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Review

Chatbot for Health Care and Oncology Applications Using Artificial Intelligence and Machine Learning: Systematic Review

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Abstract

Background: Chatbot is a timely topic applied in various fields, including medicine and health care, for human-like knowledge transfer and communication. Machine learning, a subset of artificial intelligence, has been proven particularly applicable in health care, with the ability for complex dialog management and conversational flexibility.

Objective: This review article aims to report on the recent advances and current trends in chatbot technology in medicine. A brief historical overview, along with the developmental progress and design characteristics, is first introduced. The focus will be on cancer therapy, with in-depth discussions and examples of diagnosis, treatment, monitoring, patient support, workflow efficiency, and health promotion. In addition, this paper will explore the limitations and areas of concern, highlighting ethical, moral, security, technical, and regulatory standards and evaluation issues to explain the hesitancy in implementation.

Methods: A search of the literature published in the past 20 years was conducted using the IEEE Xplore, PubMed, Web of Science, Scopus, and OVID databases. The screening of chatbots was guided by the open-access Botlist directory for health care components and further divided according to the following criteria: diagnosis, treatment, monitoring, support, workflow, and health promotion.

Results: Even after addressing these issues and establishing the safety or efficacy of chatbots, human elements in health care will not be replaceable. Therefore, chatbots have the potential to be integrated into clinical practice by working alongside health practitioners to reduce costs, refine workflow efficiencies, and improve patient outcomes. Other applications in pandemic support, global health, and education are yet to be fully explored.

Conclusions: Further research and interdisciplinary collaboration could advance this technology to dramatically improve the quality of care for patients, rebalance the workload for clinicians, and revolutionize the practice of medicine.

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KEYWORDS

chatbot; artificial intelligence; machine learning; health; medicine; communication; diagnosis; cancer therapy; ethics; medical biophysics; mobile phone

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Introduction

Background

Artificial intelligence (AI) is at the forefront of transforming numerous aspects of our lives by modifying the way we analyze information and improving decision-making through problem solving, reasoning, and learning. Machine learning (ML) is a subset of AI that improves its performance based on the data provided to a generic algorithm from experience rather than defining rules in traditional approaches [1]. Advancements in ML have provided benefits in terms of accuracy, decision-making, quick processing, cost-effectiveness, and handling of complex data [2]. Chatbots, also known as chatter robots, smart bots, conversational agents, digital assistants, or intellectual agents, are prime examples of AI systems that have evolved from ML. The Oxford dictionary defines a chatbot as "a computer program that can hold a conversation with a person, usually over the internet." They can also be physical entities designed to socially interact with humans or other robots. Predetermined responses are then generated by analyzing user input, on text or spoken ground, and accessing relevant knowledge [3]. Problems arise when dealing with more complex situations in dynamic environments and managing social conversational practices according to specific contexts and unique communication strategies [4].

Given these effectual benefits, it is not surprising that chatbots have rapidly evolved over the past 2 decades and integrated themselves into numerous fields, such as entertainment, travel, gaming, robotics, and security. Chatbots have been proven to be particularly applicable in various health care components that usually involve face-to-face interactions. With their ability for complex dialog management and conversational flexibility, integration of chatbot technology into clinical practice may reduce costs, refine workflow efficiencies, and improve patient outcomes [5]. A web-based, self-report survey examining physicians' perspectives found positive benefits of health care chatbots in managing one's own health; for improved physical, psychological, and behavioral outcomes; and most notably, for administrative purposes [6]. In light of the opportunities provided by this relatively new technology, potential limitations and areas of concern may arise that could potentially harm users. Concerns regarding accuracy, cybersecurity, lack of empathy, and technological maturity are reported as potential factors associated with the delay in chatbot acceptability or integration into health care [7].

Objectives

This narrative review paper reports on health care components for chatbots, with a focus on cancer therapy. The rest of this paper is organized as follows: first, we introduce the developmental progress with a general overview of the architecture, design concepts, and types of chatbots; the main *Results* section focuses on the role that chatbots play in areas related to oncology, such as diagnosis, treatment, monitoring, support, workflow efficiency, and health promotion; and the *Discussion* section analyzes potential limitations and concerns for successful implementation while addressing future applications and research topics.

Methods

This review focuses on articles from peer-reviewed journals and conference proceedings. The following databases were searched from October to December 2020 for relevant and current studies from 2000 to 2020: IEEE Xplore, PubMed, Web of Science, Scopus, and OVID. The literature search used the following key terms: *chatbot*, *chatter robot*, *conversational agent*, *artificial intelligence*, and *machine learning*. For further refinement, these key terms were combined with more specific terms aligned with the focus of the paper. This included *healthcare*, *cancer therapy*, *oncology*, *diagnosis*, *treatment*, *radiation therapy*, and *radiotherapy*. The searches were not limited by language or study design. Letters and technical reports were excluded from the search. The full list of sources and search strategies is available from the authors.

The screening of chatbots was guided by a systematic review process from the Botlist directory during the period of January 2021. This directory was chosen as it was open-access and categorized the chatbots under many different categories (ie, health care, communication, and entertainment) and contained many commonly used messaging services (ie, Facebook Messenger, Discord, Slack, Kik, and Skype). A total of 78 chatbots were identified for health care components and further divided according to the following criteria: diagnosis, treatment, monitoring, support, workflow, and health promotion. It should be noted that using the health filters from a web directory limits the results to the search strategy and marketing label. Thus, the results from equivalent studies may differ when repeated.

Results

Chatbot History and Evolution

The idea of a chatbot was first introduced in 1950 when Alan Turing proposed the question, "Can machines think?" [8]. The earliest forms were designed to pass the Turing test and mimic human conversations as much as possible. In 1966, ELIZA (MIT Artificial Intelligence Library) was the first known chatbot developed to act as a psychotherapist, using pattern matching and template-based responses to converse in a question-based format [9]. Improvements were made to build a more human-like and personalized entity by incorporating a personality in PARRY (developed Kenneth Colby) that simulated a paranoid patient [10]. One of the most well-known chatbots is ALICE, developed in 1995 by Richard Wallace, which uses a pattern-matching technique to retrieve example sentences from output templates and avoid inappropriate responses [11]. A renewed interest in AI and advances in ML have led to the growing use and availability of chatbots in various fields [12]. SmarterChild (ActiveBuddy, Inc) [13] became widely accessible through messenger apps, followed by more familiar web-based assistants using voice-activated systems, such as Apple Siri, Amazon Alexa, Google Assistant, and Microsoft Cortana. On the basis of our analysis (Figure 1), the most popular developments of chatbots for health care purposes are diagnostics, patient support (ie, mental health counseling), and health promotion. Some of these applications will be further explored in the following section for cancer applications.

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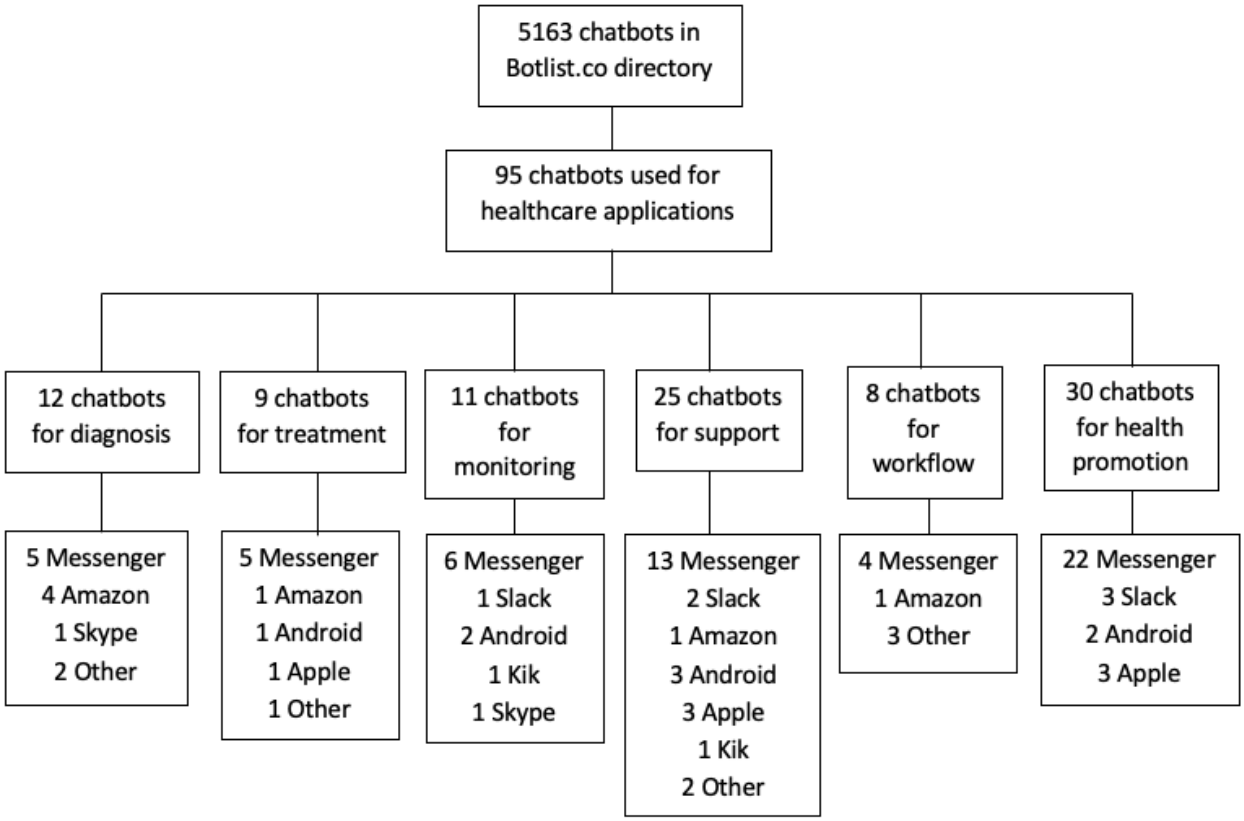
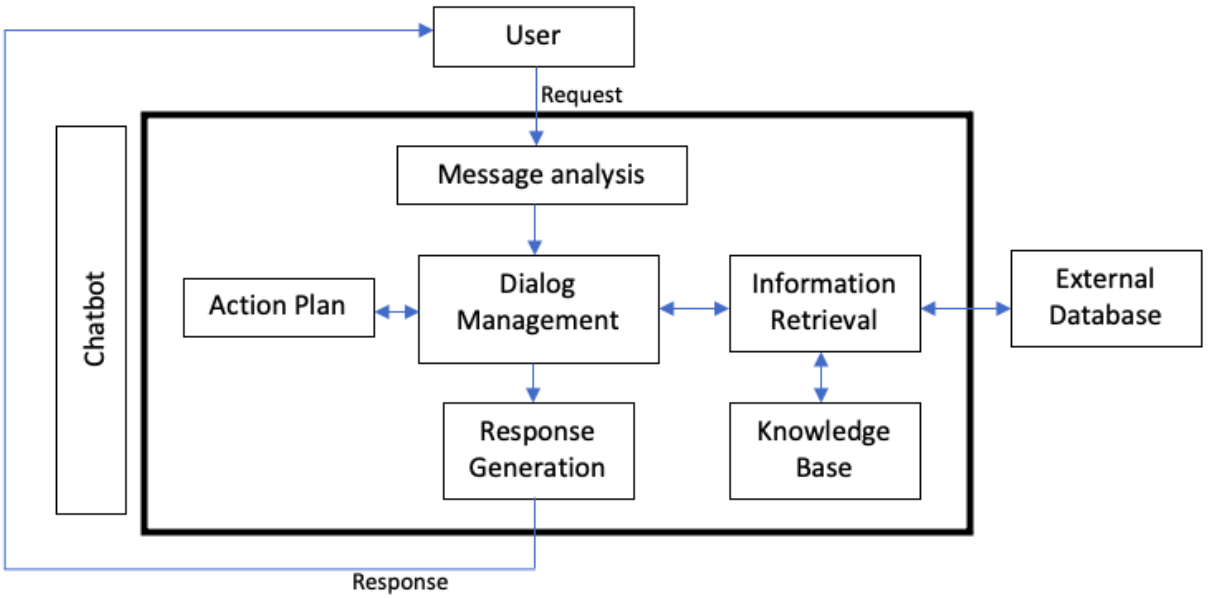
Figure 1. Search and screening for health care chatbots. Chatbots using more than one platform are included.



Chatbot General Architecture

Although there are a variety of techniques for the development of chatbots, the general layout is relatively straightforward. As a computer application that uses ML to mimic human conversation, the underlying concept is similar for all types with 4 essential stages (input processing, input understanding, response generation, and response selection) [14]. A simplified general chatbot architecture is illustrated in Figure 2. First, the user makes a request, in text or speech format, which is received and interpreted by the chatbot. From there, the processed information could be remembered, or more details could be requested for clarification. After the request is understood, the requested actions are performed, and the data of interest are retrieved from the database or external sources [15].

Figure 2. Schematic representation of general chatbot architecture.



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Chatbot Types

With the vast number of algorithms, tools, and platforms available, understanding the different types and end purposes of these chatbots will assist developers in choosing the optimal tools when designing them to fit the specific needs of users. These categories are not exclusive, as chatbots may possess multiple characteristics, making the process more variable. The 5 main types are described below [15]. Textbox 1 describes some examples of the recommended apps for each type of chatbot but are not limited to the ones specified.

Knowledge domain classification is based on accessible knowledge or the data used to train the chatbot. Under this category are the open domain for general topics and the closed domain focusing on more specific information. Service-provided classification is dependent on sentimental proximity to the user and the amount of intimate interaction dependent on the task performed. This can be further divided into interpersonal for providing services to transmit information, intrapersonal for companionship or personal support to humans, and interagent to communicate with other chatbots [14]. The next classification is based on goals with the aim of achievement, subdivided into informative, conversational, and task based. Response generation chatbots, further classified as rule based, retrieval based, and generative, account for the process of analyzing inputs and generating responses [16]. Finally, human-aided classification incorporates human computation, which provides more flexibility and robustness but lacks the speed to accommodate more requests [17].

Textbox 1. Recommended health care components for the different types of chatbots.

Knowledge domain

- Open domain: responding to more general and broader topics that can be easily searched within databases; may be the preferred chatbot type for routine symptom screening, connecting to providers or services, or health promotion apps
- Closed domain: responding to complex or specific questions requiring more in-depth research; may be the preferred chatbot type for treatment planning or recommendation

Service provided

- Interpersonal: used mainly to transmit information without much intimate connection with users; may be the preferred chatbot type for imaging diagnostics or hereditary assessment where the main duty is to relay factual information to users
- Intrapersonal: tailored for companionship or support; may be the preferred chatbot type for counseling, emotional support, or health promotion that requires a sense of human touch
- Interagent: used for communicating with other chatbots or computer systems; may be the preferred chatbot type for administration purposes when transferring patient information between locations

Goal based

- Informative: designed to provide information from warehouse database or inventory entry; may be the preferred chatbot type for connecting patients with resources or remote patient monitoring
- Conversational: built with the purpose of conversing with users as naturally as possible; may be the preferred chatbot type for counseling, emotional support, or health promotion
- Task based: only performs 1 specific task where actions are predetermined; may be the preferred chatbot type for screening and diagnostics

Response generation

- Uses pattern matching when the domain is narrow and sufficient data are available to train the system; may be the preferred chatbot type for screening and diagnostics

Human aided

- Incorporates human computation that increases flexibility and robustness but decreases speed; may be the preferred chatbot type for most apps except for support or workflow efficiency, where speed is an essential factor in the delivery of care

Chatbots in Cancer Therapy

Overview

Cancer has become a major health crisis and is the second leading cause of death in the United States [18]. The exponentially increasing number of patients with cancer each year may be because of a combination of carcinogens in the environment and improved quality of care. The latter aspect could explain why cancer is slowly becoming a chronic disease that is manageable over time [19]. Added life expectancy poses new challenges for both patients and the health care team. For example, many patients now require extended at-home support and monitoring, whereas health care workers deal with an increased workload. Although clinicians' knowledge base in the use of scientific evidence to guide decision-making has expanded, there are still many other facets to the quality of care that has yet to catch up. Key areas of focus are safety, effectiveness, timeliness, efficiency, equitability, and patient-centered care [20].

Chatbots have the potential to address many of the current concerns regarding cancer care mentioned above. This includes

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the triple aim of health care that encompasses improving the experience of care, improving the health of populations, and reducing per capita costs [21]. Chatbots can improve the quality or experience of care by providing efficient, equitable, and personalized medical services. We can think of them as intermediaries between physicians for facilitating the history taking of sensitive and intimate information before consultations. They could also be thought of as decision aids that deliver regular feedback on disease progression and treatment reactions to help clinicians better understand individual conditions. Preventative measures of cancer have become a priority worldwide, as early detection and treatment alone have not been effective in eliminating this disease [22]. Physical, psychological, and behavioral improvements of underserved or vulnerable populations may even be possible through chatbots, as they are so readily accessible through common messaging platforms. Health promotion use, such as lifestyle coaching, healthy eating, and smoking cessation, has been one of the most common chatbots according to our search. In addition, chatbots could help save a significant amount of health care costs and resources. Newer therapeutic innovations have come with a heavy price tag, and out-of-pocket expenses have placed a significant strain on patients' financial well-being [23]. With chatbots implemented in cancer care, consultations for minor health concerns may be avoided, which allows clinicians to spend more time with patients who need their attention the most. Costs may also be reduced by delivering medical services more efficiently. For example, the workflow can be streamlined by assisting physicians in administrative tasks, such as scheduling appointments, providing medical information, or locating clinics.

With the rapidly increasing applications of chatbots in health care, this section will explore several areas of development and innovation in cancer care. Various examples of current chatbots provided below will illustrate their ability to tackle the triple aim of health care. The specific use case of chatbots in oncology with examples of actual products and proposed designs are outlined in Table 1.

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Table 1. Use case for chatbots in oncology, with examples of current specific applications or proposed designs.

Use case and application, chatbot	Function
Screening and diagnosis	
Imaging diagnostic	
Medical Sieve [24]	Examines radiological images to aid clinicians with diagnosis
Symptom screening	
Quro [25]	Presynopsis based on symptoms and history to predict user conditions
Buoy Health [26]	Assists in identifying the cause of illnesses and provides medical advice
Harshitha breast cancer screening [27]	Dialog flow to give an initial analysis of breast cancer symptoms
Babylon [28]	Symptom checker
Your.md [28]	Symptom checker
Ada [28]	Symptom checker
Hereditary assessment	
ItRuns [29]	Gathers family history information at the population level to determine the risk of hereditary cancer
Treatment	
Patient treatment recommendation	
Mathew [30]	Identifies symptoms, predicts the disease using a symptom–disease data set, and recommends a suitable treatment
Madhu [31]	Provides a list of available treatments for various diseases and informs the user of the composition and prescribed use of the medications
Connecting patients with providers or resources	
Divya [32]	Engages patients regarding their symptoms to provide a personalized diagnosis and connects with appropriate medical service
Rarhi [33]	Provides a diagnosis based on symptoms, measures the seriousness, and connects with a physician
Physician treatment planning	
Watson for Oncology [34]	Examines data from records and medical notes to generate an evidence-based treatment plan for oncologists
Monitoring	
Remote patient monitoring	
STREAMD [35]	Provides access to care instructions and educational information
Conversa [35]	Provides access to care instructions and educational information
Memora Health [35]	Provides access to care instructions and educational information
AiCure [36]	Coaches patients to manage their condition and adhere to instructions
Infinity [37]	Assesses health outcomes and impact of phone-based monitoring for patients with cancer aged ≥65 years
Vik [38,39]	Addresses patients' daily needs and concerns
Support	
Counseling	
Vivobot [40]	Cognitive and behavioral intervention for positive psychology skills and promoting well-being
Emotional support	
Youper [26]	Daily emotional support and mental health tracking
Wysa [26]	Daily emotional support and mental health tracking
Replika [26]	Daily emotional support and mental health tracking
Unmind [26]	Daily emotional support and mental health tracking

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Use case and application, chatbot	Function
Shim [26]	Daily emotional support and mental health tracking
Woebot [41]	Daily emotional support and mental health tracking
Workflow efficiency	
Administration	
Sense.ly [42]	Assists in monitoring appointments, manages patients' conditions, and suggests therapies
Careskore [42]	Tracks vitals and anticipates the need for hospital admissions
Mandy [43]	Assists health care staff by automating the patient intake process
Patient encounter	
HOLMeS [44]	Supports diagnosis, chooses the proper treatment pathway, and provides prevention check-ups
Health promotion	
General lifestyle coaching	
SWITCHes [45]	Tracks patients' progress, provides insight to physicians, and suggests suitable activities
CoachAI [46]	Tracks patients' progress, provides insight to physicians, and suggests suitable activities
WeightMentor [47]	Provides self-help motivation for weight loss maintenance and allows for open conversation
Healthy eating	
Health Hero [48]	Guides in making informed decisions around food choices to change unhealthy eating habits
Tasteful Bot [48]	Guides in making informed decisions around food choices to change unhealthy eating habits
Forksy [48]	Guides in making informed decisions around food choices to change unhealthy eating habits
SLOWbot [49]	Guides in making informed decisions around food choices to change unhealthy eating habits
Smoking cessation	
SMAG [50]	Cognitive behavioral therapy
Bella [51]	Coaches to help quit smoking

Diagnostics and Screening

An accurate diagnosis is critical for appropriate care to be administered. In terms of cancer diagnostics, AI-based computer vision is a function often used in chatbots that can recognize subtle patterns from images. This would increase physicians' confidence when identifying cancer types, as even highly trained individuals may not always agree on the diagnosis [52]. Studies have shown that the interpretation of medical images for the diagnosis of tumors performs equally well or better with AI compared with experts [53-56]. In addition, automated diagnosis may be useful when there are not enough specialists to review the images. This was made possible through deep learning algorithms in combination with the increasing availability of databases for the tasks of detection, segmentation, and classification [57]. For example, Medical Sieve (IBM Corp) is a chatbot that examines radiological images to aid and communicate with cardiologists and radiologists to identify issues quickly and reliably [24]. Similarly, InnerEye (Microsoft Corp) is a computer-assisted image diagnostic chatbot that recognizes cancers and diseases within the eye but does not directly interact with the user like a chatbot [42]. Even with the rapid advancements of AI in cancer imaging, a major issue is the lack of a gold standard [58].

From the patient's perspective, various chatbots have been designed for symptom screening and self-diagnosis. The ability of patients to be directed to urgent referral pathways through early warning signs has been a promising market. Decreased wait times in accessing health care services have been found to correlate with improved patient outcomes and satisfaction [59-61]. The automated chatbot, Quro (Quro Medical, Inc), provides presynopsis based on symptoms and history to predict user conditions (average precision approximately 0.82) without a form-based data entry system [25]. In addition to diagnosis, Buoy Health (Buoy Health, Inc) assists users in identifying the cause of their illness and provides medical advice [26]. Another chatbot designed by Harshitha et al [27] uses dialog flow to provide an initial analysis of breast cancer symptoms. It has been proven to be 95% accurate in differentiating between normal and cancerous images. Even with promising results, there are still potential areas for improvement. A study of 3 mobile app–based chatbot symptom checkers, Babylon (Babylon Health, Inc), Your.md (Healthily, Inc), and Ada (Ada, Inc), indicated that sensitivity remained low at 33% for the detection of head and neck cancer [28]. The number of studies assessing the development, implementation, and effectiveness are still relatively limited compared with the diversity of chatbots currently available. Further studies are required to establish the efficacy across various conditions and populations. Nonetheless, chatbots for self-diagnosis are an effective way of advising patients as the first point of contact if accuracy and sensitivity requirements can be satisfied.

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Early cancer detection can lead to higher survival rates and improved quality of life. Inherited factors are present in 5% to 10% of cancers, including breast, colorectal, prostate, and rare tumor syndromes [62]. Family history collection is a proven way of easily accessing the genetic disposition of developing cancer to inform risk-stratified decision-making, clinical decisions, and cancer prevention [63]. The web-based chatbot ItRuns (ItRunsInMyFamily) gathers family history information at the population level to determine the risk of hereditary cancer [29]. We have yet to find a chatbot that incorporates deep learning to process large and complex data sets at a cellular level. Although not able to directly converse with users, DeepTarget [64] and deepMirGene [65] are capable of performing miRNA and target predictions using expression data with higher accuracy compared with non–deep learning models. With the advent of phenotype–genotype predictions, chatbots for genetic screening would greatly benefit from image recognition. New screening biomarkers are also being discovered at a rapid speed, so continual integration and algorithm training are required. These findings align with studies that demonstrate that chatbots have the potential to improve user experience and accessibility and provide accurate data collection [66].

Treatment

Chatbots are now able to provide patients with treatment and medication information after diagnosis without having to directly contact a physician. Such a system was proposed by Mathew et al [30] that identifies the symptoms, predicts the disease using a symptom–disease data set, and recommends a suitable treatment. Although this may seem as an attractive option for patients looking for a fast solution, computers are still prone to errors, and bypassing professional inspection may be an area of concern. Chatbots may also be an effective resource for patients who want to learn why a certain treatment is necessary. Madhu et al [31] proposed an interactive chatbot app that provides a list of available treatments for various diseases, including cancer. This system also informs the user of the composition and prescribed use of medications to help select the best course of action. The diagnosis and course of treatment for cancer are complex, so a more realistic system would be a chatbot used to connect users with appropriate specialists or resources. A text-to-text chatbot by Divya et al [32] engages patients regarding their medical symptoms to provide a personalized diagnosis and connects the user with the appropriate physician if major diseases are detected. Rarhi et al [33] proposed a similar design that provides a diagnosis based on symptoms, measures the seriousness, and connects users with a physician if needed [33]. In general, these systems may greatly help individuals in conducting daily check-ups, increase awareness of their health status, and encourage users to seek medical assistance for early intervention.

Chatbots have also been used by physicians during treatment planning. For example, IBM's Watson for Oncology examines data from records and medical notes to generate an evidence-based treatment plan for oncologists [34]. Studies have shown that Watson for Oncology still cannot replace experts at this moment, as quite a few cases are not consistent with experts (approximately 73% concordant) [67,68]. Nonetheless, this could be an effective decision-making tool for cancer therapy to standardize treatments. Although not specifically an oncology app, another chatbot example for clinicians' use is the chatbot Safedrugbot (Safe In Breastfeeding) [69]. This is a chat messaging service for health professionals offering assistance with appropriate drug use information during breastfeeding. Promising progress has also been made in using AI for radiotherapy to reduce the workload of radiation staff or identify at-risk patients by collecting outcomes before and after treatment [70]. An ideal chatbot for health care professionals' use would be able to accurately detect diseases and provide the proper course of recommendations, which are functions currently limited by time and budgetary constraints. Continual algorithm training and updates would be necessary because of the constant improvements in current standards of care. Further refinements and testing for the accuracy of algorithms are required before clinical implementation [71]. This area holds tremendous potential, as an estimated ≥50% of all patients with cancer have used radiotherapy during the course of their treatment.

Patient Monitoring

Chatbots have been implemented in remote patient monitoring for postoperative care and follow-ups. The health care sector is among the most overwhelmed by those needing continued support outside hospital settings, as most patients newly diagnosed with cancer are aged ≥65 years [72]. The integration of this application would improve patients' quality of life and relieve the burden on health care providers through better disease management, reducing the cost of visits and allowing timely follow-ups. In terms of cancer therapy, remote monitoring can support patients by enabling higher dose chemotherapy drug delivery, reducing secondary hospitalizations, and providing health benefits after surgery [73-75].

StreamMD (StreamMD, Inc), Conversa (Conversa Health, Inc), and Memora Health (Memora Health, Inc) are chatbots that function on existing messaging platforms that provide patients with immediate access to care instructions and educational information [35]. To ensure that patients adhere to instructions, AiCure (AiCure, Inc) uses a smartphone webcam to coach them in managing their condition. Recently, a chatbot architecture was proposed for patient support based on microservices to provide personalized eHealth functionalities and data storage [36]. Several studies have supported the application of chatbots for patient monitoring [76]. The semiautomized messaging chatbot Infinity (Facebook, Inc) was used to assess the health outcomes and health care impacts of phone-based monitoring for patients with cancer aged ≥65 years. After 2 years of implementation, there was a 97% satisfactory rate, and 87% considered monitoring useful, with the most reported benefit being treatment management and moral support [37]. Similar results were discovered in 2 studies using Vik (WeFight, Inc), a text-based chatbot that responds to the daily needs and concerns of patients and their relatives with personal insights. A 1-year prospective study of 4737 patients with breast cancer reported a 94% overall satisfaction rate [38]. A more in-depth analysis of the 132,970 messages showed that users were more likely to answer multiple-choice questions compared with open-ended ones, chatbots improved treatment compliance rate

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by >20% (P=.04), and intimate or sensitive topics were openly discussed. An area of concern is that retention rates drastically decreased to 31% by the end of this study. The other study was a phase 3, blind, noninferiority randomized controlled trial (n=132) to assess the level of patient satisfaction with the answers provided by chatbots versus those by physicians [39]. Using 12 frequently asked questions on breast cancer, participants were split into 2 groups to rate the quality of answers from chatbots or physicians. Among patients with breast cancer in treatment or remission, chatbot answers were shown to be noninferior (P<.001), with a success rate of 69% compared with 64% in the physician groups. Concerns regarding the chatbot's ability to successfully answer more complex questions or detect differences between major and minor symptoms still remain to be addressed.

Further refinements and large-scale implementations are still required to determine the benefits across different populations and sectors in health care [26]. Although overall satisfaction is found to be relatively high, there is still room for improvement by taking into account user feedback tailored to the patient's changing needs during recovery. In combination with wearable technology and affordable software, chatbots have great potential to affect patient monitoring solutions.

Patient Support

The prevalence of cancer is increasing along with the number of survivors of cancer, partly because of improved treatment techniques and early detection [77]. These individuals experience added health problems, such as infections, chronic diseases, psychological issues, and sleep disturbances, which often require specific needs that are not met by many practitioners (ie, medical, psychosocial, informational, and proactive contact) [78]. A number of these individuals require support after hospitalization or treatment periods. Maintaining autonomy and living in a self-sustaining way within their home environment is especially important for older populations [79]. Implementation of chatbots may address some of these concerns, such as reducing the burden on the health care system and supporting independent living.

With psychiatric disorders affecting at least 35% of patients with cancer, comprehensive cancer care now includes psychosocial support to reduce distress and foster a better quality of life [80]. The first chatbot was designed for individuals with psychological issues [9]; however, they continue to be used for emotional support and psychiatric counseling with their ability to express sympathy and empathy [81]. Health-based chatbots delivered through mobile apps, such as Woebot (Woebot Health, Inc), Youper (Youper, Inc), Wysa (Wysa, Ltd), Replika (Luka, Inc), Unmind (Unmind, Inc), and Shim (Shim, Inc), offer daily emotional support and mental health tracking [26]. A study performed on Woebot, developed based on cognitive behavioral therapy, showed that depressive symptoms were significantly reduced, and participants were more receptive than in traditional therapies [41]. This agreed with the Shim results, also using the same type of therapy, which showed that the intervention was highly engaging, improved well-being, and reduced stress [82]. When another chatbot was developed based on the structured association technique counseling method, the user's motivation was enhanced, and stress was reduced [83]. Similarly, a graph-based chatbot has been proposed to identify the mood of users through sentimental analysis and provide human-like responses to comfort patients [84]. Vivobot (HopeLab, Inc) provides cognitive and behavioral interventions to deliver positive psychology skills and promote well-being. This psychiatric counseling chatbot was effective in engaging users and reducing anxiety in young adults after cancer treatment [40]. The limitation to the abovementioned studies was that most participants were young adults, most likely because of the platform on which the chatbots were available. In addition, longer follow-up periods with larger and more diverse sample sizes are needed for future studies. Chatbots used for psychological support hold great potential, as individuals are more comfortable disclosing personal information when no judgments are formed, even if users could still discriminate their responses from that of humans [82,85].

Workflow Efficiency

Electronic health records have improved data availability but also increased the complexity of the clinical workflow, contributing to ineffective treatment plans and uninformed management [86]. A streamlined process using ML techniques would allow clinicians to spend more time with patients by decreasing the time spent on data entry through the ease of documentation, exposing relevant patient information from the chart, automatically authorizing payment, or reducing medical errors [58]. For example, Mandy is a chatbot that assists health care staff by automating the patient intake process [43]. Using a combination of data-driven natural language processing with knowledge-driven diagnostics, this chatbot interviews the patient, understands their chief complaints, and submits reports to physicians for further analysis [43]. Similarly, Sense.ly (Sense.ly, Inc) acts as a web-based nurse to assist in monitoring appointments, managing patients' conditions, and suggesting therapies. Another chatbot that reduces the burden on clinicians and decreases wait time is Careskore (CareShore, Inc), which tracks vitals and anticipates the need for hospital admissions [42]. Chatbots have also been proposed to autonomize patient encounters through several advanced eHealth services. In addition to collecting data and providing bookings, Health OnLine Medical Suggestions or HOLMES (Wipro, Inc) interacts with patients to support diagnosis, choose the proper treatment pathway, and provide prevention check-ups [44]. Although the use of chatbots in health care and cancer therapy has the potential to enhance clinician efficiency, reimbursement codes for practitioners are still lacking before universal implementation. In addition, studies will need to be conducted to validate the effectiveness of chatbots in streamlining workflow for different health care settings. Nonetheless, chatbots hold great potential to complement telemedicine by streamlining medical administration and autonomizing patient encounters.

Health Promotion

Survivors of cancer, particularly those who underwent treatment during childhood, are more susceptible to adverse health risks and medical complications. Consequently, promoting a healthy lifestyle early on is imperative to maintain quality of life, reduce mortality, and decrease the risk of secondary cancers [87].

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According to the analysis from the web directory, health promotion chatbots are the most commonly available; however, most of them are only available on a single platform. Thus, interoperability on multiple common platforms is essential for adoption by various types of users across different age groups. In addition, voice and image recognition should also be considered, as most chatbots are still text based.

Healthy diets and weight control are key to successful disease management, as obesity is a significant risk factor for chronic conditions. Chatbots have been incorporated into health coaching systems to address health behavior modifications. For example, CoachAI and Smart Wireless Interactive Health System used chatbot technology to track patients' progress, provide insight to physicians, and suggest suitable activities [45,46]. Another app is Weight Mentor, which provides self-help motivation for weight loss maintenance and allows for open conversation without being affected by emotions [47]. Health Hero (Health Hero, Inc), Tasteful Bot (Facebook, Inc), Forksy (Facebook, Inc), and SLOWbot (iaso heath, Inc) guide users to make informed decisions on food choices to change unhealthy eating habits [48,49]. The effectiveness of these apps cannot be concluded, as a more rigorous analysis of the development, evaluation, and implementation is required. Nevertheless, chatbots are emerging as a solution for healthy lifestyle promotion through access and human-like communication while maintaining anonymity.

Most would assume that survivors of cancer would be more inclined to practice health protection behaviors with extra guidance from health professionals; however, the results have been surprising. Smoking accounts for at least 30% of all cancer deaths; however, up to 50% of survivors continue to smoke [88]. The benefit of using chatbots for smoking cessation across various age groups has been highlighted in numerous studies showing improved motivation, accessibility, and adherence to treatment, which have led to increased smoking abstinence [89-91]. The cognitive behavioral therapy–based chatbot SMAG, supporting users over the Facebook social network, resulted in a 10% higher cessation rate compared with control groups [50]. Motivational interview–based chatbots have been proposed with promising results, where a significant number of patients showed an increase in their confidence and readiness to quit smoking after 1 week [92]. No studies have been found to assess the effectiveness of chatbots for smoking cessation in terms of ethnic, racial, geographic, or socioeconomic status differences. Creating chatbots with prespecified answers is simple; however, the problem becomes more complex when answers are open. Bella, one of the most advanced text-based chatbots on the market advertised as a coach for adults, gets stuck when responses are not prompted [51]. Therefore, the reaction to unexpected responses is still an area in progress. Given all the uncertainties, chatbots hold potential for those looking to quit smoking, as they prove to be more acceptable for users when dealing with stigmatized health issues compared with general practitioners [7].

Discussion

Challenges and Limitations

AI and ML have advanced at an impressive rate and have revealed the potential of chatbots in health care and clinical settings. AI technology outperforms humans in terms of image recognition, risk stratification, improved processing, and 24/7 assistance with data and analysis. However, there is no machine substitute for higher-level interactions, critical thinking, and ambiguity [93]. Chatbots create added complexity that must be identified, addressed, and mitigated before their universal adoption in health care.

Hesitancy from physicians and poor adoption by patients is a major barrier to overcome, which could be explained by many of the factors discussed in this section. A cross-sectional web-based survey of 100 practicing physicians gathered the perceptions of chatbots in health care [6]. Although a wide variety of beneficial aspects were reported (ie, management of health and administration), an equal number of concerns were present. Over 70% of physicians believe that chatbots cannot effectively care for all the patients' needs, cannot display human emotion, cannot provide detailed treatment plans, and pose a risk if patients self-diagnose or do not fully comprehend their diagnosis. If the limitations of chatbots are better understood and mitigated, the fears of adopting this technology in health care may slowly subside. The *Discussion* section ends by exploring the challenges and questions for health care professionals, patients, and policy makers.

Moral and Ethical Constraints

The use of chatbots in health care presents a novel set of moral and ethical challenges that must be addressed for the public to fully embrace this technology. Issues to consider are privacy or confidentiality, informed consent, and fairness. Each of these concerns is addressed below. Although efforts have been made to address these concerns, current guidelines and policies are still far behind the rapid technological advances [94].

Health care data are highly sensitive because of the risk of stigmatization and discrimination if the information is wrongfully disclosed. The ability of chatbots to ensure privacy is especially important, as vast amounts of personal and medical information are often collected without users being aware, including voice recognition and geographical tracking. The public's lack of confidence is not surprising, given the increased frequency and magnitude of high-profile security breaches and inappropriate use of data [95]. Unlike financial data that becomes obsolete after being stolen, medical data are particularly valuable, as they are not perishable. Privacy threats may break the trust that is essential to the therapeutic physician–patient relationship and inhibit open communication of relevant clinical information for proper diagnosis and treatment [96].

Chatbots experience the *BlackBox* problem, which is similar to many computing systems programmed using ML that are trained on massive data sets to produce multiple layers of connections. Although they are capable of solving complex problems that are unimaginable by humans, these systems remain highly

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opaque, and the resulting solutions may be unintuitive. This means that the systems' behavior is hard to explain by merely looking inside, and understanding exactly how they are programmed is nearly impossible. For both users and developers, transparency becomes an issue, as they are not able to fully understand the solution or intervene to predictably change the chatbot's behavior [97]. With the novelty and complexity of chatbots, obtaining valid informed consent where patients can make their own health-related risk and benefit assessments becomes problematic [98]. Without sufficient transparency, deciding how certain decisions are made or how errors may occur reduces the reliability of the diagnostic process. The *Black Box* problem also poses a concern to patient autonomy by potentially undermining the shared decision-making between physicians and patients [99]. The chatbot's personalized suggestions are based on algorithms and refined based on the user's past responses. The removal of options may slowly reduce the patient's awareness of alternatives and interfere with free choice [100].

Finally, the issue of fairness arises with algorithm bias when data used to train and test chatbots do not accurately reflect the people they represent [101]. As the AI field lacks diversity, bias at the level of the algorithm and modeling choices may be overlooked by developers [102]. In a study using 2 cases, differences in prediction accuracy were shown concerning gender and insurance type for intensive care unit mortality and psychiatric readmissions [103]. On a larger scale, this may exacerbate barriers to health care for minorities or underprivileged individuals, leading to worse health outcomes. Identifying the source of algorithm bias is crucial for addressing health care disparities between various demographic groups and improving data collection.

Chances for Errors

Although studies have shown that AI technologies make fewer mistakes than humans in terms of diagnosis and decision-making, they still bear inherent risks for medical errors [104]. The interpretation of speech remains prone to errors because of the complexity of background information, accuracy of linguistic unit segmentation, variability in acoustic channels, and linguistic ambiguity with homophones or semantic expressions. Chatbots are unable to efficiently cope with these errors because of the lack of common sense and the inability to properly model real-world knowledge [105]. Another factor that contributes to errors and inaccurate predictions is the large, noisy data sets used to train modern models because large quantities of high-quality, representative data are often unavailable [58]. In addition to the concern of accuracy and validity, addressing clinical utility and effectiveness of improving patients' quality of life is just as important. With the increased use of diagnostic chatbots, the risk of overconfidence and overtreatment may cause more harm than benefit [99]. There is still clear potential for improved decision-making, as diagnostic deep learning algorithms were found to be equivalent to health care professionals in classifying diseases in terms of accuracy [106]. These issues presented above all raise the question of who is legally liable for medical errors. Avoiding responsibility becomes easier when numerous individuals are involved at multiple stages, from development to clinical applications [107]. Although the law has been lagging and litigation is still a gray area, determining legal liability becomes increasingly pressing as chatbots become more accessible in health care.

Regulatory Considerations

Regulatory standards have been developed to accommodate for rapid modifications and ensure the safety and effectiveness of AI technology, including chatbots. The US Food and Drug Administration has recognized the distinctiveness of chatbots compared with traditional medical devices by defining the software within the medical device category and has outlined its approach through the Digital Health Innovation Action Plan [108]. With the growing number of AI algorithms approved by the Food and Drug Administration, they opened public consultations for setting performance targets, monitoring performance, and reviewing when performance strays from preset parameters [102]. The American Medical Association has also adopted the Augmented Intelligence in Health Care policy for the appropriate integration of AI into health care by emphasizing the design approach and enhancement of human intelligence [109]. An area of concern is that chatbots are not covered under the Health Insurance Portability and Accountability Act; therefore, users' data may be unknowingly sold, traded, and marketed by companies [110]. On the other hand, overregulation may diminish the value of chatbots and decrease the freedom for innovators. Consequently, balancing these opposing aspects is essential to promote benefits and reduce harm to the health care system and society.

Future Directions

Chatbots' robustness of integrating and learning from large clinical data sets, along with its ability to seamlessly communicate with users, contributes to its widespread integration in various health care components. Given the current status and challenges of cancer care, chatbots will likely be a key player in this field's continual improvement. More specifically, they hold promise in addressing the triple aim of health care by improving the quality of care, bettering the health of populations, and reducing the burden or cost of our health care system. Beyond cancer care, there is an increasing number of creative ways in which chatbots could be applicable to health care. During the COVID-19 pandemic, chatbots were already deployed to share information, suggest behavior, and offer emotional support. They have the potential to prevent misinformation, detect symptoms, and lessen the mental health burden during global pandemics [111]. At the global health level, chatbots have emerged as a socially responsible technology to provide equal access to quality health care and break down the barriers between the rich and poor [112]. To further advance medicine and knowledge, the use of chatbots in education for learning and assessments is crucial for providing objective feedback, personalized content, and cost-effective evaluations [113]. For example, the development of the Einstein app as a web-based physics teacher enables interactive learning and evaluations but is still far from being perfect [114]. Given chatbots' diverse applications in numerous aspects of health care, further research and interdisciplinary collaboration to

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advance this technology could revolutionize the practice of medicine.

On the basis of the discussion above, the following features are general directions of future suggestions for improvements in chatbots within cancer care in no particular order of importance:

1. Patients with cancer may feel vulnerable or fear discrimination from employers or society [115]. Security of sensitive information must be held to the highest standards, especially when personal health information is shared between providers and hospital systems.
2. An increasing number of patients are bringing internet-based information to consultations that are not critically assessed for trustworthiness or credibility. If used correctly, the additional health information could enhance understanding, improve the ability to manage their conditions, and increase confidence during interaction with physicians [116]. Unfortunately, this is often not the case, and most patients are not adequately informed regarding the proper screening of information. Ways to address this challenge include promoting awareness and developing patient management guidelines. Chatbots also have the potential to become a key player in their ability to screen for credible information. They could help vulnerable individuals critically navigate web-based cancer information, especially for the older or more chronic populations that tend to be less technologically adept.
3. Current applications of chatbots as computerized decision support systems for diagnosis and treatment are relatively limited. The targeted audience for most has been for patients' use, and few are designed to aid physicians at the point of care. Medical Sieve and Watson for Oncology are the only chatbots found in our search that are designed specifically for clinicians. There are far more AI tools in the market to help with clinical decision-making without the ability to interact with users [117]. With the rapid data collection from electronic health records, real-time predictions, and links to clinical recommendations, adding chatbot functionalities to current decision aids will only improve patient-centered care and streamline the workflow for clinicians.
4. More concrete evidence of high quality and accuracy across a broad range of conditions and populations entails more representative training data reflecting racial biases and developing peer-reviewed algorithms to reduce the *Black Box* problem.
5. Integration into the health care system, particularly with telemedicine, for seamless delivery from the beginning to the end does not mean replacing in-person care but rather complementing the health care workflow to ensure patients receive continuity and coordination of care.
6. Reimbursement of chatbot services to physicians who decide to implement this technology into their practice will likely increase adoption rates. Organizations and health providers will likely profit because chatbots allow for a more efficient and reduced cost of delivery.
7. Continual training of chatbots as new knowledge is uncovered, such as symptom patterns or standard of care, is needed.
8. As the Vik study found that users were more likely to respond to multiple-choice questions over open-ended ones [38], chatbot developers should move toward the choice with higher response rates. Studies, surveys, and focus groups should continue to be conducted to determine the best ways to converse with users.
9. Universal adoption of various technical features, such as training with additional languages, image recognition, voice recognition, user feedback to improve services according to needs, access on multiple common platforms, and reacting to unexpected responses, need to be considered.

The ability to accurately measure performance is critical for continuous feedback and improvement of chatbots, especially the high standards and vulnerable individuals served in health care. Given that the introduction of chatbots to cancer care is relatively recent, rigorous evidence-based research is lacking. Standardized indicators of success between users and chatbots need to be implemented by regulatory agencies before adoption. Once the primary purpose is defined, common quality indicators to consider are the success rate of a given action, nonresponse rate, comprehension quality, response accuracy, retention or adoption rates, engagement, and satisfaction level. The ultimate goal is to assess whether chatbots positively affect and address the 3 aims of health care. Regular quality checks are especially critical for chatbots acting as decision aids because they can have a major impact on patients' health outcomes.

Review Limitations

The systematic literature review and chatbot database search includes a few limitations. The literature review and chatbot search were all conducted by a single reviewer, which could have potentially introduced bias and limited findings. In addition, our review explored a broad range of health care topics, and some areas could have been elaborated upon and explored more deeply. Furthermore, only a limited number of studies were included for each subtopic of chatbots for oncology apps because of the scarcity of studies addressing this topic. Future studies should consider refining the search strategy to identify other potentially relevant sources that may have been overlooked and assign multiple reviews to limit individual bias.

Conclusions

As illustrated in this review, these chatbots' potential in cancer diagnostics and treatment, patient monitoring and support, clinical workflow efficiency, and health promotion have yet to be fully explored. Numerous risks and challenges will continue to arise that require careful navigation with the rapid advancements in chatbots. Consequently, weighing the gains versus threats with a critical eye is imperative. Even after laying down the proper foundations for using chatbots safely and effectively, the human element in the practice of medicine is irreplaceable and will always be present. Health care professionals have the responsibility of understanding both the benefits and risks associated with chatbots and, in turn, educating their patients.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
ML: machine learning

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Viewpoint

Secondhand Smoke Exposure of Expectant Mothers in China: Factoring in the Role of Culture in Data Collection

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Abstract

Cancer is the leading cause of death worldwide. Tobacco smoking, including secondhand smoking, causes cancer and is responsible for over 22% of global cancer deaths. The adverse impacts of secondhand smoke are more pronounced for expectant mothers, and can deteriorate both mothers' and infants' health and well-being. Research suggests that secondhand smoke significantly increases expectant mothers' risk of miscarriage, cancer, and other chronic disease conditions, and exposes their unborn babies to an increased likelihood of having life-long poor health. In China, a pregnant woman's family members, such as her husband, parents, or in-laws, are the most likely people to be smoking around her. Due to traditional Chinese cultural practices, even though some expectant mothers understand the harm of secondhand smoke, they may be reluctant to report their family members' smoking behaviors. Resulting in severe underreporting, this compromises health experts' ability to understand the severity of the issue. This paper proposes a novel approach to measure secondhand smoke exposure of pregnant women in the Chinese context. The proposed system could act as a stepping stone that inspires creative methods to help researchers more accurately measure secondhand smoking rates of expectant mothers in China. This, in turn, could help health experts better establish cancer control measures for expectant mothers and decrease their cancer risk.

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KEYWORDS

cancer; secondhand smoking; secondhand smoke; expectant mothers; pregnant women; China; transitional Chinese culture; "doing the month"; smoking; pregnancy; women; China; culture; behavior

Background

Cancer is the leading cause of death worldwide [1]. Tobacco smoking, including secondhand smoking, causes cancer and is responsible for over 22% of global cancer deaths [2]. In 2017 alone, 62.9 million disability-adjusted life years were lost in China due to cancer [3]. With the current prevalence of smoking, the situation is expected to worsen in the future [4]. China has the largest population of tobacco smokers worldwide—one in every three smokers across the globe is Chinese [4]. Different from other human addictions (eg, opioids), tobacco smoking not only harms smokers' health but also harms the health of individuals exposed to secondhand smoke [5].

While smoking has been declining in China (eg, among Chinese adults aged 30-69 years, 11.0% of smokers quit in 2010 compared to 4.2% quit rates in 1996), secondhand smoking remains a persistent public health issue that harms people's health and well-being [6]. Secondhand smoking can be

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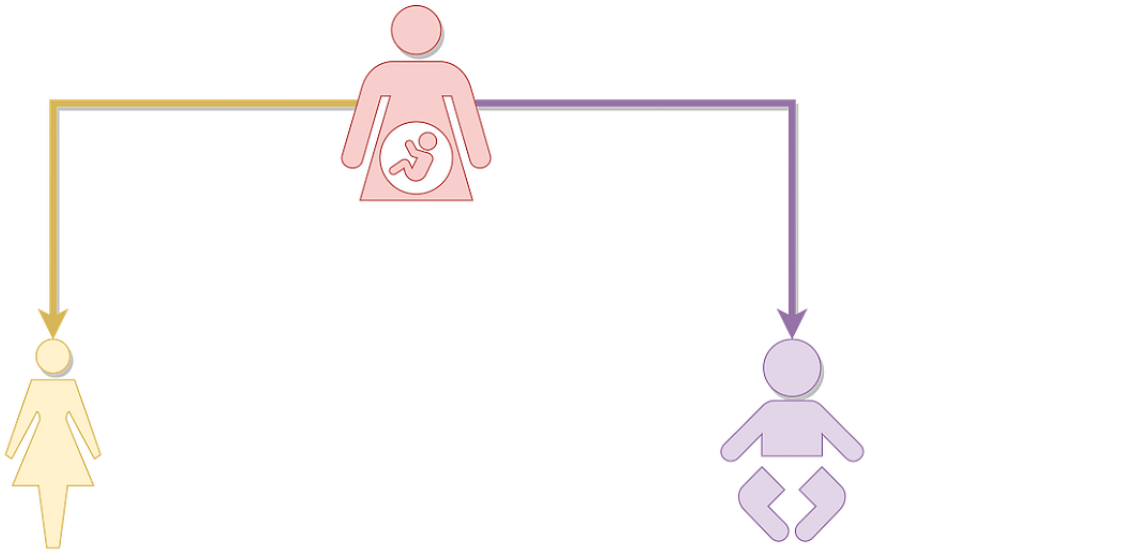
understood as nonsmokers' exposure to smoke from tobacco products due to regular contact with smokers in close proximity to them [7]. Individuals subjected to secondhand smoke face unique health challenges despite not smoking cigarettes. They are exposed to the same set of detrimental health consequences associated with tobacco smoking, ranging from physical health consequences (eg, an elevated risk of cancer) to pronounced psychological health challenges [8].

Danger of Secondhand Smoke for Expectant Mothers

Recent evidence shows that Chinese women exposed to secondhand smoke often experience a significant decline in cognitive functions, such as memory, that can last up to two years [9]. However, the situation might be worse for expectant mothers. Women may experience various health issues during pregnancy including venous thromboembolism, diabetes, hypertension, and heart disease; in addition, women are at increased risk of domestic violence when pregnant [10-12]. Additionally, for this community, exposure to toxic materials often results in harm to both the women themselves and their unborn babies [13-15]. In other words, exposure to harmful substances, such as toxic secondhand smoke, harms pregnant women at a time when health risks are more likely to affect their long-term health outcomes, in addition to causing substantial harm to their unborn babies' health [16-18]. Furthermore, secondhand smoke and its adverse effects are associated with an increased risk of infant mortality, including sudden infant death syndrome [19] (Figure 1).

Figure 1. A schematic representation of the increased health risks of secondhand smoking for expectant mothers and their infants.



- Coughing
- Headaches
- Eye and nasal irritation
- Sore throat
- Other complications during pregnancy
- Increased risk (25%-30%) for severe illness from COVID-19
- Stroke
- Heart attack
- Angina
- Complete heart failure
- Increased risk of chronic obstructive pulmonary disease
- Increased risk of other breathing problems
- Infections and complications after birth
- Cancers (eg, lung cancer risk increased by 20%-30%)

- Breastfeeding discontinuation
- Low birth weight
- Reduced neonatal head circumference
- Delayed mental development in early childhood
- Sudden infant death syndrome

"Doing the Month": A Unique Risk Factor for Secondhand Smoke Exposure

Secondhand smoking might have an even more significant impact on expectant Chinese women due to cultural practices. In China, it is common practice for partners, parents, or in-laws to take care of the pregnant woman during and beyond pregnancy to meet her basic needs [20]. Owing partially to traditional Chinese culture and social norms, immediately after women give birth to their babies, these helpers are also expected to attend to the needs and wants of women and their newborn infants during the "doing the month" ritual [21]. When followed stringently, "doing the month," a traditional Chinese cultural practice that dates back more than 2000 years, requires women to follow an extensive list of rules. These rules include not

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leaving the house, refraining from contacting water or wind (eg, not washing one's hair, taking full-body showers, or opening the window), and not consuming foods that have a "cold" nature, among other things, for a full month [22]. In a recent study of 2615 Chinese women, researchers found that 60.5% of women surveyed did not go outside during the first month after childbirth, while 30.4% of the women only went outside once or twice [23].

Due to the physical constraints of the "doing the month" practice, understandably, women who follow the custom closely often have to rely on help from family members or formal caregivers [24]. Though "doing the month" can cause significant discomfort, with some customs not supported by scientific evidence, a considerable number of young Chinese mothers still practice the ritual, following the customs of their ancestors [25]. It is common to receive support from husbands and senior members of a family during pregnancy and throughout the "doing the month" ritual [24], which can result in many family members living in the same household for some time. Although this arrangement can offer women substantial help, the extended time spent in close proximity may introduce a series of risk factors into a household [26]. Despite public smoking rates declining due to recent antismoking public policies, one unintended consequence is that smokers are more likely to smoke indoors [27], which affects people who may not be able to leave such an environment.

Deeply rooted in traditional Chinese culture is the consensus that young adults are expected to avoid correcting the behavior of seniors, even if the behavior is known to be health-damaging [28]. This cultural norm might be more pronounced when it comes to behaviors related to in-laws, so as to not appear confrontational and disrespectful. Regardless, these health-damaging behaviors, such as secondhand smoking, may harm women and their infants [28]. Furthermore, though women's rights are steadily improving in China, it is essential to acknowledge that women's overall welfare and well-being is still primarily overshadowed by that of men [29].

However, positive changes are occurring. A growing body of literature suggests that there has been a change in Chinese people's attitudes and behaviors toward complying with traditional Chinese cultural values and social norms in recent years. Research finds that though the influence of traditional Chinese culture on Chinese social norms and practices (such as collectivism) is still ongoing and tangible, its hold over young adults is waning [30]. Furthermore, as the number of working women increases, more women gain financial freedom, bringing equal rights and gender equality to the forefront [31]. Overall, accumulating evidence indicates that values that are cherished by older Chinese generations might no longer be valued to the same degree by their younger counterparts [32].

Measuring Smoking Around Expectant Mothers

This cultural shift may have an impact on how pregnant women address issues such as being exposed to harm through secondhand smoke from their husbands and older family members [33]. Due to recent cultural shifts, pregnant Chinese women are more likely to be aware of the devastating effects secondhand smoke can have on themselves and their unborn babies. These shifts may eventually result in mothers persuading their husbands or senior family members to change their smoking behaviors; mothers may even find a way to avoid these toxic environments filled with secondhand smoke. However, while this social phenomenon may be occurring, it is difficult to capture in a nonintrusive research setting [34]. Owing partially to ingrained cultural values and social norms, pregnant Chinese women may be reluctant to share their norm-defying behaviors toward their senior family members with researchers.

What might be possible, however, is to gauge this phenomenon from a different yet closely related angle. To this end, we propose a new method to gauge pregnant women's rates of secondhand smoking. Different from traditional methods, which ask people how often they are exposed to secondhand smoke directly, we believe that a pregnant woman's exposure to secondhand smoke may be more accurately gauged by asking about the smoking frequency of the woman's family members (ie, husbands and other relatives) when they are in close proximity to the woman, especially during the "doing the month" period. In other words, there might be discrepancies in secondhand smoking rates reported by pregnant women due to deep-rooted cultural influences (eg, not wanting to accuse their family members, who play a pivotal role in the "doing the month" ritual, of reckless health behaviors that might harm the health and well-being of the expectant mothers, unborn children, and smokers themselves).

One way to gauge potential discrepancies in secondhand smoking rates reported by expectant mothers is by comparing these rates with smoking rates reported by the family members of these women. That is to say, rather than asking pregnant women about their exposure to secondhand smoke, more accurate information may be gleaned by directly asking family members about smoking frequency and duration in the presence of the pregnant woman. To further ensure that secondhand smoking faced by expectant mothers can be captured accurately, we believe it is important to collect data from expectant mothers and their family members separately (eg, survey conducted individually, rather than as a family unit), so that the role of social pressure in influencing survey results will be limited.

Protecting pregnant women from the harm of secondhand smoking safeguards the health and well-being of unborn children. Research that focuses on understanding women's exposure to secondhand smoke and the various factors that contribute to their experience of secondhand smoking is urgently needed. The proposed approach is tangible and realistic from a research perspective. Understanding the relationship between traditional Chinese cultural values and social norms, women's awareness of secondhand smoking and their background information (eg, education levels), and the women's actual exposure to secondhand smoke from their husbands and other family members can help researchers obtain valuable insights needed to develop intervention measures to protect this vulnerable population [35].

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Concluding Remarks

In 2018, it is estimated that 4,285,033 new cancer cases were diagnosed in China, among which 1,919,023 were female [3]. Mounting evidence suggests that tobacco smoking increases the risk of many types of cancers [1]. Different from environmental factors such as air pollution, which might be more difficult to control and contain [36], tobacco smoking can be curbed in a timely and cost-effective manner [37], as seen in successful tobacco control interventions established in countries such as the United States. This insight is particularly promising for expectant mothers, as the adverse impacts of secondhand smoke are more pronounced for this population, and can harm both the mother's and the infant's health and well-being [13-18]. However, to develop a tailored and targeted tobacco control plan, health experts and government officials need to understand how much secondhand smoke expectant mothers are exposed to. We hope that the current proposed methods and future improved measures will lead to a better understanding of how much secondhand smoke expectant mothers are exposed to, as that knowledge is essential for designing and deploying effective interventions to protect expectant mothers and their infants from the harms of smoking and risk of cancer.

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Authors' Contributions

ZS conceived the work, reviewed the literature, and drafted and edited the manuscript. DMD, JA, LS, YC, and LY reviewed the literature and edited the manuscript. All authors approved the manuscript for submission.

Conflicts of Interest

None declared.

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Viewpoint

First-line Advanced Cutaneous Melanoma Treatments: Where Do We Stand?

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Abstract

Cutaneous melanoma has always been a dreaded diagnosis because of its high mortality rate and its proclivity for invasiveness and metastasis. Historically, advanced melanoma treatment has been limited to chemotherapy and nonspecific immunotherapy agents that display poor curative potential and high toxicity. However, during the last decade, the evolving understanding of the mutational burden of melanoma and immune system evasion mechanisms has led to the development of targeted therapy and specific immunotherapy agents that have transformed the landscape of advanced melanoma treatment. Despite the considerable strides in understanding the clinical implications of these agents, there is a scarcity of randomized clinical trials that directly compare the efficacy of the aforementioned agents; hence, there are no clear preferences among the available first-line options. In addition, the introduction of these agents was associated with a variety of dermatologic adverse events, some of which have shown a detrimental effect on the continuity of treatment. This holds especially true in light of the current fragmentation of care provided by the managing health care professionals. In this study, we attempt to summarize the current understanding of first-line treatments. In addition, the paper describes the indirect comparative evidence that aids in bridging the gap in the literature. Furthermore, this paper sheds light on the impact of the scarcity of dermatology specialist input in the management of dermatologic adverse events associated with advanced melanoma treatment. It also looks into the potential avenues where dermatologic input can bridge the gap in the care provided by oncologists, thus standardizing the care provided to patients with melanoma presenting with dermatologic adverse events.

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KEYWORDS

advanced cutaneous melanoma; first-line treatments; immunotherapy; targeted therapy; combinational therapy; dermatologic adverse events; cutaneous side effects

Introduction

Melanoma is a malignant transformation of the melanocytes. It accounts for approximately 1% of all skin cancers; however, it carries the highest mortality rate among all skin cancers [1,2]. The high mortality rate of melanoma is mainly because of its early metastatic potential and aggressive nature [3]. Surgery has been shown to be a successful treatment for localized melanomas; however, advanced cases have a grim prognosis [3]. In the last decade, medical management of advanced melanoma has transformed the life expectancy of patients with melanoma. The introduction of novel agents, namely immunotherapy and targeted therapy, has increased the median overall survival (OS) by 10-fold, from an average of 6 months to >5 years [4,5]. Targeted therapy comprises agents that directly inhibit mutated kinases, namely BRAF and mitogen-activated protein kinase kinase, which have been implicated in the growth and survival of cancerous melanocytes. However, the efficacy of BRAF inhibitor (BRAFi) and mitogen-activated protein kinase kinase inhibitor (MEKi) monotherapies is limited by early resistance and an upsurge in treatment-associated skin tumors. Consequently, a combined BRAFi plus MEKi approach

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was trialed, which resulted in superior survival rates while minimizing the aforementioned limitations.

In addition, specific immunotherapy agents were developed following Nobel Prize-winning discoveries that outlined the pivotal role of certain immune downregulatory signals that facilitate tumor growth. Hitherto, several single and combined treatments have been approved as first-line therapy for advanced melanoma.

It is worth mentioning that BRAF status testing is imperative to the treatment choice; in general, immunotherapy is offered to both patients with BRAF-positive and BRAF-negative melanoma, whereas targeted therapy (BRAFi and MEKi) is only used for patients who test positive for the BRAF mutation [6-8].

Immunotherapy in Clinical Practice

Currently, there are 3 types of immunotherapy treatments approved for unresectable or metastatic melanoma treatment regardless of the BRAF status: 2 anti–programmed death 1 (PD-1) agents, namely nivolumab and pembrolizumab; a single anti–programmed death 1 ligand (PD-L1) agent, atezolizumab; and a single anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA4) agent, ipilimumab [6,7,9].

CheckMate 067, a phase 3 double-blind randomized controlled trial (RCT), demonstrated the superiority of nivolumab with or without ipilimumab over ipilimumab monotherapy. Because of the study design, nivolumab plus ipilimumab combination therapy was not directly tested against nivolumab monotherapy. However, indirect analysis suggested that adding ipilimumab to nivolumab monotherapy achieved higher progression-free survival (PFS) and response rates, whereas no significant difference was reported in OS (Table 1) [5]. Therefore, both nivolumab-containing groups have been approved as first-line treatments [6,7].

Table 1. Summary of the 5-year efficacy results of CheckMate 067 along with the reported dermatologic adverse events[a].

Study group	Nivolumab plus ipilimumab	Nivolumab	Ipilimumab
Overall survival			
Value, median (months)	>60	36.9	19.9
HR[b]	0.52[c]	0.63[d]	N/A[e]
Progression-free survival			
Value, median (months)	11.5	6.9	2.9
HR	0.42[c]	0.53[d]	N/A
Adverse events (all grade), %	96	87	86
Adverse events (grade ≥3), %	59	23	28
Dermatologic adverse events			
Rash (all grade), %	30	24	22
Rash (grade ≥3), %	3	<1	2
Pruritus (all grade), %	36	23	36
Pruritus (grade ≥3), %	2	<1	<1
Vitiligo (all grade), %	9	11	5
Vitiligo (grade ≥3), %	0	<1	0
Dry skin (all grade), %	5	5	4
Dry skin (grade ≥3), %	0	0	0
Maculopapular rash (all grade), %	12	5	12
Maculopapular rash (grade ≥3), %	2	1	<1

[a]Adapted from Larkin et al [5].

[b]HR: hazard ratio.

[c]Nivolumab plus ipilimumab versus ipilimumab.

[d]Nivolumab versus ipilimumab.

[e]N/A: not applicable.

However, the enhanced efficacy of combined immunotherapy comes with added adverse events [5]. Therefore, the choice between combined and single agent immunotherapy must be tailored to the patient's circumstances, considering different factors, such as the patient's health status (absence of autoimmune diseases or other comorbidities that might aggravate

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the immune-related adverse events) and the patient's willingness to tolerate the added toxicity associated with combination therapy. Furthermore, the availability of support services that can monitor and manage adverse events should be considered [7].

Patients with advanced melanoma were recruited in CheckMate 067 regardless of the tumor's BRAF status; hence, nivolumab plus ipilimumab combination therapy and nivolumab monotherapy were approved for both BRAF-positive and BRAF-negative melanomas. Of note, the percentage of BRAF-positive melanomas in CheckMate 067 was 31.5%, which is lower than the reported prevalence of BRAF mutations among patients with melanoma (approximately 60%) [5,10]. Hence, the overall results might be a misrepresentation of the BRAF-positive subgroup which are known to have worse prognosis.

In KEYNOTE-006, a phase 3 open label RCT, pembrolizumab monotherapy has been shown to improve PFS, OS, and response rates compared with ipilimumab monotherapy (Table 2) [11]. As with nivolumab monotherapy, pembrolizumab monotherapy is recommended as a first-line therapy if the added side effects of combination immunotherapy cannot be tolerated [6,7]. The tolerable adverse events profile of pembrolizumab paralleled with its associated long-term survival rate nominates it as a potential candidate for combined immunotherapy and combined targeted therapy plus immunotherapy. However, there are no published data that support its use in a combined regimen.

Table 2. Summary of the 5-year efficacy results of KEYNOTE-006 along with the reported dermatologic adverse events[a].

Study group	Pembrolizumab[b]	Ipilimumab
Overall survival		
Value, median (months)	32.7	15.9
HR[c]	0.75[d]	N/A[e]
Progression-free survival		
Value, median (months)	8.4	3.4
HR	0.57[d]	N/A
Adverse events (all grade), %	77-82	74
Adverse events (grade ≥3), %	17	20
Dermatologic adverse events		
Rash (all grade), %	16-17	16
Rash (grade ≥3), %	0	0
Pruritus (all grade), %	20	26
Pruritus (grade ≥3), %	0	0

[a]Adapted from Schachter et al [12] and Robert et al [11].

[b]Compiled results of the 2 pembrolizumab doses studied in KEYNOTE-006.

[c]HR: hazard ratio.

[d]Pembrolizumab versus ipilimumab.

[e]N/A: not applicable.

To date, the following are approved first-line immunotherapy treatments for unresectable or metastatic melanoma irrespective of BRAF mutation status: nivolumab plus ipilimumab combination, nivolumab monotherapy, and pembrolizumab monotherapy [8]. Patients with BRAF-positive advanced melanoma are offered additional first-line treatment options, namely combined BRAFi plus MEKi regimens, as discussed below.

Targeted Therapy in Clinical Practice

In total, 3 BRAFi have been approved for unresectable or metastatic melanoma, namely vemurafenib, dabrafenib, and encorafenib. In addition, 3 MEKi, namely cobimetinib, trametinib, and binimetinib, have been approved for use along with the aforementioned BRAFi agents. The superiority of combined BRAFi plus MEKi therapy over BRAFi monotherapy was established in the coBRIM, COMBI-d, COMBI-v, and COLUMBUS RCTs (Tables 3-5) [13-15]. Moreover, the addition of MEKi to BRAFi monotherapies has been shown to mitigate the high resistance rates and high toxicities associated with BRAFi monotherapy and overcome the limited response rates and early resistance in MEKi monotherapies. In light of these results, BRAFi plus MEKi combination supplanted targeted monotherapy regimens as first-line systemic treatments for advanced melanoma [16-19]. To date, there is no evidence available from head-to-head trials that compare the 3 approved BRAFi plus MEKi combination regimens, namely vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib. The following section attempts to compare these lines of treatment using indirect and comparative analyses.

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Table 3. Summary of the coBRIM efficacy results along with the reported dermatologic adverse events[a].

Study group	Cobimetinib plus vemurafenib	Vemurafenib
Overall survival		
Value, median (months)	22.3	17.4
HR[b]	0.70[c]	N/A[d]
Progression-free survival		
Value, median (months)	12.3	7.2
HR	0.58[c]	N/A
Adverse events (all grade), %	99.2	98
Adverse events (grade ≥3), %	75.3	61.4
Dermatologic adverse events		
Rash (all grade), %	72.5	67.5
Rash (grade ≥3), %	17	16.3
Photosensitivity (all grade), %	47.8	37.8
Photosensitivity (grade ≥3), %	4.5	0
Alopecia (all grade), %	16.6	30.5
Alopecia (grade ≥3), %	0.4	0.4
Hyperkeratosis (all grade), %	10.1	27.2
Hyperkeratosis (grade ≥3), %	0.4	2.4
Squamous cell carcinoma (all grade), %	4	12.6
Squamous cell carcinoma (grade ≥3), %	3.6	12.6
Keratoacanthoma (all grade), %	1.6	9.3
Keratoacanthoma (grade ≥3), %	1.2	8.5

[a]Adapted from Ascierto et al [13].

[b]HR: hazard ratio.

[c]Cobimetinib plus vemurafenib versus vemurafenib.

[d]N/A: not applicable.

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Table 4. Summary of the COMBI-d efficacy results along with the reported dermatologic adverse events[a].

Study group	Dabrafenib plus trametinib	Dabrafenib
Overall survival		
Value, median (months)	25.1	18.7
HR[b]	0.71[c]	N/A[d]
Progression-free survival		
Value, median (months)	11.0	8.8
HR	0.67[c]	N/A
Adverse events (all grade), %	87	90
Adverse events (grade ≥3), %	32	30
Dermatologic adverse events		
Rash (all grade), %	24	20
Rash (grade ≥3), %	0	<1
Dry skin (all grade), %	9	14
Dry skin (grade ≥3), %	0	0
Pruritus (all grade), %	7	11
Pruritus (grade ≥3), %	0	0
Alopecia (all grade), %	5	26
Alopecia (grade ≥3), %	0	0
Hyperkeratosis (all grade), %	6	33
Hyperkeratosis (grade ≥3), %	0	<1
Skin papilloma (all grade), %	1	18
Skin papilloma (grade ≥3), %	0	0
Dermatitis acneiform (all grade), %	8	3
Dermatitis acneiform (grade ≥3), %	0	0
Squamous cell carcinoma (all grade), %	3	9
Squamous cell carcinoma (grade ≥3), %	3	9
New primary melanoma (all grade), %	<1	2
New primary melanoma (grade ≥3), %	<1	<1

[a]Adapted from Long et al [14].

[b]HR: hazard ratio.

[c]Dabrafenib plus trametinib versus trametinib.

[d]N/A: not applicable.

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Table 5. Summary of the COLUMBUS efficacy results along with the reported dermatologic adverse events[a].

Study group	Encorafenib plus binimetinib	Encorafenib	Vemurafenib
Overall survival			
Value, median (months)	33.6	23.5	16.9
HR[b]	0.61[c]	0.76[d]	N/A[e]
Progression-free survival			
Value, median (months)	14.9	9.6	7.3
HR	0.51[c]	0.68[d]	N/A
Adverse events (all grade), %	98.4	99.5	100
Adverse events (grade ≥3), %	68.2	67.7	65.6
Dermatologic adverse events			
Rash (all grade), %	16.1	20.8	30.1
Rash (grade ≥3), %	1.6	2.1	3.2
Pruritus (all grade), %	12.5	21.9	10.8
Pruritus (grade ≥3), %	0.5	0.5	0
Hyperkeratosis (all grade), %	15.1	40.1	29
Hyperkeratosis (grade ≥3), %	0.5	3.6	0
Dry skin (all grade), %	16.1	30.2	23.1
Dry skin (grade ≥3), %	0	0.5	0
Alopecia (all grade), %	14.6	56.3	37.6
Alopecia (grade ≥3), %	0	0	0
Palmoplantar erythrodysesthesia syndrome (all grade), %	7.3	51.6	14
Palmoplantar erythrodysesthesia syndrome (grade ≥3), %	0	13.5	1.1
Photosensitivity (all grade), %	3.6	3.6	25.3
Photosensitivity (grade ≥3), %	0.5	0	1.1
Palmoplantar keratoderma (all grade), %	9.9	26.6	17.7
Palmoplantar keratoderma (grade ≥3), %	0	2.1	1.1
Keratosis pilaris (all grade), %	4.7	3.6	25.3
Keratosis pilaris (grade ≥3), %	0.5	0	1.1
Papilloma[f] (all grade), %	7	10	19
Papilloma[f] (grade ≥3), %	N/A	N/A	N/A
Squamous cell carcinoma[f] (all grade), %	3	8	17
Squamous cell carcinoma[f] (grade ≥3), %	N/A	N/A	N/A
Basal cell carcinoma[f] (all grade), %	2	1	2
Basal cell carcinoma[f] (grade ≥3), %	N/A	N/A	N/A

[a]Adapted from Ascierto et al [15] and Gogas et al [20].

[b]HR: hazard ratio.

[c]Encorafenib plus binimetinib versus vemurafenib.

[d]Encorafenib versus vemurafenib.

[e]N/A: not applicable.

[f]These dermatologic adverse events were reported separately by Gogas et al [20] as all grade dermatologic adverse events with no further breakdown.

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Comparing Current Targeted Therapy Combinations

To date, no direct studies have been conducted that would prioritize dabrafenib plus trametinib over vemurafenib plus cobimetinib or vice versa. coBRIM, which compared vemurafenib plus cobimetinib and vemurafenib monotherapy, and COMBI-v, which compared dabrafenib plus trametinib and vemurafenib monotherapy, share some similarities in study design features and control groups. On the basis of these similarities, Galván ‐ Banqueri et al [21] conducted an indirect comparison between the 2 combined regimens and concluded that there were no significant differences in OS and PFS. The similarities in PFS and OS were also reported in a systematic review and network meta-analysis by Garzón ‐ Orjuela et al [22]. However, this study highlighted disparities in safety profiles; dabrafenib plus trametinib was found to be safer because of the lower risk of grade 3 and grade 4 adverse events, such as ocular adverse events (serous retinopathy) and elevated liver enzymes.

Indirect comparisons should be interpreted cautiously, as even similarly designed trials might exhibit some degree of discrepancy that would discredit any conclusions made. In case of coBRIM and COMBI-v, there were differences in the inclusion criteria, study end points (PFS was the primary end point in coBRIM and secondary in COMBI-d), and allowance of patient crossover between study arms [13,23].

In COLUMBUS, a phase 3 open label RCT, encorafenib plus binimetinib displayed unprecedented efficacy rates for a BRAFi plus MEKi combination therapy (median OS of 33.6 months and median PFS of 14.9 months), especially in median OS. In comparison, dabrafenib plus trametinib treatment achieved a median OS of 25.1 months and a median PFS of 11 months, which was similar to the vemurafenib plus cobimetinib combination results, yielding 22.3 and 12.3 months for median OS and PFS, respectively (Tables 3-5) [13-15].

The National Institute for Health and Care Excellence (UK) recruited Pierre Fabre, a pharmaceutical company, to compare the clinical efficacy and cost-effectiveness of encorafenib plus binimetinib and dabrafenib plus trametinib by evaluating the direct and indirect evidence. The results showed that there were no significant differences in the clinical outcomes between the 2 BRAFi plus MEKi combinations; however, encorafenib plus binimetinib was shown to be more cost-effective. Hence, it was recommended by the National Institute for Health and Care Excellence for BRAF-positive advanced melanomas [24].

The study designs of COLUMBUS, coBRIM, COMBI-d, and COMBI-v had a notable difference in patient characteristics, which might suggest the added benefit of certain targeted therapy combinations in select patient subcategories. Unlike coBRIM, COMBI-d, and COMBI-v, the COLUMBUS trial allowed the recruitment of previously treated patients, including those who were previously treated with BRAFi monotherapies [13,25-27]. This shows that the clinical outcomes were achieved in a cohort that might have developed resistance or progressed with previous BRAFi agents. It also enhances the external validity of the results and establishes encorafenib plus binimetinib as an effective second-line treatment for patients who have progressed in previous systemic treatments.

Of note, the number of patients with elevated levels of lactate dehydrogenase (a negative prognostic factor) involved in COLUMBUS was lower than in other trials, which might indicate that the patients enrolled had a *healthier* baseline. However, apart from the disparity in lactate dehydrogenase levels, the other prognostic factors were comparable. In addition, vemurafenib monotherapy was a common control group in COLUMBUS, COMBI-v, and coBRIM and produced comparable results, which negates any significant differences between study participants [13,25,26].

Pharmacokinetic analysis of the available BRAFi revealed significant differences. Delord et al [28] compared encorafenib, dabrafenib, and vemurafenib in a preclinical setting (cell lines and xenograft melanoma tumors) and showed that although all 3 agents were able to inhibit BRAF V600E kinase activity at the same concentration, encorafenib had a markedly prolonged half-life (>30 hours) compared with that of dabrafenib (2 hours) and vemurafenib (0.5 hours). This translated to increased drug availability, prolonged target suppression, and enhanced potency. Delord et al [28] demonstrated the increased potency of encorafenib by showing that the half-maximal inhibitory concentration (IC_{50}) was achieved with a lower concentration of encorafenib (<40 nmol/L) compared with that of dabrafenib (<100 nmol/L) and vemurafenib (<1 µmol/L) [28]. The prolonged half-life and superior potency of encorafenib might explain the prolonged median OS of encorafenib plus binimetinib evident in the COLUMBUS trial. Additional research should delineate the impact of the pharmacokinetic profile on the onset and overall onset of resistance, a notable limiting factor of BRAFi and MEKi [17].

The frequency of certain dermatologic adverse events varied considerably between the monotherapy groups in the COLUMBUS trial and across other BRAF trials, which might point to the presence of molecular differences in same-group agents (Tables 3-5) [13-15]. One such difference is the variability of kinase inhibition among BRAF isotypes. Encorafenib was shown to exhibit similar inhibition on both mutated and wild-type BRAF isotypes, whereas both dabrafenib and vemurafenib inhibited mutated BRAF kinase more efficiently with minimal inhibition of wild-type BRAF kinase [29]. The uneven inhibition leads to the hyperstimulation of wild-type BRAF kinase manifesting clinically as the paradoxical rise of BRAFi-associated dermatologic adverse events, such as squamous cell carcinoma, primary melanoma, and papillomas [29,30]. Adelmann et al [29] introduced the term *paradox indices*, which estimates a therapeutic window that represents the concentration range within which maximum inhibition of BRAF is achieved while maintaining the lowest paradoxical activation of the downstream kinase extracellular signal-regulated kinase (ERK), the culprit kinase that drives treatment-induced dermatologic adverse events in wild-type BRAF tissues [31]. Encorafenib had the highest paradox index (50), representing the most potent agent with the widest safety margin, followed by those of dabrafenib (10) and vemurafenib

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(5.5) [29]. The clinical results corresponded with the reported paradox indices, as vemurafenib-associated squamous cell carcinoma was twice as common compared with the encorafenib group; similar disparities were noted in papilloma and keratosis pilaris (Table 5).

The unique pharmacokinetic profile of encorafenib could also explain the disparity in the prevalence of nondermatologic adverse events. For instance, pyrexia was shown to be the most common adverse event and a substantial limiting factor among patients treated with dabrafenib plus trametinib, causing the most treatment interruptions (30%), dose reductions (14%), and permanent terminations (3%) [26]. COLUMBUS trial revealed a sizable decrease in pyrexia incidence in the encorafenib plus binimetinib group (18%) compared with that in the dabrafenib plus trametinib group (53%) in the COMBI-v trial [20,26]. In addition, COLUMBUS showed that vemurafenib (an agent used in the vemurafenib plus cobimetinib combination) monotherapy group had an approximately 2-fold increase in pyrexia (30%) compared with the encorafenib monotherapy group (16%) [20]. Both findings suggest that encorafenib plus binimetinib is, potentially, the safest BRAFi plus MEKi currently offered for treatment-induced pyrexia. Given the lack of direct evidence, detailed comparisons of other critical adverse events, especially those that impose the greatest threat of treatment interruption, are much needed to help navigate the available treatments. To date, all 3 combinations have been approved as first-line treatments for BRAF-positive advanced melanoma, especially in rapidly deteriorating cases [6,32].

Immunotherapy Versus Targeted Therapy

To date, no evidence is available from head-to-head trials that compare immunotherapy and targeted therapy for BRAF-positive melanomas. Ugurel et al [33] conducted an exploratory analysis comparing the PFS and OS of landmark trials assessing advanced melanoma treatments. The study included 25 prospective clinical trials from 2002 to 2017, producing 83 Kaplan-Meier survival curves. Ugurel et al [33] showed that there was a high concordance among the survival curves of different agents within the same group of both targeted and immunotherapy agents used as first-line therapies. However, the survival data of the second or higher treatment lines showed lower concordance. Moreover, the combined BRAFi plus MEKi had superior PFS rates compared with those of combined immunotherapy at 6 months (72.3% vs 63.8%). In addition, the OS rates of combined BRAFi plus MEKi were also higher at 12 months (76.6%) than those of the combined immunotherapy (73.1%). However, the OS rate curves crossed over in favor of combined immunotherapy at 24 months, yielding 62.9% compared with 53.3% in combined BRAFi plus MEKi [33]. It is worth mentioning that the analysis of Ugurel et al [33] only included trials that evaluated treatments of BRAF-positive melanoma that were published up to January 1, 2017; hence, the results of the aforementioned analysis did not account for agents approved more recently, such as encorafenib plus binimetninb.

Moreover, the 5-year update of CheckMate 067 demonstrated the long-term survival benefit of nivolumab groups in patients with BRAF-positive melanoma. The combination arm reported a median OS of >60 months (median OS has not been reached yet), representing the longest median OS of all the currently available first-line treatments, followed by nivolumab monotherapy, which achieved a median OS of 45.5 months (Tables 1-5) [5]. Conversely, the 5-year combined pooled data of COMBI-d and COMBI-v revealed that the median OS at 5 years was 25.9 months in patients with BRAF-positive melanoma on combined dabrafenib plus trametinib treatment [23]. Comparing the results from Checkmate 067 and COMBI-v or COMBI-d would not present tangible evidence because of the discrepancy in the characteristics of study populations [5,23].

The inferior 24-month survival outcome of targeted therapy reported in the analysis of Ugurel et al [33] and the considerable difference in the 5-year median survival between the nivolumab groups and the dabrafenib plus trametinib combination group delineate the acquired resistance phenomenon associated with targeted therapy, which became eminent approximately 6 months after treatment initiation [5,17,23].

Similarly, the lower PFS and OS rates of immunotherapy during the first year of treatment depicted in the findings of Ugurel et al [33] displayed the primary resistance phenomenon associated with immunotherapy agents [34]. It is worth mentioning that the 5-year compiled data of CheckMate 067 denote a steadily increasing rate in complete response, regardless of the BRAF status, which might suggest the reversibility of immunotherapy-associated resistance [5].

Furthermore, studies have shown that BRAFi plus MEKi agents displayed a more pronounced therapeutic effect in patients with high lactate dehydrogenase. Conversely, immunotherapy was more effective in patients with normal levels of lactate dehydrogenase [35,36].

These findings suggest the superiority of combined BRAFi plus MEKi as an *acute* treatment especially in aggressive melanomas, while supporting the superior role of immunotherapy as a *maintenance* therapy. Furthermore, these findings suggest the benefit of sequential therapy, where treatment could be initiated by BRAFi plus MEKi and then maintained by immunotherapy, thus harvesting the benefits of both lines of therapy. This approach is corroborated by the 5-year analysis of the pooled data of COMBI-d and COMBI-v trials, which showed that a complete response was observed in patients who were treated with immunotherapy following dabrafenib plus trametinib therapy administered in the aforementioned trials [23]. This regimen is currently being studied in ImmunoCobiVem (ClinicalTrials.gov NCT02902029), a clinical trial assessing the efficacy and safety of sequential treatment with cobimetinib plus vemurafenib followed by atezolizumab.

The European Society for Medical Oncology recommends the use of immunotherapy in unresectable melanoma regardless of the BRAF mutation status, as long as the immunotherapy can be safely administered, meaning that melanoma is not progressing very quickly and there is no imminent threat to any function or organ [6]. The US National Comprehensive Cancer Network recommends both immunotherapy and targeted therapy as first-line treatments for unresectable melanoma; however, targeted therapy is preferred for rapidly deteriorating

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BRAF-positive melanomas [7]. Studies comparing targeted and immunotherapy agents as first-line treatment are yet to be published; such results will conceivably shape the guidelines of this dynamic field.

Combined Targeted and Immunotherapy Regimen

On July 30, 2020, the United States Food and Drug Administration approved atezolizumab combined with vemurafenib plus cobimetinib as first-line treatment for unresectable melanoma. This is the first approved combined treatment regimen that incorporates targeted therapy and immunotherapy [9].

Atezolizumab is a PD-L1 inhibitor that has been approved as a monotherapy to treat other solid cancers, including breast and urothelial cancers [37,38]. Atezolizumab monotherapy has also been investigated in a phase 1 trial for the treatment of advanced melanoma. In this study, Hamid et al [39] showed that atezolizumab achieved a median OS of 23 months. In addition, the median response duration exceeded 5 years, while maintaining a tolerable safety profile. The response durability and tolerability presented atezolizumab as a promising agent for melanoma treatment.

However, the recent approval of atezolizumab was based on the results of IMspire150, a phase 3 double-blind RCT that assessed the efficacy and safety of atezolizumab plus vemurafenib plus cobimetinib versus vemurafenib plus cobimetinib plus placebo. Both arms were initially treated with the vemurafenib plus cobimetinib combination for the first cycle (a 28-day cycle), after which the intervention group was commenced on atezolizumab, whereas the control group was given a matched placebo. The PFS of the triple agent group was 15.1 months, which was significantly longer than that of the dual agent group (10.6 months) [40]. Interestingly, the PFS curves of the 2 groups parted ways after 7 months of treatment, at approximately the same time that the acquired resistance of BRAFi plus MEKi becomes apparent, highlighting the added benefit of incorporating immunotherapy with combined targeted therapy [17,33,40]. In addition, the median duration of response was prolonged in the triple agent arm. At the time of the interim analysis, the death rate of the triple agent group was 36% compared with 43% in the control group. Accordingly, the OS rate at 24 months was predicted to be 60% and 53% for the triple and dual agent groups, respectively [40].

Notably, immune-mediated adverse events, which required systemic corticosteroids, were more frequent in the triplet group. These adverse events include dermatitis acneiform, acne, pneumonitis, uveitis, hyperthyroidism, and raised liver enzymes. Other dermatologic adverse events, such as photosensitivity reactions, rash, pruritus, dry skin, and sunburn were also reported in the triplet group [40].

The higher toxicity of the triple agent treatment was also portrayed in KEYNOTE-022, a phase 2 double-blind RCT that evaluated the addition of pembrolizumab to dabrafenib plus trametinib combined therapy. The study showed that the triple agent group had a superior median PFS of 16.0 months versus 10.3 months in the dabrafenib plus trametinib only group. However, the *P* value threshold for statistical significance (*P*=.003) was not achieved for PFS (*P*=.04). However, the triple agent group had a higher rate of patients with complete response (18.3%) compared with that in the dual agent group (13.3%). Furthermore, the triple agent group displayed improved response duration; however, it was associated with higher toxicity, leading to more frequent treatment discontinuations [41].

In light of the added toxicity of the triple agent approach and the lack of mature data that demonstrate the OS benefit of the triple therapy, guidelines are yet to outline the exact role of this regimen in treating BRAF-positive melanoma and the implications it has on the currently available dual agent options [42]. The results of other ongoing trials that evaluate the triple agent approach, such as ImmunoCobiVem (ClinicalTrials.gov NCT02902029) and COMBI-I (ClinicalTrials.gov NCT02967692), will aid in delineating the role of combined immunotherapy and targeted therapy in melanoma treatment.

Treatment-associated toxicity is pivotal in shaping current and future guidelines, particularly for adverse events that have been detrimental to treatment continuation. In fact, treatment-associated dermatologic adverse events have been ranked high for both frequency and severity. Dermatologic adverse events present in approximately 50% of patients with advanced melanoma treated with immunotherapy. Targeted therapy-related dermatologic adverse events occur in 90% of the patients who are treated, rendering dermatologic adverse events not only one of the most frequently reported adverse events but also one of the most common reasons for treatment interruption [32,43]. Immunotherapy-related dermatologic adverse events include maculopapular rash, vitiligo, and pruritus [44]. In contrast, dermatologic adverse events associated with targeted therapy are not only more common but also are more clinically relevant [32]. Targeted therapy-induced dermatologic adverse events, which are responsible for most treatment interruptions include proliferative cutaneous neoplasms, rash, and photosensitivity reactions [45].

Dermatologic Adverse Events: A Challenge in Clinical Practice

Advanced melanoma treatment-related dermatologic adverse events are mainly managed by oncologists and dermatologists. However, the former are more involved in the management of dermatologic adverse events, as advanced cutaneous melanoma cases are referred to oncology care, with minimal care provided by dermatologists.

Furthermore, the literature shows that there is hesitancy in requesting dermatology input when managing dermatologic adverse events despite the challenges that they present in clinical practice, including dose reduction or, more importantly, treatment interruption or termination [46-48]. The following are 3 studies that showcase this phenomenon and illustrate the degree of dermatology specialist input in managing oncology treatment-related dermatologic adverse events.

In a French study by Peuvrel et al [46], 67 nondermatologist health care professionals who manage patients with cancer on

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targeted therapy were surveyed. Although there was consistency in treating common, uncomplicated cases, greater disparity was evident in managing complex cases, such as secondary skin infection or cases associated with radiodermatitis. Moreover, the study revealed that dermatologic consultations were prompted mainly if dermatologic adverse events were exacerbated or were persistent for >2 weeks. It also identified that nondermatologists struggled to grade dermatologic adverse events and manage those located in skin appendages, such as nails and the scalp. Less than half of the respondents would refer to a dermatologist if they needed help in managing cutaneous side effects.

The disparity in management and latency in seeking specialist input was echoed in a German study by Hassel et al [47] where oncologists and dermato-oncologists were provided with pictures and medical history of a patient with an acneiform rash, a dermatologic adverse event associated with targeted therapy and were asked to provide information on grading and treatment strategies. The results showed that dermato-oncologists had a more liberal use of local antibiotics (P=.006) and isotretinoin (P=.002). However, the data showed that dermato-oncologists delayed targeted therapy less often because of skin toxicity (P=.009). Despite these discrepancies, only 9% of the oncologists referred the patient to a dermatologist [47].

Finally, in the Unites States, Boone et al [48] surveyed 110 oncology clinicians who manage patients on targeted therapy. Of the health practitioners surveyed, 17% reported rash in approximately 90% of their patients: 32% had terminated treatment because of rash, and 60% had to reduce the dose. Despite the high rate of rash causing considerable treatment disruptions, only 8% of those surveyed requested dermatology consultations and fewer than half actively treated mild rashes [48].

Although it might be inappropriate to draw generalizations from questionnaire-based studies, the aforementioned studies provide insight into the oncology practice in different parts of the world. All of these studies revealed a delay in seeking dermatology consultations despite facing challenging dermatologic adverse events that led to treatment disruptions. However, the questionnaires did not account for the impact of late dermatology consultations on the physical and psychological well-being of the patients, nor did they account for the implications of any untreated dermatologic adverse events, which have been shown to be detrimental to the patients' quality of life [49,50].

Dermatologic adverse events have been shown to cause notable treatment termination and dose reduction, which might hinder clinical resolution and lead to disease progression [45]. Late dermatology consultations, if acquired, attempt to alleviate clinical symptoms of severe or persistent dermatologic adverse events; however, they may not reverse the negative connotations that patients have toward the treatment regimens, which may result in poor compliance. Moreover, late dermatology consultations will only allow melanoma treatment continuation when the dermatologic adverse events are controlled and will have a limited role in certain dermatologic adverse events that persist even after treatment termination. Therefore, a more proactive role is needed from dermatologists to screen for and manage early dermatologic adverse events to ensure maximal clinical benefit of melanoma treatment.

Furthermore, immunotherapy landmark trials excluded patients with autoimmune diseases, including autoimmune dermatitis; hence, no recommendations can be made regarding patients with ongoing autoimmune skin diseases [5,12]. However, observational studies have not only shown an exacerbation of autoimmune dermatitis, such as psoriasis, in patients undergoing immunotherapy treatment but have also reported new cases in previously healthy patients [51,52]. This alludes to the importance of integrated dermato-oncology evaluation before treatment commencement, especially in patients with ongoing autoimmune dermatitis or those predisposed to develop such diseases.

The American Academy of Dermatology recommends a collaborative approach between dermatologists and oncologists to limit treatment interruptions and improve patients' quality of life. The academy also recommends routine dermatologic assessments to be carried out depending on the agent used, age of the patient, and predisposition to skin cancer, including any previous history of skin cancer or sun damage. In the recent American Academy of Dermatology guidelines for treating melanoma, dermatologic assessments were specifically recommended for 3 patient subgroups. First, patients on BRAFi monotherapy (targeted therapy) should be assessed every 2-4 weeks for the first 3 months. Second, patients on immunotherapy should be assessed during the first month of treatment, with additional assessments as needed. Finally, patients with autoimmune dermatitis, such as atopic dermatitis, should be assessed before therapy commencement for counseling and treatment [32]. Moreover, the US National Comprehensive Cancer Network recommends regular dermatology assessments and referrals for patients with melanoma on targeted therapy [7]. In the United Kingdom, dermatologic adverse events are managed primarily by oncologists, and there are no recommendations for routine dermatologic evaluations.

Closing the Gap Between Dermatologists and Oncologists

Collaborative efforts between dermatologists and oncologists should be established throughout the treatment period. This is especially true because of the rapid pace of developments in advanced melanoma management, including the approval of novel agents, approval of new combinations of existing agents, and adaptation of unresectable melanoma treatments in adjuvant and neoadjuvant settings. In addition, many of these agents are widely used in other oncology disciplines. These factors contribute to the increasing patient pool, which might benefit from a more unanimous treatment approach.

Several clinical models have been implemented to improve the quality of care provided to patients with cancer, presenting with dermatologic adverse events. For instance, in North America, cutaneous oncology clinics have been established, which are run by trained dermatologists who manage dermatologic adverse events. Furthermore, several European countries have adopted dermato-oncology training programs that equip dermatologists

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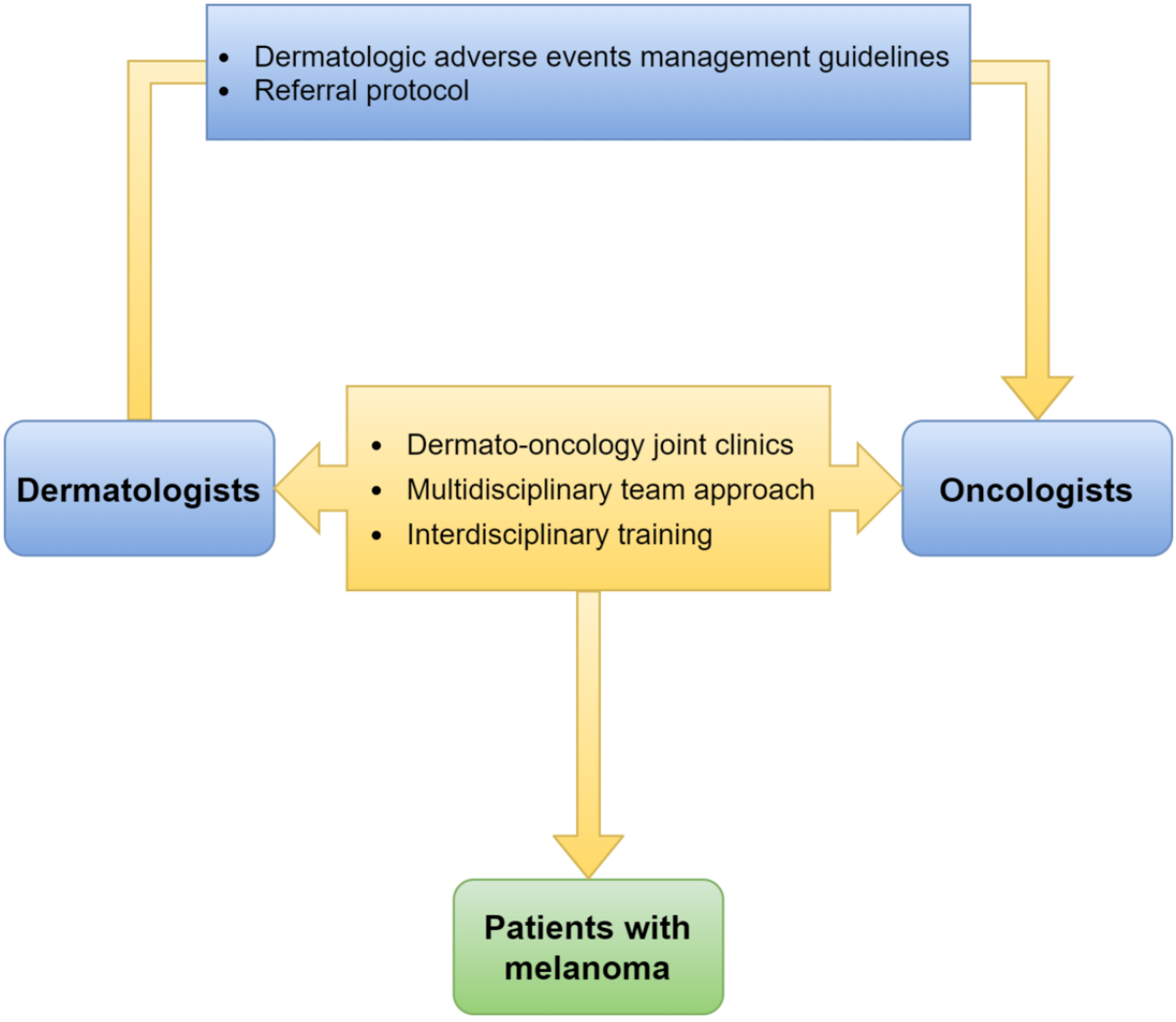
with the means to diagnose and treat dermatologic adverse events associated with different cancer treatments. In contrast, the United Kingdom offers dermato-oncology services, such as transplant skin clinics that provide routine skin assessments that screen and manage dermatologic adverse events. However, these clinics are limited to certain tertiary hospitals, with no routine dermatology input provided in other hospitals [53].

Several proposed steps at the institutional level, if applied, should contribute to improved and holistic care for patients with advanced melanoma (Figure 1). First, a wider range of hospitals should implement dermato-oncology joint clinics. Second, a multidisciplinary team approach should be incorporated throughout the treatment period. In addition, pretreatment dermatologic evaluations should be incorporated into the care of patients with advanced melanoma who have ongoing autoimmune dermatitis and those who are predisposed to develop such diseases. Third, dermato-oncology interdisciplinary training should be established as part of specialist training or as an independent fellowship program, which will allow the transfer of expertise between the 2 specialties. These efforts will provide dermatologists and oncologists with a better understanding of the characteristics of these agents, enabling them to recognize and manage early signs of serious dermatologic adverse events, thereby limiting unnecessary treatment interruptions.

Figure 1. Proposed steps to improve the quality of care provided to patients with melanoma.



On the departmental scale, dermatologists should formulate easy-to-follow management guidelines for common dermatologic adverse events, thus creating a higher degree of independence among oncologists when faced with dermatologic adverse events. Moreover, these guidelines should highlight the scenarios that mandate dermatology referrals, thereby facilitating the universality of care across hospitals.

Conclusions

Because of the novelty of targeted therapy and immunotherapy, there are no mature data from head-to-head trials that compare targeted therapy and immunotherapy or delineate the role of combined or sequential targeted and immunotherapy regimens. Indirect data analyses suggest that combined targeted therapy has an advantageous therapeutic effect on rapidly developing,

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prognostically poor melanomas, whereas immunotherapy agents show a more durable long-term melanoma growth inhibition. Further direct comparative studies will undoubtedly offer a better understanding of the ideal treatment approach for advanced cutaneous melanoma.

Incidentally, dermatologic adverse events are among the most frequently reported adverse events with targeted therapy and immunotherapy. Because of the unclear role of dermatologists in managing dermatologic adverse events in the current guidelines, managing oncologists are faced with a plethora of treatment-related dermatologic adverse events that have been shown to be detrimental to treatment continuity and patients' quality of life. Hence, evidence-based guidelines that incorporate dermato-oncology management are much needed to improve the quality of care provided to patients with advanced melanoma.

Conflicts of Interest

None declared.

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Abbreviations

BRAFi: BRAF inhibitor
CTLA4: cytotoxic T-lymphocyte-associated protein 4
ERK: extracellular signal-regulated kinase
MEKi: mitogen-activated protein kinase kinase inhibitor
OS: overall survival
PD-1: programmed death 1
PD-L1: programmed death 1 ligand
PFS: progression-free survival
RCT: randomized controlled trial

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Original Paper

Measuring the Time to Deterioration for Health-Related Quality of Life in Patients With Metastatic Breast Cancer Using a Web-Based Monitoring Application: Longitudinal Cohort Study

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Abstract

Background: Health-related quality of life (HRQoL) is used to evaluate the treatment of metastatic breast cancer. In a long-term therapy setting, HRQoL can be used as an important benchmark for treatment success. With the help of digital apps, HRQoL monitoring can be extended to more remote areas and be administered on a more frequent basis.

Objective: This study aims to evaluate 3 common HRQoL questionnaires in metastasized breast cancer in terms of TTD in a digital, web-based setting. We further aim to examine the development of the HRQoL in different systemic treatment groups in each of these evaluation instruments.

Methods: A total of 192 patients with metastatic breast cancer were analyzed in this bicentric prospective online cohort study at two German university hospitals. Patients completed questionnaires on HRQoL (EuroQol Visual Analog Scale [EQ-VAS], EuroQol 5 Dimension 5 Level [EQ-5D-5L], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 item [EORTC QLQ-C30]) via an online platform over a 6-month period. Treatment schedules and medical history were retrieved from medical records. Unadjusted Cox regression analysis on treatment-related factors was performed. We conducted subgroup analyses in regard to TTD events between different treatments.

Results: The EQ-VAS showed a higher rate of deterioration after 8 weeks (84/179, 46.9%) than the EQ-5D-5L (47/163, 28.8%) and EORTC QLQ-C30 (65/176, 36.9%). Unadjusted Cox regression revealed significant connections between known metastases in the liver (P=.03, HR 1.64, 95% CI 1.06-2.52) and pleura (P=.04, HR 0.42, 95% CI 0.18-0.96) in the EQ-VAS. Significant relations between EQ-VAS events and single EQ-5D-5L items and the EQ-5D-5L summary score were demonstrated. All treatment groups significantly differed from the CDK4/6 inhibition subgroup in the EQ-VAS.

Conclusions: Compared to the EQ-5D-5L and QLQ-C30, the EQ-VAS showed a higher rate of deterioration after 8 weeks. Significant connections to certain metastatic locations were only detected in the EQ-VAS. The EQ-VAS is capable of reflecting the distinctive HRQoL profiles of different systemic treatments as well as the different aspects of HRQoL presented in the EQ-5D-5L. TTD with the EQ-VAS is an adequate mean of examining longitudinal development of HRQoL among breast cancer patients.

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KEYWORDS

eHealth; breast cancer; health-related quality of life; quality of life; time to deterioration; EQ-VAS; EQ-5D-5L; EORTC QLQ-C30

Introduction

Breast cancer is the most common cancer in women, with 1 in 8 women being affected throughout their lifetime [1]. Although there has been significant progress made both in detection and treatment, the prognosis of metastatic breast cancer remains poor. The more severe the disease, the more important palliative treatment options become that offer an acceptable health-related quality of life (HRQoL) while still providing the patient with individually optimized and life prolonging treatments [2]. There is a strong connection between HRQoL and factors such as progression of disease, progression-free survival, and the experience of adverse events during therapy [2-4]. In addition, HRQoL measurements can help with doctor-patient communication and can even be beneficial to the HRQoL itself when discussing the assessments with the physician [5]. Moreover, patients with fulfilled information needs or higher satisfaction with the received information may also display a higher degree of HRQoL [6].

Various factors can influence a patient's HRQoL making it a variable that is both difficult to unify and to diversify. The concept can mean something different to every patient, leading to a variety of interpretative possibilities. Therefore, the concept of HRQoL bares the difficulty of objectifying its content for practical decision making in medical practice. Aspects that play into the concept of HRQoL in modern medicine can vary from independence, stage of disease, the amount and severity of drug side effects to even personal fulfillment. As diverse as the topic itself are the options of evaluating it [7]. In recent years an emphasis has been made on patient-reported outcomes (PRO) as a means of collecting HRQoL data. PROs are characterized by the fact that several validated questionnaires are used simultaneously for HRQoL measurement in order to balance the respective subjectivity [8].

A PRO is "a measurement based on a report that comes directly from the patient (ie, study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else" [9]. They are an effective module in assessing a patient's well-being using paper-based and digital data collection [10]. They are useful in identifying patient distress and assessing new therapeutic methods and can hence improve care [11,12]. A previous study also observed a benefit in overall survival for patients who self-reported their symptoms in an online setting [13]. However, PRO data depend on factors that may not be health-related or influenced by individual values or other passing momentary conditions [14]. In addition, practical aspects can influence HRQoL data collection. An overflow of long questionnaires can influence compliance and motivation [15,16]. Furthermore, several studies have reported poor compliance in long-term studies [17,18]. While the findings did not show conclusively if compliance was dependent on the questionnaire format (visual analog or categorical) [17], the chosen evaluative instrument can have an influence on people's perception and adoption of it [7]. These issues play an important role when administering studies digitally, especially to a less technically inclined collective, such as older patients [19].

Therapeutic decision making, especially in palliative care, can depend on the patient's reporting of their HRQoL. As data suggest that clinicians may underestimate or miss a large part of adverse effects, there is a need for more clarity in physicians' evaluation of patient-reported content [20-23]. Changes and time to deterioration (TTD) in HRQoL have previously been used to further assess the benefits of cancer medication [24,25], again emphasizing the high potential of a differentiated evaluation of HRQoL assessments in cancer research. With metastatic breast cancer patients usually being treated for a longer period of time at the same care center, detecting change in patient-reported HRQoL presents a type of measurement that allows for long-term HRQoL screening in addition to isolated assessments. Exploring the longitudinal development of HRQoL with the TTD method may help uncover influential factors on HRQoL as well as predictive capabilities of such measurements [26]. The introduction of digital monitoring systems in the area of HRQoL offers new possibilities in reaching out to patients struggling with the effects of metastatic breast cancer and extend medical care to remote areas. However, the digital application of a longitudinal measurement system needs to be evaluated in terms of effectiveness, acceptance and presentation. Low compliance can be a challenge in longitudinal digital studies [18], and aspects concerning patients' expectation regarding quality of life such as response shift can influence the TTD [27].

This study aimed to evaluate 3 common HRQoL questionnaires (EuroQol Visual Analog Scale [EQ-VAS], EuroQol 5 Dimension 5 Level [EQ-5D-5L], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 item [EORTC QLQ-C30]) in a sample of women with metastasized breast cancer in terms of TTD in a digital, web-based setting. We further examined the development of the HRQoL in different systemic treatment groups.

Methods

Study Design and Sample

The PEPPER study (Patient Engagement Pilotstudie Mammakarzinom-individualisierte und Ressourcen-effiziente Patient-Reported Outcomes Erfassung durch digitale Therapieunterstuetzungssysteme) was conducted from December 2016 to August 2019 at two German university hospitals (University Hospitals of Heidelberg and Tübingen). It was designed as a bicentric prospective cohort study collecting longitudinal information on HRQoL, physical symptoms, and PROs of metastatic breast cancer patients via the online platform PiiA (Patient-informiert-interaktiv-Arzt, Figure 1) over a 6-month period. The assessments were scheduled weekly for

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the first 8 weeks of the cohort study and 4 times monthly for the last 4 months (see Table 1). The digital assessment of QoL allowed for evaluation not bound to treatment schedule and the inclusion of patients not living in close proximity to the care center. Participants were identified through a screening process of their medical history and then approached at their next scheduled appointment. Criteria of eligibility were ≥18 years of age, a sufficient level of the German language, metastatic breast cancer in progressive or stable state of disease undergoing any form of systemic therapy, patients with therapy change, active enrollment in the PRAEGNANT study (a German metastatic breast cancer registry network), and written consent. Exclusion criteria covered patients who were not eligible for observation due to severe comorbidities or unavailability according to the treating physician, patients who were not able to handle a tablet computer or were unable to write as well as patients who were not able to understand the nature and extent of the trial and the procedures required.

The patients assessed for eligibility were radiologically assessed for disease progression every 3 months until death or loss to follow-up using the Response Evaluation Criteria in Solid Tumors [28]. The patients assessed for eligibility were divided into 2 subgroups—patients with stable disease or partial response and those with early progressive disease at the first trimonthly follow-up evaluation.

Upon confirmation of participation, patients were asked to complete the baseline visit on-site on a tablet provided by the staff. Skilled staff was available throughout the baseline visit in person and via email during the entire study period to provide technical support. Further parts of the study were completed on their preferred device at home. Participants of the study were reminded of upcoming or uncompleted visits via email or telephone. The study was conducted in German. Ethics approval was granted by the ethical committees of the University of Heidelberg (S-598/2016) and Tübingen (191/2017BO2).

Figure 1. Example of an assessment section on the Patient-informiert-interaktiv-Arzt portal.

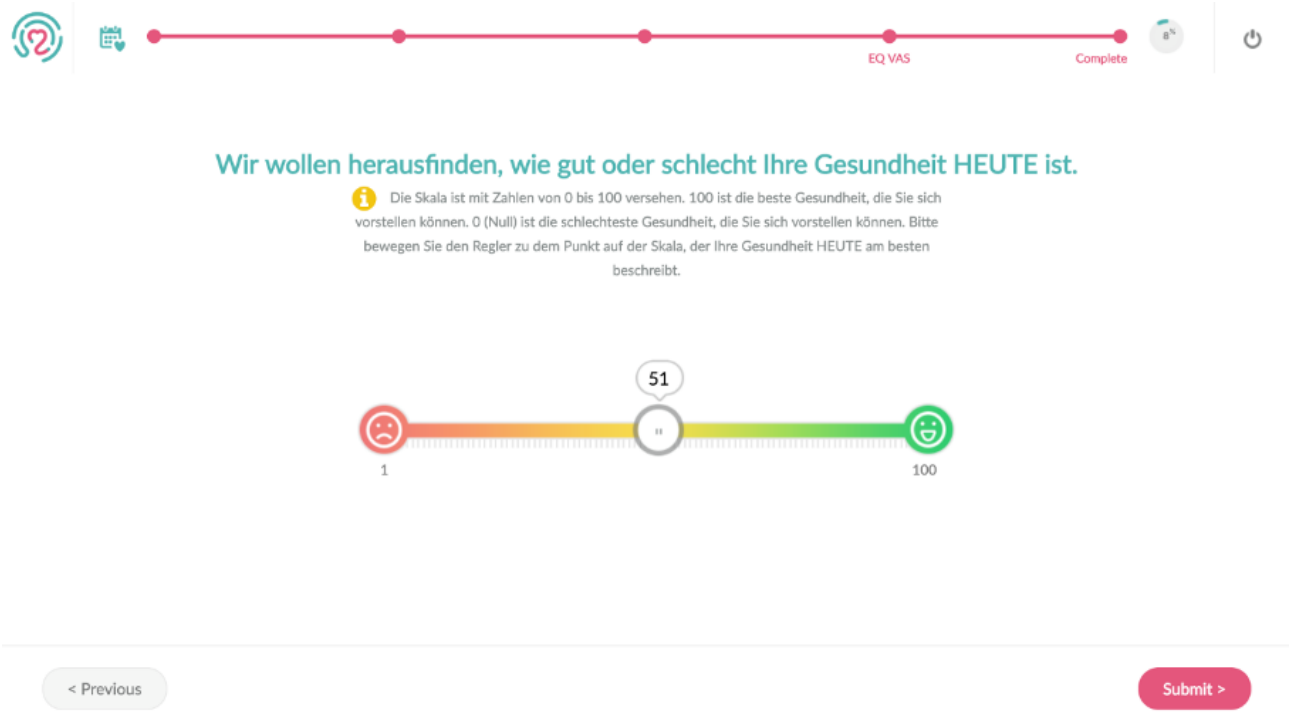

Table 1. Implementation of questionnaires.

Visit	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Week	0	1	2	3	4	5	6	7	8	12	16	20	24
EQ-VAS[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EORTC QLQ-C30[c]	✓	—[d]	—	—	✓	—	—	—	✓	✓	✓	✓	✓

[a]EQ-VAS: EuroQol Visual Analog Scale.

[b]EQ-5D-5L: EuroQol 5 Dimension 5 Level.

[c]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 item.

[d]Not applicable.

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Quantitative Data Collection and Questionnaires

Sociodemographic data was gathered at baseline via the online platform PiiA. In addition, treatment regiments and medical history were retrieved by analyzing medical records of the particular university hospital. To evaluate the QoL of the patients, 3 assessment instruments were used in this study.

We administered 3 common HRQoL questionnaires (EQ-VAS, EQ-5D-5L, EORTC QLQ-C30) over a 6-month period (see Table 1). A TTD event is defined as the decline in HRQoL score in the respective questionnaire score by the corresponding minimally important difference (MID) in comparison to the baseline score.

The EQ-VAS is a global self-evaluation of the state of health on a visual analog scale from 0 (worst imaginable state of health) to 100 (best imaginable state of health). It thereby offers a global and momentary insight into the patients' overall self-reported well-being. The EQ-VAS can be administered as part of the EQ-5D questionnaire [29,30]. A difference of ≥7 points was the MID for deterioration detection, which has previously been established in similar studies [24,25,31,32].

The EQ-5D-5L is a validated questionnaire consisting of 5 questions, each with 5 options, encompassing aspects such as mobility and self-reliance as parts of its HRQoL definition [33]. The EQ-5D-5L is a validated instrument in assessing HRQoL in German [29,34] and has shown to be of use in detecting changes in the state of health of breast cancer patients [35]. The EQ-5D-5L can be summarized using a score ranking from <0 (worst possible HRQoL) to 1 (best possible HRQoL) [33]. A decrease in ≥0.08 points was regarded as a MID for deterioration as described previously [24,25,31,32]. The average completion time for the EQ-5D-5L ranges from 25 to 75 seconds, while the EQ-VAS can be answered in just 5 to 15 seconds.

The EORTC QLQ-C30 constitutes a more detailed questionnaire in regard to HRQoL and is a valid tool in measuring the HRQoL in cancer patients [36]. Consisting of 30 items, the EORTC QLQ-C30 encompasses 5 questions about self-reliance in everyday situations, 23 questions about physical complaints and their impact on HRQoL and social interactions on 4-point Likert scales as well as two global items on the HRQoL and state of health, each on a 7-point Likert scale. The average time to completion of this questionnaire is estimated to range from 150 to 450 seconds. The QLQ-C30 is summed up using a summary score [37]. The questionnaire has previously been found to be a valid instrument in assessing HRQoL in breast cancer patients via an eHealth medium [38]. In accordance with similar studies, a decline of ≥10 points was regarded as deterioration [24,31,39-41]. The pattern, in which questionnaires were implemented in the study, is depicted in Table 1.

Treatment Line Grouping

Data about their current treatment regime was assembled from the participants' medical history. The various lines of treatment were divided into the following 4 groups: cyclin-dependent kinase (CDK) 4/6 inhibition therapy (including any form of endocrine therapy in combination with a CDK4/6 inhibitor), human epidermal growth factor receptor 2 (HER2)-targeted therapy (including trastuzumab, pertuzumab, trastuzumab emtansine, and lapatinib alone or in combination with chemotherapy), chemotherapy (intravenous or oral) alone, and endocrine therapy alone.

Statistical Analysis

We used the programming language R (version 3.6.1, R Foundation for Statistical Computing) for all analyses [42]. Socioeconomic characteristics, questionnaire data, and treatment schedules were first described descriptively using absolute and relative frequencies, means, and standard deviations.

TTD was defined as time to the first clinically meaningful deterioration in the respective HRQoL assessment tool and was illustrated using Kaplan-Meier plots. Furthermore, univariable, unadjusted Cox regression was applied to examine the influence of state of disease and similar characteristics on the TTD for all questionnaires. Moreover, we examined the aforementioned systemic treatment groups as to their TTD events for the EQ-VAS and the EQ-5D-5L using unadjusted Cox regression. Furthermore, predetermined systemic treatment groups within each HRQoL questionnaire were compared using linear mixed models.

Thereupon, EQ-VAS scores were compared to the different questions of the EQ-5D-5L as well as to the EQ-5D-5L summary score. For the patients who experienced a TTD event in the EQ-VAS, the difference of the values between the time of the event and the baseline visit in the respected EQ-5D-5L item were compared by applying the 1-sample Wilcoxon signed-rank test. Thereafter, this difference was compared to the differences of patients without a TTD event using the 2-sample Wilcoxon rank-sum test. In all analyses, $P<.05$ (2-tailed) was considered indicative of statistically significant differences.

Results

Sociodemographic Characteristics and State of Disease

A total of 192 patients with metastatic breast cancer were analyzed in this bicentric prospective online cohort study at two German university hospitals. During the first 8 weeks of the study, 21.9% (42/192) of participants completed every visit with a satisfactory completion rate of ≥80% showing a considerable loss of patients during follow-up in the overall study. However, the percentage of completed questionnaires after 8 weeks in comparison to baseline was higher with 62.7% (104/166) for the EQ-VAS, 73.2% (82/112) for the EQ-5D, and 62.4% (103/165) for the QLQ-C30. The number of completed questionnaires for each visit are included in Multimedia Appendix 1. The sociodemographic characteristics of this collective are shown in Table 2. The average age at study inclusion was 54.3 years. A total of 49.5% (95/192, 25 missing) of patients had a high education level (university entrance qualification or higher), and 69.8% (134/192, 25 missing) received public health insurance.

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Table 2. Sociodemographic characteristics (n=192).

Characteristic	Value
Age at study inclusion (years), mean (SD)	54.3 (10.1)
Age at primary diagnosis (years), mean (SD)	47.3 (10.0)
Education, n (%)	
University entrance qualification or higher	95 (49.5)
Lower than university entrance	72 (37.5)
Missing	25 (13.0)
Health insurance, n (%)	
Public	134 (69.8)
Private	33 (17.2)
Missing	25 (13.0)
Marital status, n (%)	
Married/in a relationship	142 (74.0)
Not married/in a relationship	23 (12.0)
Missing	27 (14.1)
Children, n (%)	
Yes	128 (66.7)
No	39 (20.3)
Missing	25 (13.0)

The mean age of initial diagnosis was 47.3 years. The average duration between initial diagnosis and study inclusion was 66.6 months. A total of 29.7% (57/192, 57 missing) of patients were already in metastatic stage at initial diagnosis of breast cancer. Further information on the metastatic situation at study enrollment and state of disease of the primary tumor according to TNM classifications can be seen in Table 3.

The median number of different treatment regiments before inclusion was 3 (range 0-13, Q1-Q3 2-4) and on average patients received 1 (0-10, 1-2) different chemotherapeutic treatment lines prior to enrollment in the study. Within the first 3 months of study participation, 46 patients (46/192, 24.0%, 11 missing) were diagnosed with disease progression and 21 patients (21/192, 10.9%, 10 missing) experienced a change in treatment. The systemic treatment line patients followed throughout this period is shown in Table 3.

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Table 3. State of disease and treatment regiments.

Characteristic	Value
Difference between initial diagnosis of breast cancer and study inclusion (months), median (Q1-Q3)	66.6 (29.4-127.4)
Difference between initial diagnosis of breast cancer metastases and study inclusion (months), median (Q1-Q3)	21.5 (6.8-40.1)
Characteristics of primary tumor (TNM classification), n (%)	
c/y/pT[a]PT[b]	
0	7 (3.6)
1	46 (24.0)
2	60 (31.3)
3	15 (7.8)
4	7 (3.6)
Other or N/A	57 (29.7)
c/y/pN[c]PT	
+	35 (18.2)
0	23 (12.0)
1	32 (16.7)
2	13 (6.8)
3	6 (3.1)
Other or N/A	83 (43.2)
M[d]PT	
1	57 (29.7)
0	78 (40.6)
N/A	57(29.7)
Breast cancer subtype of primary tumor, n (%)	
Hormone receptor positive + HER2[e] neu negative	101 (52.6)
HER2 neu positive	63 (32.8)
Triple negative	14 (7.3)
N/A	14 (7.3)
Metastases diagnosed at study inclusion, n (%)	
Brain	6 (3.1)
Lymph nodes	53 (27.6)
Bone	108 (56.3)
Lung	55 (28.6)
Pleura	20 (10.4)
Liver	66 (34.4)
Peritoneum	9 (4.7)
Skin	10 (5.2)
Other	15 (7.8)
N/A	4 (2.1)
Previous treatment regiments before study inclusion (Q1-Q3)	
Number of treatment regiments, median	3 (2-4)
Number of chemotherapeutic treatment lines, median	1 (1-2)
Systemic treatment groups during study period, n (%)	

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Characteristic	Value
CDK[f] 4/6 inhibitors +/– endocrine therapy	41 (21.4)
Chemotherapy	62 (32.3)
Endocrine therapy	18 (9.4)
HER2-targeted therapy	54 (28.1)
N/A	17 (8.9)

[a]c/y/pT: Clinical/after neoadjuvant therapy/pathologic classification of tumor extent and size.

[b]PT: Primary tumor.

[c]c/y/pN: Clinical/after neoadjuvant therapy/pathologic classification of regional lymph node involvement.

[d]M: Metastatic spread.

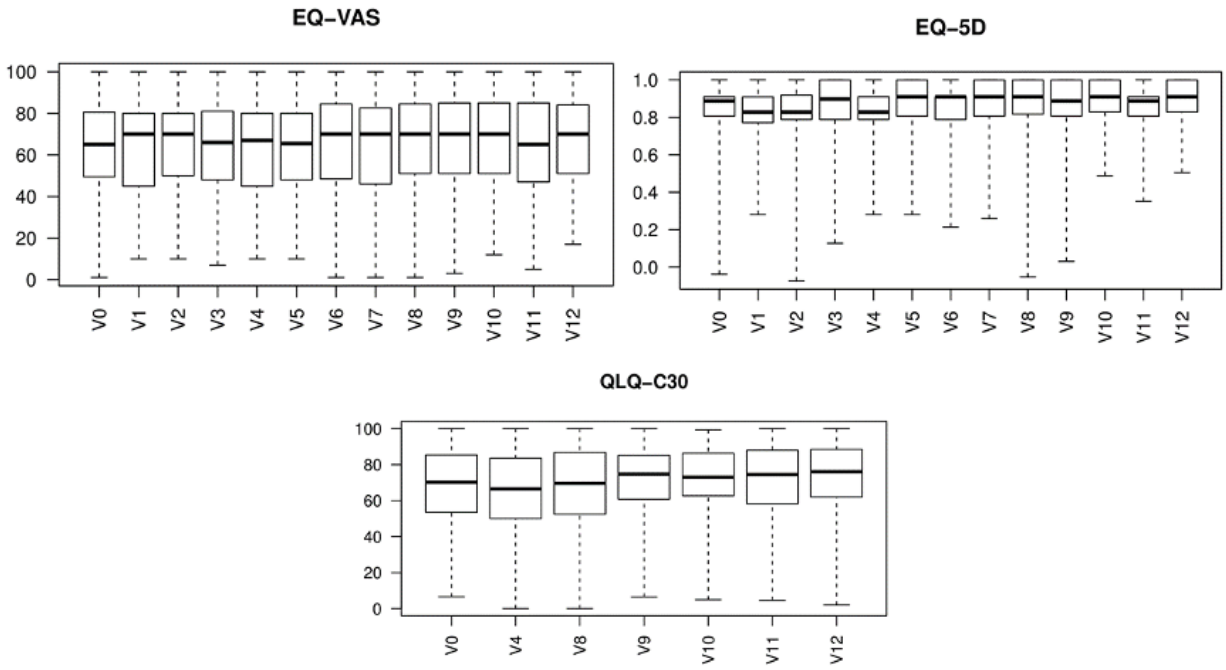
[e]HER2: human epidermal growth factor receptor 2.

[f]CDK: cyclin-dependent kinase.

Questionnaire Data

Figure 2 shows the overall state of health at the different visits. On average, patients reported a health status in the upper half of the possible range in each of the questionnaires and at all visits. Furthermore, the differences observed throughout the 6-month study period are fairly small in all questionnaires, indicating a low degree of change in HRQoL during the study period. The EQ-VAS consistently showed a higher variance than the other questionnaires during the entire study period.

Figure 2. Box plots representing (a) EQ-VAS results at baseline and 12 visits, (b) EQ-5D-5L results at baseline and 12 visits, and (c) EORTC-QLQ-C30 results at baseline and 6 visits. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 item; EQ-5D-5L: EuroQol 5 Dimension 5 Level; EQ-VAS: EuroQol Visual Analog Scale.



TTD With Regression Results

The rate of deterioration (number of patients with deterioration divided by the total number of patients) amounted to 0.47 in the EQ-VAS (84/179), representing the highest rate of TTD events in our sample with an average TTD of 8 weeks. We could identify a rate of deterioration of 0.29 (47/163) in the EQ-5D-5L and 0.37 (65/176) in the QLQ-C30.

Univariate Cox regression analysis on pathologic and treatment-related factors showed a connection between known metastases in the liver (P=.03) and pleura (P=.04) at the time of study inclusion and deterioration, as well as a vague link to the clinical diagnoses of disease progression within the first 3 months of the study in the EQ-VAS (P=.11). As can be seen in Figure 3, patients with diagnosed disease progression (hazard ratio [HR] 1.48) showed a higher rate of TTD events in the EQ-VAS than in case of no progression with a nonsignificant P value (P=.11), as seen in Figure 3. For the other questionnaires, we could not detect a link between the reviewed criteria and deterioration. The results of the univariate Cox regression analysis can be found in Table 4. A univariate Cox

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regression analysis with results adjusted for age and progression can be found in Multimedia Appendix 1.

Figure 3. Kaplan-Meier estimation for stable and progressive state of disease representing (a) EQ-VAS, (b) EQ-5D-5L, and (c) EORTC-QLQ-C30. EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 item; EQ-5D-5L: EuroQol 5 Dimension 5 Level; EQ-VAS: EuroQol Visual Analog Scale.

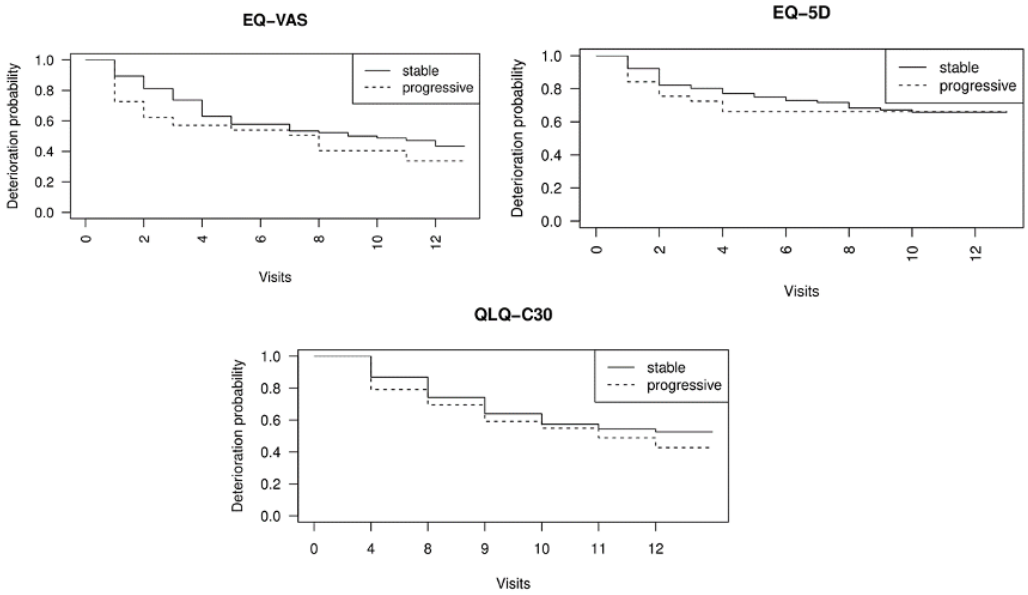

Table 4. Univariate Cox regression analysis.

Variable	EQ-VAS[a]		EQ-5D-5L[b]		EORTC QLQ-C30[c]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	0.99 (0.97-1.02)	.583	0.98 (0.95-1.01)	.20	1.00 (0.98-1.03)	.83
Metastasis						
Brain	1.71 (0.74-3.94)	.21	0.32 (0.04-2.31)	.26	1.16 (0.42-3.2)	.78
Lymph nodes	1.20 (0.77-1.87)	.42	1.42 (0.79-2.54)	.23	0.95 (0.56-1.63)	.86
Bone	0.83 (0.54-1.29)	.41	0.85 (0.47-1.53)	.59	1.4 (0.81-2.43)	.22
Lung	1.09 (0.69-1.69)	.71	0.73 (0.39-1.37)	.33	0.97 (0.57-1.65)	.91
Pleura	0.42 (0.18-0.96)	.04	0.43 (0.13-1.39)	.16	0.90 (0.41-1.98)	.79
Liver	1.64 (1.06-2.52)	.03	1.67 (0.94-2.99)	.08	0.87 (0.51-1.47)	.61
Peritoneum	0.96 (0.35-2.63)	.94	0.78 (0.19-3.2)	.73	1.39 (0.5-3.84)	.52
Skin	0.55 (0.2-1.52)	.25	0.82 (0.25-2.65)	.74	0.41 (0.1-1.7)	.22
Other	0.67 (0.32-1.39)	.28	0.73 (0.26-2.04)	.55	1.79 (0.93-3.46)	.08
Progression	1.48 (0.91-2.37)	.11	1.15 (0.60-2.23)	.34	1.05 (0.58-1.88)	.88
Systemic group						
CDK[d] 4/6 inhibitors +/– endocrine therapy	Reference	Ref	Ref	Ref	Ref	Ref
Chemotherapy	1.72 (0.77-3.85)	.19	1.48 (0.41-5.32)	.55	0.43 (0.2-0.94)	.03
Endocrine therapy	2.29 (0.93-5.65)	.07	0.69 (0.11-4.21)	.69	0.60 (0.25-1.5)	.29
HER2[e]-targeted therapy	1.7 (0.76-3.83)	.20	1.42 (0.38-5.4)	.60	0.54 (0.25-1.15)	.11

[a]EQ-VAS: EuroQol Visual Analog Scale.

[b]EQ-5D-5L: EuroQol 5 Dimension 5 Level.

[c]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 item.

[d]CDK: cyclin-dependent kinase.

[e]HER2: human epidermal growth factor receptor 2.

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Systemic Treatment Groups

We divided the patients into 4 groups according to the treatment that they received during the first 3 months of the study. We then proceeded to use Cox regression to compare the subgroups with each other in terms of the TTD. This revealed a difference between CDK4/6 inhibitor therapy and mere endocrine therapy in the EQ-VAS (*P*=.07) and between CDK4/6 inhibitor therapy and chemotherapy in the QLQ-C30 (*P*=.03; see Table 4).

Using a linear mixed model, we proceeded to compare the predetermined systemic treatment groups within each HRQoL questionnaire. For the EQ-VAS and EQ-5D-5L, a significant difference between treatment groups could be detected. In the EQ-VAS, all treatment groups showed a significant difference in comparison to CDK4/6 inhibitor therapy during the examination period (see Table 5). A similar difference showed in our analyses of these subgroups using the QLQ-C30 summary score. An increase in the difference of EQ-VAS values in comparison to baseline is visible for patients receiving CDK4/6 inhibitors. For the EQ-5D-5L, a significant difference between patients receiving chemotherapy and HER2-targeted therapy could be encountered. All results of the subgroup analysis can be examined in Table 5.

Table 5. Linear mixed model and post hoc analysis results for therapeutic subgroup comparison (cyclin-dependent kinase 4/6 inhibitors +/– endocrine therapy = group 1, chemotherapy = group 2, endocrine therapy = group 3, human epidermal growth factor receptor 2-targeted therapy = group 4); scale of the respective tool in brackets.

Group comparison	EQ-VAS[a] (0-100)		EQ-5D-5L[b] (0-1)		EORTC QLQ-C30[c] (0-100)	
	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
Overall	—[d]	<.001	—	.002	—	.048
2-1	–14.41	<.001	–0.06	.03	8.91	.04
3-1	–12.62	<.001	–0.26	.79	1.74	.97
4-1	–10.58	<.001	0.01	.99	3.37	.75
3-2	1.80	.81	0.04	.47	–7.17	.23
4-2	3.83	.09	0.07	.002	–5.54	.29
4-3	2.03	.75	0.03	.58	1.63	.97

[a]EQ-VAS: EuroQol Visual Analog Scale.

[b]EQ-5D-5L: EuroQol 5 Dimension 5 Level.

[c]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 item.

[d]Not applicable.

Event Comparison Between the EQ-VAS and the EQ-5D-5L and Patients Without TTD Events

For each patient who showed deterioration in the EQ-VAS, a Wilcoxon signed-rank test with continuity correction was conducted to examine whether significant differences in singular questions and the summary score of the EQ-5D-5L could be detected. In Table 6 it can be seen that for several EQ-5D-5L items such a significant relation could be registered. Thereupon, a 2-sample Wilcoxon rank-sum test was performed comparing the deteriorating patients to the rest of the sample group to further differentiate between significant subgroup and collective deterioration. The results are depicted in Table 6.

Table 6. Results of the Wilcoxon signed rank test and the 2-sample Wilcoxon rank-sum test.

EQ-5D-5L[a] scale	Event: baseline		Event: remaining time steps	
	Mean difference (CI)	*P* value[b]	Mean difference (CI)	*P* value[c]
Mobility	0.28 (0.09 to 0.48)	.005	0.34 (0.14 to 0.54)	.001
Selfcare	0.15 (–0.01 to 0.31)	.06	0.12 (–0.03 to 0.29)	.12
Activities	0.26 (0.05 to 0.47)	.02	0.29 (0.07 to 0.51)	.01
Pain	0.26 (0.07 to 0.45)	.009	0.27 (0.07 to 0.47)	.008
Anxiety	0.26 (–0.04 to 0.56)	.09	0.23 (–0.07 to 0.54)	.13
Summary score	–0.06 (–0.11 to –0.01)	.02	–0.06 (–0.11 to –0.01)	.03

[a]EQ-5D-5L: EuroQol 5 Dimension 5 Level.

[b]Wilcoxon signed-rank text.

[c]Wilcoxon rank-sum test.

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Discussion

Objective and Main Findings

In this study, we aimed to examine the longitudinal development of HRQoL using the TTD method in 3 different HRQoL questionnaires among breast cancer patients. We also applied Cox regression to determine possible influencing factors and used the Wilcoxon signed-rank test and the 2-sample Wilcoxon rank-sum test to distinguish our findings further. We then compared common systemic treatment groups in breast cancer treatment to emphasize our results. Mainly, we found the EQ-VAS showing a higher rate of deterioration than the other questionnaires in the same collective. Furthermore, in our sample the EQ-VAS offered a higher variance than the other questionnaires, allowing for more distinction between higher and lower outcome patients than the other instruments. A TTD event in the EQ-VAS also shows relations to disease related determinants as well as clear differentiation both individually between the EQ-VAS and the EQ-5D-5L items and from patients who did not experience a TTD event.

TTD With Regression Results

The highest rate of deterioration using TTD method could be detected in the EQ-VAS, a visual analog scale. The MID that were used for deterioration detection have been previously used in other studies [24,25,31,32,39-41]. Nonetheless, it should be noted that the sample size for the EQ-VAS was bigger than for the other questionnaires, especially the EQ-5D-5L. It has been described that long questionnaires can result in lower compliance [16]. This might be explained by the length and timing of the other questionnaires: the other 2 instruments are more extensive and the QLQ-C30 was only included on a monthly basis. Implementing the QLQ-C30 on a monthly rather than a weekly basis was an effort to ensure compliance and motivation as this questionnaire is much longer than the other assessments and as this analysis only constitutes a secondary aim of this study. However, this may have resulted in patient loss within the interval and fewer opportunities to apply the TTD method on this questionnaire. Apart from this, due to the small sample size and the limited HRQoL variance in all questionnaires, we did not perform tests to compare the precision of the questionnaires among each other. Therefore, it cannot be concluded that the EQ-VAS is advantageous in the longitudinal investigation of HRQoL compared to the other questionnaires examined. However, although overall completion rates deteriorated over time as expected, the EQ-VAS showed a higher completion rate than the EQ-5D-5L, which were both included in the visits on a weekly basis. Hence, it can be concluded that the EQ-VAS as a single visual analog scale with decisive wording offers an easy application of HRQoL monitoring in a digital setting.

Using univariate Cox regression analysis on the pathologic and treatment-related factors we discovered a link between metastases in the liver (P=.03) and pleura (P=.04) at the time of study inclusion and deterioration in HRQoL only in the EQ-VAS. As metastases in other organs result in further symptoms, a decrease of HRQoL in this state of disease is very plausible. Patients with progressive disease showed a tendency of a shortened TTD in the EQ-VAS (HR 1.48) when compared to the EQ-5D-5L (HR 1.15) and the QLQ-C30 (HR 1.05). This corresponds to previous research that describes a negative impact of disease progression on HRQoL [3]. This connection might show possible predictive capabilities of this method when using the EQ-VAS, as it may be more sensitive to disease progression than the other questionnaires.

Event Comparison Between the EQ-VAS and EQ-5D-5L

With the EQ-5D-5L and EORTC QLQ-C30 showing less deterioration events in comparison to the EQ-VAS and no significant connections to the above-described factors, we proceeded to further investigate the significance of a TTD event in the EQ-VAS. To accomplish this, we first applied a Wilcoxon signed-rank test with continuity correction. We observed significant changes for patients with an EQ-VAS event in several EQ-5D-5L items. This indicates an internal consistency of deterioration in HRQoL for individuals with an EQ-VAS TTD event among the several different aspects of HRQoL presented in the EQ-5D-5L. Moreover, it offers an assurance that aspects of the HRQoL definition of the EQ-5D-5L are reflected in the open formulation of the EQ-VAS. As the analysis showed only a vague relation to the anxiety question of the EQ-5D-5L, it might suggest a capability of the EQ-VAS to better reflect physical rather than mental aspects of HRQoL in breast cancer patients. However, the EQ-VAS has previously been reported to show a lower score in patients with anxiety and depressive disorders in comparison to healthy participants [43]. Nonetheless, in this sample a TTD event in the EQ-VAS was more strongly reflected in physical aspects of the EQ-5D-5L.

Thereupon, we performed a 2-sample Wilcoxon rank-sum test to contrast patients who experienced a TTD event in the EQ-VAS with patients who experienced no TTD event by comparing their respective differences in the EQ-5D-5L. As these analyses were significant for most items and the overall score, a clear distinction of patients with a TTD event to the inconspicuous participants became apparent. These analyses show that TTD events did not occur randomly but show that patients with a TTD event in the EQ-VAS significantly differ from the rest of the study population. This further supports the EQ-VAS as a valid screening instrument to implement TTD for longitudinal HRQoL management.

Systemic Treatment Groups

Cox regression analyses revealed a vague statistical difference between patients receiving CDK4/6 inhibitors and patients undergoing endocrine therapy alone. As other studies reported factors such as pain reduction and advantageous tumor response for patients receiving a CDK4/6 inhibitor in addition to endocrine therapy, our findings offer a plausible reflection of CDK4/6 inhibitors' HRQoL profile [44,45]. Furthermore, the combination with CDK4/6 inhibitors and endocrine therapy has shown to be beneficial in regard to progression-free survival when compared to endocrine therapy alone, which in turn represents an important factor in HRQoL [3,46].

From further examination of the EQ-VAS score using a linear mixed model (Table 5), we again found that CDK4/6 inhibition

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therapy significantly differs from the other treatment groups. Patients receiving CDK4/6 inhibition therapy showed an overall positive difference to baseline in the EQ-VAS during the entire study period, whereas the other groups showed a steady or even declining level of HRQoL on the questionnaire. As it has previously been reported that patients under CDK4/6 inhibitors have a slower rate of deterioration in HRQoL and experience milder side effects, our findings are reinforced by previous research [47,48]. This again supports our finding that a longitudinal observation of HRQoL through the EQ-VAS questionnaire is an adequate mean of measurement for this variable.

Further investigation of the EQ-5D-5L uncovered a significant difference between patients under chemotherapy and patients receiving HER2-targeted therapy. It has previously been described that patients who receive a combination of HER2-targeted therapy and chemotherapy exhibit better HRQoL than patients who only receive chemotherapy [49,50]. It has also been reported that the addition of HER2-targeted medication to a chemotherapy schedule can result in the improvement of adverse effects [49]. As can be seen in Multimedia Appendix 1, both groups showed a greater variance in the EQ-5D-5L than the other groups. For the subgroup undergoing HER2-targeted therapy, several extreme outliers with a high positive difference to baseline contribute to the distinction of this group. On the other hand, the boxplots for the chemotherapy subgroup show a discrete tendency toward a reduction in HRQoL on the EQ-5D-5L, which complements previous research.

This subgroup analysis therefore consolidates the representativeness of both our sample and our finding that measuring the TTD can be an adequate method to observe HRQoL, especially with the EQ-VAS.

However, not all treatment groups were of equal size and not all of these groups showed an adequate retention rate in their assessments. Therefore, these findings must be interpreted with proper caution, but in the context of previous studies in this area still represent an important impulse of future research.

Limitations

Our analysis is based on a relatively small sample size. This might result from poor compliance, length of questionnaire or technical difficulties which, when present, were quickly resolved by the staff [15,16].

In addition, we did not account for response shift ("a change in the meaning of one's self evaluation of a target construct" [51]) as this was a secondary aim of this study. However, there are studies that show that by not considering response shift, HRQoL levels can lead to misinterpretation [52,53]. We also defined TTD events in relation to the baseline score. When assessing HRQoL, using the time until definitive deterioration has also been suggested in a metastatic setting [54]. In accordance with previous research in the field of longitudinal HRQoL monitoring and per not accounting for response shift in our analyses, we decided to apply the TTD method using the baseline score as reference [24,25,27,31,41,54].

Therefore, more research is needed to consolidate our findings. Moreover, all questionnaires were administered digitally only. However, the equivalence of electronic and paper-based PRO measurements has previously been established [10]. Furthermore, we detected a rather high and steady level of well-being among all questionnaires in our descriptive analysis, which limits the variance of these findings. We only included patients with internet access at home, as per inclusion criteria. Hence, older patients who are not as technologically inclined were not eligible for participation. Therefore, with an average age of 54.3 years, our sample does not reflect the average age of breast cancer patients [55]. Furthermore, as Heidelberg and Tübingen reflect economically strong regions in Germany, our sample showed a higher percentage of private health insurance and higher education than the general public [56-58]. As private health insurance in Germany is only available if you have a higher income, it can be concluded that our sample shows a bias in regard to its socioeconomic profile [56]. In addition, the order of the questionnaires remained the same throughout the study and was not randomized.

Conclusions

In comparison to the EQ-5D-5L and QLQ-C30, the EQ-VAS showed a higher rate of deterioration, significant connections between deterioration and certain locations of metastases, and a better discrimination between progressive and stable disease (HR 1.48). In addition, known differences in HRQoL profiles of various treatment regiments were reflected in the EQ-VAS. We suggest that using the TTD method with the EQ-VAS is an adequate means of examining longitudinal development of HRQoL among breast cancer patients in a digital setting and constitutes a reasonable addition to breast cancer therapy.

Acknowledgments

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Authors' Contributions

KB wrote the manuscript and was involved in data collection along with LS. KB, MF, and TMD planned the data analysis. MF performed the data analysis. MW, TMD, LS, AS, TE, JG, and AH were involved in project development and coordination.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Supplemental tables and figure.
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Abbreviations

CDK: cyclin-dependent kinase
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 item
EQ-5D-5L: EuroQol 5 Dimension 5 Level
EQ-VAS: EuroQol Visual Analog Scale

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HER2: human epidermal growth factor receptor 2
HR: hazard ratio
HRQoL: health-related quality of life
MID: minimally important difference
PEPPER study: Patient Engagement Pilotstudie Mammakarzinom - individualisierte und Ressourcen-effiziente Patient-Reported Outcomes Erfassung durch digitale Therapieunterstuetzungssysteme
PiiA: Patient-informiert-interaktiv-Arzt
PRO: patient-reported outcome
TTD: time to deterioration

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Original Paper

Technology-Based Interventions for Cancer Caregivers: Concept Analysis

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Abstract

Background: Cancer is a taxing chronic disease that demands substantial care, most of which is shouldered by informal caregivers. As a result, cancer caregivers often have to manage considerable challenges that could result in severe physical and psychological health consequences. Technology-based interventions have the potential to address many, if not all, of the obstacles caregivers encounter while caring for patients with cancer. However, although the application of technology-based interventions is on the rise, the term is seldom defined in research or practice. Considering that the lack of conceptual clarity of the term could compromise the effectiveness of technology-based interventions for cancer caregivers, timely research is needed to bridge this gap.

Objective: This study aims to clarify the meaning of technology-based interventions in the context of cancer caregiving and provide a definition that can be used by cancer caregivers, patients, clinicians, and researchers to facilitate evidence-based research and practice.

Methods: The 8-step concept analysis method by Walker and Avant was used to analyze the concept of technology-based interventions in the context of cancer caregiving. PubMed, PsycINFO, CINAHL, and Scopus were searched for studies that examined technology-based interventions for cancer caregivers.

Results: The defining attributes of technology-based interventions were recognized as being accessible, affordable, convenient, and user-friendly. On the basis of insights gained on the defining attributes, antecedents to, and consequences of technology-based interventions through the concept analysis process, technology-based interventions were defined as the use of technology to design, develop, and deliver health promotion contents and strategies aimed at inducing or improving positive physical or psychological health outcomes in cancer caregivers.

Conclusions: This study clarified the meaning of technology-based interventions in the context of cancer caregiving and provided a clear definition that can be used by caregivers, patients, clinicians, and researchers to facilitate evidence-based oncology practice. A clear conceptualization of technology-based interventions lays foundations for better intervention design and research outcomes, which in turn have the potential to help health care professionals address the needs and preferences of cancer caregivers more cost-effectively.

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KEYWORDS

concept analysis; caregivers; cancer; oncology; technology-based interventions; mobile phone

Introduction

Background

Cancer does not discriminate—it is prevalent across demographics and geographies [1]. Cancer is also pernicious—it could overwhelm the physiological health and psychological well-being of patients with cancer and cancer caregivers [2-7]. Informal caregivers, for instance, often have to shoulder a considerable amount of care burden—depending on the disease trajectory of the patients, approximately 55%-95% of caregivers shoulder mental health disorders such as distress [8-10]. In the context of this study, the term *health care professionals* describes health care personnel, including doctors, nurses, and all other formal caregivers, whereas *informal cancer caregivers*, *cancer caregivers*, and *caregivers* are used interchangeably, referring to informal cancer caregivers such as family and friends, who often regularly provide a wide range of assistance to a patient with cancer. Although, overall, a variety of interventions hold promise to alleviate caregiver burden, ranging from print materials and face-to-face consultations to telephone-based assistance [11-20], technology-based interventions are considered the most practical and promising solution available to caregivers.

The Critical Role of Technology-Based Interventions

The emphasis on technology-based interventions for cancer caregivers has become particularly pronounced amid the COVID-19 pandemic, a global health crisis that has effectively crippled many, if not all, of the traditional health care services available to patients and caregivers [21-23]. During the pandemic, many cancer caregivers have found much-needed solace and support in technology-based health care services, ranging from online support groups to videoconferencing with patients or health care professionals [24-26]. It is important to note that there is a growing body of research investigating the benefits of technology-based health solutions [24-29]. For instance, a systematic review revealed that caregivers significantly improved their cancer knowledge and communication outcomes after receiving technology-based interventions [27]. Throughout the pandemic, many scholars worried about whether the lack of *personal touch* might undermine technology-based interventions [28]. However, it is worth noting that, although face-to-face interactions have advantages, the social dynamics of these consultations could also hinder health care outcomes. For instance, in a study that compared the intervention efficacy of face-to-face consultations and technology-based interventions, researchers found that, among these 2 types of interventions, caregivers were more likely to truthfully report their stress symptoms to a web-based support system and have these symptoms addressed and treated [29].

The Importance of Conceptual Clarity

Although research on technology-based interventions for caregivers is gaining momentum, it faces many obstacles [30]. One of the most prominent hurdles that could considerably undermine the research field is the lack of a clear and consistent definition of the term *technology-based interventions*. It is important to note that, although the application of technology-based interventions is on the rise, the term is seldom defined when applied in cancer research or practice. A review of the literature [31-34] shows that alarmingly, much of the research on technology-based interventions for patients with cancer fails to provide a clear definition of the term to shed light on key questions: (1) Are technology-based interventions the same as terms such as *web-based interventions*? (2) What are the key characteristics of technology-based interventions? (3) What constitutes a technology-based intervention? The lack of conceptual clarity of the term *technology-based interventions* could substantially undermine the research field, as one of the most espoused truisms in academia is arguably that, particularly in light of scientific integrity and solidarity, scholars cannot measure what they cannot define [35-37]. As one scholar, the prominent British physicist and mathematician Lord William Thomson Kelvin, succinctly put it, “What is not defined cannot be measured. What is not measured cannot be improved. What is not improved is always degraded” [38].

Technology-Based Interventions and Related Terms

Overview

Before further elaborating on the urgent need for a clear definition of the term *technology-based interventions*, it is critical to shed light on why there is an urgent need to analyze and define the concept—similar terms (eg, digital health) applied in the research field often harbor deep-rooted issues that could cause confusion among scholars. Overall, a kaleidoscope of terms, such as *digital health*, *eHealth*, and *mobile health (mHealth*), has been used to describe a wide range of health solutions available to cancer caregivers [39-43]. These terms often refer to health solutions in the form of health services or products that are enabled by the internet (eg, emails and web-based appointments), multifunctional devices that are elevated by the connectivity of the internet (eg, smartphones such as the iPhone), or tools and services built upon other networking opportunities (eg, Amazon devices, such as Echo and Tile, developed on low-bandwidth networks such as the Sidewalk framework [44] or Bluetooth technologies). On the surface, these terms seem to describe various technology-based interventions in accordance with their unique characteristics, such as how the term mHealth can be used to refer to smartphone-based health interventions. However, a closer examination of these concepts reveals deep-rooted research issues.

Too Broad, Too Narrow, and Too Many Overlaps in Related Terms

To begin with, because of a lack of clear and consistent definitions, these terms can mean different things to different audiences—depending on the specific research contexts, they can be either extremely broad or narrow given that their meanings could vary widely as the research contexts shift (eg, example applications [39-43]). This is particularly true as

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technology-based tools or services become increasingly flexible and versatile. For instance, depending on the research context, terms such as *digital health*, *eHealth*, and *mHealth* can refer to a broad spectrum of health solutions, ranging from video-based materials on self-care or cancer care management (eg, television programs), web- or telephone-based communication with a wider support circle (eg, health care professionals), journaling in any or many enabling devices, or a hybrid or multicomponent intervention that consists of divergent forms of technology-based interventions [39-43].

At the same time, these terms can be too narrow. For instance, *mHealth* is often adopted to describe smartphone-, tablet-, and app-based health solutions [41] but not for interventions that involve laptop computers or smartwatches, even though they both possess similar defining functions to those of smartphones and tablets (eg, devices that can be easily carried and work on the go). The same applies for terms such as *digital health*, *eHealth*, *mHealth*—as researchers or caregivers' definitions of *digital* vary, for instance, *digital health* can refer to network connectivity in one study and to characteristics of the intervention or the delivery platform in another [45-48]. These *too broad* or *too narrow* issues lead to the conclusion that these terms might be further complicated by the fact that these terms are often not mutually exclusive [32,49,50]. For instance, video-based interventions can be delivered via DVD, television, computer, smartphone, or even electronic health records [49], which means that, because of a lack of conceptual clarity, these interventions can be described as any of the following: digital health, eHealth, or mHealth interventions. Overall, in contrast to technology-based interventions, terms such as *digital health*, *eHealth*, and *mHealth* are plagued by (1) a lack of definition and consensus regarding the scope of *digital health*, *eHealth*, and *mHealth*; (2) the absence of consistency in the interpretations of the meanings of *digital*, *electronic*, and *mobile*; and (3) the flexibility and versatility of technology opportunities that are often categorized as *digital health*, *eHealth*, and *mHealth* (eg, video-based interventions that can be delivered via mobile devices, desktop computers, and televisions).

It is important to underscore that these drawbacks also apply to terms such as *technology-mediated interventions*, *internet-based interventions*, and *web-based interventions* that have been used in cancer research [51], in contrast to more embracing terms such as *technology-based* and concepts such as *mediated*, *web*, or *internet* that are more flexible, versatile, and open to interpretation. Overall, compared with terms such as *digital*, *electronic*, and *mobile*, *technology* is a more focused and confined description of health solutions that incorporate technological elements. In other words, even though it also lacks conceptual clarity, the term *technology-based interventions* only faces one issue: the lack of a clearly defined conceptualization. These insights combined underscore the importance of establishing conceptual clarity for the term *technology-based interventions first*, before venturing into research on broader concepts such as *digital health*, *eHealth*, and *mHealth*.

Technology-Based Interventions: The Need for Conceptual Clarity

One of the most concerning phenomena in cancer research on technology-based interventions is the fact that several studies have investigated the concept without clearly defining and delineating its conceptual parameters [52-55]. In other words, without a clearly delineated conceptual definition of the term, a wide range of measurements have been used for technology-based interventions [30]. This practice is extremely worrisome and problematic. Without large-scale systematic reviews or meta-analysis studies [56-58], it is difficult to determine the degree of discrepancies between the true effects of technology-based interventions and what has been measured and reported. What is clear, however, is that the lack of definitions, compounded by the heterogeneity of the measures adopted to gauge the barely or poorly defined concept, could substantially undermine the reproducibility and replicability of research on technology-based interventions [56-58], not to mention the quality of review studies on technology-based interventions for cancer caregivers.

The importance of reproducibility and replicability in research cannot be overstated [35]. These 2 research criteria are indispensable to scientific research, ranging from concept building, evidence collection, and data analysis to the interpretation and application of research findings [35-37]. In essence, reproducibility and replicability are instrumental in advancing the literature, elevating the research field, and building the collective knowledge base of the society [35]. However, because of barely or poorly defined key research concepts, researchers might risk missing the valuable opportunity to (1) understand and interpret current research findings on technology-based interventions for cancer caregivers, (2) pinpoint effective components of the interventions, and (3) apply these components to future intervention studies to further the research field [35-37]. Thus, to bridge the research gap, this study aims to examine technology-based interventions in the context of cancer caregiving via the lens of concept analysis.

Objective

The aim of our study is to explore the meaning of technology-based interventions in the context of cancer caregiving and provide a definition.

Methods

Concept Analysis

One of the most well-accepted and widely adopted approaches to establish conceptual clarity is concept analysis [59-61]. Concept analysis is an important analytical tool in understanding the nuanced conceptual and theoretical meaning of a term [59], which could be understood as a research process that "entails the systematic examination of the attributes or characteristics of a given concept for the purpose of clarifying the meaning of that concept" [61]. Conceptual clarity of key research variables is indispensable to the development of science and research. In other words, concept analysis generates a structured meaning that establishes rules and guidelines for the correct use and

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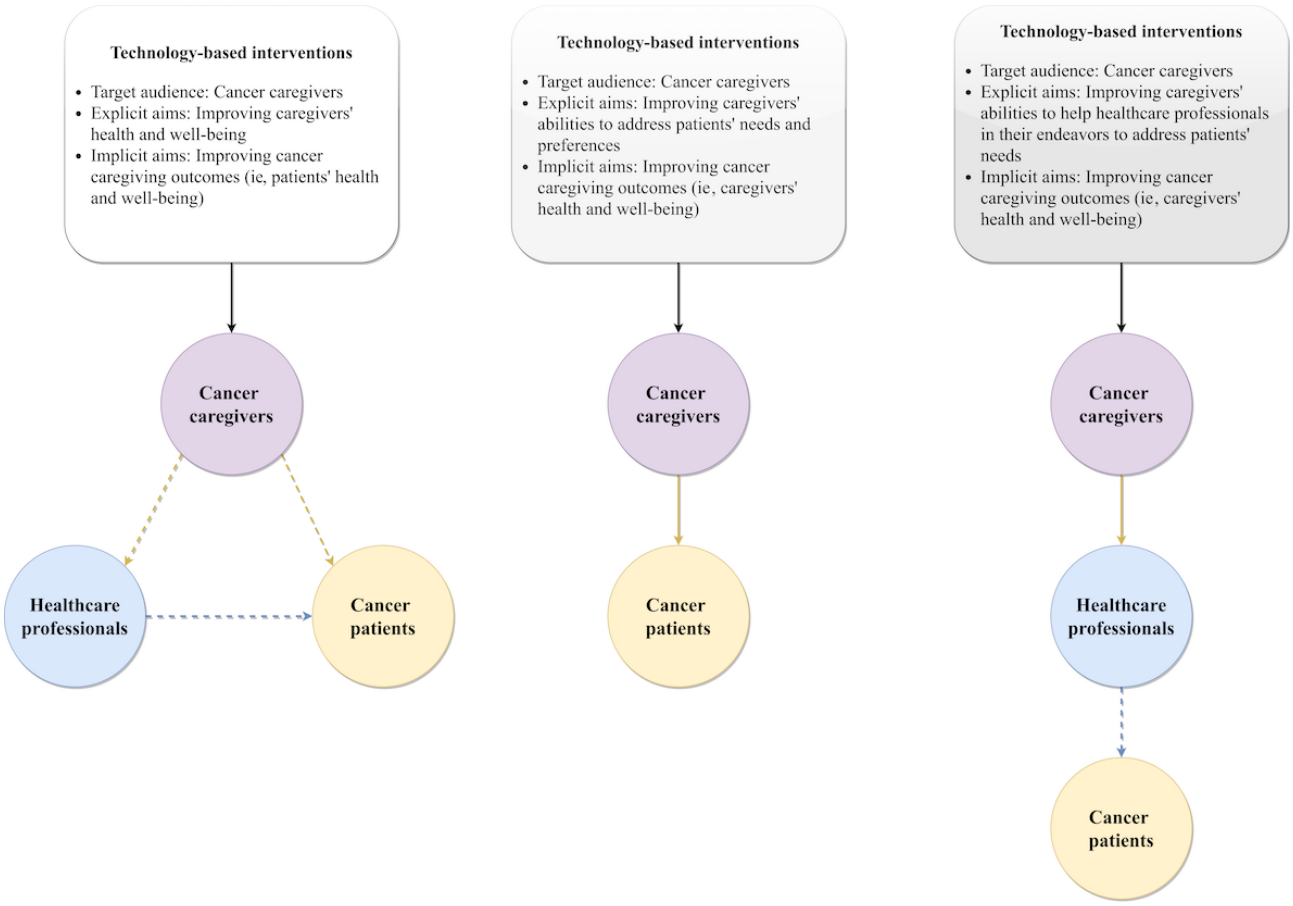
applications of the concept. In this study, the concept analysis method was adopted to clarify the meaning of technology-based interventions in the context of cancer caregiving and to provide a definition that can be used by cancer caregivers, patients, clinicians, and researchers to facilitate evidence-based research and practice.

Technology-Based Interventions

A review of the literature shows that technology-based interventions for cancer caregivers can be categorized into 3 groups in terms of the explicit aims they focus on the following: (1) helping the caregivers themselves, (2) helping caregivers help the patients, and (3) helping caregivers to facilitate the abilities of health care professionals to improve the patient-provider relationship or the health outcomes of patients with cancer. On the surface, these 3 subgroups of technology-based interventions for cancer caregivers seem to have substantial divergences. However, it is important to note that the similarities between these subgroups are more pronounced and meaningful: (1) all of these interventions have cancer caregivers as their first-degree target audience, (2) these subgroups share the same intervention mechanisms, and (3) their overall aims are in line with one another—to improve the abilities of caregivers, patients, and health care professionals to better address the caregiving needs and preferences of patients with cancer and in turn, patients health and quality of life. Thus, all these subgroups of interventions were considered in this study. A framework that can help health care professionals better understand these interventions is shown in Figure 1.

Figure 1. A framework of subgroups of technology-based interventions with cancer caregivers as the target audience.



Theoretical Framework

Although there are many concept analysis approaches available in the literature, the method by Walker and Avant [59] was adopted as the theoretical framework in this study. The decision was based on the following considerations: (1) the method by Walker and Avant is the most used concept analysis framework [60]—and adopting this method could help facilitate research replicability in the field, (2) using a method that the audience is familiar with can help the readership better focus on the gist of the study—clarifying and defining the concept of technology-based interventions in cancer caregiving, which in turn could (3) help readers better understand the need for a clear definition of technology-based interventions and the merits of the concept analysis methodology, and (4) the method by Walker and Avant is more linear and structured compared with other models [62], which can help researchers build a more straightforward presentation of the research process and study findings.

There are 8 steps in the concept analysis method by Walker and Avant [59]: (1) selecting the concepts; (2) determining the aim of the research; (3) identifying available uses of the concepts; (4) determining the defining attributes of the concepts; (5) constructing a model case example; (6) creating borderline, related, and contrary case examples; (7) presenting antecedents and consequences; and (8) defining empirical referents. The definitions of key concept analysis terms adopted in this study

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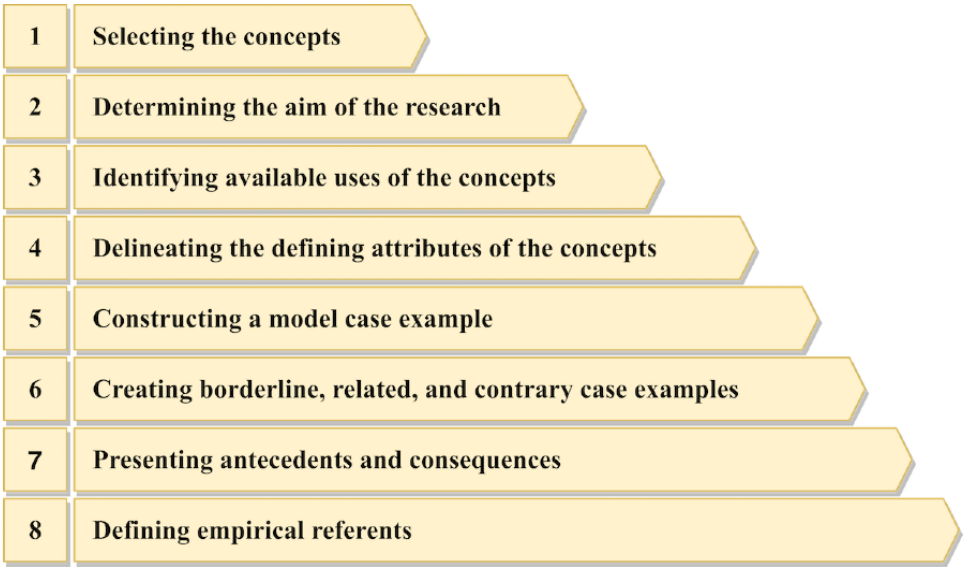
can be found in Textbox 1. To better illustrate the research procedures, we also created a schematic figure to delineate the methodological steps we took to obtain our research findings (Figure 2).

Textbox 1. Definitions of key terms of the concept analysis method adopted in the study.

Concept and definition

- Defining attribute: recurring characteristics of the concept
- Antecedent: occurrence that happened before, and that directly shape, the concept
- Consequence: occurrence that happened as a result of, and are directly influenced by, the concept
- Model case: real-life and often paradigmatic use of concept cases that reflects the essence of the concept
- Related case: cases that have characteristics that are similar to the concept at face value but are different from the concept at its core upon close examination
- Borderline case: cases that contain most, but not all, of the key attributes of the concept
- Contrary case: cases that represent what the concept is not (eg, have little or none of the defining attributes of the concept)
- Empirical referent: real-world phenomena that demonstrate the concept

Figure 2. A schematic representation of the concept analysis procedures adopted in the study.



Search Strategy and Data Analysis

On the basis of the guidelines by Walker and Avant [59], a literature synthesis was adopted to capture available conceptual dimensions of technology-based interventions. An extensive and cross-disciplinary review of the literature was conducted to capture the full breadth of technology-based interventions. Partially because of a lack of relevant literature, publications in the fields of computer science, psychology, and behavioral sciences were all included in the review. The databases PubMed, PsycINFO, CINAHL, and Scopus were searched between June and July 2020. The search terms used were as follows: *(cancer/tumor) AND (caregiver/carer/family/spouse/partner) AND (technology-based intervention OR trial/treatment/therapy)*; search terms varied slightly in different databases.

Both the research objectives and search terms were developed in 2 stages. The first research stage was where we accidentally encountered the conceptualization issue associated with the term *technology-based interventions*. Our initial research objective was to conduct a systematic review study on technology-based interventions for cancer caregivers [24]. During this process, we found that, although there is a rich body of research on technology-based interventions for cancer caregivers, most of the authors fail to offer a clear conceptualization of the term. As we delved deeper into the issue, we realized that our team also had yet to develop a clearly delineated definition of technology-based interventions—we assumed that we knew what we ventured out to study. This revelation, combined with insights gained from additional research on the subject matter, yielded the conclusion that a concept analysis study was needed to proceed with our original research plan, which was contingent on an evidence-based and clearly defined conceptualization of the term *technology-based interventions.* Thus, to address this research gap, we conducted this study. To date, 3 sets of search terms have been developed and used specifically for this study: 1 for the systematic review, 1 to search for definitions, and 1 for our concept analysis.

The search terms were developed based on insights gained from the literature, web-based group discussions, and brainstorming

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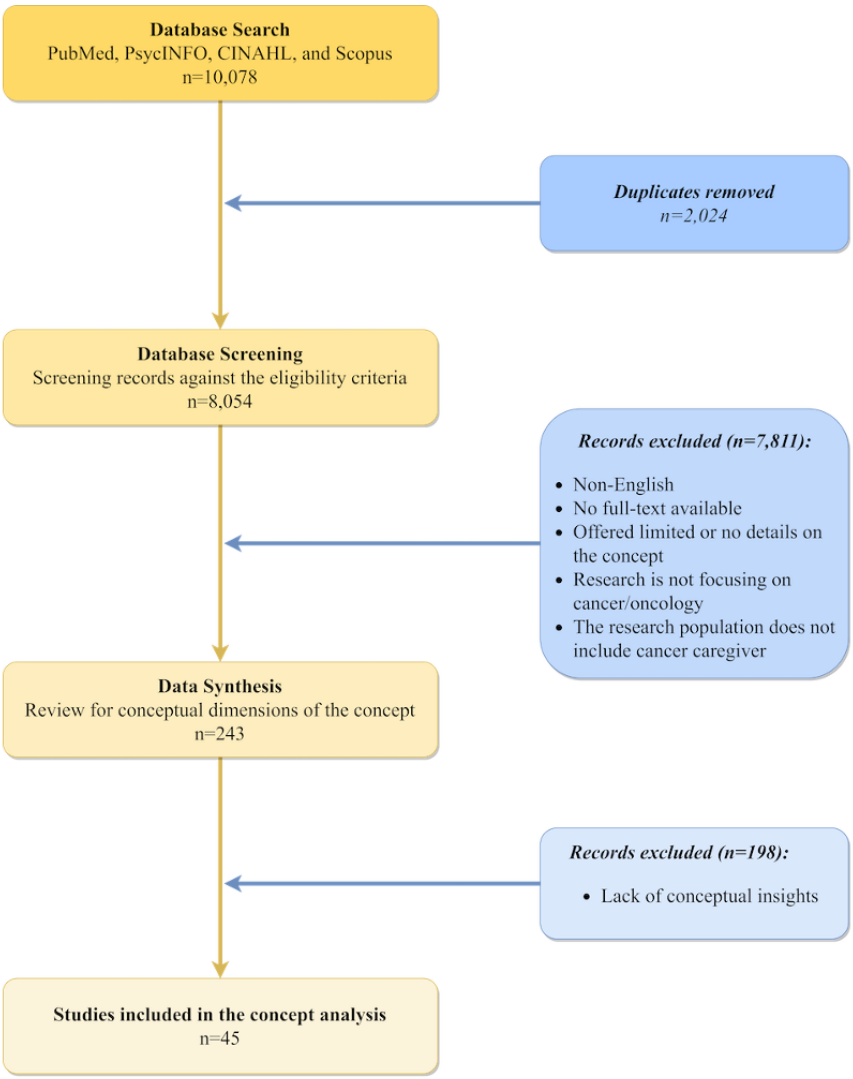
sessions (including all authors and the school's academic librarian) as well as examples set by previous literature [63]. Articles were reviewed for broad research focus (eg, research context and design) and detailed descriptions of technology-based interventions (eg, the role of technology in the intervention). Key information (eg, use of technology and intervention content) from eligible articles was extracted and analyzed. Two principal reviewers (ZS and XL) conducted the review. Discrepancies were resolved via group discussions that included all authors until a consensus was reached. Through this process of synthesis and comparison, a clear conceptualization of the term emerged. The details of the data screening and analysis processes are illustrated in Figure 3.

Figure 3. Data screening and analysis flowchart.



Eligibility Criteria

Articles were excluded if they failed to provide conceptual insights on technology-based interventions; more specifically, the exclusion criteria were as follows: the study was (1) not written in English, (2) not peer-reviewed, (3) not focusing on technology-based interventions (eg, papers focusing on face-to-face strategies for cancer caregivers), and (4) not centering on cancer caregivers. The inclusion criteria are listed in Textbox 2.

Textbox 2. Study inclusion criteria.

Inclusion criteria

- Participants: informal cancer caregivers
- Language: English
- Study type: journal articles
- Study context: discussing technology-based interventions for cancer caregivers
- Intervention: technology-based; cancer caregivers being either the sole or one of the key target audiences

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Results

Overview

The reviewed articles consisted of titles, abstracts, and full-text articles in English from 2010 to 2020, resulting in 10,078 records. The key articles included in the review are listed in Multimedia Appendix 1 [19,27,31-34,45,64-101]. A total of 45 articles met the eligibility criteria (Multimedia Appendix 1). In addition, a manual search of the reference lists of eligible articles located further articles of relevance. Drawing insights from the literature [102-104], Google Scholar was used to reverse-trace articles that cited papers included in the final review as an additional measure to ensure a comprehensive literature search strategy. On the basis of the study results, the concept of technology-based interventions was defined as the use of technology to design, develop, and deliver health promotion contents and strategies aimed at inducing or improving positive physical or psychological health outcomes in cancer caregivers. In the following sections, detailed information on the use of the concept, defining attributes, relevant cases, antecedents and consequences, as well as empirical referents is presented and discussed.

Use of the Concept

Overall, the available definitions of technology-based interventions often revolve around 2 components: the use of technology and the purpose of the intervention. Limited emphasis placed on aspects such as the integration of technology into the intervention or end-user involvement in the application of the technology complicates the research area. When examining the effectiveness of behavioral interventions, researchers define technology-based interventions as approaches that use "information and communication technology applications to promote behavioral outcomes" [105]. Researchers also discussed technology-based interventions in terms of the technology platforms they adopted. In a study focusing on mental health, the term *technology-based intervention* is used synonymously with the concept of *internet-based interventions* [106]. The study outlines that both approaches *include computer-based and web-based interventions, text messaging, interactive voice recognition, smartphone apps, and emerging technologies* [48].

Some definitions allow technology platforms integrated with technology-based interventions to be more inclusive, where platforms such as computers, web-based apps, mobile phones, and wearable sensors are all considered possible venues for intervention delivery [107-110]. In addition to the emphasis on the use of technology, technology-based interventions are often defined with a focus on intervention objectives and projected outcomes. Aiming to examine the influence of an intervention on informal caregivers of stroke survivors, researchers describe technology-based interventions as "some form of telepractice that uses information and communication technologies to help eliminate distance barriers and to help with scheduling logistics, thus extending the scope for provision of quality healthcare" [111]. Overall, although promising studies are emerging in the literature, there is a dearth of insights that could provide conceptual clarity to the term *technology-based interventions*, particularly in the cancer caregiving research field.

Defining Attributes

Defining attributes are recurring themes that mirror *the heart of concept analysis* [43]. On the basis of insights gained from the literature review and data synthesis, *accessible* [64,65,112], *affordable* [66,112], *convenient* [66,67,113], and *user-friendly* [40,68-71,114] were identified as the defining attributes of technology-based interventions. Although additional characteristics were identified, these attributes were the most frequent traits found across the interventions analyzed. One of the key attributes of technology-based interventions was accessibility: compared with conventional solutions, technology-based interventions can be accessed whenever and wherever [64,65,112]. In other words, cancer caregivers can access technology-based interventions without having to worry about transportation or other logistical issues (eg, availability of appointments).

The second defining attribute of technology-based interventions was affordability. In addition to resources related to transportation, considering that many technology-based interventions can be accessed free of cost (eg, smartphone app [115]), caregivers often do not have to worry about financial resources needed for them to adopt these interventions [66,112]. The ability to be accessed whenever and wherever and often without charge subsequently makes technology-based interventions convenient to use and access [66,67,113]. In addition to these traits (ie, accessible, affordable, and convenient), technology-based interventions often adopt a user-friendly design to improve user engagement [40,68-71,114], such as incorporating gamification mechanisms that can improve the user experience of cancer caregivers while learning ways to improve their health and well-being.

Another aspect of being user-friendly centered on the respect technology-based interventions have for end-user input—some interventions were developed in a co-design fashion, where health promotion strategies were discussed and built by cancer caregivers, health care professionals, and academic scholars collaboratively [69]. This method is an important participatory approach for intervention development, and it has many advantages, the most noticeable ones centering on the ability of the co-design to yield more optimal anticipated outcomes and less unintended consequences compared with interventions that only involve limited groups of stakeholders [116-118]. Although it is difficult to determine which of these defining attributes is the most appealing to cancer caregivers, it is clear that these characteristics have collectively made technology-based interventions appealing to cancer caregivers.

Relevant Cases

Model Case and Contrary Case

To make the comparison more apparent, an example scenario that incorporates these 2 types of cases is constructed in this paper. The cases were developed according to the instructions given by Walker and Avant [59] and insights were drawn from the literature [119-121]. The first example relates to usual care and is the contrary case. At the same time, resources such as

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Doctor Carer, which possess the key defining attributes of technology-based interventions by being accessible, affordable, convenient, and user-friendly, are the example of the model case. Details of the example case can be found in Textbox 3.

Textbox 3. Details of the model and contrary case example.

Case example

Angie is a 35-year-old Latina living in a rural Texas city that has a well-built Hispanic community. She has been worrying ever since she was informed that her mother has cervical cancer. After her brother died in a factory accident, Angie became the breadwinner of her family; she works 3 jobs to support her parents and her 2 adolescent children from a previous marriage. Though self-reliant, Angie often feels helpless, as she knows nothing about how to take care of her mother or how to establish a functioning *new normal* for her family. Angie wishes she lived outside of a rural context; traveling 200 miles to and from the closest cancer clinic has a taxing impact on her family and her career. Help and hope seem to be too far away. Angie shared her concerns with a woman she met at the clinic. Eva, now her best friend, showed Angie free resources available via smartphone. Angie was overwhelmed. Using her smartphone, Angie registered with almost all available cancer websites, watched hundreds of hours of YouTube tutorials and caregiver stories, and downloaded over 2 dozen medical apps on her phone to learn more about how to be a caregiver to her mother. Angie just downloaded an app called *Doctor Carer*, which can connect her with volunteer cancer doctors for free. She hopes this app can provide her with the answers she desperately needs and bring her one step closer to feeling less overwhelmed.

Borderline Case and Related Case

According to Walker and Avant [59], a borderline case could be understood as a case with most but not all defining attributes of the concept. In contrast, a related case has traits that are similar but different from those inherent to the concept. The aim of developing the following scenario, one that embodies both a borderline case and a related case, is to compare and contrast these 2 types of cases. In contrast to the cases mentioned in the section *Model Case and Contrary Case*, the comparison in this section will focus on the influence of the caregiver on the patient. In this scenario, the borderline case is represented by the communication between Kacey (the patient with cancer) and her friend Ann (the cancer caregiver), whereas the related case is depicted by Ann's use and adoption of the interactive multimedia e-book, *Compendium of Materia Medica*. Details of the borderline case and related case examples are presented in Textbox 4. To further shed light on these 4 types of cases and their connected functionality in explaining the concept of technology-based interventions, a comparison of the model case, contrary case, related case, and borderline case was conducted and is discussed in Table 1.

Textbox 4. Details of the example borderline and related cases.

Case example

Kacey is a 25-year-old aspiring actress living in Los Angeles, California. She is also a patient with breast cancer; diagnosed with stage I breast cancer a week ago. Although the diagnosis brought chaos to Kacey's life, her social support systems have kept her afloat. Ann, Kacey's best friend since high school, has been an unwavering source of support to Kacey. Whenever Kacey is in distress, Ann is there for her, talking, videoconferencing, and interacting on social media with her to help her weather through tough times. Kacey is unable to afford insurance and, therefore, is uninsured for the moment. Disappointed by the limited resources that are available to her, Kacey was determined to find alternative health care resources she could explore. Recently, she was mesmerized by the documentaries and books Ann shared with her. Kacey was impressed by what the documentaries argued, and she has planned to stop consuming meat and adopt a vegan diet starting next week. She intends to use the rest of this week to design her own diet. Kacey bought one of the e-books Ann mentioned to her, *Compendium of Materia Medica*, as soon as she read its description. The book has a very detailed account of foods that have beneficial properties to the human body, along with suggestions on what to eat under various circumstances. The book is better than an encyclopedia; it has texts, illustrations, and interactive media embedded in it to enhance the learning experience. Kacey knows she has a long fight ahead of her. But she is hopeful.

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Table 1. Comparison of the differences among the model case, contrary case, related case, and borderline case.

Parameter	Model case	Contrary case	Related case	Borderline case
Definition	Real-life and often paradigmatic use of concept cases that reflects the essence of the concept	Case that represent what the concept is not—have little or none of the defining attributes of the concept.	Case that have characteristics similar to the concept at face value but different from the concept at its core upon close examination.	Case that contain most, but not all, of the key attributes of the concept.
Example	Resources like *Doctor Carer* mentioned in Angie's caregiving experience	Usual care mentioned in Angie's caregiving experience.	Ann's use and adoption of the interactive multimedia e-book *Compendium of Materia Medica.*	The communication between Ann and her friend Kacey.
Defining attribute	The use of technology to design, develop, and deliver health promotion contents and strategies aimed at inducing or improving positive physical or psychological health outcomes in cancer caregivers	In-person communicated and delivered health promotion contents and strategies; no technology is involved.	Nontailored interventions that are not designed, developed, or delivered based on Ann's needs and preferences as Kacey's informal cancer caregiver	Not all caregiver–patient communication is about the caregiving experience or the cancer continuum, enabled or delivered via technology.
Detailed rationale	*Doctor Carer* is an intervention that possesses all the defining attributes of technology-based interventions.	No technology is needed for in-person communicated interventions to occur, which means that, although it is an intervention nonetheless, it is not a technology-based intervention.	Like all interventions, technology-based interventions are intentionally designed and delivered to address the needs and wants of caregivers. Either the book *Compendium of Materia Medica* or its digitalization is intentionally created with caregivers like Ann in mind.	For Ann, communicating with Kacey can occur either in person or via technology-based methods, and it may not necessarily have an impact on her caregiving experience.

Antecedents and Consequences

In this section, whenever antecedents and consequences are mentioned, they refer to *antecedents to technology-based interventions* and *consequences of technology-based interventions*, respectively. Two types of antecedents to technology-based interventions were identified. First, antecedents to the need for interventions involve factors such as cancer-related psychosocial distress [72] and lack of couple-based interventions [65]. Second, antecedents to the adoption of technology-based interventions operate as opposed to conventional interventions and take into consideration the physical or geographical constraints [64] and the prevalence of technology, such as smartphones [66]. In addition, resonating with these antecedents, 2 types of consequences of technology-based interventions were found. First, consequences of the intervention stimuli as a whole addressed aspects such as improved quality of life [68] and reduced stress [69] among caregivers. Second, focused on consequences of the use of technology-based interventions rather than conventional interventions such as positive Google Analytics results [69] and intention to use the telemedicine tool in the future [67]. Detailed information on the identified antecedents and consequences is presented in Table 2.

Table 2. Antecedents to and consequences of technology-based interventions.

Type	Category
Antecedents	
Antecedents to the need for interventions	• Cancer-related psychosocial needs [72] • Lack of couple-based interventions [65] • Neglect of psychosocial concerns of family caregivers [87]
Antecedents to the need for technology-based interventions	• Physical constraints [64] • Prevalence of smartphones [66] • Feasibility of internet- or web-based interventions [71]
Consequences	
Consequences of the intervention as a whole	• Improved quality of life [68] • Reduced stress [91] • Improved marital communication, confidence, and skills [85]
Consequences of the use of technology-based interventions	• Positive Google Analytics results [69] • Intention to use the app in the future [67] • Bring positive effect or healthier psychosocial states in patients [76]

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Empirical Referents

Empirical referents can be considered real-world demonstrations of a concept [59]. For technology-based interventions, empirical referents can be interventional medical apps developed for caregivers. In 2017, there were an estimated 325,000 medical apps available on smartphones, which could translate into over 3.7 billion medical app downloads among smartphone users [122]. Of these 325,000 apps, those that are commercially available, interventional in nature, and designed for cancer caregivers could be considered empirical referents to technology-based interventions.

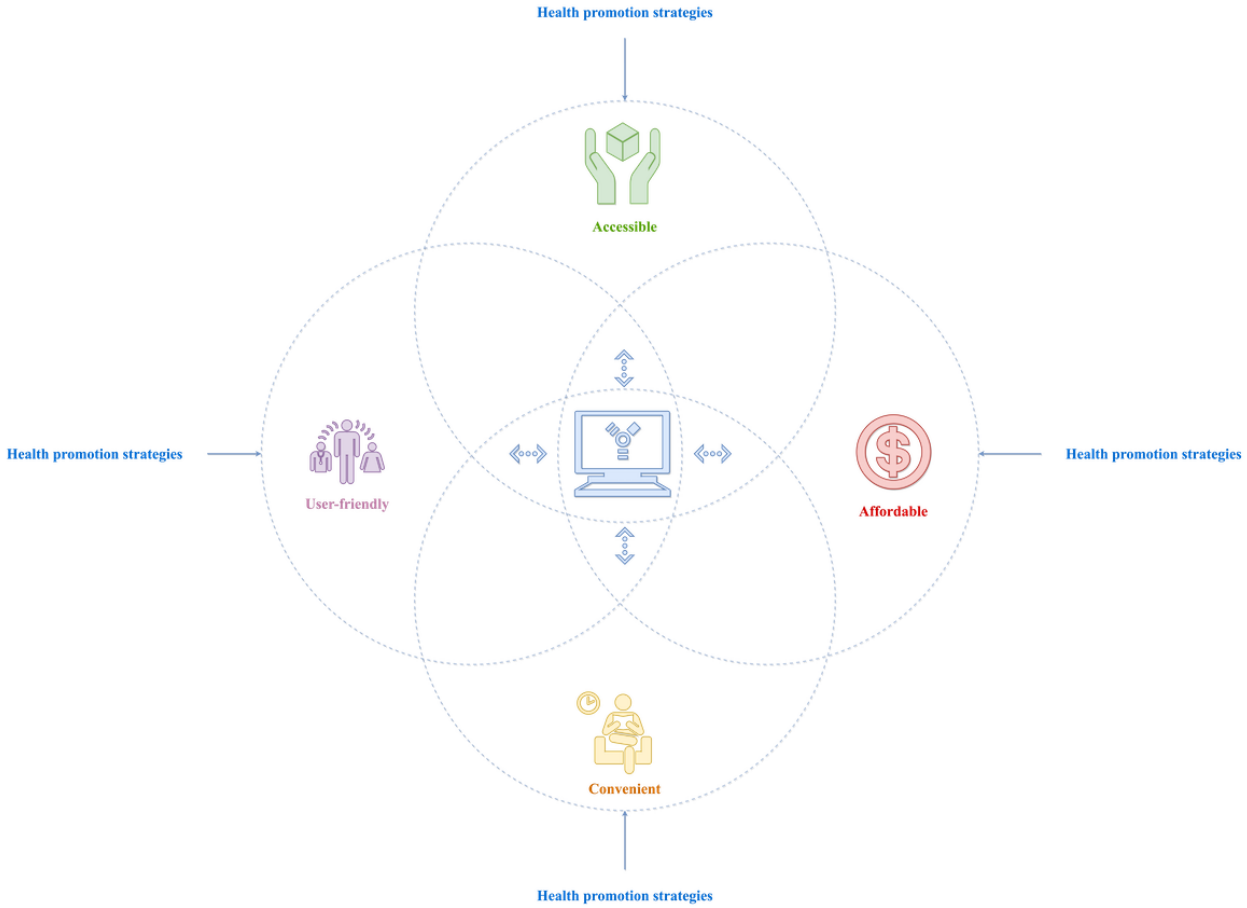
Discussion

Principal Findings

Although technology-based interventions are essential to health care research and practice, there is a lack of definition of the concept, particularly in the context of cancer caregiving. In this paper, we set out to clarify the meaning of technology-based interventions in the context of cancer caregiving and provide a definition that can facilitate evidence-based oncology research and practice. Considering that the lack of conceptual clarity of the term could undermine the effectiveness of technology-based interventions in addressing the health challenges of cancer caregivers, timely research is needed to bridge the gap. To the best of our knowledge, this is the first study to examine technology-based interventions from a concept analysis perspective. Aiming to obtain conceptual clarity for the term, we adopted the method by Walker and Avant [59] as the guiding framework; carefully reviewed the literature; identified defining attributes; and developed key case examples, antecedents, and consequences that are indispensable to the conceptual infrastructure of technology-based interventions.

The key defining attributes that characterize technology-based interventions are *accessible*, *affordable*, *convenient*, and *user-friendly*. Combining the identified antecedents and consequences, the following definition was proposed: technology-based interventions are defined as the use of technology to design, develop, and deliver health promotion contents and strategies aimed at inducing or improving positive physical or psychological health outcomes in cancer caregivers. A detailed illustration of the interplay of the key defining attributes that characterize the concept of technology-based interventions is shown in Figure 4. Overall, Figure 4 underscores that, in essence, technology-based interventions are health promotion strategies augmented with technology platforms to make them more effective (ie, accessible, affordable, convenient, and user-friendly) in improving the health and well-being of cancer caregivers.

Figure 4. A schematic representation of the technology-based intervention attributes.



This definition and the defining attributes could be a solution to address some of the critical issues regarding the conceptualization of the term, both in the current and broader research contexts of technology-based interventions [123,124],

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which compromises the ability of the existing research to enrich the literature. A growing number of papers have begun to acknowledge and address the importance of adopting clear and structured methodological procedures and frameworks to ensure research reproducibility and replicability [125,126]. The absence of a clear definition could lead to poor replicability and low comparability of intervention studies, which in turn, limits the applicability and generalizability of these studies and their corresponding interventions [35]. Viewed as a mechanism to connect current research findings and generate new insights, systematic review research has the potential to further contribute to the growth of research inquiry [56].

However, evidence suggests that systematic review studies often fall victim to the lack of conceptual definitions in the literature [126]. Results show that 40%-89% of poorly described interventions are not replicable, which means that they cannot be adequately used in systematic reviews or offer substantial contributions to the development of the research field [127]. The availability of a clear definition of the research topic enables research studies to report their findings accurately and meaningfully to facilitate further research endeavors, such as systematic reviews and meta-analysis studies [126,127]. From this perspective, the results of this study offer opportunities to address key methodological issues in the literature, such as a lack of conceptual definitions of technology-based interventions in cancer caregiving research. By offering a clear and concise definition of technology-based interventions that clarifies the process using systematically identified antecedents, defining attributes, and consequences, the findings of this study can help guide future interventions that aim to improve the well-being and health outcomes of cancer caregivers.

The findings of this study underscore that technology-based interventions should be clearly conceptualized in terms of the following aspects: (1) the use of technology in the intervention (ie, as the communication platform), (2) the key components the intervention incorporates (ie, technology as the communication platform and health promotion strategies as the content), (3) the relationship between the key components (ie, a communication platform and content symbiosis; the role of technology is flexible, ranging from *managing* to *supporting* the intervention content), (4) the purpose of the intervention (ie, to produce health solutions for cancer caregivers), and (5) the defining characteristics of technology-based interventions (ie, accessible, affordable, convenient, and user-friendly key traits inherent to technology and the audience-centered communication approach). Overall, the insights provided by this study can help researchers better understand and interpret outcomes and technology-based interventions, identify effective intervention strategies, and apply them to future studies that have the potential to further improve the health outcomes of cancer caregivers.

Limitations

Although this study fills significant voids in the literature, it is not without limitations. A concept analysis approach was adopted in this study to conduct a structured and comprehensive literature search. We conducted our literature search in the PubMed, PsycINFO, CINAHL, and Scopus databases for eligible articles and manually screened the articles that were referenced or cited in these articles. Although these databases are comprehensive, it is possible that articles were indexed exclusively in other databases that were not included in the analysis. We did not follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) procedures [128] in presenting our data screening process. Rather, we modeled our flowchart based on example concept analyses [129] that used a more linear and simplified data screening process. Although our choice of data screening flowchart was justified, we understand that this screening procedure may not meet the expectations of some readers. In our future research endeavors, we will adopt the PRISMA procedures to ensure detailed screening information is presented in the manuscript. Finally, this concept analysis only included articles published in English. This eligibility criterion may further limit our data pool.

Conclusions

Technology-based interventions play an increasingly important role in addressing the health and well-being of caregivers across the cancer continuum. Although technology-based interventions can offer substantial benefits to patients with cancer and their caregivers, many limitations could hinder the design, development, and deployment of these interventions. The results of our study offer much-needed conceptual clarity on the term, which in turn, could help build a more rigorous and robust research environment for investigations on technology-based interventions, both in the context of cancer caregiving and beyond. Overall, conveying a clear definition of technology-based interventions to researchers, health care practitioners, and cancer caregivers is a foundational step in establishing a collaborative and coordinated effort to develop and deploy cost-effective interventions. On the basis of the study findings, technology-based interventions are defined as the use of technology to design, develop, and deliver health promotion contents and strategies aimed at inducing or improving positive physical or psychological health outcomes in cancer caregivers. We believe this definition serves as a key step toward a mutual ground that elevates comparability between interventions and outcomes, which in turn, could further advance the research field and the knowledge base.

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Conflicts of Interest

None declared.

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Multimedia Appendix 1
Key articles included in the review.
[DOCX File , 66 KB - cancer_v7i4e22140_app1.docx]

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Abbreviations

mHealth: mobile health

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Original Paper

Oncology Patients' Experiences With Novel Electronic Patient Portals to Support Care and Treatment: Qualitative Study With Early Users and Nonusers of Portals in Alberta, Canada

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Abstract

Background: With the current proliferation of clinical information technologies internationally, patient portals are increasingly being adopted in health care. Research, conducted mostly in the United States, shows that oncology patients have a keen interest in portals to gain access to and track comprehensive personal health information. In Canada, patient portals are relatively new and research into their use and effects is currently emerging. There is a need to understand oncology patients' experiences of using eHealth tools and to ground these experiences in local sociopolitical contexts of technology implementation, while seeking to devise strategies to enhance portal benefits.

Objective: The purpose of this study was to explore the experiences of oncology patients and their family caregivers when using electronic patient portals to support their health care needs. We focused on how Alberta's unique, 2-portal context shapes experiences of early portal adopters and nonadopters, in anticipation of a province-wide rollout of a clinical information system in oncology facilities.

Methods: This qualitative descriptive study employed individual semistructured interviews and demographic surveys with 11 participants. Interviews were audio-recorded and transcribed verbatim. Data were analyzed thematically. The study was approved by the University of Alberta Human Research Ethics Board.

Results: Participants currently living with nonactive cancer discussed an online patient portal as one among many tools (including the internet, phone, videoconferencing, print-out reports) available to make sense of their diagnosis and treatment, maintain connections with health care providers, and engage with information. In the Fall of 2020, most participants had access to 1 of 2 of Alberta's patient portals and identified ways in which this portal was supportive (or not) of their ongoing health care needs. Four major themes, reflecting the participants' broader concerns within which the portal use was occurring, were generated from the data: (1) experiencing doubt and the desire for transparency; (2) seeking to become an informed and active member of the health care team; (3) encountering complexity; and (4) emphasizing the importance of the patient–provider relationship.

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Conclusions: Although people diagnosed with cancer and their family caregivers considered an online patient portal as beneficial, they identified several areas that limit how portals support their oncology care. Providers of health care portals are invited to recognize these limitations and work toward addressing them.

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KEYWORDS

patient portal; MyChart; health information and communication technology; eHealth; personal health information; oncology; cancer care; Canada; qualitative; context of technology implementation

Introduction

Background

Clinical information technologies and consumer eHealth tools are becoming an essential part of health care delivery. Patients are eager to have electronic access to their personal health information, and expectations to manage their own health have increased [1]. eHealth refers to the application of digital health technologies and includes telehealth and remote monitoring, the use of mobile devices, ePrescribing, health information technology systems, electronic health records, and more [2]. The use of eHealth and the internet has the potential to augment health care services by educating and empowering patients, making health care more equitable by extending services, expediting access to medical information, and ensuring the information provided is evidence based [3]. Furthermore, eHealth is transforming the way patients and providers communicate, establish rapport, and receive care, as virtual medical appointments become more commonplace (a movement catalyzed as a result of the COVID-19 pandemic) and as patients have immediate access to medical information.

Patient portals are secure computerized applications that give citizens access to some of their personal health information stored in health providers' electronic health record, via electronic devices such as computers, cellphones, and tablets. Personal health information available via portals typically includes laboratory results, medications, immunizations, allergies, diagnostic results, and medical visit notes [4]. Other portal features include secure messaging with health care providers, appointment self-scheduling, and requesting medication refills. Different jurisdictions may choose to enable different portal features and set restrictions (ie, immediate test result release versus embargo period).

In addition to portals, digital platforms, including the internet, enable access to health-related information and peer support groups. The internet is often used as a primary source of health-related information, generating concerns about misinformation among health care providers [1]. To address this concern, patient portals that provide hyperlinks to credible information (eg, medication side effects, explanation of laboratory tests) have been suggested as a preferred source of information.

In Canada, patient portals are becoming more available, but the actual use is challenging to estimate. In Alberta, a Canadian province with a population of more than 4.4 million people, 2 province-wide patient portals were launched in 2019: MyHealth Records and MyAHS Connect (MAC; described later in the paper). As of March 31, 2021, approximately 565,000 Albertans had created a MyHealth Records account and more than 38,000 Albertans had access to the MyAHS Connect portal [5]. The latter figure denotes the total number of patients who either started using or could *potentially* start using MyAHS Connect as this portal was gradually becoming available across the health care sites these patients visited.

The patient portal use in Alberta may not necessarily be representative of the overall population in Canada. For example, in 2019, the Canadian Medical Association reported that virtual care and online patient portals were used by 1% of Canadians [6]. The same year, researchers at the University Health Network (UHN) in Toronto, Canada, reported the annual adoption rate of approximately 65%, with 43,000 "myUHN" patient portal registrations during the first 14 months [7]. Attempts to reconcile these numbers should be made with caution. On the one hand, reports of portal adoption are often based on a nonconservative definition of portal use, meaning activating a portal account or logging in once. On the other hand, all sources from 2019 cited above reflect a pre-COVID-19 pandemic situation. During the pandemic, virtual care and portal adoption have been on the rise.

Canadian research to demonstrate the impact of patient portals is emerging. Similar to international studies, Canadian research suggests that there are benefits to using portals [1]. Patients often value portals, as this technology provides them with detailed information about their health and stimulates and informs conversations with their health care providers [8,9]. Furthermore, being able to schedule appointments, request medication prescription renewals, and access medical information allow patients to feel more involved in the management of care [9]. Health care providers comment that portals give patients the opportunity to actively participate in the management of their care and that patients are better prepared for medical appointments, as they have additional time to look up medical results and develop pertinent questions [9]. Portals may also benefit health care systems, as patients might be more willing to follow medical advice and more diligent with refilling medication prescriptions [9].

Despite these benefits, there are barriers to portal implementation and use. Limited health and digital literacy and lack of computer or internet access increase health inequities and further marginalize selected population groups [10]. Test results may be misinterpreted by patients, generating anxiety and increasing the demand on health care professionals to provide reassurance and clarification to their patients [11]. In addition, health care organizations have reported concerns

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regarding limited financial resources to implement patient portals [12].

Patient portal use is known to be the highest among patients diagnosed with cancer. The Canadian Cancer Society [13] predicts that approximately 1 in 2 Canadians will be diagnosed with cancer in their lifetime, and about 1 in 4 will die of the disease. With the steady year-on-year increase in cancer diagnoses, online patient portals are becoming more desirable to augment the coordination of care for oncology patients [14]. Cancer treatment and the cancer diagnosis, in and of itself, result in a wide range of self-management challenges, such as monitoring side effects and scheduling numerous medical appointments. Oncology patients have a keen interest in portals, as they require comprehensive health information, have blood work done regularly, and often are, or are expected to be, active participants in managing their condition [14,15]. They report that using portals allows them to feel more in control of their situation, be better prepared for medical appointments, and provides them with the opportunity to advocate for their needs [16]. Yet, some oncology patients view portals with reservations. For example, with the immediate release of laboratory and imaging results via a portal, patients may discover that their cancer has metastasized. Given the implications of living with cancer, oncology patients are often viewing these results during times of despair, thereby compounding feelings of fear and uncertainty [17].

The objective of this study was to explore how patients diagnosed with cancer use online resources for care and treatment in the Canadian province of Alberta. Specifically, we were interested in patients' awareness and use of the novel electronic patient portals in Alberta's unique, 2-portal context.

The Context and Setting of This Study

When reporting research on patient portals, it is important to clearly outline characteristics and functions of specific portals and describe sociopolitical and organizational contexts of portal implementation and utilization [18]. Below we describe the complicated context of portal implementation in Alberta, Canada, where this study was performed.

In March 2019, Alberta's Ministry of Health (Alberta Health) released a provincial patient portal called MyHealth Records (later, its component called My Personal Records [MPR] became a patient portal per se) allowing all Albertans 14 years and older to access some of their health information online, most notably immunization records and common laboratory results [19]. MyHealth Records requires a multistep process to create an account and authenticate (as described in detail below). All patient information is supplied to MyHealth Records from a provincial electronic medical record (EMR) called Netcare. Although useful to health care providers, Netcare EMR is a "view-only" system.

In November 2019, Alberta Health Services (AHS), the province's integrated health authority, launched Wave One of the clinical information system, Connect Care (AHS' name for its project to implement the EPIC system), in some acute care teaching hospitals and ambulatory clinics in Edmonton. Connect Care implementation is an ongoing ambitious process consisting of 9 waves (from 2019 to 2023), with 3 waves already launched, aiming to achieve the *one patient one record* goal for the province. Unlike clinical information systems implemented in a single health care facility or across a few facilities, Connect Care is envisioned to span the entire province with the population of more than 4.4 million people and to replace existing fragmented EMRs. One of the future waves will include oncology facilities across the province. As a component of Connect Care, AHS offers a tethered patient portal called MyAHS Connect (MAC; known as MyChart during the pilot stage, as described below) to enable patients registered with AHS facilities to access their personal health information [20].

In preparation for Connect Care launch, from 2015 to 2019, the AHS piloted its tethered patient portal called MyChart (EPIC) in select Edmonton clinics. Patients who used MyChart during the pilot stage were mostly satisfied with the portal and described it as an easy-to-use, efficient tool that improved accuracy of data sharing and allowed for easier communication [8,21]. Although a sign-up process presented initial challenges for some patients, overall, it was easy to create a MyChart account, including obtaining proxy access. With Wave One of Connect Care in 2019, AHS initially made an arrangement for existing MyChart users to be "grandparented" into the new, Connect Care–enabled patient portal. However, due to the tensions between the 2 macro-level portal implementers, access to the portal for these existing users was interrupted either temporarily (they had to create a new account) or permanently (for some parent proxies who accessed their children's information). In early 2020, MyChart was renamed MyAHS Connect and the access to this portal was streamlined with the Government's MyHealth Records patient portal, which affected the ease of enrollment for AHS patients, as described below. A chronology of major events in Alberta, up to April 2019, leading to the unique, 2-portal context in the province is presented in Avdagovska et al [22].

Thus, at the time of our study in the Fall of 2020, Albertans who were patients attending AHS facilities could enroll to view their personal health information via one or both online portals accessible through the Government of Alberta website under the aegis of MyHealth Records: (1) a provincial citizen portal My Personal Records (MPR) linked with a "view-only," legacy EMR; and (2) the MyAHS Connect (MAC) portal tethered to a Connect Care–enabled EMR. (Refer to Multimedia Appendix 1 for a table comparing portal features in Alberta. Portal functionalities are categorized based on Ammenwerth et al [23] with adaptations).

To sign up for MyHealth Records, citizens must access the Government of Alberta website, register for a MyAlberta Digital ID (MADI), and confirm their identity by uploading an Alberta driver's license or Alberta ID card. Within 10 days, one receives a verification code in the mail and is able to complete MADI registration online. A person then has to provide his/her personal health number (each legal resident has this number to access the Canadian publicly funded health care system) to set up access to the My Personal Records portal. To access the MyAHS Connect portal, in addition to the above steps, a patient must be attending an AHS health care facility that has launched Connect Care, and be offered or indicate their interest in

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becoming a portal user to the facility's personnel, who will provide further instructions (ie, a website link to enter personal information to get access to MyAHS Connect) [24].

Of note, AHS facilities, in which Connect Care is being implemented, include hospitals, outpatient clinics, continuing care facilities, cancer centers, mental health facilities, and some community health sites across the province. By contrast, some primary and community care sites, and family physicians are not officially part of AHS and additional efforts will be required to link these sites to Connect Care.

As is evident from the above description, for the public, major challenges in accessing Alberta's portals include a complicated sign-up process, terminological confusion with many variants of official and colloquially used portal names and abbreviations, additional steps for proxy access for parents of sick children (as children under 14 years of age cannot have a MADI account), and what appears as the existence of 2 parallel portals.

Apart from a few studies conducted during the MyChart pilot stage [8,21], there is limited understanding of the use and effects of patient portals in Alberta. The research question guiding this study focused on patients diagnosed with cancer to explore their experiences of using online resources to support their cancer treatment and care, and in particular patients' awareness and use of the novel electronic patient portals in Alberta, Canada. We sought to understand how Alberta's unique, 2-portal context shapes experiences of early portal adopters and nonadopters, in anticipation of a province-wide rollout of a clinical information system in oncology facilities.

Methods

Design

This qualitative descriptive study [25] involved in-depth semistructured interviews with oncology patients and their family caregivers to provide a comprehensive summary of the phenomenon under study. Broadly, our theoretical assumptions informing the study relate to the *technology-in-practice, sociomaterial* perspective [26,27]. This perspective conceptualizes technologies as active artifacts whose role and effects can be better understood in their relation to other human and nonhuman actors in a person's situated reality. The technology-in-practice perspective helps to avoid both the uncritically enthusiastic rhetoric of technological progress as always beneficial and an equally unwarranted negative technological determinism (eg, cold technology eliminates warm human touch). Rather, a researcher is guided to study how technological objects are used or not used in everyday life *in connection* with other human and nonhuman actors; what human actors do with those objects; and what those objects *do*, what effects they produce. Ethical approval for this study was obtained from the Research Ethics Board at the University of Alberta (Pro00098299).

Sample and Recruitment Strategy

Using convenience, purposive sampling, we recruited 11 participants who had been previously or were presently diagnosed with cancer or their family caregivers, were residents of Alberta, and spoke English. Our primary interest was the experiences of patients diagnosed with cancer. However, it is well known that in the context of oncology care, family involvement (eg, informal and unpaid caregiving provided typically by close family members) can be significant. Thus, we reasoned that eligibility criteria inclusive of family members of people diagnosed with cancer may attract more than 1 person from the same family unit. For instance, a patient in an active stage of cancer might choose to participate with the assistance of a family member. As described below, only 1 participant in our sample self-identified as not diagnosed with cancer but as a family caregiver with past experiences of caregiving, and rather than excluding this person, we interviewed him and clearly marked his data in the findings as provided by a family caregiver.

A recruitment email was sent twice, 1 month apart, to more than 100 members of the Cancer Care Alberta Patient and Family Advisory Network. This Network is a group of volunteers, often retired professionals, actively interested in providing their opinion to AHS on various health-service related topics. We reasoned that the Network is a group of accessible informants with direct experience with cancer, who moreover are likely to be aware about the novel patient portals. The portals have not been widely advertised in the province, and thus we targeted a group that is generally more informed about health service innovations in Alberta. Interested individuals contacted the lead author (ADS) directly over email or phone to schedule the initial consent meeting. All 11 respondents who took part in the individual consent meetings agreed to participate in the study.

Data Collection

From August to November 2020, each participant completed an online demographic survey and took part in a semistructured interview over the phone. We developed the interview guide to be aligned with the technology-in-practice perspective. That is, rather than asking participants who self-identified as portal users to explain how the portal is helpful and why it is good, we asked a broad opening question about using (or not) online tools and resources while living with a cancer diagnosis. We further asked participants to describe situations in which they used the internet or the portal, for example, "What happened that you needed to use an online tool?," "What did you look for?," "How did you use the information?." An interview guide was used to evoke detailed responses from all participants [28]. Interviews ranged from 27 to 68 minutes in length, with an average time of 48 minutes, and were audio-recorded and transcribed verbatim. During the interviews, the interviewer (ADS) took reflective notes to enhance credibility and trustworthiness of the study, as personal beliefs and preconceived notions were brought forth [29]. The interviewer did not know and had no interaction with the participants prior to the study.

Data Analysis and Rigor

An inductive thematic analysis was undertaken [30,31]. Transcripts were coded by the lead author. All codes and associated quotes were compared and contrasted to identify similarities and differences across the data set. Codes were then grouped into preliminary categories and themes, and were finalized once all codes and preliminary categories were reviewed and discussed with 2 other members of the research

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team (VC and OP) until a consensus was achieved, ensuring the qualitative rigor of the study [32]. Data analysis occurred simultaneously with data collection until no new codes were identified.

Saturation, or the point in the data collection process when participants provide similar information [33], was reached at diverse points for different themes. For example, by the fifth interview all participants talked about the uncertain future they face once diagnosed with cancer and how they searched the internet for health-related information and how they desired transparency when communicating with health care providers. These ideas are expressed in what we identified as Theme 1. By the ninth interview we had consistently heard that most portal users were trying to gain independence by being able to access information via a portal, using the portal to prepare for appointments, and disliking incomplete information and poor organization of the portal webpages. This too shaped subsequent themes.

One of the trustworthiness criteria in qualitative research relates to the expertise and experiences of researchers [33]. To present a compelling account of the phenomenon under study, researchers need to strike a balance between possessing knowledge of the field of study (eg, to create data collection tools, understand the context) and delineating between their own assumptions and participants' experiences. Our research team brought relevant expertise and self-awareness to this study: one of the members of the research team had received cancer care recently, adding an important patient perspective during team discussions. Another academic member of the research team (OP) focuses on eHealth and portal technology implementation, contributing expertise in this area. Authors from Cancer Care Alberta (AHS) include a member of the Executive Leadership Team (PJR), a scientist (LW), and an oncologist (JCE), each of whom have interests and experience in exploring innovations in models of cancer care.

Results

Participant Characteristics

Participants included 8 females and 3 males within the age range from mid-20s to late-70s. Most participants were aged 60 and above. Except for 1 family caregiver, all of the participants had been diagnosed with some form of blood-borne, tissue, organ, or lymphatic cancer. All participants reported level of education above high school, with 6 possessing university degrees. Nearly half of the participants had previously worked or were currently working in health care. All participants spoke English as their primary language, and 9 self-identified as white. All participants classified themselves as proficient users of computers, who employ internet daily for a variety of purposes such as emailing, online banking, shopping, and health information seeking.

Seven participants were enrolled in and used a portal: 1 person used both My Personal Records (MPR) and MyAHS Connect (MAC); 5 used My Personal Records only, as MyAHS Connect was not launched at their health care facilities yet; and 1 person used MyChart in the past (precursor to MyAHS Connect) and was in the process of creating her MyHealth Records/My Personal Records account.

Only 2 of 7 portal users originally learned about the portals from the public sources such as newspapers and media, whereas the majority learned about the portals from volunteering on the patient advisory committees for health services. Three participants were not aware of the portal(s) prior to the study. The only participant who did not sign up for a My Personal Records provincial portal despite being aware about it had frequent follow-up meetings with his oncologist where blood work was reviewed, which seemed sufficient in terms of accessing personal health information for this participant.

At the time of this study, all participants experienced relatively stable health (ie, active cancer treatments were completed), and used the portals from a couple of times per month to once every few months. Four participants reported having other chronic conditions, which also motivated some of them to use a portal regularly.

In the interviews, participants discussed an online patient portal as one among many tools (including the internet, phone, videoconferencing/telemedicine, print-out reports) available to make sense of cancer diagnosis, treatment, and prognosis; maintain connection with health care providers; and interact with the information. Thematic analysis of interview transcripts generated 4 key themes *reflecting the participants' broader concerns within which the portal use was situated*: (1) experiencing doubt and the desire for transparency, (2) seeking to become an informed and active member of the health care team, (3) encountering complexity, and (4) emphasizing the importance of the patient–provider relationship.

Theme 1: Experiencing Doubt and the Desire for Transparency

Overview

Several participants described using portals and the internet to reveal what they believed was the "hidden truth" about their condition. Experiencing doubt and the desire for transparency were articulated through the following subthemes: an uncertain future and transparency of health information versus withholding information.

Subtheme 1A: The Uncertain Future

Many participants voiced their concerns about not knowing what their future held. They used a patient portal and the internet to look for certainty. For example, when participants were asked what one was looking for or hoping to achieve while using the internet, a family caregiver replied, "My uncle I think was just wanting to know what other people had to say, what was the collective wisdom on this...am I gonna survive it?" Similarly, a woman in her 20s said the following about accessing information on social media:

> *There's just so many people out there like you and sometimes it inspires a sense of hope, these people survived, I can do it too type of thing, but other times...it can cause some harm because if you see a really sad story, you're like shoot, what if that happens to me?*

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Most participants found patient portals useful for accessing personal medical information, particularly test results. The words of a 60-year-old woman who used My Personal Records (MPR) exemplify an attitude of several participants: "The way I'm wired, I freeze if I don't know the information; I freeze. Information keeps me moving forward...[this] is the best way to summarize how I use the portal, and how I use the internet." To clarify medical terminology encountered in the portal and to search for additional information, all participants commonly turned to the internet (eg, the Mayo Clinic and WebMD websites). Participants' preferences varied: some used Wikipedia as a starting place and then triangulated information from various sources; others sought out open access scientific research.

However, participants realized that neither generic nor personal medical information such as test result numbers in the portal provide definitive answers or allow them to understand the prognosis of their illness. For this, participants relied on their health care providers and were very sensitive to what their providers disclosed and withheld.

Subtheme 1B: Transparency of Health Information Versus Withholding Information

Access to medical information via a portal addressed only a fraction of what participants living with cancer felt was necessary for them. Participants often equated transparency of information with openness of their health care providers. The majority of the participants stressed the importance of receiving clear and unambiguous health information. A 64-year-old woman emphasized this notion by saying:

> *When you've got an oncology patient, for the most part,...those people really have to buy-in to the health care system, they're there for a long time, not a good time, and they want full knowledge, they want to be able to get confirmed...what's the word I want...full consent, knowledgeable consent.*

Comparably, a 68-year-old woman disclosed how she used nonverbal cues to attain openness during a telehealth videoconference: "When I asked him [oncologist] a question, I could look to see if he was covering anything, you know, if he was trying to protect me from some information, I could tell that on his face." (This video call was enabled by other technologies, not via the portals, as My Personal Records does not provide video visits with health care providers). Participants implied that honesty and full transparency are inextricably intertwined; both are paramount to the provision of care and to the development of trustworthy patient–provider relationships. As a 72-year-old man stated:

> *We don't want secrecy, we want openness. The health system is all about the patients and without the patients you don't have a business....If you've got an open thing of information on both sides of the conversation, you can overcome objections so much more honestly.*

It is noteworthy that many participants wondered if their health care provider was withholding information from them as a means of protection. A 45-year-old woman said, "Because you know, you always think that maybe, are they [health care providers] telling you everything? Are they hiding something?" As a result, some participants relied on the portal and other online sources, such as social forums and websites that provide cancer-specific information, to uncover the "hidden truth." A 60-year-old man used the internet to verify if the information he was given by his doctors was true:

> *I was getting statistics on the type of treatment that I was going to get and it had a success rate of well over 90% and sometimes it's the old saying, that if it sounds too good to be true than it probably is, well I guess I checked it [the internet] to cross reference that and to make sure that they are telling me the truth about it.*

Another 60-year-old participant echoed the aforementioned concern and described how she used My Personal Records to cross-check the information she received from her doctor:

> *You [the patient] do get left behind and I think what the portal can do...is make sure I'm asking the right questions, like why is that high and [the doctor is] not mentioning it?...to say I don't trust the system is too extreme, but I don't trust that people don't make mistakes.*

Most of the participants acknowledged the importance of having truthful information, often obtained from a combination of sources that assisted them during decision-making processes.

Theme 2: Seeking to Become an Informed and Active Member of the Health Care Team

Overview

Much noted benefits of patient portals were having access to laboratory test results and a medication list. Participants wanted to use portals to become well-informed and better prepared for medical appointments with their oncologists; however, they felt that having access to limited information supplied via the portal prevented this from occurring. Although the portal allowed participants to feel more in control of their situation, it did not necessarily equip them to be full participants in their care because of limited information provided in the portal. Subthemes for this category included seeking control through independence, accountability for managing one's health, and preparation for medical appointments.

Subtheme 2A: Seeking Control Through Independence

Prior to the adoption of portals, participants received relevant personal health information entirely through their health care providers. Portals allowed them to access test results independently and thereby made them feel more in control of their situation. A 64-year-old woman who used My Personal Records (MPR) said,

> *Until some of these portals were coming up, I kept a written log, I asked for copies of lab results, especially when they were abnormal. And that's not necessary now, it's all there online, and it is fully accessible in Alberta. [She continued] I guess it [a portal] just gives you a sense of control which I think, when you're a patient you often feel like you don't have a*

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> *lot, so even just giving you that sense so you really felt like you were part of the team.*

Reiterating this point, another participant familiar with My Personal Records, who in the past was a family caregiver, spoke hypothetically about how portals might be helpful for oncology patients:

> *Portals would help them [family/friends with cancer] feel more in control of what can sometimes feel like a situation where you don't have any control. Cause you know, you're always waiting for somebody else to tell you what's next, and how this is gonna go, was your scan clear, was there something on it? You can go and check them yourself.*

Subtheme 2B: Accountability in Relation to Managing One's Health

Many participants believed that being a self-advocate and taking ownership for their own health was part of their responsibility as a patient. An online patient portal both required and promoted self-responsibility. A 64-year-old woman said,

> *One of the things I have found dealing with long-term residual results from cancer treatment is: if you're not your own advocate, if you don't stay on top of it yourself, then ...you can get lost in the shuffle. And so, to me, there is a personal responsibility for keeping on top of everything.*

Although all 6 of the participants who accessed My Personal Records appreciated having the ability to independently look up their laboratory results and immunization records, many found it particularly challenging to track their health status, as the information provided to them within the portal was fragmented. A 68-year-old woman said with irony in her voice: "We want people to take responsibility for their own health and yet we are not giving them all the information." Many participants wanted to be able to read unredacted clinic-visit summaries, doctor's notes, referrals, and diagnostic results in full detail—regardless of how harsh those details were. However, at the time of the study, the amount of information supplied to the My Personal Records patient portal from Alberta's EMR was very limited.

A man in his 70s shared that one of the reasons he did not access this portal was because of missing information (at the time of the study in the Fall of 2020): "PSA [prostate-specific antigen] is not available and for prostate cancer people that are in active treatment the first thing that the patient will look at is, what's my PSA?" By contrast, a woman who had access to both portals appreciated viewing diagnostic imaging reports such as scans and X-rays provided by MyAHS Connect (whereas they were unavailable in My Personal Records). This participant found that printing out her imaging report for a muscular-skeletal injury she had been dealing with recently, and taking the report to her physiotherapist, made communication easier for her with her care provider. It also increased the accuracy of information conveyed.

Many of the participants recognized inequality in the distribution of health information. A 68-year-old woman stressed: "If we really think patients are part of the health care team then we need to give them the same information as the other members." Being their own advocate and having equal access to medical information were considered essential components in terms of managing one's health. Yet, most of the participants felt that My Personal Records, in its current form, was "lacking in execution."

Subtheme 2C: Preparation for Medical Appointments

Given the time constraints of medical appointments with oncologists, participants really valued their appointments. For example, a 64-year-old woman said: "[A portal] allows me to be more knowledgeable when I go into a meeting or an appointment because I have specific pinpoint questions, so that I'm not wasting their [oncologists'] time." Many participants used the portal and other online sources as a means of preparing for their appointments. A 74-year-old man shared his perception of the internet's potential: "It is all intended to help the individual become more conscious of their situation...so that they can be more effective in their dialogue with their oncologist." The portal and internet sites allowed participants to assume a more active role during their appointments, as having access to information prior to the meeting fostered meaningful dialogue with their oncologist. A 45-year-old woman discussed how she used My Personal Records to prepare for her appointments, "When you go see an oncologist the time is very short....So, if I go in and I already know, ok my test results were good, then my set of questions are gonna be this."

By contrast, some participants felt that the information provided to them via My Personal Records neither prepared them for their appointments nor promoted conversations within the multidisciplinary health care team. For example, a 39-year-old woman disclosed that having access to incomplete information did not increase her confidence going into an appointment:

> *It [the portal] didn't really give me that ability to come into the appointment ready, which is what I would want out of this, is for me to come into appointments more knowledgeable, for me to be able to talk with my doctor more back and forth versus him coming in with all the information.*

Theme 3: Encountering Complexity

Overview

All participants encountered multiple complexities when navigating the portal technology and when piecing together information. Because of the difficulty of comprehending medical jargon and unexplained information in the My Personal Records (MPR) portal, all 6 participants who used this portal turned to the internet to gather information about their medical condition. During the interviews, it was apparent how challenging the portal names were for participants, not to mention the fact that there are 2 different portals housed on the same My Health Alberta Government website. One woman felt exasperated trying to make sense of all the names, official and colloquial, she previously heard as being used (often interchangeably) to refer to a website with patient's health information: "my health Alberta; my health; my health records; my personal records; mhr; portal; my ahs connect; my ahs; mac..." And this list does not include a mobile app version for MyAHS Connect called

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"MyChart by Epic." A sense of encountering complexity and feeling lost were expressed through the following subthemes: a counterintuitive tool and difficulties comprehending information.

Subtheme 3A: A Counterintuitive Tool

The majority of the participants who accessed My Personal Records discussed diverse difficulties they experienced, such as poor organization of the webpage and nonintuitive navigation. A 39-year-old woman, who reported using the portal since early 2019 when it was launched, described it as "not patient-friendly." She elaborated by describing the layout of the page with medication prescriptions: "It had dates, but it didn't really seem like they were in order or I couldn't really determine what the order was supposed to be, it didn't really make sense." Similar problems were reported by a 60-year-old woman: "Occasionally I want to check [my medications], especially the one-off prescriptions, the ones you have to spend hours digging through the data to find out what you were prescribed, like when I had a bladder infection."

The way laboratory results were displayed in My Personal Records garnered even stronger criticism: "It just sucks," mentioned a participant and then elaborated:

> *You can't just pick a test and then get the entire bit of information...Like my mom is following her one blood test every month...If she wants to track how that one test is doing, she has to keep a written log because otherwise she has to keep going back and searching, and searching through all of the multiple blood tests she gets...I think it [My Personal Records] was designed by a computer programmer who didn't understand how people used their data.*

Similarly, a 68-year-old woman, who used to work in health care and self-identified as highly computer literate, described her attempt to make sense of the laboratory results page: "You can't just look at it and see it on one page; that really frustrates me. And if I recall correctly, it's organized in a weird way."

Because of the perception of poor organization of the webpage and its "cluttered" interface, participants described the portal as difficult to navigate. A 68-year-old woman quoted above, summed up her frustration: "There's too much stuff on it and so you have to kind of figure things out." She continued, "[Unlike MPR] I like nice, simple, clean...here's what I'm looking for, click on that, ok there it is." Navigating the complicated interface deterred a 39-year-old woman from using My Personal Records: "I found it pretty hard to navigate...I just didn't find it helpful, near as helpful as I expected it to be or hoped it would be, so I haven't really gone back."

In addition, participants described the multistep sign-up process as being somewhat "cumbersome." Waiting for a code to arrive in the email felt to some like a "drag." Further, a 45-year-old woman shared:

> *I had trouble signing in when [the portal became available] because you were supposed to scan your driver's license or something, I don't know, something wasn't working so I actually had to try about three or four times.*

Although most of the participants felt that the sign-up process was disconcerting, many appreciated, from a security standpoint, how careful the Government was at protecting information. As one person expressed, "It was worth it to go through the steps to know it was secure."

Only 3 participants considered My Personal Records as "easy to navigate" (1 of these individuals was also referring to MyAHS Connect), while others expressed the need for a simpler portal. "The biggest thing is that they're [portals should be] intuitive." Another individual said, "They [should not] be difficult, portals are only as good as they've been created and set up and if it's difficult to maneuver through it, it's gonna turn people off."

Subtheme 3B: Difficulties Comprehending Information

All 7 participants who used a portal encountered unfamiliar medical terminology or incomplete information and relied on the internet at some point to fill the gap. A 77-year-old woman, who previously worked as a health care provider, described having difficulty interpreting radiology reports within MyAHS Connect: "Some of these radiology words are a bit challenging and I've got a health care background, so if I can't figure it out, what about the general public?" Comparably, a 39-year-old woman said, referring to a disjuncture between vaccine's names commonly used in colloquial language and vaccine's scientific names used in the portal: "I didn't know...the technical name of the immunization...was that flu shot, was that Twinrix, was that the things that we call them, the layman's terms. It was...too technical for a patient, it wasn't patient friendly." The same participant, who self-identified as health literate and computer-savvy and came across as very articulate, nevertheless mentioned the following about laboratory results: "It would be great if I could see all of them, or if I could understand them."

As a consequence of encountering medical jargon and incomplete information, participants either gravitated toward the internet to understand the information or turned away from the portal altogether. For example, a 68-year-old woman described a situation in which she used the internet to understand why a laboratory result was abnormal: "That's when I would go to Wikipedia [as a starting place] and I would check to see why my GFR [glomerular filtration rate] was low."

The main difference between the information provided within the portal and on the internet, however, was that the portals did not generate suspicions of falsification. As a 72-year-old man said,

> *The patient portal is a reflection of what's actually happened to you. The internet is a morass of good information and misinformation and it depends on your intellect or the space you're in mentally as to how you interpret that.*

When navigating the portal, participants noted fragmented and often perplexing information, but knew that the information within the portal was about them.

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Theme 4: Emphasizing the Importance of the Patient–Provider Relationship

Overview

Perhaps paradoxically, patients' access to their personal health information via portals and an increased sense of independence have generated a greater emphasis on the value of patient–provider relationships. Although many participants voiced concerns about health care providers potentially withholding information as a means of protection or "sugar-coating" (as 1 participant has put it), participants still trusted and valued their professional advice. While the findings did not directly suggest that trust influenced patient portal use, they did highlight the importance of in-person interactions and having health care providers assist patients with interpreting information from the portals and other online sources. The subthemes for this category include trust and the essence of in-person interactions and the need for additional information.

Subtheme 4A: Trust and the Essence of In-person Interactions

Although participants appreciated having access to their personal health information, they did not want portals to replace the relationship they had with their oncologist, family doctor, or a nurse. The development of a trusting relationship between the patient and health provider was mainly attributed to in-person interactions. A 68-year-old woman stated, "I wouldn't want it [the portal] to replace my relationship with my physician." She continued, "I feel like I need to trust them. That relationship really matters and I'm not somebody who prefers to use technology for my relationships, I prefer it face-to-face."

Participants described the importance of in-person interactions when receiving unpleasant news. A 72-year-old man rhetorically asked, "You should never have an internet message saying—'you've got stomach cancer, report to your doctor'—that should never happen; that's a human touch, right?" Comparably, a family caregiver said, "How it [a message] gets delivered, who you're hearing it from, how you're hearing it, makes a big difference in how you're going to build your own frame of reference to go forward." She continued, "They're [health care providers] trained, they know how to deliver news like that and how to support people."

Subtheme 4B: The Need for Additional Information

Most of the participants relied on their physician and nurses to provide them with necessary information, or to explain its significance, to understand and manage their medical condition. A 45-year-old woman shared: "My neutrophils, whenever I'm on my medication, is low. It doesn't alarm me [when I see it in the portal] because I know my doctor's seen it so if he was concerned about it then he would tell me." Some of the participants did, however, recognize that their health care providers are also busy attending to other patients. A 60-year-old man said, "I found the doctors I was dealing with were also dealing with hundreds of other people." Not having a health care provider available to interpret information significantly impacted the participants' lives. A woman in her 20s who did not have a portal account shared her reality:

> *They'll [health care providers] take weeks to get back to you and I think running on such high anxiety levels is simply something I can't do. It really hinders every aspect of my life; I can't function normally until I get the clear you know? It's like debilitating fear.*

Enlisting the help of formal supports, such as their oncologist, helped alleviate anxiety. A family caregiver shared, "She's got a great family physician who will get all of her results and interpret them for her so when she actually talks to the oncologist she's already in a state of receptivity, she's more relaxed." Similarly, another participant described her reaction to reading the word "metastases" on a radiology report within MyAHS Connect: "It made me very nervous." She continued, "[but] now I know to ignore that because my doctor says, no, that's not the case." Participants acknowledged the importance of attending their medical appointments; for example, 1 woman stated, "That's why we go to the specialist, to tie it all together."

Discussion

Summary of Key Findings

The aim of this study was to explore the experiences of oncology patients or their family caregivers with electronic patient portals available in Alberta for health-related purposes. As far as we know, this is the first empirical study set in the unique context of a 2-portal system in Alberta, Canada, that illustrates how the tensions between the macro-level portal policy makers [22] are manifested in patient experiences with portal technology. At the time of the study, the provincial Government's webpage with the access to MyHealth Records housed 2 portals. A provincial portal, My Personal Records (MPR; implemented by the Government per se), was available to adult Albertans, and most participants in our study used it. By contrast, a provincial health authority's (AHS) clinical information system, Connect Care (EPIC) and its MyAHS Connect patient portal (MAC; known as MyChart in 2015-2019 during the pilot stage and implemented independently from the Government), had not been launched across Alberta's oncology facilities. However, some oncology patients attending other clinics for concomitant health concerns might have had access to MyAHS Connect through those non-oncology facilities. One participant in our study used both portals.

One concern raised frequently by the participants was the lack of awareness of the portals in Alberta. Many pointed out that the portals were not well advertised. In fact, 3 participants who did not use the portals did not know they existed until enrolling in the study. Further, the overall terminological morass with portal names and an excessively complicated sign-up/authentication process are characteristics of the 2-portal context in the province. This influences the public perception and creates a barrier to portal adoption.

Our data do not permit robust comparison between the 2 portals (eg, webpage layout, navigation, filtering of test results); however, participants expressed frustration about the existing layout of My Personal Records, while MyAHS Connect was appreciated for providing access not only to laboratory tests but also to diagnostic images.

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Findings of this study point to patients' desire for transparency. Although portals and other digital platforms were considered as beneficial tools in accessing health information, these tools did not provide its users with direct information regarding their prognosis and future. Many of the participants used these tools as a means of triangulating or supplementing the information provided by their health care providers. Several participants wondered if their health care providers were withholding information from them as a means of protection; therefore, they used the portals and the internet to cross-check the information. Although the majority of participants felt that having access to health information enabled them to be more knowledgeable, prepared, and in control, some felt that having limited access to information prevented them from becoming active participants of their health. Moreover, many of the participants described how personal interactions had profound effects on the development of trusting patient–provider relationships and that they did not want portals or any other online tools to replace that.

Participants in our study did not regard searching for health information or using a portal in separation from their ongoing lives as people living with cancer. Related to the *technology-in-practice* perspective [26,27], we found that the portal joins the net of relations consisting of health care providers (especially oncologists and nurses), information, medical visits, diagnostic tests, prescribed drugs, family life, etc. The usefulness of portals (or not) is weighed by their ability to answer questions, link pieces of information, offer continuity through displaying comprehensive information, and make communication effortless. The organization of portal webpages and their content produce multiple and shifting effects such as increasing or alleviating anxiety, positioning a portal user as a tech-savvy or an "illiterate," and enhancing or undermining trust in health services.

Comparison With Other Literature

Supporting our findings, Kooij et al [12] noted a significant tension between the aims of protecting information privacy and facilitating portal uptake among end users. In the Netherlands, a portal sign up for patients that requires the use of the Government-issued unique digital identifier and a multistep authorization and verification is a notable barrier to portal uptake and use [12].

The evidence on the implementation and uptake of patient portals is unequivocal about the facilitating factors, such as creating awareness about the portal, easy sign-up process, intuitive navigation, explanation of medical terms, and the use of lay language [18]. Yet, all these facilitators were lacking at the time of the study.

Participants in our study emphasized the importance of the patient–provider relationship, a parallel finding to Alpert et al's [17] study from the United States. In our study, the majority of the participants relied on their family doctor or oncologist to interpret information from the portals or the internet and to try to resolve feelings of uncertainty and distress. Similar findings were reported by Baudendistel et al's [34] study in Germany, where health care providers shared their concerns of patients developing anxiety and uncertainty during the absence of professionals to interpret results presented within portals. Several participants preferred in-person interactions for communicating about their condition. The importance of communication in oncology is equally emphasized in several other American studies [9,35,36].

At the time of our study, participants lived with nonactive cancer, had infrequent diagnostic tests, and accessed the portal occasionally. With the exception of 1 person, they did not report situations when they viewed abnormal test results in real time, before their oncologist evaluated the results and had a chance to follow-up with them. By contrast, the research literature is replete with examples of concerns expressed by patients and health care providers about immediate result release. For example, the overwhelming majority of oncologists in an outpatient department at the Stanford Cancer Care Center felt that patient's online access to abnormal results had negative consequences, but opinions were mixed for normal results [11]. Furthermore, half of the oncologists reported that sharing online results had worsened their communications with patients [11]. In another study, the timing of result release was identified by oncologists and nurses in a cancer care center in New York as particularly important for patients, as some results may indicate the recurrence or progression of disease, generating patient anxiety [37]. Physicians were clear about the necessity to quickly aid patients in interpreting test results to prevent or reduce anxiety [11].

Numerous studies suggest that electronic portals improve patient health outcomes [38,39]. Patient empowerment facilitated by the use of portals and other online tools is a recurring theme in the literature [3,9,38,40,41]. It is said that the provision of health information, especially laboratory results, allows patients to feel more involved in the management of their care, thereby empowering them [9,42]. Our findings complicate and add nuance to the aforementioned literature. Similar to findings reported in Ammenwerth et al [23], portals did not necessarily foster feelings of empowerment. Participants spoke of the challenges they encountered when attempting to become an informed and active member of the health care team. While access to health information allowed participants to prepare for their medical appointments and feel in control [17,43], many of them struggled to make sense of the fragmented information. Moreover, many of the participants discussed the need for access to information to self-manage in their daily life. Therefore, to foster feelings of empowerment, other conditions should be in place in addition to having access to one's personal health information. It is possible that the language of empowerment is preferred by researchers, but people living with cancer seem to describe their experiences in other ways.

Recommendations for Research

Contrary to some existing research, in our study, participants who used a portal did not describe feelings of empowerment. We wondered: do portals and other online tools actually foster feelings of empowerment or does this notion stem from the development of knowledge about one's condition and health-visit preparation skills? The interchangeable use of the terms *engagement* and *empowerment* has further added to the complexity of measuring this concept [42]. Future research

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might explore both engagement and empowerment and clearly define how these terms are understood.

Further, ethnographic fieldwork is promising for understanding why portals are used or abandoned by patients and involves examining whether and how patients use health technology in daily life, what practical arrangements (consisting of people and things) they create to support living with chronic health conditions, and how technology can support what Jeannette Pols calls a *good life* for patients [44]. Talking about *good* life with technology, Pols, a social scientist, philosopher, and health care researcher, means that the new health technology (eg, a portal) is not inherently good. Its effects and outcomes are not predetermined but instead are produced as the result of interactions among various human and nonhuman elements in everyday life. This draws attention to particularities [45], and to the necessity for accommodations, the ability to undertake and undergo small changes and adjustments from/by technological systems, humans, health care practices, and policies. What Pols might ask of portal implementers, policy makers, health care organizations, and researchers interested in the success of eHealth tools is to—amidst the focus on health care standardization, "generalizable outcomes," "universal values," and "general trends" [45]—make space to attend to particularities of patients' lives to understand what arrangements make a portal valuable versus meaningless.

A noteworthy finding of the study was that some participants used the portal and the internet to counter the lack of transparency perceived in health care. Future studies can explore how trust can be developed and sustained within online environments. Transparency is seldom discussed in health care despite being a common concern and potential ethical issue that directly impacts patient care [46]. Full disclosure of information may promote better quality care, augment trust, and promote better health outcomes [47].

Future research could also examine portal platforms and compare them across Canada, as some provinces work with different vendors and develop their own portals. Comparing portal implementation across the country could assist with the identification of best practices and help guide improvement strategies to reduce costs and maximize benefits.

Once Connect Care is launched within Alberta cancer care facilities and patients receive access to MyAHS Connect (MAC), it will be essential to understand patients' experiences with the 2-portal terrain as well as health professionals' perspectives working within the context of oncology care. Some areas that will need to be considered include access to the portal (ensuring an easier sign-up process) and ways to balance transparency with the potential psychological impact of information that is distressing, unclear, or can be misinterpreted. With increased portal use and the expansion of the potential information that can be accessed by both the patient and their families via a proxy access, further questions arise. These questions also highlight the ease of use and the security of the data.

Recommendations for Practice

One key recommendation is to improve public awareness and health care providers' awareness about portals and their ability to promote them. Further, developing an education program (eg, video tutorials and posters) can facilitate portal uptake. Health care providers also require portal training, as it may allow them to assist patients who require further support with accessing supplementary resources and navigating portals. Education programs aiming to increase citizens' digital and health literacy may assist patients to develop confidence, critically analyze health information, and allow them to make informed decisions that optimize their health [48]. Health care providers are at the forefront of patient education and might be in the optimal positions to tailor education sessions to individual capacity [49]; however, health care providers require organizational support and would need to co-design educational materials with patients and family members.

Our study did not include perspectives of oncology service providers; however, it is well known that the collection, storage, and analysis of patient-reported quality of life and outcome measures is an ongoing process in the oncology context. Patient portals provide a convenient venue to support these organizational goals, making it easier for patients to complete before- and after-visit questionnaires. The success of this undertaking depends on patient's uptake of the portal technology. Our findings indicate that even highly educated and literate individuals with computer skills might be deterred from the difficult-to-navigate portals containing fragmented information.

Recommendations for Policy

A patient-friendly version of the portal with a simpler interface, and one that is designed with an understanding of *how* patients use information, is needed. However, explaining the significance of laboratory values and providing direction on what to do after being informed about an abnormal result lie beyond the portal's affordances; it is the role of the clinician. Portal policies should be developed with the appreciation of the role of clinicians, who often need to mediate between the patient and the portal.

It will be interesting to observe how the Alberta Government's My Personal Record and the health authority's MyAHS Connect coevolve and how this process shapes experiences of portal users. Another important consideration is the timing of releasing test results into the portals. Many oncology patients prefer discussing the results with the oncologist first to prevent feelings of distress. Lastly, an essential recommendation for practice and policy is that portals cannot streamline or replace the patient–provider relationship, as this relationship can provide both trusting and individualized care [50].

Limitations

There are a few limitations to this study. All participants spoke English as their primary language; therefore, this study did not account for challenges that may have been faced by individuals who speak English as an additional language, or who are unable to speak English. Further, our convenience sample comprised individuals from the Alberta Patient and Family Advisory Network for oncology. These tend to be well-educated individuals (often former health care professionals) who regularly use computers and the internet and are active participants in managing their health. Lastly, our recruitment

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relied exclusively on email invitation (with 1 reminder). This approach may have excluded individuals and groups who do not use computers and who, by extension, will likely not be able to use portals.

The strength of this study was a sample comprising individuals of diverse age, from the 20s to the late 70s. Further, patient portals are new to Alberta, Canada, and it is informative to learn from the experiences of early adopters. The detailed description of portal features and the context of portal implementation provided earlier in this paper will help readers judge the degree of transferability of our findings. Indeed, we want to stress that the differences in portal features and design across jurisdictions should be taken into consideration in research on portals.

Conclusion

In Canada, the objective of using eHealth is to encourage Canadians to live healthier by offering online tools that securely connect its users with valid, up-to-date health information to augment understanding and management of personal health [2]. With the growth of cancer diagnoses today, patient portals are becoming more desirable to strengthen the coordination of care for oncology patients [11]. Although literature foregrounds the benefits that portals can offer patients, the findings of this study suggest that more effort is needed to move from the portal deployment to making it an integral tool in the lives of people living with cancer. It is noteworthy that patient portals cannot replace the patient–provider relationship, but rather serve as an additional means of accessing information and assisting oncology patients to cope with their condition.

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Authors' Contributions

OP led conceptualization of the project and with ADS submitted the ethics application. OP also drafted the original version of the survey and interview guide. ADS conducted participant recruitment, data collection, the initial data analysis, and drafted an early version of the manuscript. ADS and OP contributed equally to the substantive content of the original manuscript. ADS, VC, and OP helped refine data analysis. VC provided necessary guidance to ADS throughout the process and helped revise interview guide and manuscript drafts. PJR, LW, and JCE were involved in project conceptualization, grant funding application, and survey development; they also added substantive content to the original draft and reviewed subsequent versions. OP led a revision process, executed by her and VC with input from ADS and PJR. All coauthors approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Comparison of main patient portal features in Alberta, Canada, as of Fall 2020.
[DOC File , 55 KB - cancer_v7i4e32609_app1.doc]

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Abbreviations

AHS: Alberta Health Services
EMR: electronic medical record
MAC: MyAHS Connect (AHS' Connect Care portal)
MADI: MyAlberta Digital ID
MPR: My Personal Records (Alberta Health [government] portal)
UHN: University Health Network

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Review

Computer-Based Decision Tools for Shared Therapeutic Decision-making in Oncology: Systematic Review

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Abstract

Background: Therapeutic decision-making in oncology is a complex process because physicians must consider many forms of medical data and protocols. Another challenge for physicians is to clearly communicate their decision-making process to patients to ensure informed consent. Computer-based decision tools have the potential to play a valuable role in supporting this process.

Objective: This systematic review aims to investigate the extent to which computer-based decision tools have been successfully adopted in oncology consultations to improve patient-physician joint therapeutic decision-making.

Methods: This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist and guidelines. A literature search was conducted on February 4, 2021, across the Cochrane Database of Systematic Reviews (from 2005 to January 28, 2021), the Cochrane Central Register of Controlled Trials (December 2020), MEDLINE (from 1946 to February 4, 2021), Embase (from 1947 to February 4, 2021), Web of Science (from 1900 to 2021), Scopus (from 1969 to 2021), and PubMed (from 1991 to 2021). We used a *snowball* approach to identify additional studies by searching the reference lists of the studies included for full-text review. Additional supplementary searches of relevant journals and gray literature websites were conducted. The reviewers screened the articles eligible for review for quality and inclusion before data extraction.

Results: There are relatively few studies looking at the use of computer-based decision tools in oncology consultations. Of the 4431 unique articles obtained from the searches, only 10 (0.22%) satisfied the selection criteria. From the 10 selected studies, 8 computer-based decision tools were identified. Of the 10 studies, 6 (60%) were conducted in the United States. Communication and information-sharing were improved between physicians and patients. However, physicians did not change their habits to take advantage of computer-assisted decision-making tools or the information they provide. On average, the use of these computer-based decision tools added approximately 5 minutes to the total length of consultations. In addition, some physicians felt that the technology increased patients' anxiety.

Conclusions: Of the 10 selected studies, 6 (60%) demonstrated positive outcomes, 1 (10%) showed negative results, and 3 (30%) were neutral. Adoption of computer-based decision tools during oncology consultations continues to be low. This review shows that information-sharing and communication between physicians and patients can be improved with the assistance of technology. However, the lack of integration with electronic health records is a barrier. This review provides key requirements for enhancing the chance of success of future computer-based decision tools. However, it does not show the effects of health care

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policies, regulations, or business administration on physicians' propensity to adopt the technology. Nevertheless, it is important that future research address the influence of these higher-level factors as well.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42021226087; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226087

(JMIR Cancer 2021;7(4):e31616) doi:10.2196/31616

KEYWORDS

oncology; cancer; computer-based; decision support; decision-making; system; tool; machine learning; artificial intelligence; uncertainty; shared decision-making

Introduction

Background

As patients continue to play a more active role in the management of their health, the person-centered model of care has been promoted as a strategy to improve the quality of health care systems [1]. Along with ensuring that all clinical decisions are guided by the patient's values, the goal of the person-centered model is to respect and respond to the individual's preferences and needs. This motivates physicians and patients to coordinate their activities, share information, and reach shared therapeutic decisions [2]. This review takes a person-centered approach for the important and challenging case of consultations involving patients with cancer. Patients have come to expect their treating physicians to explain the benefits, as well as the risks, of the therapies recommended to them. Furthermore, patients prefer to be engaged in the therapeutic decision-making process [3,4], except when they are very ill [5,6], rather than permitting their physicians to choose therapies for them. Patients may also want to be given the chance to consider their options and to choose between accepting or refusing a therapy.

Medical consultations in oncology are a multipart process that involves shared decision-making between the patient and the physician. Bomhof-Roordink et al [7] have articulated this process in their model of shared decision-making. A physician starts the anticancer treatment recommendation process by learning about the patient's preferences, before or during consultations, which they need to consider along with the evidence of efficacy of each potential treatment option. Next, the physician needs to engage the patient in reviewing the potential benefits and risks of the key therapeutic choices available. After collaboratively and carefully examining the situation, the physician provides treatment recommendations. However, the ultimate course of action may be chosen by the patient alone or by the physician when the patient does not want to decide [7].

As the choice of diagnostic modalities and therapies grows, the clinical decision-making process has become extremely complex [8]. Faced with large volumes of fragmented information, physicians must reconstruct, identify, and consider the portion of information that they share with their patients. In addition, physicians need to decide how to best inform their patients and obtain their consent [9]. Hence, physicians need clinical information that is organized and presented in a way that is easy for them to interpret and share in discussions with their patients.

Once physicians have determined what they need to share, they need to be able to show the relevant information to their patients in such a way that the patient can understand the meaning of the different benefits and risks of each therapeutic choice [5,10]. When physicians can summarize information that is relevant to patients' diseases and their survival, explain highly uncertain situations, and manage their interactions with patients well, then patients can more easily understand their physicians' recommendations and choose their preferred therapy or care pathway. This step establishes the foundation for informed consent in shared therapeutic decision-making.

With the intention to support patients, as well as physicians, in this challenging therapeutic decision-making process, paper-based decision tools have been developed [8]. They have been designed to enhance patient-physician communications and interactions. In addition to the incorporation of research results, for example, evidence from clinical trials, paper-based decision tools inform both physicians and patients of the risks, benefits, and outcomes of the available therapies [6,11,12]. Furthermore, paper-based decision tools have a long tradition in supporting clinical decision-making. They have been shown to improve patients' knowledge, accuracy of perceived potential risks, understanding of prognosis, treatment goals, and health outcomes [8]. Moreover, in practices where paper-based decision tools are used, they are well accepted [11]. However, paper-based decision tools can be difficult to update when new therapies are rapidly being developed and adopted. Furthermore, increasing the use of genetic testing and the introduction of advanced molecular medicine in routine clinical practice has generated an expanding body of knowledge that increases the complexity of the decision-making process [2]. Thus, it is recommended that physicians and patients use computer-based decision tools to improve the process outlined above [2].

Hunt et al [13] defined a computer-based decision tool as follows: "any software designed to directly aid in clinical decision-making in which characteristics of individual patients are matched to a computerized knowledge base for the purpose of generating patient-specific assessments or recommendations that are then presented to clinicians for consideration."

Research to create computer-based clinical decision tools has a long history. For example, as far back as 1973, Shortliffe et al [14] published a paper on this topic. Shortliffe [15] believed that with computer-based decision tools, knowledge can be integrated and disseminated to physicians. Similarly, computer-based decision tools may aid in packaging relevant clinical information and therapeutic choices for presentation to

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individual patients [16]. They may also simplify patient-physician communications [8]. On the basis of these perceived benefits, several computer-based decision tools have been developed to assist therapeutic decision-making during oncology consultations [17].

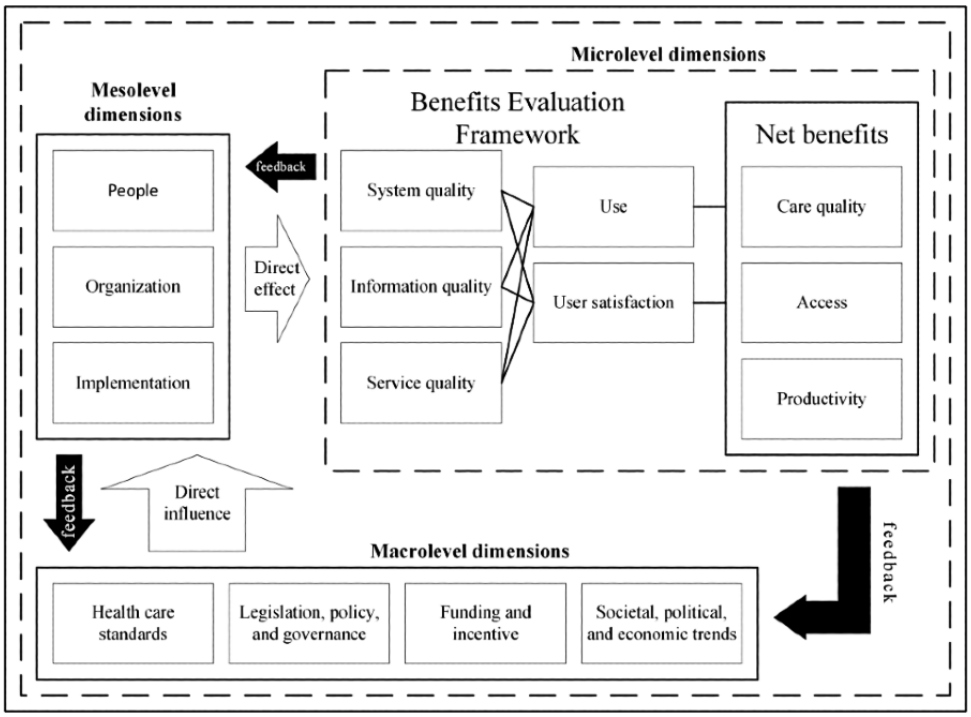
For example, Shortliffe et al [18] developed a computer-based decision tool to guide physicians treating patients with cancer. The technology consists of a computer user interface that enables physicians to review patients' historical data and test results, enter new information about patients, and query the computer system for anticancer therapy recommendations. The implemented computer technology was initially based on the IF-THEN rule algorithm: for example, "IF: there is evidence of disease extension THEN: refer the patient to lymphoma clinic" [18]. However, more recently, computer-based decision tools have been redeveloped for oncology consultations by applying artificial-intelligence–based machine learning software technologies to improve the accuracy of the recommended anticancer therapies [16].

It is unclear at what level computer-based decision tools are adopted by oncology physicians. There have been a small number of reviews about computer-based clinical decision tools [19-21]. Pawloski et al [21] reported patients' outcomes from a treatment delivery viewpoint. Beauchemin et al [20] described decision tools broadly and included nursing care delivery in their study. In contrast, Mazo et al [19] provided an overview of decision tools for breast cancer. However, none of the reviews addressed physicians' propensity to adopt computer-based decision tools during oncology consultations. The aim of this review is to identify and categorize the factors that influence physicians' propensity to adopt computer-based decision tools in oncology consultations by using the Clinical Adoption Framework (CAF) [22,23].

Conceptual Model

The CAF, as shown in Figure 1, is an extension of the Benefits Evaluation Framework (Canada Health Infoway), which was adapted from the DeLone and McLean information system success measurement model, as cited in the study by Lau et al [22].

Figure 1. Clinical Adoption Framework with the micro-, meso-, and macrolevel dimensions, which could influence the successful adoption of health information systems, and the associated conceptualized feedback loops [22,24].



Conceptually, the CAF is made up of micro-, meso-, and macrolevels. At the microlevel, the focus is on the dimension of quality, which measures success factors such as information completeness, accuracy, relevance and comprehension, system features, performance, security, responsiveness, support services, and leadership; user behavior, intention to use the technology, and user satisfaction; and net benefits, which refer to patient safety, risk, effectiveness, compliance, health outcomes, efficiency and capability, cost and savings, availability and access to services, and patient and clinician participation [24].

The mesolevel dimensions directly influence microlevel users' propensity to adopt the technology. It addresses people's characteristics and their expectations, roles, and responsibilities; technology system and organizational fit, strategy, culture, structure or processes, information infrastructure, and return on value; and implementation stages, project management approaches, and technology fit with present and future operations [24].

The macrolevel dimensions directly affect the mesolevel factors, which in turn affect the success of adoption at the microlevel. At the macrolevel, governance, legislations, regulations, and policies; health care and professional practice standards; funding and incentive payments; and trends in public expectations as well as sociopolitical and economic climates with respect to

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technologies and the whole health care system influence adoption [24].

In addition, as indicated in Figure 1, there is a feedback loop at each level of the CAF. The results of each level are fed back to higher and lower levels of the conceptual model, that is, the outcomes of microlevel factors influence the meso- and macrolevel factors. Similarly, mesolevel factors influence higher macrolevel and lower microlevel factors, and macrolevel factors affect mesolevel factors [24]. Consequently, the CAF represents a technical, social, political, and economic system that must contend with constant internal and external forces that dynamically affect propensity to implement and adopt computerized information systems in health care settings.

The research questions are as follows: (1) What is the extent of adoption of computer-based decision tools in oncology consultations? (2) Is there a difference in levels of adoption by country and period? (3) What factors may have influenced the adoption of the technology? (4) What are the lessons learned to improve adoption of the technology?

Methods

This systematic review was registered on PROSPERO (CRD42021226087), the International Prospective Register of Systematic Reviews [25].

Search Strategy and Inclusion Criteria

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [26] and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist, guidelines, and statements [27]. In addition, with the assistance of medical sciences librarians, the search strategy was constructed by applying the PICOC framework [28,29]:

- P (population): only physicians treating patients with cancer were included. Other clinicians such as nurses, pharmacists, or supportive care professionals were excluded.
- I (intervention): only computer-based decision tools used to assist oncology consultations were included. Paper-based tools or digital tools such as websites that are used solely and independently by patients who seek information outside consultations with their treating physicians were not included.
- C (comparison): usual care, which means health care based on traditional paper pamphlets, video recordings, or using standard data collection in electronic health record systems.
- O (outcomes): adoption of the technology for use during oncology consultations, that is, physicians use the information provided by computer-based decision tools as part of their routine medical practice to deliver oncology care.
- C (context): assisting shared decision-making during the selection of anticancer therapy, that is, physicians and patients use the information provided by the technology to collaborate and discuss the benefits and potential harms of each treatment option before agreeing on a final treatment plan. In this context, use of the technology does not mean only the physician needs to physically operate or view information on the computer screen. The physician may provide access to the technology to the patient or another care provider to assist the patient enter personal information or understand the information provided. The physician can then use the additional information provided by the patient to facilitate discussions and decision-making during the consultation.

On February 4, 2021, 1 reviewer (AY) used the OvidSP platform (Health First) to search the following databases: Cochrane Database of Systematic Reviews (from 2005 to January 28, 2021), Cochrane Central Register of Controlled Trials (December 2020), MEDLINE (from 1946 to February 4, 2021), and Embase (from 1947 to February 4, 2021). In addition, on the same day, the databases of Web of Science (from 1900 to 2021), Scopus (from 1969 to 2021), and PubMed (from 1991 to 2021) were searched. After relevant articles were selected for inclusion in this review, the reference list and citations of each article were inspected for additional articles. The *snowball* search was conducted using Scopus and Google Scholar. Further searches for relevant articles were conducted by browsing the *BMC Medical Informatics and Decision Making* journal website, along with searches of gray literature websites [30-33]. The detailed Boolean expressions of the search strategy are provided in Multimedia Appendix 1.

Study Selection

A single review author (AY) removed duplicates and screened the titles and abstracts of all retrieved articles for relevance in accordance with the criteria of the research questions. Similarly, another 2 review authors (JK and TS) independently assessed the eligibility of a randomly selected sample of articles from a subset of the retrieved articles to judge their eligibility for inclusion or exclusion in the review. Disagreement among the 3 review authors was resolved through discussion.

First, guided by the evidence-based medicine pyramid [34], articles that used a study design within the categories of randomized controlled trials, cohort studies, case-control studies, and case series or reports were included for review, whereas articles that were published as conference papers or abstracts, protocols, commentaries, editorials, letters, or opinions were excluded because of their perceived low quality. No limitation on language was imposed. For articles that were not published in the English language, attempts were made to translate them into English by using a web-based translator [35]. Second, studies that met the following key criteria were included: (1) the study was conducted in an oncology consultation setting, (2) it involved distinct real-world computer-based decision tool use by oncology physicians, (3) a computer-based decision tool assisted patient-physician communications to share information and to agree on an anticancer therapy; and (4) the elements of the effectiveness of a computer-based decision tool in oncology consultations were reported.

Data Extraction

A data extraction spreadsheet to capture study information was developed a priori by 3 reviewers. The selected studies were then screened by 1 review author, and relevant qualitative data were extracted. The spreadsheet was populated in accordance

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with the requirements of the review questions. As more experience was gained with data extraction, the review authors iteratively adjusted the required variables in the spreadsheet. The final set of data variables required to answer the review questions was as follows: study; study design and participant sample size; computer-based decision tool versus comparator; clinical setting context and country; primary objective; and study outcomes (Table 1).

Table 1. Overview of the included studies, ordered with the most recent first (N=10).

Study	Study design and participant sample size	Computer-based decision tool versus comparator	Clinical setting context, country	Primary objective	Study outcomes[a]
Wyatt et al [36], 2019	Pre- and postsurvey patients (n=290), postsurvey patients (n=447)	TakeTheWind versus no comparison	Breast cancer clinic (n=1), United States	To assess utility, ease of use, and impact of decision tool	*Patients preferred shared decision-making* and written material, disliked tablet computers, and had trouble navigating and accessing the tool.
Yao et al [37], 2019	Longitudinal, prospective before-and-after study; CDT[b]-arm patients (n=63), surgeons (n=2); UC[c]-arm patients (n=57), surgeons (n=3)	In-visit decision aid versus UC	Breast surgery clinics (n=5), institution (n=1), United States	To measure impact on knowledge, preferences, and involvement	*Patients had more discussions regarding their treatment with surgeons and had less surgery.* (Anxiety, distress, fear, quality of life, and concerns regarding body image were unchanged) compared with UC.
Cuypers et al [38], 2019	RCT[d]; CDT-arm hospitals (n=9), UC-arm hospitals (n=9), academic medical center (n=1)	Prostaat versus UC	Prostate cancer hospitals (n=18), academic medical center (n=1), the Netherlands	To understand implementation and use of CDT	*Improved physician-patient communication about preferences and values*
Raj et al [39], 2017	Controlled before-and-after study; before-implementation patients (n=80), after-implementation patients (n=134)	COMBAT versus paper	Pain management at outpatient cancer clinic, Norway	To evaluate improvement in pain management	(No change in physicians' behavior and no improvement in pain management)
Yao et al [40], 2017	Prospective pre-post study; CDT-arm patients (n=97), UC-arm patients (n=114)	In-visit decision aid versus UC	Breast surgery at hospitals (n=3), United States	To examine effects on shared information and treatment choice	*Higher knowledge levels in the CDT group than in the UC group*
Miles et al [41], 2017	Mixed-methods randomized trial; patients (n=13)	Openclinical versus no comparison	Colorectal cancer outpatient oncology department, United Kingdom	To examine acceptability, usefulness, and areas of improvement	*CDT was accepted and found useful by patients* but needed improved presentation of information.
Henton et al [42], 2017	Usability study; patients with prostate cancer (n=7), patients with colorectal cancer (n=7)	SEER*CSC[e] versus no comparison	Prostate and colorectal cancer centers (n=4), United States	To understand patients' information needs and preferences	CDT lacked features to facilitate patient-physician discussions and was time consuming for data entry.
Morgan et al [43], 2015	Prospective study; patients (n=25)	Morgan versus no comparison	Breast cancer center, Canada	To assess satisfaction and knowledge retention	*Knowledge retention was high, and patients were highly satisfied.*
Siminoff et al [44], 2006	RCT; physicians (n=58), patient-physician pairs (n=405)	Adjuvant! versus UC pamphlet	Breast cancer oncology practices (n=14), United States	To examine impact on treatment decisions and practice	CDT added 5 minutes to total consultation time *and was found more useful than a pamphlet.*
Peele et al [45], 2005	RCT; physicians (n=56), CDT-arm patients (n=250), UC-arm patients (n=182)	Adjuvant! versus UC pamphlet	Breast cancer practices, academic (n=5), community-based (n=9), United States	To examine impact on women's adjuvant therapeutic decision	*Fewer women with low tumor severity chose adjuvant therapy.*

[a]To represent the key outcomes of each study, the following formatting has been adopted: *italic text* represents positive outcomes, normal text represents negative outcomes, and normal text within parentheses represents neutral outcomes.

[b]CDT: computer-based decision tool.

[c]UC: usual care.

[d]RCT: randomized controlled trial.

[e]SEER*CSC: Surveillance, Epidemiology, and End Results Cancer Survival Calculator.

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Risk-of-Bias Assessment

Using the Cochrane risk-of-bias tools for randomized controlled trials and nonrandomized studies, 1 review author assessed the risk of bias of the included studies [26]. The tool for randomized controlled trials [46] assesses studies on each of these 6 domains: (1) randomization processes, (2) identification or recruitment of participants into clusters, (3) deviations from the intended intervention, (4) missing outcome data, (5) measurement of the outcome, and (6) selection of the reported result. The tool for nonrandomized studies [47] assesses studies on each of these 7 domains: (1) due to confounding, (2) selection of participants into the study, (3) classification of intervention, (4) deviations from the intended intervention, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported result. Finally, the judgment in each domain is carried forward to an overall risk of bias for each study. The tools highlighted some risk of bias in all the selected studies.

Data Synthesis

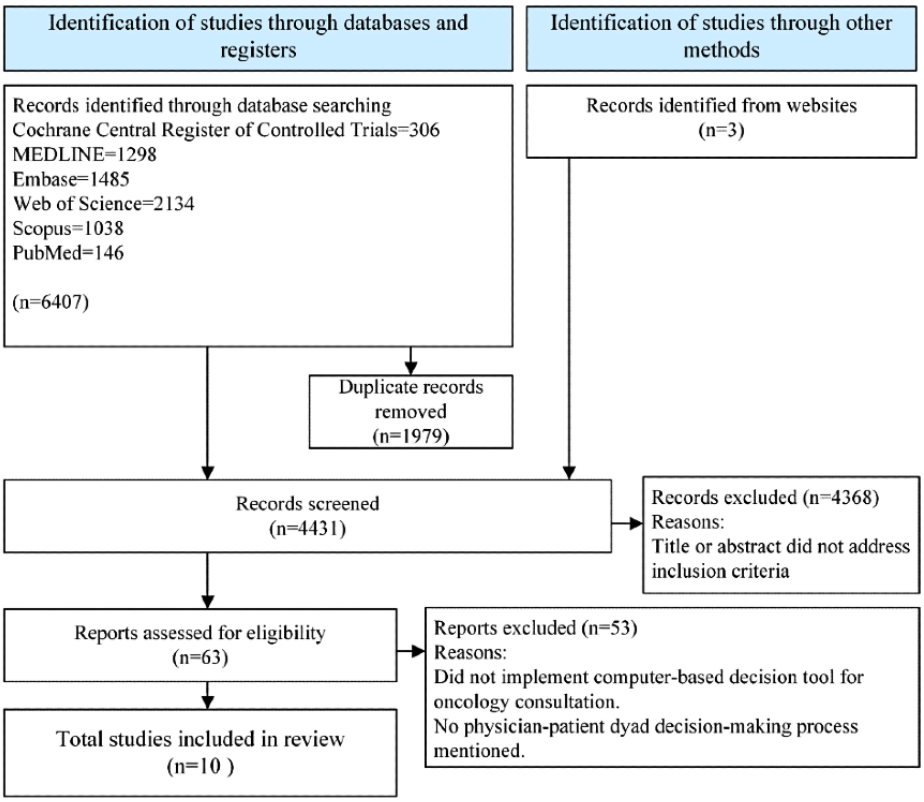
The articles included in this study reported a high diversity of functionalities and features of computer-based decision tools. Therefore, the reported outcomes of the studies were grouped according to the dimensions of the CAF [22]. The results within each group were subsequently assessed and combined into a common set of factors that directly affect physicians' propensity to adopt computer-based decision tools in oncology consultations.

Results

Search Results and Study Characteristics

The initial searches in the aforementioned databases retrieved 6407 articles (Figure 2). Browsing searches and inspections of reference lists and citations identified 3 additional articles. Of the 6407 articles retrieved through database search, 1979 (30.89%) duplicates were removed. Of the remaining total 4431 articles, 4368 (98.58%) were excluded after titles and abstracts were screened. Next, the full-text articles were assessed for eligibility, and of the 63 articles, 53 (84%) were excluded. A total of 10 studies were thus included in this review.

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flowchart of the study selection process and results.



When the 10 selected studies for review were assessed by using the Cochrane risk-of-bias tools, they all exhibited some level of risk of bias. Of the 10 studies, 3 (30%) were randomized controlled trials [38,44,45], and 1 (10%) was a mixed-methods randomized study [41] (Multimedia Appendix 2, Table S1 [38,41,44,45]). All (4/4, 100%) the randomized studies included a high risk of bias because of the practices observed when assigning participants, adhering to the intervention, and accounting for missing outcome data. Of the 10 studies, 6 (60%) were nonrandomized studies (Multimedia Appendix 2, Table S2 [36,37,39,40,42,43]). Of these 6 nonrandomized studies, 1 (17%) [39] included a moderate risk of bias, whereas the remaining 5 (83%) [36,37,40,42,43] included serious risk of bias due to confounding [36,37,40], bias in selecting participants [43], bias in accounting for missing data, and measurement of outcomes [42].

Table 1 includes significant details gathered from the reviewed studies. Of the 10 studies, 6 (60%) were conducted in the United States, and 1 (10%) each was conducted in Canada, the Netherlands, Norway, and the United Kingdom. In all, 8

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different computer-based decision tools were used across the 10 studies.

A summary of the identified computer-based decision tools from the review is provided in Table 2. The details include the name of the computer-based decision tool, country where each evaluation was conducted, categories of disease that were handled, types of decision that were settled, number of studies that were conducted for each computer-based decision tool, and bibliographical references. Of the 8 computer-based decision tools, 4 (50%) were evaluated for breast cancer consultations; 1 (13%) each for colorectal, prostate cancer, and cancer pain; and 1 (13%) for breast or colorectal cancer.

Table 2. Summary of 8 identified computer-based decision tools from 10 reviewed studies.

Name of computer-based decision tool	Country	Disease category	Type of decision	Number of studies	Reference
Adjuvant!	United States	Breast cancer	Take adjuvant chemotherapy or not	2	[44,45]
In-visit decision aid	United States	Breast cancer	Choose surgical option	2	[37,40]
Morgan	Canada	Breast cancer	Educate patients about adjuvant systemic therapy	1	[43]
TakeTheWind	United States	Breast cancer	Choose surgical option	1	[36]
SEER*CSC[a]	United States	Breast or colorectal cancer	Estimate patient prognosis	1	[42]
Openclinical	United Kingdom	Colorectal cancer	Take adjuvant chemotherapy or not	1	[41]
COMBAT	Norway	Cancer pain	Choose opioid dose and pain management option	1	[39]
Prostaat	Netherlands	Prostate cancer	Choose surgical and radiotherapy or no treatment	1	[38]

[a]SEER*CSC: Surveillance, Epidemiology, and End Results Cancer Survival Calculator.

Factors Influencing Adoption of a Computer-Based Decision Tool

Levels of Impact

The factors that influenced the adoption of computer-based decision tools during oncology consultations were identified from the 10 selected studies. An initial 16 distinct influential factors were collected from the review and mapped to the categories of the CAF as shown in Figure 3. Afterward, these 16 factors were expanded to show their levels of impact on adoption as shown in Multimedia Appendix 3 [36-45] and in the following sections [22].

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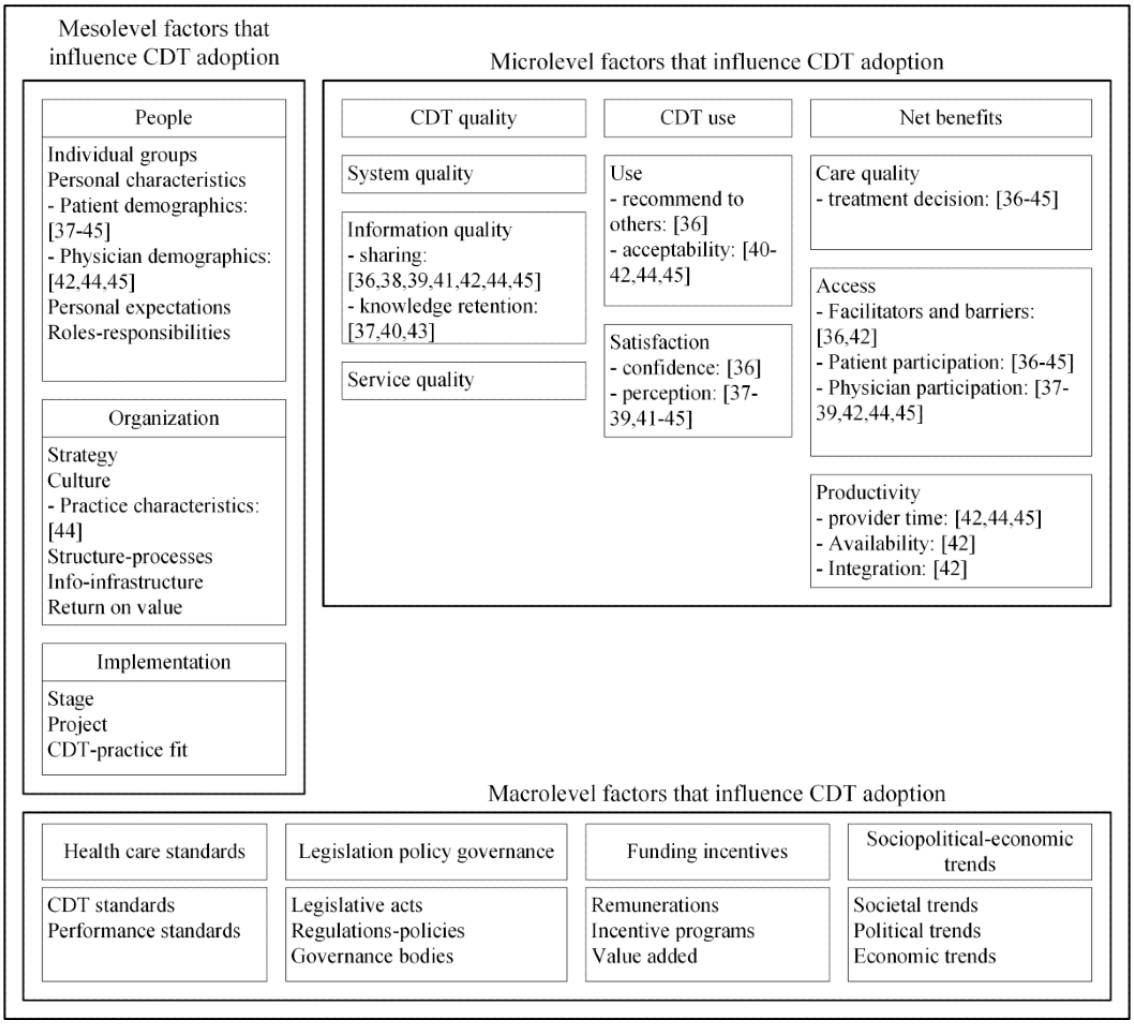
Figure 3. Micro-, meso-, and macrolevel factors that influence computer-based decision tool adoption [22]. CDT: computer-based decision tool.



Microlevel

Quality of System, Information, and Service

At the microlevel, no system or service quality factors were identified. However, information quality factors included information-sharing and knowledge retention. Transfer of information between patients and physicians was assessed by 30% (3/10) of the studies, which reported that patients retained a high level of treatment knowledge after consultations with physicians who used a computer-based decision tool [37,40,43]. Of the 10 studies, 5 (50%) assessed the level of information-sharing. Of these 5 studies, 1 (20%) found that 81.4% of the physicians considered the information provided by the computer-based decision tool useful [44], 2 (40%) reported that patients found the information about treatment options useful [36,41], and the remaining 2 (40%) reported that physicians did not use the information provided by the computer-based decision tool [39,42]. Of the remaining 5 studies, 1 (20%) reported that 65% of the patients read all information provided about treatment comparisons, and 71% of the patients indicated that they discussed the summary that was provided by the computer-based decision tool in consultation with their physicians [38]. A few physicians believed that some patients were made more anxious by the information, did not understand key information [44], were confused by the information provided, or felt that the information provided was conflicting [41]. In addition, some physicians did not value or benefit from the information provided by the computer-based decision tool [39].

Use and User Satisfaction

All 10 reviewed studies discussed use and user satisfaction. The use factors included recommendation and acceptability of use. Of the 10 studies, 1 (10%) [36] reported that when patients were introduced to the technology, 92% indicated that they liked it and would recommend its use to other patients. The feature that they liked the most was the *presence of helpful information*, followed by *ease of navigation* and *confidence in the treatment plan*. After consultations with physicians who used the technology, patients experienced a positive increase in confidence by an average of 0.8 points on a 10-point scale compared with when the technology was not used, and this was statistically significant [36]. However, the study also pointed out that some patients found navigating the technology difficult, disliked the use of tablet computers, and preferred written or printed material [36]. Similarly, another study (1/10, 10%) reported that 22% of the patients preferred consultations with paper-based decision tools [38]. In other cases, physicians provided patients with external access through web technologies to educate and prepare them for discussions about therapeutic choices during consultations. In these cases, other care providers

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such as nurses were also able to help by walking patients through the information provided by the technology and helped them increase their understanding of the benefits and risks of the different therapies on offer. Of the 10 studies, 4 (40%) reported that this practice was positively acceptable to both physicians and patients, although patients reportedly found the language of computer-based decision tools too complex [41,42,44,45]. Physicians found that their patients communicated better and engaged more in discussions. They felt that they were able to refine their understanding of their patients' preferences, whereas patients felt that their perspectives were made clearer and reflected more accurately [44]. Patients' satisfaction with consultations and clinic visits when computer-based decision tools were used was estimated to have a mean satisfaction score of 4.53 (SD 0.1) out of a maximum score of 5 [43]. However, of the 10 studies, 3 (30%) disclosed that computer-based decision tools did not improve therapeutic decision-making or found no statistically significant difference between decisions made using the technology and usual care and did not change physicians' usual behavior [37,39,40].

Net Benefits in Terms of Care Quality, Access, and Productivity

Of the 10 studies, 8 (80%) referred to care quality factors as net benefits of computer-based decision tools. The studies [36-41,44,45] measured the proportion of patients who received various types of treatment. Siminoff et al [44] indicated that the difference in the proportion of patients receiving various types of therapy was statistically insignificant but stated that the adoption of computer-based decision tools during oncology consultations influenced 86.2% of the patients' treatment decisions. The authors also declared that 84.6% of the patients in technology-assisted consultations accepted treatment compared with 89.5% of the patients in usual care. Furthermore, Peele et al [45] reported that only 58% of the women in consultations with technology accepted adjuvant therapy, an additional treatment to enhance the effectiveness of an initial medical treatment, compared with 87% of the women in usual care, and Yao et al [37] reported that 15.9% of the patients with low tumor severity in technology-assisted consultations accepted treatment compared with 24.6% in usual care. Similarly, Miles et al [41] reported that when technology was used in consultations, 11 out of 12 patients declined chemotherapy.

In contrast, of the 10 studies, 3 (30%) reported that patients in consultations with computer-based decision tools received more treatments than those in usual care. In a computer-based decision tool study for prostate cancer, 71% of the patients received treatment [38]. In a study for breast cancer treatment, 21.7% of the patients underwent surgery compared with 15.8% in usual care [37]. In addition, significantly more patients with high tumor severity chose adjuvant therapy in the computer-based decision tool group [45].

Of the 10 studies, 1 (10%) examined the effects of technology-assisted consultations on cancer pain intensity [39]. The authors observed no significant difference in pain intensity when technology was used compared with before its introduction. In addition, after 3 weeks of follow-up care, the authors noted that there was a lack of efficacy when the technology was used.

Of the 10 studies, 2 (20%) discussed access factors. The first study collected information on the facilitators and barriers to local adoption and implementation of a computer-based decision tool [42]. The study mentioned that the facilitators or barriers included existing channels, processes, and provider preferences. Users revealed that they did not access the technology because of lack of incentives or infrastructure, time, information about treatment, integration with the electronic health record system, availability of the technology on their desktops, and their own habits or preferences [42]. The second study produced a nonprioritized list of the facilitators and barriers to access [36]. The study identified that users needed to enter their username and password to log in, or they encountered technical issues every time they tried to use the technology; users had difficulty connecting wirelessly to the internet; and users were being provided information that they had already received on paper or during consultation [36].

Productivity factors covered the length of consultations. Of the 10 studies, 1 (10%) measured physicians' productivity in terms of the effect of a computer-based decision tool on the length of consultations [44], and it found that an average of 5 minutes was added to the length of consultations.

Meso- and Macrolevels

Of the 10 studies, 9 (90%) identified patient demographics, 3 (30%) identified physician demographics, and 1 (10%) identified practice characteristics as mesolevel factors. However, there were no factors identified that explicitly influenced adoption at the mesolevel. At the macrolevel, there were no health care standards; legislations; policies; governance; funding incentives; or societal, political, or economic factors identified that explicitly influenced adoption.

Summary of Key Findings

The results of this review showed that of the 8 identified computer-based decision tools, 4 (50%) were developed and studied in the United States, as shown in Table 2 [36,37,40,42,44,45]. Next, to determine whether a study was positive, negative, or neutral, the greater than or equal (≥) 50% rule, as cited in the study by Lau et al [22], was adopted. Consequently, of the 10 studies, 6 (60%) reported positive results for computer-based decision tools [37,38,41,43-45], whereas only 1 (10%) reported negative results [42]; 3 (30%) were neutral [36,39,40].

The CAF was extended to accommodate factors that influenced physicians' propensity to adopt computer-based decision tools in oncology consultations. Of the 83 factors at the microlevel, 20 (24%) were identified as influential (Multimedia Appendix 3). Of these 20 factors, Textbox 1 reports 11 (55%) that were identified as positively affecting physicians, Textbox 2 reports 7 (35%) that negatively affected physicians, and Textbox 3 reports 2 (10%) that had no effect on physicians.

The studies did not explicitly provide evidence of meso- and macrolevel factors that influenced physicians' propensity to adopt computer-based decision tools.

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Textbox 1. The positive factors that influenced physicians' propensity to adopt computer-based decision tools (N=11).

Factors that were identified as positively affecting physicians

- Access
  - Factor 1: treatment decisions were influenced by recommendations from physicians.
  - Factor 2: information provided by the technology was given to patients by physicians.
  - Factor 3: treatment information and the relationship with survival were included to facilitate conversation with patients.
  - Factor 4: technology helped physicians to understand patients' treatment preferences.
  - Factor 5: information provided by the technology was useful to physicians.
  - Factor 6: a copy of the information produced by the technology was used for reference during consultations.
- Information quality
  - Factor 7: physician-patient communication about preferences and values was improved.
  - Factor 8: physicians reviewed information provided by the technology with patients during consultations.
- Satisfaction
  - Factor 9: physicians believed that patients became more engaged in discussion and understood the information.
- Use
  - Factor 10: physicians reported that the technology was useful for their patients.
  - Factor 11: the technology was used in routine practice in academic and community practices.

Textbox 2. The negative factors that influenced physicians' propensity to adopt computer-based decision tools (N=7).

Factors that were identified as negatively affecting physicians

- Access
  - Factor 12: the technology did not provide all the information that the physicians wanted.
  - Factor 13: the technology was not readily available on the physicians' desktop.
  - Factor 14: the technology was not integrated with the electronic health record.
- Information quality
  - Factor 15: physicians did not take advantage of the information conveyed through the technology.
  - Factor 16: physicians were not able to share information and treatment alternatives with their patients.
- Productivity
  - Factor 17: the technology added 5 minutes to total consultation time.
- Satisfaction
  - Factor 18: some physicians perceived that the technology made patients somewhat more anxious.

Textbox 3. The factors that showed that the use of computer-based decision tools had no effect on physicians' propensity to adopt the technology (N=2).

Factors that were identified as not affecting physicians

- Access
  - Factor 19: no significant change in physicians' behavior.
- Care quality
  - Factor 20: no significant change in prescribed drug dosage between preintervention and intervention periods.

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Discussion

Making Sense of the Adoption Success of Computer-Based Decision Tools in Oncology Consultations

This review has 3 aims: (1) to understand the different levels and periods of adoption of computer-based decision tools during oncology consultations across the world, (2) to identify the factors that influenced the adoption of the technology by physicians, and (3) to learn how to guide future implementation and adoption of the technology in the context of shared therapeutic decision-making during oncology consultations [48].

This review showed that the development and studies of computer-based decision tools were primarily conducted in North America and Europe in the last 16 years. Although 10 studies were specifically selected for review based on the topic of computer-based decision tools that were used by physicians in oncology consultations, only 60% (6/10) of the studies addressed some aspects of the perspectives of physicians. Most of the studies focused on patients' views. Our findings of low adoption of computer-based decision tools converged with similar patterns in previous studies [49].

In all, 2 computer-based decision tools—Adjuvant! and an in-visit decision aid—were used across 40% (4/10) of the studies. Adjuvant! provided the strongest evidence of user satisfaction, information-sharing, care quality, and productivity measures. The in-visit decision aid was assessed for users' perception, knowledge retention, and treatment decision. A summary of the 8 identified computer-based decision tools is provided in Table 2.

By extending the CAF to computer-based decision tools in oncology consultations, these findings suggest that of the 20 factors, there are 11 (55%) that can facilitate physicians to adopt the technology and 7 (35%) that can stifle adoption, whereas 2 (10%) may have no effect on physicians' propensity to change and adopt the technology.

Along with helping physicians to understand their patients' treatment preferences, computer-based decision tools enable physicians to refer to information and to provide treatment information and recommendations that are related to their patients' survival. Some physicians used the technology in routine practice in academic and community practices to review information with patients during consultations. They believed that the technology is useful for their patients because their patients become more engaged in discussions and understood the information. Thus, the conversation between the physician and the patient was facilitated during consultations, and the patient-physician communication about preferences and values improved.

In contrast, some physicians perceived that computer-based decision tools made patients more anxious and added 5 minutes to their total consultation time. The study by Siminoff et al [44] gave the impression that an additional 5 minutes was insignificant. The effect, however, was subjective, depending on each physician's expectation. For a 1-hour consultation, an additional 5 minutes may be acceptable. However, the impact of adding 5 minutes to a 10-minute consultation in usual care may become objectionable. Furthermore, when the technology does not provide all the information that physicians want, is not readily available on their desktop, or is not integrated with the electronic health record, then physicians are not able to take advantage of the information conveyed through the technology. Consequently, they are not able to share information and treatment alternatives with their patients.

The findings of this review advance our understanding of the extent to which computer-based decision tools have been successfully adopted in oncology consultations. The evidence suggests that there have been very few studies that address physicians' propensity to adopt computer-based decision tools in routine oncology consultations. This review provides a starting point and direction for further investigations to incorporate computer-based decision tools in usual oncology consultations. This review also provides a guide and key lessons—as shown in Textboxes 1, 2, and 3—for the design and development of new computer-based decision tools. In addition, the review highlighted some important areas that need to be improved in future computer-based decision tools, such as integrated access with electronic medical records (Textbox 2). Some studies have reported negative outcomes with computer-based decision tools [50,51], whereas others have shown benefits [52]. In our review, of the 10 selected studies, 6 (60%) were positive, with only 1 (10%) being negative, whereas 3 (30%) were neutral. Consequently, the impact of computer-based decision tools on oncology consultations is unclear. Taken together, our findings and the findings of similar past studies [19-21,53-56] point to the need for further research in several dimensions of the CAF to uncover the value of computer-based decision tools in oncology practice.

Looking at Figure 3, it is obvious that the studies included in this review have addressed only a small set of factors among the numerous factors that could influence the adoption of computer-based decision tools in oncology consultations. Therefore, future studies will need to address additional dimensions at the meso- and macrolevels to gain a better understanding of what factors lead to successful implementation and adoption of computer-based decision tools in oncology consultations.

Review Limitations

This systematic literature review includes some limitations. First, only 10 studies were included in this review because of the dearth of studies that addressed the issues with computer-based decision tools from the perspectives of physicians. Second, the literature search was conducted by only 1 reviewer, which could have introduced bias and limited the findings. Third, the selected studies for review included a high risk of bias. Furthermore, most of the studies were conducted at nontraditional cancer centers or at health care organizations affiliated with academic institutions, which limit generalization. Fourth, our review covered a wide range of health information systems' issues, which might not have been explored sufficiently and fully explained. Future researchers should refine the search strategy to identify additional potentially relevant studies that

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may have been missed and allocate more reviewers to search the literature databases to minimize potential biases.

Conclusions

In this review, we investigated the extent to which computer-based decision tools have been adopted in oncology consultations and physicians' propensity to adopt the technology. The results of the investigation suggest that the adoption of computer-based decision tools in oncology consultations remains low. Of our 10 reviewed studies, 6 (60%) showed positive outcomes, whereas 1 (10%) showed negative outcomes, and 3 (30%) were neutral. To date, improvements have been made in communication and information-sharing between patients and physicians. However, unavailability of the information that physicians need, lack of access to the technology on physicians' desktops, and lack of integration with existing electronic health record systems are some of the findings that stifle successful adoption. Therefore, this review shows that, in addition to improving communications between physicians and patients, technology is needed to streamline the flow of information that physicians need to better inform patients. Notwithstanding the 5 minutes that would be added to the overall time of consultations, this review indicates that it is possible to create leaner oncology practices by adopting computer-based decision tools. The technology would eliminate the need to track paper-based information, making the decision-making process more streamlined and eliminating the risk of missing hard-copy paperwork. Hence, in the long run, physicians would have more time to dedicate to their patients. As a result, patients may engage more in discussions during consultations, may be better informed, and they may be more apt to provide consent for treatment.

The CAF provides the capacity to make sense of complex multidimensional factors that influence the adoption of computer-assisted decision-making in oncology consultations. Furthermore, it provides a starting point as well as a sense of direction for research in the design and development of new computer-based decision tools. Thus, this review provides a set of key factors that need to be addressed to enhance the possibility of successfully implementing and adopting computer-based decision tools in oncology consultations. However, although the review shows that it is possible at the microlevel for patients and physicians to improve their communication by using computer-based decision tools, the effects of meso- and macrolevel factors remain understudied. It is therefore important to conduct additional studies in real-world oncology consultations to understand the impact of higher-level factors on physicians' propensity to adopt computer-based decision tools.

Authors' Contributions

This review was conceived and designed by AY, PB, KAG, JK, and TS. AY performed the data collection. The data were analyzed and interpreted by AY, JK, and TS. The paper was drafted by AY, JK, KAG, and TS. Critical revision of the paper was performed by AY, JK, KAG, and TS. All authors approved the final version for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Article search results and screening.
[DOCX File , 16 KB - cancer_v7i4e31616_app1.docx]

Multimedia Appendix 2
Risk of bias in individual randomized controlled trials and nonrandomized studies of interventions.
[DOCX File , 30 KB - cancer_v7i4e31616_app2.docx]

Multimedia Appendix 3
Datasheet of microlevel factors extracted from 10 reviewed studies.
[DOCX File , 58 KB - cancer_v7i4e31616_app3.docx]

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Abbreviations

CAF: Clinical Adoption Framework
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Review

Cross-Cultural Modification Strategies for Instruments Measuring Health Beliefs About Cancer Screening: Systematic Review

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Abstract

Background: Modification is an important process by which to adapt an instrument to be used for another culture. However, it is not fully understood how best to modify an instrument to be used appropriately in another culture.

Objective: This study aims to synthesize the modification strategies used in the cross-cultural adaptation process for instruments measuring health beliefs about cancer screening.

Methods: A systematic review design was used for conducting this study. Keywords including constructs about instrument modification, health belief, and cancer screening were searched in the PubMed, Google Scholar, CINAHL, and PsycINFO databases. Bowling's checklist was used to evaluate methodological rigor of the included articles. Results were reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) approach with a narrative method.

Results: A total of 1312 articles were initially identified in the databases. After removing duplications and assessing titles, abstracts, and texts of the articles, 18 studies met the inclusion criteria for the study. Based on Flaherty's cultural equivalence model, strategies used in the modification process included rephrasing items and response options to achieve semantic equivalence; changing subjects of items, changing wording of items, adding items, and deleting items to achieve content equivalence; adding subscales and items and deleting subscales and items to achieve criterion equivalence. Solutions used to resolve disagreements in the modification process included consultation with experts or literature search, following the majority, and consultation with the author who developed the scales.

Conclusions: This study provides guidance for researchers who want to modify an instrument to be used in another culture. It can potentially give cross-cultural researchers insight into modification strategies and a better understanding of the modification process in cross-cultural instrument adaptation. More research could be done to help researchers better modify cross-cultural instruments to achieve cultural equivalence.

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KEYWORDS

cancer screening; health beliefs; instrument modification; strategy; systematic review

Introduction

Cancer is one of the leading causes of death in the world [1]. In 2018, there were 18.1 million new cases and 9.5 million cancer-related deaths globally [1]. By 2040, the number of new cancer cases is expected to rise to 29.5 million and the number of cancer-related deaths is estimated to climb to 16.4 million [1]. An effective tool to reduce deaths from cancer [2], screening helps detect cancer at the early stage and reveal cancer before symptoms appear [3]. For more than a half century, cancer screening has been an essential component to decrease the burden of morbidity and mortality from cancer [4].

Although cancer screening has proven to be an effective way to detect cancer at the early stage, the use of cancer screenings is not optimal among several populations [4]. Previous research showed that the uptake of cancer screening was associated with health belief of cancer screening [5]. Beliefs and attitudes about cancer screening, such as mistrust of cancer screening and the

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health care system, beliefs toward the cancer screening process or illness, and fatalistic beliefs, are important factors influencing the participation of high-risk populations in cancer screening [6-10]. Among minority ethnic groups, traditional cultural values, health beliefs about concepts of preventive health, fear of cancer screening, belief that cancer screening is unnecessary unless one is ill, misconceptions concerning one's susceptibility to cancer, and stigmatization may also deter high-risk populations from getting cancer screening [11].

Based on the health belief model, health belief of cancer screening can be measured by 6 constructs, including perceived severity and susceptibility of cancer, perceived benefits and barriers of cancer screening, self-efficacy, and cues to action of cancer screening [12]. Previous researchers have developed several instruments to measure these constructs on health beliefs of cancer screening [13,14]. One of the most widely used scales [15] is Champion's Health Belief Model Scale, originally developed to measure the health beliefs of US populations toward breast cancer screening [14]. Later it was translated and modified to different language versions to test health beliefs of cancer screening in other countries and cultures (eg, other groups of people who hold similar values and beliefs about health behaviors) [16].

Cross-cultural instrument adaptation includes 2 necessary steps, instrument translation and instrument modification [17]. Adapting an instrument to be used in another culture is not merely translating the instrument to another language. Since cultural backgrounds vary among different population groups, modifying the instrument to meet the cultural equivalence is essential for ensuring the reliability and validity of translated instruments [18]. According to Flaherty et al [19], a 5-stage equivalence should be met to maintain the integrity of the translated instrument: (1) semantic equivalence ensures the meaning of each item remains conceptually and idiomatically the same, (2) content equivalence ensures the content of each item in the instrument has consistent cultural relevance, (3) technical equivalence ensures the methods of data collection (interviews, observation, or self-report) elicit comparable data, (4) criterion equivalence establishes the normative interpretation of the variable, and (5) conceptual equivalence ensures the same theoretical construct is being measured in each culture.

Compared to a newly developed instrument, using various modification methods to adapt an existing instrument to be used in the target population is a cost efficient and time-saving choice [17]. Although reasons for considering modifications in the adaptation process, including missing concepts or dimensions, different meaning of concepts, different interpretation of terms or phrases, different style of responding, and complex or difficult respond options, were reported in a previous study [18], ways to use the modification strategies to adapt the instrument to measure health belief of cancer screening in another population/ethnicity to achieve cultural equivalence were not reported. Synthesizing the modification strategies used in the cross-cultural instrument adaptation process will provide general guidance to help novice researchers gain deeper insight into the instrument modification process.

The purpose of this systematic review was to synthesize the modification strategies used in the cross-cultural instrument adaptation process measuring health belief of cancer screening for another population/ethnicity based on Flaherty's cultural equivalence model [19], especially focusing on semantic, content, and criterion equivalence. This study will provide guidance for researchers who want to modify an instrument to be used in another culture. The modification strategies synthesized in the findings of this study could be further generalized to the modification process of other instruments.

Methods

A systematic review design was used for conducting this study. Keywords including constructs about instrument modification, health belief, and cancer screening were searched in the PubMed, Google Scholar, CINAHL, and PsycINFO databases in June 2020. Detailed keywords from each construct included (1) instrument modification: instrument, modify, revise, adapt, adaptation, refinement, refine; (2) health belief: perception, attitude, belief, perspective; and (3) cancer screening: cancer, screening, prevent, prevention. Equivalent index terms with the same meanings were also searched. Inclusion criteria for the articles were (1) peer-reviewed articles, (2) reported instrument modification process about health beliefs toward cancer screening, and (3) published in the English language (which could be read by the authors). The exclusion criteria were (1) informal articles such as commentary, letter to the editor, and conference abstract and (2) constructs from the health belief model not included.

For identifying relevant studies, keywords were applied to search the full text of articles in the databases. Titles and abstracts of the articles were read further to exclude irrelevant studies. Articles in the reference list of selected articles were also searched. Inclusion and exclusion criteria were evaluated during the process. Information on the purpose, sample, setting, methods, results, and discussion of the included articles was extracted and entered into the table of evidence. Bowling's checklist was used to evaluate methodological rigor of the included articles [20]. The studies' aims, methods, results, and conclusions were evaluated by assessing the 20 items in Bowling's checklist. Results in the study were reported using a narrative method following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [21] (see Multimedia Appendix 1 for PRISMA checklist).

Results

Search Findings

A total of 1312 articles were initially identified in the databases. After removing duplications, the titles and abstracts of the articles were assessed further, and 1293 articles were excluded in the process. Out of the 19 remaining articles screened, 1 article was further excluded because it focused on the cultural beliefs of cancer screening instead of health beliefs of cancer screening. In total, 18 studies met the inclusion criteria and were included in the study [22-39] (Figure 1).

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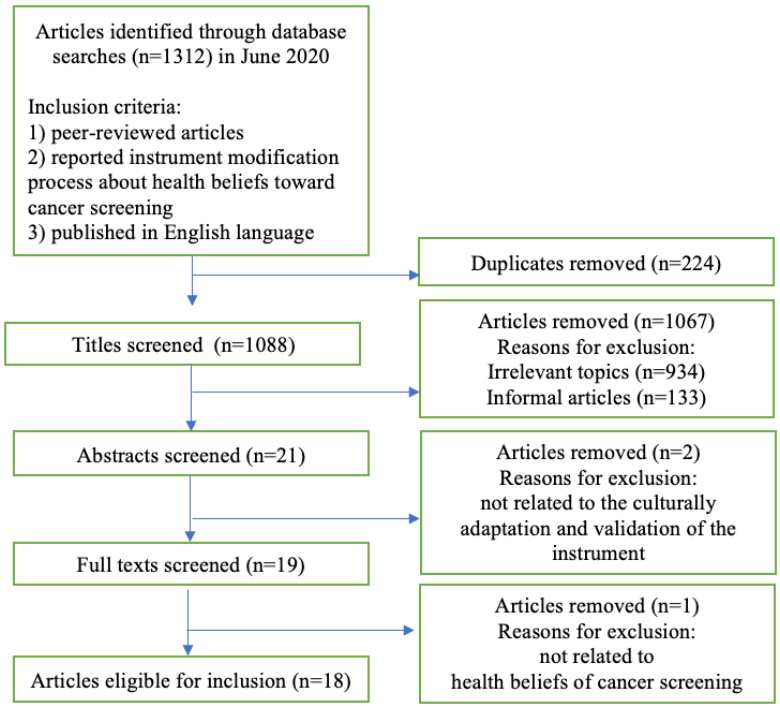
Figure 1. PRISMA flowchart documenting study selection process.



Study Characteristics

Among the 18 reviewed studies (Table 1), 5 were conducted in Turkey [22-26], 3 in Iran [27-29], 2 in the United States [30,31], and 1 each in Mexico [32], Indonesia [33], Malta [34], South Korea [35], Jordan [36], Malaysia [37], the city of Kaunas in Lithuania [38], and Cyprus [39]. The publication years of the studies ranged from 2001 to 2020. The sample size of the studies ranged from 15 to 656. Convenience sampling [22,25,28,32-35] and random sampling methods [23,27,29,36,37] were the most frequently used recruitment methods. Champion's Health Belief Model Scale [14] was most commonly (17/18) adapted in the studies. The remaining study [30] created their scale by combining an adapted health belief scale from Menon et al [40] and a severity scale by Champion [41]. All studies were guided by the health belief model. Sixteen studies were about health beliefs of breast cancer screening and 2 studies were about health beliefs of colorectal and cervical cancer screening. All adapted instruments in the studies were proved to be valid and reliable through the validation process.

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Table 1. Study characteristics for the included articles.

Study authors and citation	Modification strategies
Gozum and Aydin [22]	Rephrasing words in the items (S[a])
Guvenc et al [23]	Adding items (C[b])
Karayurt and Dramalı [24]	Rephrasing words in the items (S)
Secginli and Nahcivan [25]	Rephrasing words in the items (S)
Yilmaz and Sayin [26]	Rephrasing words in the items (S); deleting parts of the sentences in the items (C)
Hashemian et al [27]	Deleting parts of the sentences in the items (C); deleting items (C); adding items (C)
Kharameh et al [28]	Rephrasing words in the items (S); deleting items (C)
Taymoori and Berry [29]	Rephrasing words in the items (S); deleting parts of the sentences in the item (C); changing the subject of the items (C); changing the response options (S)
Lee and Lee [30]	Rephrasing words in the items (S); deleting parts of the sentences in the items (C); changing the response options (S)
Medina-Shepherd and Kleier [31]	Rephrasing words in the items (S)
Juárez-García et al [32]	Changing the response options (S); deleting items (C); adding items (C)
Dewi [33]	Rephrasing words in the items (S); deleting subscales (Cr[c]); adding subscales (Cr)
Marmarà et al [34]	Rephrasing words in the items (S); changing the subject of the items (C); deleting subscales (Cr); deleting items (C); adding subscales (Cr)
Lee et al [35]	Rephrasing words in the items (S)
Mikhail and Petro-Nustas [36]	Minor changes in the wording of the items (S); adding items (C)
Parsa et al [37]	Adding subscales (Cr)
Zelviene and Bogusevicius [38]	Rephrasing words in the items (S); deleting parts of the sentences in the items (C)
Tsangari and Petro-Nustas [39]	Minor changes in the wording of the items (S)

[a]S: semantic.

[b]C: content.

[c]CR: criterion.

Data Evaluation and Extraction

The quality of the reviewed articles was evaluated by the first author and verified by the second author using Bowling's checklist (Table 2). Data evaluation results showed the studies either had excellent or fair quality. All studies met 11 to 17 criteria on the checklist, although certain limitations existed (eg, generalizability of the findings to other populations: scales translated to one language cannot be used for another population speaking another language).

During the data evaluation process, the first author extracted relevant data from the reviewed articles and entered data into the Excel (Microsoft Corp) table of evidence, summarized correlated information into themes, and classified data into different categories. The second author checked the data and categories to ensure the findings were synthesized in a reliable way.

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Table 2. Quantitative studies critical appraisal checklist [20].

	Criteria	Yes	No
1	Aims and objectives clearly stated	18	0
2	Hypothesis/research questions clearly specified	10	8
3	Dependent and independent variables clearly stated	3	15
4	Variables adequately operationalized	14	4
5	Design adequately described	12	6
6	Method appropriate	18	0
7	Instruments used tested for reliability and validity	18	0
8	Source of sample, inclusion/exclusion, response rates described	14	4
9	Statistical errors discussed	4	14
10	Ethical considerations described	13	5
11	Study was piloted	15	3
12	Statistically analysis appropriate	18	0
13	Results reported and clear	18	0
14	Results reported related to hypothesis and literature	18	0
15	Limitations reported	13	5
16	Conclusions do not go beyond limit of data and results	18	0
17	Findings able to be generalized	0	18
18	Implications discussed	18	0
19	Existing conflicts of interest with sponsor identified	0	18
20	Data available for scrutiny and reanalysis	0	18

Modification Strategies

According to Flaherty's cultural equivalence model, strategies used in the modification process were categorized by the equivalence type, especially semantic, content, and criterion equivalence (Table 3).

Table 3. Modification strategies used in the studies.

Equivalence type	Strategies
Semantic equivalence	• Rephrasing items • Rephrasing response options
Content equivalence	• Changing subjects of items • Changing wording of items • Adding items • Deleting items
Criterion equivalence	• Adding subscales and items • Deleting subscales and items

Semantic Equivalence

Semantic equivalence requires the meaning of each item in the adapted instrument to be similar to the meaning of the original item [19]. When aiming to achieve this type of cultural equivalence, rephrasing items and response options were frequently used in the reviewed studies.

Rephrasing Items

Upon reading expert and participant comments about the scales, the authors simplified and modified some wordings of items during the modification phase [28,33,36,39]. This strategy was frequently used in the reviewed studies (eg, some words in the items were replaced by other words, and medical terms were replaced by generally known terms).

To reach cultural accuracy of items, some words in the items were replaced by other words. Following one participant's suggestion, in the study to adapt a Korean version of Champion's Health Belief Model Scale, the word "hok" was changed into "meongwooli." Even though both words meant lump or mass in Korean, the authors asserted the modification

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helped the women in the study to better understand the content of the instrument [35]. To accurately measure Turkish women's health belief of breast cancer screening, the word "komik" (meaning funny) was changed into "tuhaf" (another expression of funny), and "gizlilik" (meaning privacy) was changed into "mahremiyet" (another expression of privacy) per expert suggestions. This change increased the consistency between the translated version and original version of the instrument [25]. The item "When I do breast screening examination, I feel good about myself" was changed to "I feel self-satisfied" as it was closer to the Iranian meaning than "feel good" [29].

Another strategy used to reach cross-cultural semantic equivalence was rephrasing medical terms to generally known terms. This strategy was used in the study conducted to measure health beliefs of colorectal cancer screening among Korean Americans [30]. The medical term "fecal occult blood test" was replaced with lay language "stool blood test," as the medical term might be difficult to understand for participants not employed in a health-related field [30]. In the Turkish Health Belief Model Scale [26], the term "lump" was translated to "kitle" initially and changed to "sert yumrubeze," a lay-language word that has a similar meaning to "kitle" and would be understood by Turkish women [26]. In the Maltese Health Belief Model Scale [34], "mammografija" was changed to "mammogram" and "nipil" was translated to "nipple" because "mammogram" and "nipple" are generally known terms with similar meanings to "mammografija" and "nipil" in Maltese. A similar strategy was used in the study conducted among Hispanic women [31]. The authors changed the original term of breast, "mama," to "seno," a word with similar meaning, since "seno" would be most understood in all Hispanic groups.

To avoid causing misunderstanding, confusion, and anxiety, some instrument items were changed by reversing direction of the meaning. This strategy was used in one study conducted with Maltese women [34]. The item "...will last for a short time" with reverse scoring was replaced with "...will last for a long time." Then scores on the item did not have to be reversed.

Rephrasing Response Options

To increase clarity and achieve semantic equivalence, wordings of response options in the instruments may need to change. This strategy was used in 3 studies [29,30,32]. To adequately measure Mexican women's health belief toward breast cancer screening, the response options were amended to 4=yes, 3=I think so, 2=I don't think so, and 1=no, since the original response options were found to be problematic for the participants [32]. Also, instead of using the original response options (from "strongly disagree" to "strongly agree"), the Farsi Health Belief Model Scale used "not at all true" to "very true" for the perceived severity, susceptibility, benefits, and barriers subscales and "never" to "always" for the health motivation subscale, since most of the participants in the pretest phase reported problems with the format of response options [29]. Furthermore, the response option in the scale to measure Korean Americans' health beliefs about colorectal cancer screening, "neutral" was changed to "so-so" per expert advice and suggestions in the published literature [30].

Content Equivalence

Content equivalence requires the content of each item in the adapted instrument to be relevant or appropriate to each cultural group or population under study [19]. This type of cross-cultural equivalence was usually achieved by changing subjects of items, changing wording of items, adding items, or deleting items.

Changing Subjects of Items

This strategy was used to achieve content equivalence by making the meanings of the items relevant or appropriate. It could avoid arousing fatalistic thoughts that were commonly present among minority populations. This strategy was used in the study conducted with Maltese women [34]. The item "My illness has serious...consequences" was replaced with "Breast cancer has serious...consequences." The participants were asked to report their personal views about breast cancer instead of an illness personally affecting them [34]. Another strategy used in the study was using the third person pronoun instead of the first person pronoun to avoid arousing fatalistic thought. In some cultures, people believe that expressing an ominous event in the first person indicates that the event will occur [29]. In the Iranian Health Belief Model Scale [29], the first person pronoun in the item "If I developed breast cancer, I would not live longer than 5 years" was changed to the third person pronoun: "If someone developed breast cancer, she would not live longer than 5 years." Similarly, changes were also made to another 3 items in the perceived severity scale in this study [29].

Changing Wording of Items

To modify items measuring the sizes of breast lumps in Champion's Health Belief Model Scale ("I am able to find a breast lump which is the size of a quarter/dime/pea"), different items or coins familiar to the target population were used. In the Indonesian Health Belief Model Scale, "quarter" and "dime" were changed to "walnut" and "hazelnut," respectively, because the sizes of a walnut and hazelnut are commonly known in Indonesia [33]. To find equal sizes to "quarter, dime, and pea," the words were translated into "chickpea, hazelnut, and walnut" in the Turkish Health Belief Model Scale [25]. To represent dime and quarter in Iranian culture, the authors used "filbert" and "rather greater than filbert," since "filbert" is commonly known in Iran culture [29]. In addition, the authors used different sizes of Turkish coins equalized to the sizes of the American quarter and dime, and the sizes of the original quarter and dime were given in centimeters in another study with Turkish women [26]. Similarly, wordings about the size of a palpable lump were also changed according to the sizes of currencies in Kaunas [38] and South Korea [35] in 2 other studies.

Adding Items

To increase the cultural sensitivity of the adapted instrument, thus increasing the scale's content equivalence, entire items or parts of items were added to the adapted instrument.

Adding entire items to the modified scale was a common strategy used in the reviewed studies. In the Iranian Health Belief Model Scale, the item "I am more likely than the average woman to get breast cancer" was added to the adapted instrument because this item was maintained in the previous version of Champion's scale and also because of the special

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features of the participants in the study (who had a family history of breast cancer) [27]. Furthermore, 4 items, (I don't know where to go for mammography; I don't have any problem with my breasts, I don't need mammography; I do self-examination of the breasts, so there is no need for mammography; and I don't have enough money for mammography) were added to the subscale of perceived barriers per participant discussion [27]. In addition, per expert suggestions, 2 items concerning awareness of the age and frequency at which mammograms should be undertaken were added to the self-efficacy subscale of the Mexican Health Belief Model Scale. Two items concerning myths were added to the barrier subscale. Two items concerning risk factors for cancer were added to the susceptibility subscale, and one item on drug use avoidance was added to the health motivation subscale [32].

To make the meaning of the items clear and easily understandable, additional words of explanation were added as part of some items. In the study conducted with Korean Americans, the explanation "not wanting to let other people know that you are doing the stool blood test or handling stool for the test" was added to the item "not having privacy would keep you from having a stool blood test," since privacy could be interpreted as several different Korean words depending on the context [30]. Also, the item, "I have other problems more important than having a stool blood test," was expanded to "Having a stool blood test is not the most urgent and important problem I have, which keeps me from doing it" because several participants reported they did not understand its meaning [30]. In the Turkish Health Belief Model Scale [26], the term "radyasyon" was explained as "radiation, x-ray/in other words radyasyon-rontgen" because some women in the target population would not know the word radiation since general understanding of the word was "x-ray." Similarly, in the same study, "mammography" was expanded to "mammography" and "breast x-ray" in the modified scale because many women in Turkey do not know about early diagnostic methods for breast cancer, especially mammography [26]. Furthermore, in the translated Kaunas instrument, after pretesting with 10 women, 2 alternatives of the original word meaning "privacy," solitude and severalty, were written with the original meaning next to the item "I don't have enough privacy to do breast examination" [38].

Deleting Items

Deleting entire items or parts of items was a common strategy used in the studies to achieve content equivalence. Entire items in the reviewed studies were removed due to redundancy, irrelevance, or inaccuracy or a low content validity index at the item level. In one study, the item "I am too old to need a routine mammogram" was deleted because the Iranian women (n=200) in the study were younger (mean age 46.15 [SD 7.26] years, range 28 to 69 years) than the participants in the original Champion study (aged 50 years and older) [27]. Furthermore, the item "I don't know how to go about getting a mammogram" was eliminated because the city was quite small [27]. Similarly, 2 items, "Breast cancer will last for a long time" and "I expect to have breast cancer for the rest of my life," were removed in another study because the 2 items were found to confuse the Maltese participants and cause consistent heightened anxiety in responders [34]. Finally, the item "receiving a mammogram prior to breast screening" was deleted from a study to avoid overlap [34].

To reach cross-cultural content equivalence, parts of sentences in items from the original instruments were deleted. The terms "boyfriend" and "partner" in the item "Breast cancer would threaten a relationship with my boyfriend, husband, or partner" were deleted in 2 studies with Iranian women because sexual relationship outside the marriage is forbidden by Islamic rules and religious norm [29]. Furthermore, the word "blood" in the item describing "stool blood test" was deleted to emphasize that a stool sample was needed because some Korean American participants wrongly thought the test required blood to be taken [30].

Criterion Equivalence

Criterion equivalence requires the interpretation of an instrument's relationship to established independent criteria for a certain event to be the same across cultures. This type of equivalence was usually achieved by adding subscales or items and deleting subscales.

Adding Subscales or Items

In the Maltese Health Belief Model Scale, the authors added subscales concerning the impact of sociodemographic and socioeconomic factors (eg, items about education level and income) on women's breast screening behavior to acknowledge the contributions of those criteria to breast cancer screening [34]. A cues to action subscale (such as physician recommendations and family history), often omitted from empirical studies using Champion's Health Belief Model Scale, was added because the authors thought cues to action were important criteria through which to examine the health belief of Maltese toward breast cancer screening [34]. In the Turkish Health Belief Model Scale, 4 items (cost, fatalism, preference for female health care professionals, and distance from the health center) thought to be appropriate to Turkish culture were added to the barrier subscale [23]. Furthermore, to test Jordan women's fatalistic beliefs about breast cancer, the item "If I get sick with breast cancer, I believe this is my fate and practicing breast screening examination will not change my fate regardless of when the tumor is detected" was added to the barrier subscale [36].

Deleting Subscales or Items

In the reviewed studies, some subscales in the Health Belief Model Scale were deleted to increase cultural sensitivity. When the literature search indicated that most Maltese women perceived breast cancer to be a serious threat, the perceived severity scale was removed from the Maltese Health Belief Model Scale because the authors determined that perceived severity was not a criterion for examining the health belief of Maltese women toward breast cancer screening [34]. In addition, the item "people who perform mammograms are rude to women" was eliminated because participants believed that a sense of shame prevents them from receiving mammography instead of the issue of obscenity, and the statement lacked compatibility with Iranian culture [27].

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Disagreement Solution Strategies

If a disagreement arose and panel members could not reach consensus on the translated items, solution strategies included consultation with experts, literature search, following the majority, and consultation with the author who developed the scales.

Consultation With Experts or Literature Search

This strategy was used in one study aiming to measure the health belief of Korean Americans toward colorectal cancer screening [30]. When the primary investigator and translation committee members encountered difficulty reaching a consensus on translation, they either sought guidance from an expert or literature published in both Korean and English to solve the dispute [30].

Following the Majority

This strategy was used in one study conducted with Hispanic women. The terms used for marital status aroused a disagreement over the comment from an expert panel member. The expert did not believe that every Hispanic would understand *estado civil* to mean marital status. However, a consensus was reached by the majority of the panel and the term *estado civil* was used in the translated instrument [31].

Consultation With the Author Who Developed the Scales

When meanings of the items in the original scale were not stated clearly, consulting with the author who developed the scales may provide clarification. In a study conducted with Korean Americans, some participants did not understand the meaning of the term "privacy" in the barrier items. Hence, the primary investigator consulted with the author who developed the barrier scale. The author clarified the meaning of privacy, and the item was rephrased accordingly [30].

Discussion

Summary

This study synthesized the modification strategies used in the instrument adaptation process to achieve cultural equivalence and provided solutions to the divergence in the instrument modification process. The instrument that measured health beliefs about cancer screening was used as an example in the study. To our knowledge, this is the first study to date investigating the modification strategies used in the adaptation process of instruments measuring health beliefs of cancer screening. The modification strategies to achieve cultural equivalence summarized in this study could help researchers gain insight into the instrument modification process.

To reach cross-cultural equivalence of the adapted instruments, modification is an essential step. According to Medina-Shepherd and Kleier [31], studies using cross-cultural instruments without the process of modification may have problems with validity. To make the instrument culturally appropriate, researchers must use words that are preferred and commonly used by the target population. If appropriate attention is not given to word choice, the instrument may be meaningless to participants from the target population, and accurate responses might not be obtained [42]. Therefore, changes and adaptation of the items in the source language may be necessary to achieve cultural equivalence in the target language.

According to the literature, the strategies used in the adaptation process generally included 3 types of modifications—changing, deleting, and adding—and 2 levels—scale level and item level, which consisted of modification of the question statement and response options).

First, rephrasing items or response options was a basic strategy in instrument modification to achieve semantic equivalence [28,33,36,39]. Following expert and participant suggestions, changes to wording could be made on specific items and response options. In addition, medical terms may need to be rephrased to generally known terms to enhance understanding, and confusing items may need to change their directions of meaning. In the instrument modification process, clarity is an important criterion that should be considered. If a statement in the modified instrument is not clearly understood by the participants or causes confusion, the wording should be further changed or modified to reach accuracy at the item level [35]. Medical terms not well known in the lay population need to be modified to give participants more insight into the instrument questions [30]. Replacing the medical term with a generally known term [34] or adding an explanation to the medical term can assure an easier understanding. Changing the direction of the meaning can lessen confusion caused by the statement as well [34]. Although changing the wording of an instrument is easily achieved, cross-cultural researchers still need to use this strategy with careful consideration. Consultation with experts and participants from the target population is still the most important step to validate the modification.

Second, changing subjects of items, changing wordings, and adding or deleting items could help the adapted instrument achieve content equivalence with the original items. Some item subjects may be not appropriate in the instrument due to fatalistic thoughts of participants, and the subjects may need to be changed. Adding relevant items and deleting irrelevant statements were also important strategies to reach content equivalence. In the literature reviewed in this study, items tended to be added to increase cultural sensitivity and clarity and deleted to decrease redundancy, irrelevance, or inaccuracy or increase the content validity index at the item level. In the instrument modification process, items in the original scale suitable to the initial cultural context may not be suitable to the other cultural context. Selecting relevant items and deleting irrelevant items could lessen confusion and make the scale more meaningful [32]. Expanding the incomplete statement by adding an explanation or instruction for answering the question could help participants fully and clearly answer the question [30], increasing the response rate for each item. However, adding or deleting items should be carefully considered since the modification may impact the instrument's reliability and validity. Pilot testing of modified instrument's validities (content, construct, predictive, and face validity) and reliabilities (internal consistency and test-retest reliability and item-total subscale correlations) is necessary before launching the modified instrument into formal use.

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In addition, the strategies of adding and deleting subscales and items were often used to achieve cross-cultural criterion equivalence. In the literature reviewed in this study, the specific reason for adding and deleting subscales and items was to increase cultural sensitivity and clarity. This strategy should be used with careful consideration. Unless supported by a comprehensive literature review or updated theoretical framework that reflects a changed base of the instrument, adding or deleting subscales and items could significantly impact the validity of the adapted instrument.

Furthermore, disagreement solution strategies for the modification process included consultation with experts or literature search, following the majority, and consultation with the author who developed the scales. Using an appropriate solution strategy to solve a disagreement arising in the modification process can clarify the vague meanings of items and further increase the validity of the items. During the modification process, it is best to have a research team with bilingual professionals who are familiar with the cultures for which the instrument was originally developed and to which it will later be adapted. If it is possible, the primary investigators for the instrument modification should be the ones who are bilingual, bicultural, and familiar with the concepts measured in the instrument. This could facilitate the instrument modification process and help meet challenges that emerge during the process.

Limitation

This systematic review has some limitations. First, we used a narrative rather than a meta-analysis method to summarize data. As such, our findings cannot be used to recommend the optimal strategies for modifying instruments used in the cross-cultural research. Second, we reviewed only articles written in English, which may have biased the data and restricted our findings. Limiting the review to English language articles may introduce a language bias and lead to erroneous conclusions [43]. However, since 92.50% of scientific literature is written in English [44], the language bias may have little impact on this study. Third, modification strategies synthesized in this study may not be able to reflect other factors impacting the modification process. Factors such as personal experience and expertise of the researcher, translator, or interpreter; educational level and health literacy of the target population; and cultural integration and assimilation levels between populations should also be considered in the modification process.

Future Direction of Research

Instrument modification is an important part of cross-cultural research. Adapting an instrument developed for another culture to be used in the target population can save time, add value to the original instrument, and promote science achievements to circulate around the world. With the development of science, factors impacting the cross-culture instrument modification change accordingly. For example, instruments used for online and offline cancer screening (eg, paper version, telephone assessment) may differ in wording, which may impact the technical equivalence of the instrument. A systematic review of the factors that may impact the instrument modification process in the new stage of science is necessary and can help cross-cultural researchers gain a comprehensive understanding of the modification process to achieve cultural equivalency. In addition, research to update the definition of cross-cultural equivalence and a clear gold standard checklist to evaluate cultural equivalence for the instrument modification should be established for cross-cultural researchers, since Flaherty's approach was introduced several decades ago [19]. This could help to examine the cultural equivalence of the modified instrument to the original instrument and further increase the modified instrument's validity and reliability.

Conclusions

Instrument modification is a necessary process in cross-cultural instrument adaptation. This study summarized the modification strategies used to culturally adapt instruments measuring health beliefs of cancer screening to achieved cross-cultural equivalence. It can potentially give cross-cultural researchers more insight into the modification strategies and a better understanding the modification process in the cross-cultural instrument adaptation. More research needs to be done to help researchers better modify cross-cultural instruments and develop a checklist to achieve cross-cultural equivalence.

Acknowledgments

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Authors' Contributions

FL collected and analyzed the data and wrote the manuscript. EL checked the data and data analysis process and revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA checklist.
[PDF File (Adobe PDF File), 1688 KB - cancer_v7i4e28393_app1.pdf]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

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Original Paper

Exploring Cancer Survivor Needs and Preferences for Communicating Personalized Cancer Statistics From Registry Data: Qualitative Multimethod Study

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Abstract

Background: Disclosure of cancer statistics (eg, survival or incidence rates) based on a representative group of patients can help increase cancer survivors' understanding of their own diagnostic and prognostic situation, and care planning. More recently, there has been an increasing interest in the use of cancer registry data for disclosing and communicating personalized cancer statistics (tailored toward personal and clinical characteristics) to cancer survivors and relatives.

Objective: The aim of this study was to explore breast cancer (BCa) and prostate cancer (PCa) survivor needs and preferences for disclosing (what) and presenting (how) personalized statistics from a large Dutch population-based data set, the Netherlands Cancer Registry (NCR).

Methods: To elicit survivor needs and preferences for communicating personalized NCR statistics, we created different (non)interactive tools visualizing hypothetical scenarios and adopted a qualitative multimethod study design. We first conducted 2 focus groups (study 1; n=13) for collecting group data on BCa and PCa survivor needs and preferences, using noninteractive sketches of what a tool for communicating personalized statistics might look like. Based on these insights, we designed a revised interactive tool, which was used to further explore the needs and preferences of another group of cancer survivors during individual think-aloud observations and semistructured interviews (study 2; n=11). All sessions were audio-recorded, transcribed verbatim, analyzed using thematic (focus groups) and content analysis (think-aloud observations), and reported in compliance with qualitative research reporting criteria.

Results: In both studies, cancer survivors expressed the need to receive personalized statistics from a representative source, with especially a need for survival and conditional survival rates (ie, survival rate for those who have already survived for a certain period). Personalized statistics adjusted toward personal and clinical factors were deemed more relevant and useful to know than generic or average-based statistics. Participants also needed support for correctly interpreting the personalized statistics and putting them into perspective, for instance by adding contextual or comparative information. Furthermore, while thinking aloud, participants experienced a mix of positive (sense of hope) and negative emotions (feelings of distress) while viewing the personalized survival data. Overall, participants preferred simplicity and conciseness, and the ability to tailor the type of visualization and amount of (detailed) statistical information.

Conclusions: The majority of our sample of cancer survivors wanted to receive personalized statistics from the NCR. Given the variation in patient needs and preferences for presenting personalized statistics, designers of similar information tools may

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consider potential tailoring strategies on multiple levels, as well as effective ways for providing supporting information to make sure that the personalized statistics are properly understood. This is encouraging for cancer registries to address this unmet need, but also for those who are developing or implementing personalized data-driven information tools for patients and relatives.

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KEYWORDS

breast cancer; cancer statistics; personalization; prostate cancer; risk communication; cancer registry; cancer; patient needs and preferences

Introduction

Background

In cancer care, many newly diagnosed patients and survivors prefer disclosure of cancer statistics and prognostic information [1-4]. For instance, patients may wish to receive information about the chances of surviving the disease (survival data), whereas others are in need of knowing the exact number of people who are diagnosed with the same type of cancer (incidence data). Such cancer statistics are increasingly being presented on the internet through various sources, such as general cancer websites for both patients and relatives [5] and health care professionals [6], but also in decision-support tools such as patient decision aids [7] or publicly available prediction models [8]. Cancer statistics may help increase patients' understanding of their own diagnosis, prognosis, and involvement in different stages of the shared decision-making process (eg, option talk stage) with their clinician [9,10]. Moreover, both patients and clinicians may use cancer statistics to start a conversation about complex health topics such as survival or cancer recurrence, and to discuss its role in making a decision about treatment [11]. It is therefore important that patients, relatives, and clinicians have access to representative and reliable cancer statistics about topics that could contribute to informed decision making and advance care planning.

However, current cancer statistics are typically generic and population based [12-14], thereby making it hard for patients to apply the numbers to their own individual situation [15]. For instance, when a man of 50 years old is diagnosed with prostate cancer (PCa) and is asking about his life expectancy, population-based statistics about survival (which will mostly be based on substantially older men) may be of limited value. In light of the strong movements toward personalized health care [16], patient-centered care, and open access of "big health data," [17,18] there has been an increasing interest in the use of population-based cancer registries for disclosing *personalized cancer statistics* to survivors and relatives [19]. This allows survivors to be provided with more specific statistical information of certain health outcomes by comparing their own characteristics (eg, age, gender, type of tumor, tumor stage) with specific patient groups with similar characteristics. An illustrative example of this is the American Surveillance, Epidemiology, and End Results Cancer Survival Calculator (SEER*CSC) [11], which draws on an extensive cancer statistics database for communicating personalized cancer statistics (cancer incidence, survival rates) in multiple formats to patients via a publicly available web-based tool. Other initiatives that used registry data or other patient-reported data in patient–clinician communication are decision-support tools for estimating personalized health statistics, such as treatment (side) effects or quality of life outcomes [8,20,21]. Given these developments, the question arises, then, what the needs and preferences for communicating personalized cancer statistics are among cancer survivors.

Present Study and Objectives

In this study, we focus on the disclosure of personalized cancer statistics from the Netherlands Cancer Registry (NCR), a Dutch nationwide population-based registry maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR records all new cancer diagnoses and contains information about diagnosis (eg, tumor characteristics), sociodemographic (eg, age, gender), treatment, and vital status of millions of patients with cancer in the Netherlands since 1989 [22], and primarily enables health care professionals, policy makers, and others to reflect on and improve cancer care and prevention in the Netherlands. Basic and generic NCR statistics such data on incidence and survival are already being provided through websites of patient organizations, hospitals, and online cancer communities (all aimed at cancer survivors and their relatives), with more detailed NCR statistics according to site, gender, age, and region being available through the web-based tool NKR-Cijfers [6] (aimed at health care professionals). Our main project goal is to explore whether important NCR statistics on incidence, survival, and conditional survival could be disclosed via a web-based interactive tool, in which visitors (eg, patients or relatives) will have the opportunity to enter certain personal (eg, age, gender) and clinical characteristic (eg, tumor stage, years since diagnosis), with the aim of receiving personalized statistical information based on real-life patient data with similar characteristics. However, this development raises a number of questions. What types of personalized cancer statistics do cancer survivors want to receive? How should these personalized statistics be presented to patients? What potential barriers or challenges are involved in communicating personalized survival statistics to survivors via a public website? Answers to these questions will not only be useful for the development of a real-life web-based tool for displaying personalized statistics from the NCR to cancer survivors, but also for research groups outside the oncology context working on the design and implementation of similar statistical information tools based on registry or other medical data for patients and relatives.

The purpose of this study is therefore to explore the needs and preferences of breast cancer (BCa) and PCa survivors for communicating personalized cancer statistics from the NCR. Although previous research has shown that most (but not all) patients want to receive prognostic information [1-4,23], it is

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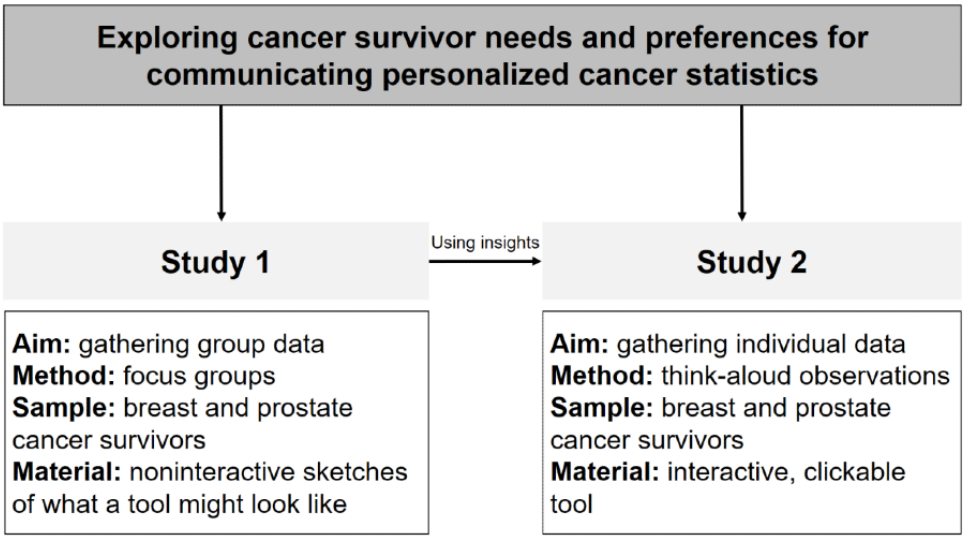
unclear which pieces of prognostic and statistical information patients wish to receive. Therefore, we first aim to explore patients' need for prognostic information on a deeper level, and more specifically by investigating *what* type of personalized cancer risks, statistics, and probabilities patients need to receive from the NCR and other data sources. Furthermore, it is much more difficult for survivors and relatives than for health care professionals to translate group-based statistics to their personal situation [24,25]. For instance, some individuals have inherently more difficulties than others in understanding numeric information, even when supported with visual aids, whereas others are experiencing emotions while processing sensitive health data such as survival or mortality rates. Hence, our second aim is to examine *how* patients want to receive personalized statistics from the NCR. To achieve our aims, we designed different (non)interactive tools to probe participant responses on their needs and preferences.

Methods

Overview

We conducted a multimethod qualitative study among BCa and PCa survivors (Figure 1). BCa and PCa are among the most prevalent types of cancer among men and women, respectively, which also makes it feasible to calculate personalized statistics based on a subgroup of patient data that is sizeable enough to provide statistically sound and meaningful information. Moreover, in general, the prognostic outcomes are relatively favorable for these 2 cancer types, thereby making it a suitable starting point for our initiative for disclosing personalized cancer statistics. We first conducted 2 focus groups (study 1) for collecting group data on needs and preferences of BCa and PCa survivors for communicating personalized NCR data, using noninteractive sketches of what a tool for communicating personalized statistics might look like. Based on these insights, we designed a revised interactive version of the tool, which was used to further explore the needs and preferences of another group of BCa and PCa survivors during individual think-aloud observations and semistructured interviews (study 2). We complied with the 32-item Consolidated Criteria for Reporting Qualitative Research (Multimedia Appendix 1) [26]. Ethical approval was granted by the Research Ethics and Data Management Committee of the Tilburg School of Humanities and Digital Sciences of Tilburg University (REDC 2019-44).

Figure 1. Overview of studies.



Study 1: Focus Groups

Overview

To explore cancer survivor needs and preferences for communicating personalized statistics from the NCR, this first study employed 2 separate focus groups (1 with BCa survivors and 1 with PCa survivors). Focus group methodology is particularly useful for exploring people's perceptions, beliefs, opinions, and attitudes about a certain topic [27].

Sampling and Recruitment

For the BCa focus group, female participants were recruited from the Dutch Breast Cancer Patient Association (Borstkankervereniging Nederland [BVN]); for the PCa focus group, male participants were identified from the Dutch Prostate Cancer Foundation (Prostaatkankerstichting [PKS]). Participants were included if they were diagnosed with BCa or PCa in the past (at least 1 year after diagnosis). Each eligible participant was approached by email by one of the representatives of the BVN or PKS. Members of our research team did not have any prior relationship with the participants at study commencement, and we were unaware of who from the patient organizations were approached to participate in the focus groups. Participants were reimbursed for their time with a €15 (US $17.4) gift card (unannounced).

Materials

To elicit patients' needs and preferences, we designed noninteractive sketches of what a tool for calculating personalized statistics from the NCR might look like (Multimedia Appendix 2). This tool consisted of 3 parts: (1) patient data entry, (2) tumor data entry, and (3) output display. The patient data entry part was the same for both cancer groups

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(eg, gender, year of birth), but the tumor data entry part differed between the 2 versions. The PCa version contained items such as year of diagnosis, prostate-specific antigen value, Gleason score (ie, the aggressiveness of the cancer), and tumor stage (ie, where the cancer is present in the body). The BCa version contained items such as year of diagnosis, tumor stage, and—in case tumor stage was unknown—metastases (ie, whether the cancer has spread beyond the breast and nearby lymph nodes to other parts of the body). The output display showed a summary of the patient and tumor characteristics filled out by the patient, followed by the personalized absolute incidence rate of their year of diagnosis, the 5- and 10-year overall survival rate, and the conditional survival rate (ie, survival rate for those who have already survived for a certain period [28]). All statistics were shown numerically, and the survival statistics were also shown visually in 4 different, conventional ways (ie, icon array, pie chart, bar chart, and line graphs). Participants could also switch between the 4 types of visualization.

Data Collection

We used a semistructured topic guide for both focus groups to facilitate discussion and elicit participants' needs and preferences for the disclosure and presentation of personalized statistics from NCR data. After a round of introduction, we first explained the purpose of the project and the NCR to the participants. We then asked them to what extent they were in need of receiving the (NCR) statistics incidence, survival, and conditional survival rates in a personalized way, either at their time of diagnosis or at a later moment. After this, we posed a final question by asking what other personalized statistics they were interested in after diagnosis and treatment. During the second part of the discussion, we showed participants sketches of what such a tool could look like (Multimedia Appendix 2). Participants were asked to take a critical look at each slide and provide comments about the tool. They were also encouraged to express their needs and preferences regarding the information presented in the data entry part and the output display of the tool.

The PCa focus group was moderated by RV (male, PhD-candidate, risk communication scientist), MvE (female, health communication scientist with expertise in qualitative research), and GG (male, PhD, with expertise in clinical data science), and the BCa focus group by RV and MvE. The moderators were not known to the participants. Both focus groups lasted 90 minutes and were conducted at the IKNL in Utrecht (The Netherlands) in November 2018 (PCa focus group) and March 2019 (BCa focus group). Field notes were taken in each focus group by RV.

Data Analysis

Qualitative data obtained from the focus groups were audio-recorded (with permission of the participants), transcribed verbatim, and analyzed thematically [29]. For this, we developed a deductive coding scheme based on the study objectives, discussion guide, and focus group content. First, 2 investigators (RV and MvE) developed a preliminary conceptual schema and codebook by independently reading the focus group transcripts. The codebook was designed to capture broad coding categories of needs and preferences for (1) disclosing different types of personalized statistics, and (2) presenting personalized statistics. Then, both investigators independently coded each transcript using MAXQDA 2020 (Verbi Software) [30], and disagreements were resolved through discussion. Finally, both investigators jointly generated a report from the coded transcripts by format to identify themes. Quotes for supporting (sub)themes were translated into English.

Study 2: Think-Aloud Observations

Overview

A think-aloud methodology was used to further assess the needs and preferences of another group of cancer survivors for communicating personalized statistics from the NCR. This involved asking participants to verbalize their thoughts, impressions, and feelings while working with a revised, clickable, and interactive version of the tool to calculate personalized cancer statistics [31]. These revisions were based on input from cancer survivors participating in the focus group (study 1). Semistructured interview techniques were used to allow participants to elaborate on their statements and experience with the tool, and to put them into context. The semistructured interviews also allowed us to capture participant preferences for a specific presentation format in case the think-aloud observations would not cover this information [32].

Sampling and Recruitment

Eligible participants were recruited from the same 2 patient organizations (BVN and PKS) as the first focus groups, and from a Dutch online cancer community (Kanker.nl [33]). Participants were included if they (1) were diagnosed with BCa or PCa in the past (at least 1 year after diagnosis), and (2) had not participated in the focus groups before. The recruitment procedure was identical to the focus groups, meaning that the members of our research team did not have any prior relationship with the participants at study commencement, and we were unaware of who from the patient organization or online cancer community were approached to participate in the think-aloud observations. Participants were reimbursed for their time with a €15 (US $17.4) gift card (unannounced).

Materials

We designed a clickable interactive version of the tool (for screenshots, see Multimedia Appendix 3), which allowed participants to manually enter patient and tumor characteristics, to view the associated personalized statistics, and to modify the type of visualization (ie, icon array [as a default option], pie chart, bar chart, and line graphs) according to their preference. Based on the input from cancer survivors during the focus groups on the sketches of the tool, the following revisions were made. First, the interactive tool now started with a supporting page, including statements such as that the statistics may contain good or bad news (taking emotional aspects into account), that the statistics were based on prior patients (taking contextual information into account), and that we could not provide exact estimates for each individual patient (taking uncertainty into account). Second, the data entry part contained explanations in plain language about certain tumor characteristics (eg, Gleason score or tumor stage). Third, the output display was kept the same, except that we now included comparative information

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by providing both generic, population-based survival statistics and the personalized survival statistics altogether. Fourth, and finally, to take the survivors' preference of amount of information into account, we created 2 tool versions: (1) a short, concise version and (2) a long, detailed version. The short version only provided the raw statistics and the minimally required explanation of the statistics on the output display, which was all presented simultaneously (Figure 2). The long version contained more textual information and gave users the option to expand texts when supplementary information was needed or to see information visually (Figure 3). All screens of the interactive tool were created using Adobe Illustrator CS6, and the tool was developed and implemented using InVision, a digital product design platform [34].

Figure 2. Example of the output display (translated to English) in the short (concise) version of the interactive tool, communicating a favorable survival rate to PCa survivors. All information is presented at the same time. PCa: prostate cancer.

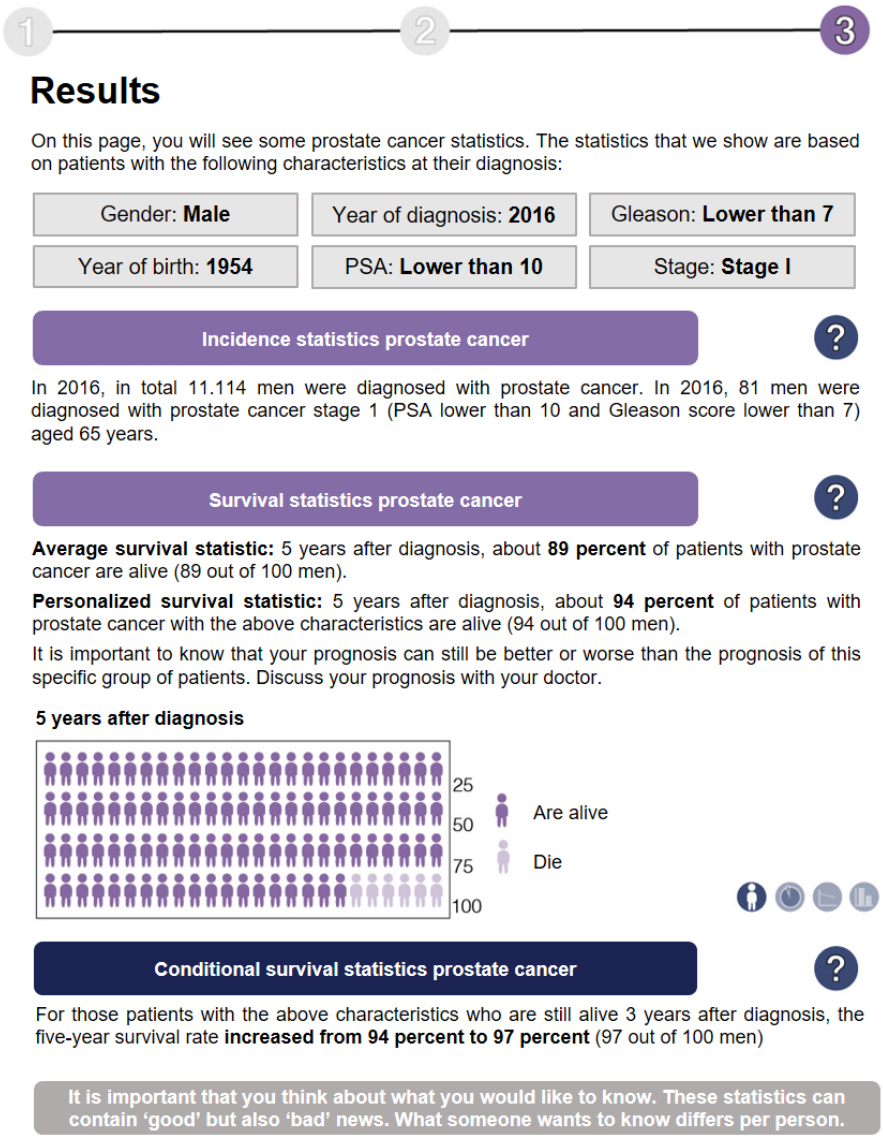

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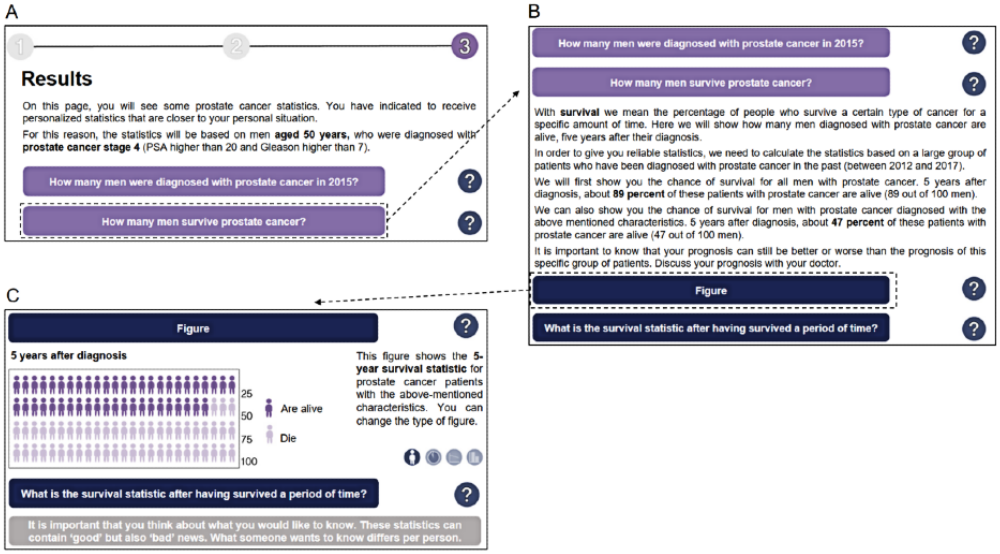
Figure 3. Example of the output display in the long (detailed) version of the interactive tool, communicating a less favorable survival rate to PCa survivors. Participants started at the left top figure (A), and could decide what type of information they wished to see (B, C). PCa: prostate cancer.



Data Collection

Each session started with an explanation of the procedure, signing informed consent, and a questionnaire that assessed sociodemographic information (age, gender, education, work, marital status, and children) and disease-related information (year of diagnosis, type of cancer). Participants were then instructed on how to think aloud. Participants were then asked to enter information into the tool and to view the results using 2 hypothetical case examples: (1) a patient with a favorable 5-year overall survival rate (89% for the BCa group and 94% for the PCa group), and (2) a patient with a less favorable overall 5-year survival rate (38% for participants with BCa and 47% for participants with PCa). Participants with PCa history would use a PCa case, and participants with BCa history would be presented with a BCa case. The case examples contained patient and disease-related information about 2 hypothetical patients [11]. We informed them that this may evoke some unpleasant memories/thoughts related to participants' own cancer (diagnostic) situation. Therefore, participants were told that (1) they always have the opportunity to withdraw their participation whenever they want to, without any negative consequences, and without providing any explanation; (2) the hypothetical personalized statistics used in this study were not real. In addition, because participants might feel anxious about reflecting on their diagnostic situation, they were referred to an online expert therapist of Kanker.nl who is specialized in dealing with cancer-related anxiety.

One case example was performed using the short version of the tool, and the other with the long version of the tool. The order and combination of the tool version with the case scenario were randomized and counterbalanced across participants. While entering the information and viewing the statistics, participants were instructed to think aloud. Prompts were used when participants fell silent (eg, "Keep talking?"), and reassuring sounds were made to enhance thinking aloud (eg, "Uhuh") [35].

After the think-aloud session, we conducted a semistructured interview to provide participants with the opportunity to elaborate on statements made during the think-aloud sessions, and to further capture participants' preferences for communicating the statistics. For this, we used a semistructured topic guide (Multimedia Appendix 4). At the end of the sessions, participants were debriefed and informed about the full purpose of the study.

The think-aloud sessions and semistructured interviews were led by 2 interviewers, RV and a research assistant (female, research assistant in communication science with expertise in new media design). Both interviewers were not known to the participants. The sessions lasted between 21 and 67 minutes (average duration 44 minutes), and were performed at either the IKNL (in Amsterdam, Rotterdam, Utrecht, or Eindhoven) or at the participants' home. Data were collected in April and May 2019. Field notes were taken from each session by RV.

Data Analysis

All think-aloud sessions and semistructured interviews were audio-recorded (with permission of the participants), transcribed verbatim, and analyzed using content analysis [36]. For this, 2 investigators (RV and MvE) developed a deductive coding scheme based on the interview guide (Multimedia Appendix 3) and the themes and subthemes that emerged from the thematic analysis of the focus group study. The same investigators then independently coded 4 transcripts, and resolved disagreements through discussion. The remaining 7 transcripts were then coded by RV. All coding activities were performed using MAXQDA 2020 (Verbi Software) [30]. Quotes for supporting the findings were translated into English.

Results

Patient Characteristics

Characteristics of participants in the 2 focus groups (n for the BCa group=9 females; n for the PCa group=4 males) and 11 think-aloud sessions (n for the patients with BCa=7 females; n for the patients with PCa=4 males) are summarized in Table 1. In both groups, there were more BCa survivors than PCa survivors (69% and 64%, respectively). The participants in both

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groups were comparable in terms of sociodemographic and disease-related characteristics (all *P* values >.20), except for the distribution of year since diagnosis (*P*=.033), with more recently diagnosed survivors in the think-aloud group.

Table 1. Participant characteristics for the focus groups and think-aloud sessions.

Characteristics	Study 1: Focus groups (n=13)	Study 2: Think-aloud observations (n=11)
Gender, n		
Female	9	7
Male	4	4
Age (years) at time of study, mean (SD)	59.8 (10.9)	57.1 (10.3)
<50	3	2
50-65	6	6
>65	4	3
Education, n		
Secondary education or practical education	2	4
College or applied university	6	4
University	5	3
Type of cancer, n		
Breast cancer	9	7
Prostate cancer	4	4
Year since diagnosis, median	9	4
0-5	4	7
6-10	3	4
>10	6	0
Work situation, n		
Work	4	5
Ill (insurance)	2	0
No work/retired	7	6
Marital status, n		
Married/partner	10	6
No partner	3	5
Children, n		
No	3	4
Yes, living with	4	2
Yes, living somewhere else	6	5

Study 1: Focus Groups

Themes Identified

Three themes were identified from the focus group data (Figure 4): (1) the need for personalized statistics, (2) the need for interpretation support, and (3) preference for information presentation. Subthemes are introduced below within each of the main themes' sections.

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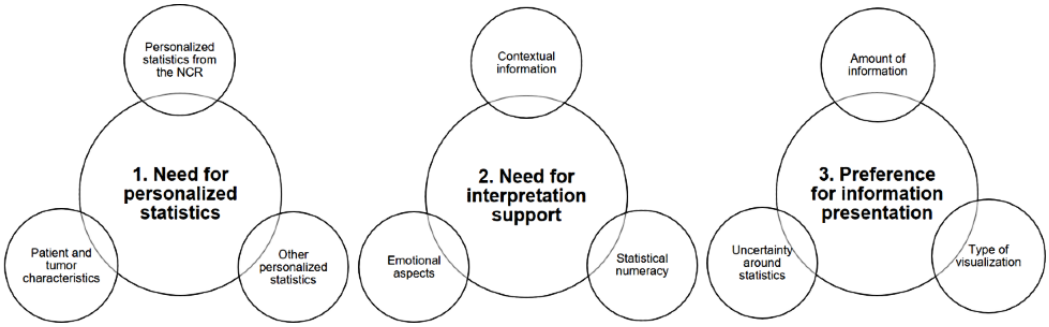
Figure 4. Schematic representation of themes and sub-themes identified from the focus group data. NCR: Netherlands Cancer Registry.



Theme 1: Need for Personalized Statistics

Summary

Participants reported the needs for receiving personalized statistics from the NCR as well as other personalized statistics, and also on how to establish this by taking several patient and tumor characteristics into account.

Personalized Statistics From the NCR

All participants found the (5- and 10-year) survival rate the most important statistic from the NCR. However, at their time of diagnosis, participants wanted to know their personalized survival chance based on their own situation. Participants mentioned that a personalized survival rate seems more relevant and useful to know than the generic or average survival rate, and that characteristics such as tumor stage and lymph nodes involvement could have a significant impact on survival rates.

> *You really want to know your personalized survival chances for your own type of cancer. So, if you are having a T4-stage cancer, you want to know the survival rate for that specific situation.* [P04, aged 71 years]

For the personalized incidence rate, participants found this type of information to be important, especially because this may help them know how many other patients like them have this specific disease and whether it is something rare or not. Being aware of the high or low incidence rate could also "help patients to see where they are in the bigger picture" [P04]. However, there were also participants who did not really see the added value of this statistic, especially because they already had been diagnosed with cancer and cannot really change this diagnosis.

> *You have already been diagnosed with breast cancer. So, what does it matter that other people also have breast cancer?* [B04, aged 55 years]

Finally, when showing personalized conditional survival rates, participants with BCa and PCa both initially found the term difficult to understand and rather confusing. However, after explaining the concept in more detail and showing them what it might look like in the tool, participants agreed that this type of statistical information might be useful to communicate. Participants mentioned that communicating the personalized conditional survival statistic "can be very reassuring and psychologically beneficial for patients" [P3]. Another participant said:

> *For instance, in the case of triple-negative for breast cancer, after having survived the first three years, your survival chance increases enormously! This could be very interesting and important to communicate [to patients].* [B03, aged 57 years]

Other Personalized Statistics

Participants' need for disclosing other personalized statistics based on NCR or other data sets spanned a broad range. Participants expressed a need for receiving information about personalized risks of treatment outcomes, such as the likelihood of experiencing treatment side effects.

> *I would have liked to know my [personalized] risk of experiencing a side effect after treatment, and whether this risk would change over time or not.* [P01, aged 72 years]

Moreover, participants reported the need for personalized statistical information about cancer recurrence, risk of cancer in the family, and impact on quality of life such as physical, cognitive, and psychosocial functioning. Furthermore, participants with BCa in particular wanted to receive statistics on the chances of getting metastatic cancer, whereas participants with PCa specifically expressed a need for treatments chosen by other patients with PCa over time and performance statistics of different hospitals.

Patient and Tumor Characteristics

Participants had several comments on the characteristics that patients should fill out, and simultaneously expressed their need for extending this with other patient and tumor features. In both groups, participants voiced concerns about asking for a patient's tumor stage, because most of the participants were unfamiliar with the term.

> *Based on my education materials from 2012, I can see that I received information about tumor grade and HER2, but not about my tumor stage.* [B04, aged 55 years]

Moreover, for the metastatic feature, patients found it important to indicate whether the tumor had spread to the lymph nodes or to other parts of the body. Participants therefore suggested providing clear explanations of the patient and tumor characteristics. Additional features proposed by the PCa survivors were information about a person's health status and information about comorbidity. Additional features requested by BCa survivors were tumor grade, HER2 status, and specific types of BCa such as triple negative. Finally, both groups asked

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for a feature dealing with a person's family history of cancer (ie, genetics).

Theme 2: Need for Interpretation Support

Summary

Both PCa and BCa survivors identified challenges that could hinder the correct interpretation of the personalized cancer statistics by future users, and expressed the following needs for supporting patients with this.

Contextual Information

Both groups of participants expressed their wishes to see supplementary information that should accompany the personalized statistics. For instance, they commented that the current survival rates are actually better than those that were displayed by the tool, because patients with newly diagnosed cancer can benefit from advances in treatment options.

> *It is important to mention that all statistics here are about the past and are based on former treatment options. You should really communicate this to users…So the current statistics can only be more positive.* [B01, aged 50 years]

Furthermore, some BCa survivors thought that providing comparative information such as the chance of 10-year cancer recurrence related to the chance of getting cancer for the first time. Similarly, the participants with PCa stated that the 5- and 10-year survival statistics for patients with cancer should be placed in context by comparing them with the survival rates of people who do not have cancer.

> *Providing the survival rate for the norm population would be very useful. The survival rate of the normal population isn't that great as well. If I see a 10-year survival rate of 21 percent for PCa patients [with stage 4], what does this 21 percent mean, and how does it compare [to the normal population]?* [P03, aged 67 years]

Statistical Numeracy

Several participants expressed their concerns about communicating personalized statistics to patients with low health or numeracy skills. They considered it important to explain that the personalized survival rates are still average statistics, and that supplementary information is highly needed especially for those patients who are lacking prior knowledge in statistics.

> *It is important that these statistics are not communicated in a scientific manner, but instead in a way that is understandable for those who do not have a background in statistics.* [P02, aged 79 years]

Emotional Aspects

Participants emphasized the importance of taking emotional aspects such as anxiety into account that may be evoked by viewing information about survival rates. Especially in the scenario with the less favorable survival statistic, some participants found the information shocking and uneasy to see and offered suggestions for adding warning statements about this.

> *I think it would be a good idea to advice people to see this information together with someone else. I could imagine that some people may find this [statistical] information emotionally difficult to interpret…Something like a disclaimer.* [B05, aged 41 years]

However, other participants did not experience this, and felt that disclosing personalized statistical information via this tool is of utmost importance for those who need it to become well informed, even though the statistics could be bad and provoke negative emotions. They felt that this would not destroy patients' hope, but instead would create a more realistic picture.

> *Those people who want hope will not read this [personalized statistical information]. I think that if you have the [statistical] information, it should become available for everyone* [B01, aged 50 years]
>
> *I have searched for statistical information all night long. Having that knowledge [statistical information] makes me feel calm* [B06, aged 63 years]

Theme 3: Preference for Information Presentation

Summary

While viewing the tool, participants reported their preferences for presenting the personalized cancer statistics in terms of type of visualization, amount of information, and uncertainty around statistics.

Type of Visualization

Regarding the different types of visualization that we used for communicating the survival rates, almost all PCa and BCa survivors expressed a preference for the icon arrays. However, 1 participant with PCa commented that the icon arrays increased levels of anxiety because "they seemed too personal" [P03]. Overall, participants found the option to switch between different types of visualization valuable and helpful.

Amount of Information

In both groups, participants shared their views on whether we should give users a conscious choice of what information they would like to see, for instance, by giving them the option to expand texts when supplementary information about specific terms or statistics is preferred. Some participants argued that this would then satisfy both users who want detailed or supplementary information about the statistics and users who want to see as little as possible. This was also true for showing the visualizations by default, or providing patients the option to decide for themselves whether they want to see the information visually or not.

> *I was thinking of the graphic. Do you always want to show this to all patients, regardless of the type? You could also first show them the textual information, and then give them the option to view the information in a graphic, and which type of graphic. Because…what if the survival rate turns out to be very low. Then the icon arrays can very confrontational.* [B01, aged 50 years]

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Uncertainty Around Statistics

Not all participants were aware of the imprecision of the statistics (ie, epistemic uncertainty), and they had conflicting views on whether or not we should disclose and communicate this. Some participants thought it might be too difficult and confusing to communicate, whereas others stated it may help patients understand that the statistics are less reliable and could be no more than an indication of what could happen. The participants with BCa showed a preference for communicating this kind of uncertainty only when calculating survival rates for small groups (eg, patients with BCa with triple-negative), or when the statistics were relatively poor (eg, less favorable survival rate). As one BCa survivor put it:

> *Here [sees a 5-year survival rate of 44% for a stage 4 BCa patient] you want to know the variation, because it may give the patient hope. If you have a poor statistic, but you see that the range is big, then you may think that you could still be on the positive side of the range. Whereas if you have a good statistic, then providing a range becomes less relevant.* [B03, aged 57 years]

This concludes the findings of the focus groups. In the next section, we will discuss the results from the think-aloud observations, which allow us to get a better insight into what cancer survivors might actually think and feel when confronted with personalized cancer statistics.

Study 2: Think-Aloud Observations

Overview

The results of the think-aloud observations are presented below, structured around the 3 main themes that were identified from the focus group data (need for personalized statistics, need for interpretation support, and preference for information presentation). Table 2 displays an overview of the main results obtained during the think-aloud observations.

Table 2. Overview of results and statements made by participants during the think-aloud sessions (N=11).

Item	Value, n (%)
Need for personalized statistics	
Mentioned that receiving personalized survival rate is valuable	9 (82)
Showed less interest in (personalized) incidence rate	11 (100)
Appreciated the conditional survival rates	10 (91)
Wanted more clinical characteristics and treatment history for specifying statistics even further	6 (55)
Need for interpretation support	
Found the supporting statements helpful and important	11 (100)
Would not recommend using verbal labels for interpreting statistics (eg, to tell patients they will receive “good or bad” news)	3 (27)
Experienced positive emotions (eg, sense of hope) while viewing the personalized statistics	9 (82)
Experienced negative emotions (eg, shocked) while viewing the personalized statistics	7 (64)
Mentioned that both favorable and unfavorable personalized statistics should be disclosed	11 (100)
Found comparative information confronting when their personalized statistics were below average	5 (45)
Appreciated comparative information when their personalized statistics were above average	5 (45)
Preference for information presentation	
Preferred icon arrays for displaying personalized survival rates	6 (55)
Preferred pie charts for displaying personalized survival rates	4 (36)
Preferred bar charts for displaying personalized survival rates	1 (9)
Appreciated the function of tailoring the type of visualization	8 (73)
Preferred a short and concise result page	10 (91)
Expressed a preference for tailoring the amount of information	5 (45)
Appreciated verbal descriptions of uncertainty around personalized statistics	5 (45)
Wanted to see confidence intervals along with the personalized statistics	2 (18)

Need for Personalized Statistics

Overall, most participants (n=9) mentioned that receiving the personalized survival rate was very valuable, of which 7 mentioned that they would use this tool after their diagnosis, and 2 only after a few years after diagnosis. Participants showed less interest in the information about cancer incidence, and 3 were even surprised by the personalized incidence rate, because they expected this statistic to be much higher. Similar to the focus group study, almost all participants (n=10) greatly appreciated the conditional survival rates, especially when initially being confronted with a less favorable survival rate. As participants put it, while thinking aloud:

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> *Well, I think this [conditional survival rate] is very valuable… Indeed, if you have survived some years after diagnosis, you are no longer part of the group of patients that died, so from that moment your chances of survival increase enormously.* [B03, aged 45 years]

> *Yes, I get it. The survival rate increased from 47 percent to 87 percent. Well, then I am a real survivor! 87 out of 100 men, that's high, isn't?* [P01, aged 68 years]

However, similar to the focus group, 6 participants expressed their need for adding more clinical characteristics and treatment history to the tool for better personalizing the statistics.

Need for Interpretation Support

All participants found the supporting statements at the start of the tool very helpful and important, as they may help users become better prepared for receiving and interpreting the statistics. However, 3 participants explicitly mentioned that we should not use labels by telling users that the numbers they will see will be good or bad news. One participant commented, while thinking aloud:

> *I do not think that you can decide for someone else whether something is good or bad news. That is not up to you. It is also relative. I mean, if you see this [survival rate] you may think it's good news, but I may think it's bad news.* [B05, aged 50 years]

The same participant offered suggestions for replacing "good or bad news" with "favorable or less favorable than expected" [B05].

Participants also experienced and expressed a mix of positive and negative emotions while viewing the personalized statistics. The majority of the participants (n=9) expressed positive emotions such as a sense of hope, while viewing the conditional survival rates (n=8), or the favorable survival rate. However, 7 participants were "shocked" or felt "uneasy" when seeing the less favorable survival rate in comparison with the favorable generic, population-based survival rate. Those participants were surprised that so few people would survive after 5 years with these specific characteristics.

> *Oh god, this [less favorable personalized survival rate] is still after five years. Well this number is very different from the generic statistic [generic, population-based survival rate]. Pff, that really sucks!* [B02, aged 60 years]

Nevertheless, participants found it important to disclose the less favorable survival rates as well to create a realistic and fair picture. Some patients (n=5) found that emotions should be taken into account, but at the same time commented that those who do not want to see the personalized statistics will not visit the tool.

> *I did not experience any feelings, but I am also a rationally and realistically oriented person. I know some women who don't want to see this kind of information, but the question is whether they will look for these statistics at all.* [B03, aged 45 years]

Furthermore, participants had mixed views on the comparative information between the personalized and generic, population-based statistics. This view typically depended on whether the personalized survival rate was above or below the generic statistic. Some participants (n=5) found the less favorable survival rate confronting when it was shown in comparison with the favorable generic survival rate. However, when participants' personalized survival rate was higher than the average, others (n=5) thought it was supportive:

> *The [generic] survival rate is 89 percent… Oh well, that is a lot. Survival rate for patients with the above characteristics is 94 percent. Okay, so my prognosis is better than the average [prognosis]. Well that's good news.* [P03, aged 60 years]

> *This [seeing both personalized and generic survival rate] is fine, and seems like an added value to me. This way, you can see whether you are below or above the average survival rate.* [P04, aged 69 years]

Participants further expressed concerns about terminology used in the tool. For instance, 7 participants were not familiar with the term "tumor stage," but rather with alternative features such as TNM stage or the presence of metastases or not. Participants further recommended to avoid complex terms such as "incidence" or "conditional survival" (Figure 2), and preferred the tool version in which these terms were explained in plain language (Figure 3).

Preference for Information Presentation

Participant preferences for visualizing the personalized survival rates were in line with those of participants in the focus group, with the majority preferring icon arrays (n=6), followed by pie (n=4) and bar charts (n=1). However, participant reactions to the "human aspect" of the icon arrays varied, with some appreciating the pictographs since the survival rates are about people, while others expressed concerns that they were too confronting. Despite this variation in preferences and (emotional) reaction, most participants appreciated the function of tailoring the type of visualization (n=8).

> *I didn't like to be confronted with this figure [icon array], because 38 percent [chance of survival]...Here you should have the option to switch between figures. When the percentage was displayed by means of a pie chart, I experienced it as less shocking than when it is presented with pictographs. I think here you should be able to make a choice in how you want to see it.* [B01, aged 54 years]

Furthermore, regarding the amount of information, most participants preferred the short and concise result page of the tool (n=10). Participants typically commented that they primarily used the tool to see statistics and survival rates as soon as possible, and therefore expected to see numerical information rather than large pieces of text. Almost half of the participants expressed a preference for tailoring the amount of information and expanding the text for certain topics (eg, complex terms, supplementary information about the NCR) if desired (n=5). Again, this was mostly preferred by participants who were shocked by the less favorable survival rates. Finally, 5

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participants appreciated the verbal descriptions of uncertainty around the statistics that we presented as part of the supporting statements, and 2 participants wanted to see confidence intervals along with the statistics.

Discussion

Principal Findings

This study aimed to explore needs and preferences of cancer survivors for communicating personalized statistics from a Dutch nationwide population-based registry, the NCR [22]. We developed different versions of a tool that allows patients to enter personal and disease-related characteristics for determining personalized incidence, survival, and conditional survival rates. We applied a qualitative multimethod study approach, by collecting group data through focus groups and individual data via think-aloud observations combined with semistructured interviews.

Our study suggests that the majority of our selective sample of cancer survivors (in both the focus group study and think-aloud sessions) have a desire to receive personalized cancer statistics. Survivors expressed an overarching desire for especially receiving tailored survival rates and conditional survival rates; they showed less interest in the personalized incidence rate, but they still thought it could be useful for some patients. Overall, the majority expressed intention to use the tool for viewing personalized statistics, regardless of the outcome. Furthermore, survivors wanted to receive a range of personalized statistics, such as personalized risk information about treatment outcomes (eg, side effects, survival, recurrence rate, or quality of life). These results support previous findings that most (but not all) patients want detailed and individualized information about their prognostic situation [2-4,37,38], with especially a strong need for personalized (conditional) survival rates and treatment outcomes (eg, risks of side effects, quality of life, or recurrence rates).

When it comes to communicating personalized statistics to patients, we found that survivors expressed a need for being provided with supporting information that should help correctly interpreting the statistics. For instance, in both focus groups and think-aloud observations, cancer survivors mentioned the importance of adding contextual information (eg, explaining the influence of treatment on survival over time, providing comparative information including generic, population-based statistics), which should help put the personalized statistics into perspective [39,40]. Next to that, survivors in the focus groups reported that they processed personalized survival statistics emotionally, and were viewing the information under the influence of emotions such as feelings of distress. Indeed, this was captured during the think-aloud observations, in which some participants were confronted by the less favorable survival statistic compared with the favorable generic survival statistic. Reminding or preparing patients about this was found to be helpful, although the use of specific interpretation labels such as “good” or “bad” news were strongly discouraged. At the same time, we observed that the disclosure of conditional survival rates had a positive effect on cancer survivors’ sense of hope, which is in line with previous work on the link between hope and disclosure of prognostic information [37].

Regarding the preference of cancer survivors for presenting the personalized statistical information, participants expressed an overarching preference for simplicity and conciseness. They found it important that the key information (survival rates) was immediately visible to them. Although some participants wished to see more information about the details of the statistics, others did not appreciate this. This challenge of finding a balance between fully informing patients about the statistics while not simultaneously overwhelming them by providing too much information has also been found elsewhere [41,42]. There were survivors who appreciated the option to tailor the amount of information, by extending texts when more detail was preferred [43], or by choosing whether or not one wants to see the visual representation of the survival statistic. Finally, regarding the type of visualization, most participants preferred the pictographs, which is in line with previous research [44], although some found the use of pictographs inappropriate and frightening for communicating survival rates [45]. We further found that the option to switch between different types of visualization was greatly appreciated by our participants, which may therefore solve the variety in presentation preferences among cancer survivors [46].

Strengths and Limitations

A strength of this study is that we employed multiple rigorous qualitative methods (focus groups and think-aloud observations combined with semistructured interviews) that complied with reporting standards [26]. The focus groups (study 1) allowed us to gather group data on cancer survivors’ needs, preferences, and perceptions about disclosing personalized cancer statistics, while the think-aloud observations (study 2) revealed spontaneous thoughts and feelings of survivors while being confronted with personalized statistics. At the same time, the think-aloud method has sometimes been criticized regarding its validity and reliability [47,48], as it may be cognitively demanding for participants to complete a task while simultaneously verbalizing their thoughts, opinions, and feelings. However, following previous research [32], we partially tackled this issue by conducting semistructured interviews after the think-aloud sessions during which participants could elaborate on their verbal statements and experiences with the tool. Even though we conducted all studies with cancer survivors (who have experience with being confronted with a cancer diagnosis), we had to make use of hypothetical case examples instead of participants’ own patient and tumor characteristics. This may have limited the ecological validity of the results, and may have influenced the emotional processes that patients did (or did not) experience while interacting with the tool.

Another limitation is that we recruited (active) cancer survivors involved in online cancer communities or patient organizations. It has been demonstrated that this selection of cancer survivors may not be fully representative of the general cancer population, as they are typically somewhat higher educated and make more extensive use of the internet [49]. Several studies suggest that lower education is associated with lower eHealth use [50]. Furthermore, we did not measure participants’ health literacy

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or numeracy skills, although some participants in our study expressed their concerns about communicating statistics to patients with low health or numeracy skills. Therefore, supplementary information or advice to discuss the results with clinician is highly needed especially for those patients who are lacking prior knowledge in statistics, or who may have less education. Despite this shortcoming, our interactive tools did comply with best practices and risk communication guidelines for communicating statistical information to the general public [24,51-54], and their content was developed by using a plain language approach (eg, using everyday language, and using logically structured and focused information) [55]. A related limitation is that we only included BCa and PCa survivors, which makes it challenging to generalize our results to other oncology populations and those patients in active treatment. However, a recent study showed that internet use and wishes for online health information and statistics do not differ between patients with different cancer types [49]. Nevertheless, for future developments and eventual release of a possible real-life web-based NCR tool, it is important to test the understanding of the tool also among the general cancer population, preferably with variation in terms of cancer type, educational background, health literacy, and numeracy skills.

Implications and Future Directions

Our results contribute to the rapidly expanding field of personalized risk communication and tailored health communication, as they further enhance our understanding of how and why we should make efforts in disclosing and communicating personalized risks statistics from registry data to patients. For instance, our data provide support for a novel recommendation of allowing users to modify the type of visualization in line with their preferences. Over the years, several best practices and communication guidelines have been developed for the delivery of risk and statistical information to patients [24,51,52,54,56], particularly with an emphasis on searching for a single-best strategy. However, preferences for certain visualizations may vary between individuals [57], and therefore tailoring the type of visual aid toward the user's preference may be a promising additional risk communication strategy to consider. Another novel finding of our study is that some of the risk communication guidelines for communicating generic, population-based statistics may yield unexpected effects when they are used for communicating risks or statistics that are personalized. For instance, icon arrays—a recommended type of visualization for explaining risks and statistics—were preferred by most participants in our study (consistent with other studies [58,59]), but they also evoked feelings of distress as they became too personal to some patients [45]. Therefore, systematic knowledge about how patients will perceive and process visual aids that communicate personalized risks statistics is needed, as well as future investigations about the effects of tailoring the type of visual aid or the amount of information on associated risk perception and comprehension outcomes.

Furthermore, our results are encouraging for research into needs and preferences of patients with cancer with respect to personalized information provision and the disclosure of big health data [11,17]. The majority of our sample expressed a need for receiving personalized statistics on different topics before and after their initial treatment, ranging from survival rates to risk information about treatment side effects. We therefore recommend further development and implementation of data-driven personalized decision aids and disease risk prediction models (either based on registry, clinical, or patient-reported outcome data) in and outside The Netherlands [8,11,15,20,21], and support their availability to patients and clinicians in daily routine practice and to laypersons on the internet. At the same time, this development comes with several challenges, which may explain why some (personalized) cancer statistics are not currently available to the general public. For instance, some additional items for personalizing survival statistics as requested by participants are not readily available within the Dutch registry (eg, information on genetic factors or comorbidity). Relatedly, increasing the number of items in this case may lead to smaller subgroups, which in turn may lead to uncertain and less reliable personalized statistics. As such, the utility of and preference for personalized statistics may differ markedly depending on how reliable the information is, and further exploration on these aspects is highly warranted.

The results of our study also have a number of novel practical implications for the design and implementation of personalized, data-driven information support tools for cancer survivors (Textbox 1). We have shown that making such tools available to patients and the general public comes with several challenges such as avoiding technical language that is needed to describe statistical or medical terms, making sure that all patients will correctly interpret the statistical information, and not overwhelming them with visualizations that display less favorable survival outcomes. A key lesson from our qualitative studies is that there does not seem to exist a single perfect communication format for the delivery of personalized cancer statistics. We therefore believe that many of the issues identified with our potential NCR tool could be solved by applying a number of different personalization techniques, such as tailoring the amount of information (eg, expanding text boxes for those who want detailed and supplementary information) [43], or tailoring the type of visualization in line with patient preferences. Furthermore, as some patients may experience difficulties with correctly interpreting the statistical information, several strategies could be taken into account such as the provision of contextual information about the statistics, or comparative information by showing average statistical outcomes of other patients.

Finally, although it has been shown that personalized statistics are typically perceived as more relevant [25], and hence better processed than generic information [60,61], our findings suggest that tool developers should not underestimate the role of affect in this process [62]. We observed that some participants processed statistical information emotionally, and expressed to be confronted by the less favorable survival rates. Making web-based prediction tools publicly available to patients and relatives thus faces the challenge of avoiding discouraging patients with less favorable survival rates of prognosis from having hope. This is especially challenging for tools that rely on automatically generated textual explanations, for instance produced by robot writers that cannot easily provide contextual information in a similar way as a doctor can do during a

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consultation [63]. However, in line with previous information needs studies, our participants indicated that for those patients who really want honest prognostic information the levels of hope will maintain, even when the news is bad [38]. We recommend tool developers to provide supporting or preparatory information about the emotional aspects, and to find ways on how to tailor automatically generated sentences and explanations on poor prognosis and treatment outcomes to patients.

Textbox 1. Recommendations for the development of tools that communicate personalized health statistics to the public.

The need for personalized statistics

Regarding the type of statistics:

- Consider communicating personalized survival statistics together with conditional survival statistics.
- Communicate not only statistics about personalized cancer incidence, but also about survival, conditional survival, and treatment outcomes (eg, side effects, quality of life).
- Consider and evaluate multiple patient (age, gender, lifestyle) and clinical (disease stage, tumor characteristics) characteristics for tailoring the statistics.

The need for interpretation support

Regarding difficulties with interpreting personalized statistical information:

- Provide contextual information about the statistics and use clear explanations on the intended use.
- Consider communicating comparative information by showing statistics of the average patient in addition to the personalized statistics.
- Use plain and appropriate language and make sure that data entry characteristics are known by patients (or at least provided by their health care providers).

Regarding emotions or feelings of distress that may arise while viewing (less favorable) statistics:

- Prepare patients for the less favorable survival statistics via reminders or warning statements.
- Avoid using evaluative labels such as “good” or “bad” survival statistics.

Preferences for information presentation

Regarding variation in preference for type of visualization:

- Incorporate multiple types of visualization for displaying the statistical information.
- Allow patients to modify the type of visualization according to their preference.

Regarding variation in preference for the amount of information:

- Keep the amount of information short and concise.
- Allow patients to tailor the amount of information, for instance, by incorporating the option to expand text for showing detailed information.

Conclusions

The majority of our sample of cancer survivors expressed a desire for receiving personalized cancer statistics such as specific and relevant data on survival and conditional survival. This is encouraging for those who are developing personalized information tools for patients that are drawing on cancer registry data or other medical databases, especially in an era of personalized health care and open access of big health data. Presenting personalized statistics to the public remains challenging and calls for tailoring strategies, as cancer survivors in our study demonstrated variation in their preferences for communicating the statistics. As a result of these findings, our research group is currently developing a real-life web-based tool that communicates personalized NCR statistics, which will be further evaluated among different stakeholders including patients, relatives, and health care providers. Given the valuable information generated in collaboration with cancer survivors, we suggest that this approach and findings can be used to design data-driven personalized information (and decision-support tools) tools for patients with cancer and other disease conditions.

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DSC/t and NWO were not involved in the study design, data collection, data analysis, report writing, and decision to submit the manuscript for publication.

Authors' Contributions

RV was responsible for conceptualization, data collection, data curation, formal analysis, methodology, writing original draft, writing-review, and editing. MvE was responsible for conceptualization, data collection, data curation, formal analysis, methodology, writing-review, and editing. GG contributed to conceptualization, data collection, writing-review, and editing. SP and LvP-F were responsible for conceptualization, supervision, writing-review, and editing. EK was responsible for conceptualization, methodology, supervision, writing-review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consolidated Criteria for Reporting Qualitative Research (COREQ).
[PDF File (Adobe PDF File), 40 KB - cancer_v7i4e25659_app1.pdf]

Multimedia Appendix 2
Sketches of a non-interactive version of the tool, used during the focus groups.
[PDF File (Adobe PDF File), 1577 KB - cancer_v7i4e25659_app2.pdf]

Multimedia Appendix 3
Screenshots of an interactive version of the tool, used during the think-aloud observations.
[PDF File (Adobe PDF File), 20079 KB - cancer_v7i4e25659_app3.pdf]

Multimedia Appendix 4
Topic guide for the semi-structured interviews.
[PDF File (Adobe PDF File), 133 KB - cancer_v7i4e25659_app4.pdf]

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Abbreviations

BCa: breast cancer
BVN: Borstkankervereniging Nederland (Dutch Breast Cancer Association)
IKNL: Netherlands Comprehensive Cancer Organisation
NCR: Netherlands Cancer Registry
PCa: prostate cancer
PKS: Prostaatkankerstichting (Dutch Prostate Cancer Foundation)
SEER*CSC: American Surveillance, Epidemiology, and End Results Cancer Survival Calculator

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Original Paper

A Digital Coaching Intervention for Cancer Survivors With Job Loss: Retrospective Study

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Abstract

Background: Returning to work is a key unmet need for working-age cancer survivors.

Objective: This study sought to evaluate return-to-work outcomes of a multidisciplinary intervention provided as routine employee support.

Methods: In a retrospective cohort analysis, patients with cancer and more than 3 months of absence from work were provided with an intervention consisting of digital resources and calls with a health coach. Propensity score matching was used to define a similar cohort of cancer patients absent from work, who were not offered the coaching intervention. The return-to-work rate as a percentage of all participants and secondary outcomes, such as the rate of death, were measured. The median time to return to work was compared between the cohorts using the Kaplan-Meier method.

Results: A total of 220 participants were enrolled in the intervention, of which 125 met the criteria for analysis. The median follow-up from cancer diagnosis was 79 weeks (IQR 60-106 weeks). In the matched control group, 22 (17.6%) participants returned to work compared with 38 (30.4%) in the intervention group (P=.02). Additionally, 19 (15.2%) matched controls died prior to claim closure compared with 13 (10.4%) in the intervention group (P=.26). The Kaplan-Meier estimated median time for the first 15% of the cohort to return to work was 87.1 weeks (95% CI 60.0-109.1 weeks) for the matched control group compared with 70.6 weeks (95% CI 52.6-79.6 weeks; P=.08) for the intervention group.

Conclusions: Patients receiving a remotely delivered coaching program in a real-world setting returned to work at a higher frequency than did control participants receiving usual care.

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KEYWORDS

cancer survivors; employment; absenteeism; mobile app; software; return to work

Introduction

Early detection and sustained improvements in the treatment of many types of cancer have markedly improved survivorship rates [1]. Approximately 45% of cancer diagnoses occur in people of working age, between 20 and 64 years old [2,3], and it is likely that the prevalence of cancer survivorship in the workforce will continue to increase.

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For working age cancer survivors, impairments in physical and mental health from the disease sequelae or side effects of treatment may reduce their participation in work [4,5]. Specifically, cancer survivors are at higher risk of unemployment [4,6,7], reduced hours, prolonged absenteeism [8,9], and impaired presenteeism [9] compared with individuals without a history of cancer. Returning to work is important for cancer survivors themselves, their employers, and the society at large [4,8,9]. For cancer survivors, returning to work can improve their sense of "normality," their self-respect [10], and their quality of life [11,12]. Conversely, prolonged job loss increases the risk of financial toxicity, resulting from decreased earnings and increased health expenditure. Financial toxicity following a cancer diagnosis is associated with emotional distress, poor treatment adherence, and a higher mortality risk [8]. From an employer and societal perspective, the return to work of knowledgeable and experienced workers enables continuity of a skilled labor pool, along with reduced productivity losses and decreased expenses like disability claim payments [13].

Factors that have been identified to adversely influence return to work include cancer diagnosis, including head and neck [5,7], central nervous system, and advanced blood and lymph malignancies [4,5]; type of work, particularly manual labor [7,10]; treatment, especially certain surgeries and systemic therapy [4,5,8]; lacking a supportive environment, including work flexibility [7,10], financial situation, and insurance availability and type [12]; and greater physical limitations [5,6]. Age and other demographics have historically had mixed influences [7], although more recently favoring successful return to work of younger employees [6] and those with higher education levels [6,8].

Return to work has therefore become a pressing issue and key unmet need of this population. A previous meta-analysis of 5 multidisciplinary interventions that covered physical, psychoeducation, and/or vocational components showed moderate evidence for improving return to work rates [14]. These interventions were provided from hospital settings to narrowly defined populations and delivered in-person, which can be both time intensive and costly. Among 3 interventions identified in a systematic review for return-to-work interventions outside of the hospital setting [15], only 1 had a suitable comparison group, but with no demonstrated effect [16]. Therefore, a paucity of evidence exists for multidisciplinary interventions provided as routine employment support that serve broad populations and adapt to the complexities and diversity of day-to-day cancer care and life in general.

In 2018, a multidisciplinary intervention delivered via digital resources and calls with a health coach was introduced by AIA Australia, a life and health insurance company, to its members with a disability insurance policy claim. This study sought to evaluate the long-term impact of the program on return-to-work outcomes as compared to usual care.

Methods

Study Design

The study is a propensity score–matched retrospective cohort analysis. Eligible AIA members were enrolled in the intervention, the CancerAid Coach Program, from October 2018 to February 2020. A comparison group was created using the below criteria and then abstracted from deidentified records of patients who did not participate in the intervention (see Multimedia Appendix 1 for a visual representation of the trial design and median times). The CancerAid online eHealth app is freely available for cancer survivors and carers for iOS [17] and Android [18].

Recruitment and Eligibility Criteria

From October 2018 to February 2020, during routine calls following lodgment of a disability claim for a cancer diagnosis, AIA staff had private conversations with potential participants to elicit their interest in participating in the intervention. Eligibility for a disability claim included patients who (1) were of working age (18-65 years); (2) held a disability insurance policy through their insurer (AIA Australia) that included coverage of a cancer diagnosis; and (3) were working prior to diagnosis and were unable to work in their regular prediagnosis capacity for at least 3 months. Program enrollment involved the AIA staff member eliciting interest and completing a secure web form, followed by automated email outreach that included consent for the use of deidentified data for research purposes [19]. The inclusion criteria were as follows: (1) completing enrollment and having at least one or more calls with a health coach; (2) a minimum follow-up time from diagnosis of 34 weeks to allow for completion of the intervention (median 10 weeks) along with delays in lodgment of the claim with the insurer (median 12 weeks) and a subsequent delay in referral to the CancerAid Coach Program (median 12 weeks); and (3) diagnosis from the top 10 most common cancer types (breast, including in situ and invasive, brain, lung, colon, ovary, pancreas, prostate, and lymphoma malignancies) to enable adequate matching. The exclusion criteria were patients whose policies were later withdrawn or who did not meet the eligibility criteria of their disability insurance policy.

Intervention and Usual Care

The CancerAid Coach Program provides a range of integrative therapies to help manage symptoms and adverse effects during or after treatment. The CancerAid Coach Program is based upon lifestyle and psychological interventions that are well established and consistent with American Society of Clinical Oncology (ASCO) guidelines (eg, diet and exercise in survivors of cancer, and peer support) [20,21] or backed by evidence from large randomized trials to improve patient outcomes (eg, digital symptom tracking) [22]. By focusing on interventions demonstrated to improve patient outcomes, it is predicted that return-to-work outcomes will also increase as patients now encounter fewer impairments in physical and mental health [5].

The CancerAid Coach Program consists of an online eHealth app (see Multimedia Appendices 2 and 3) and 3 telephone health coaching sessions delivered over a 12-week period. Additionally,

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a series of weekly messages, via email and text, are sent to participants during the period of the intervention to help reinforce key health messages on appropriate symptom tracking, exercise, diet, mindfulness, and sleep strategies. The CancerAid app allows patients to coordinate their care with tools to read about their condition, treatment options, and a broader community of cancer survivors. It also allows patients to monitor their condition, specifically in relation to being able to track their symptoms digitally and monitor their diet, exercise, sleep, and other patient-level data at home via the app.

The health coach team includes registered nurses, doctors, and allied health professionals. Coaches offer a range of interventions tailored to the needs and current stage of each patient, and use principles of behavioral change theories, such as the transtheoretical model of stages of change [23]. These interventions include inviting patients to consider their current behavior; helping them consider the impacts of making change; providing encouragement, support, and feedback on performance; encouraging patients to set further goals once existing goals are met; and finally, providing a framework of accountability. The eHealth app and regular text and email messages reinforce these interventions and help overcome many barriers to seeking face-to-face support. These interventions are applied to each of the key health messages to help improve the uptake of frequent symptom tracking, appropriate exercise and dietary intake, mindfulness, and sleep hygiene strategies.

Usual care consisted of regular phone calls with AIA staff members, for example, every few weeks, along with an optional referral to 2 rehabilitation programs consisting of support with an exercise physiologist or an occupational rehabilitation consultant. Participation in these 2 rehabilitation programs were at the patient's discretion, and participating in the CancerAid Coach Program did not preclude participation in either of these 2 rehabilitation programs.

Matched Comparison Group

The intervention group of Coach Program participants were matched on a one-to-one basis to a control group of nonparticipating insurance plan members who were otherwise eligible to participate using propensity score matching. Controls were first collected from the AIA claims database over the same period (October 2018 to February 2020) and using the same inclusion criteria as follows: (1) working age; (2) disability claim for a cancer diagnosis; (3) inability to work in their regular capacity for at least 3 months; (4) minimum follow-up time from diagnosis of 34 weeks; and (5) top 10 most common cancer types.

A logit regression model was used to calculate a propensity score for each participant, to represent the probability that they would be referred to the CancerAid group. The covariates of the propensity model included age, gender, insurance benefit type, date of cancer diagnosis, and time from diagnosis to lodgment of the claim. Using the propensity scores, CancerAid participants were matched on a one-to-one basis with the nearest-neighbor method without replacement to create a matched control group. The baseline characteristics were then reassessed for imbalance using absolute standardized mean difference.

Assessment and Outcomes

Outcome measures were derived from insurance claims data as standard business practice. Primary outcomes were rates of (1) returning to work; (2) death; and (3) claim closure, other than death or returning to work. The durations of returning to work and claim closure, commencing from the date of a cancer diagnosis, were also reported. The reasons for claim closure, other than death or returning to work, included a single lump-sum payment (compared to scheduled salary replacement), expiry of the benefit period (meaning the insurance policy had expired as set out in the policy's schedule), no longer meeting the definition of disability (ie, return to health but not work), and abandonment of the claim. A claim reported as open meant none of the previously mentioned outcomes had occurred.

Statistical Analysis

Statistical analysis was performed in R (version 4.0.3; R Foundation for Statistical Computing). Variables for propensity score matching included age, gender, cancer diagnosis, date of cancer diagnosis, time to lodgment, insurance benefit type, occupation, and geography setting. Geography settings were defined by the Australian Government as follows: 1, major cities; 2, cities and major regional centers; and 3, regional centers and other regional areas [24]. The difference in the final return to work rate was tested using a chi-squared test without Yates correction (significance $P<.05$). The time from diagnosis to return-to-work claim closure was calculated using a Kaplan-Meier model evaluated with a log-rank test (significance $P<.05$).

Results

Overview

A total of 220 participants were enrolled in the intervention, of which 125 met the criteria for this analysis (see Multimedia Appendix 4 for patient flow). A further 3749 participants who did not receive the intervention over the same period were identified from the insurer's records. Of these, 1856 control group participants met the criteria for analysis. There were observed imbalances in baseline characteristics between the intervention and control cohorts, including sex, tumor origin, geography setting, and benefit period. Based on 1:1 matching with nearest-neighbor matching, 125 intervention patients were matched to 125 control patients.

Propensity Score Results

After matching using the propensity scores, 125 intervention patients were matched to 125 control patients. The C-statistic for the logistic regression was 0.66. Covariates in the propensity match were overall well balanced, with an absolute standardized difference less than 0.1 for age, date of diagnosis, time to lodge a claim from diagnosis, and benefit period in the matched groups. The absolute standardized difference was 0.11 for gender, with 94.4% (118/125) of intervention participants being female versus 91.2% (114/125) of control participants ($P=.32$).

The occupational category and the tumor origin site were balanced between the matched groups (Table 1). There was a difference in the geographical setting between groups, with

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42.4% (53/125) of intervention participants being from major cities versus 28.8% (36/125) of control participants (P=.03). However, a separate analysis revealed there was no correlation between geographical setting and any of the primary outcomes, including return to work (P=.43), for the control and intervention groups. Geographical setting could not be addressed in propensity score matching as it does not lead to acceptable standardized mean differences between groups. Other clinical and demographic variables (age, gender, tumor origin, rehabilitation referral, and occupational category) were not statistically different between groups.

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Table 1. Baseline demographic and clinical characteristics.

Characteristic	All participants			Propensity score–matched participants			Standardized mean difference
	Control (n=1856)	Intervention (n=125)	*P* value	Control (n=125)	Intervention (n=125)	*P* value	
Age (years)			.96			.56	0.03
Median	52	53		53	53		
IQR	45-59	45-58		47-59	45-58		
Sex, n (%)			<.01			.33	0.11
Female	1513 (81.5)	114 (91.2)		118 (94.0)	114 (91.2)		
Male	343 (18.5)	11 (8.8)		7 (5.6)	11 (8.8)		
Geographical setting, n (%)			.04			.03	N/A[a]
1: major cities	663 (35.7)	53 (42.4)		36 (28.8)	53 (42.4)		
2: cities and major regional centers	668 (36.0)	31 (24.8)		48 (38.4)	31 (24.8)		
3: regional centers and areas	525 (28.3)	41 (32.8)		41 (32.8)	41 (32.8)		
Tumor origin, n (%)			.03			.27	N/A
Breast	911 (49.1)	76 (60.8)		66 (52.8)	76 (60.8)		
Brain	147 (7.9)	6 (4.8)		9 (7.2)	6 (4.8)		
Colon	258 (13.9)	17 (13.6)		15 (12)	17 (13.6)		
Hodgkin lymphoma	68 (3.7)	6 (4.8)		4 (3.2)	6 (4.8)		
Non-Hodgkin lymphoma	60 (3.2)	5 (4.0)		7 (5.6)	5 (4.0)		
Ovary	90 (4.8)	7 (5.6)		7 (5.6)	7 (5.6)		
Pancreas	71 (3.8)	5 (4.0)		4 (3.2)	5 (4.0)		
Prostate	59 (3.2)	0 (0.0)		0 (0.0)	0 (0.0)		
Rehabilitation referral, n (%)			.13			.70	N/A
No	1165 (62.8)	70 (56.0)		67 (53.6)	70 (56.0)		
Yes	691 (37.2)	55 (44.0)		58 (46.4)	55 (44.0)		
Benefit period, n (%)			.03			.70	0.01
1 year	7 (0.4)	0 (0.0)		1 (0.8)	0 (0.0)		
2 years	523 (26.4)	23 (18.4)		25 (20.0)	23 (18.4)		
5 years	120 (6.1)	7 (5.6)		4 (3.2)	7 (5.6)		
Age 60 years	616 (31.1)	51 (40.8)		43 (34.4)	51 (40.8)		
Age 65 years	216 (10.9)	7 (5.6)		9 (7.2)	7 (5.6)		
Age 67 years	486 (24.5)	35 (28.0)		42 (33.6)	35 (28.0)		
Age 70 years	3 (0.2)	0 (0.0)		1 (0.8)	0 (0.0)		
Occupation category, n (%)			.21			.37	N/A
Armed forces occupations	2 (0.1)	0 (0.0)		0 (0.0)	0 (0.0)		
Clerical support worker	206 (11.1)	16 (12.8)		16 (12.8)	16 (12.8)		
Craft and related trade worker	57 (3.1)	3 (2.4)		3 (2.4)	3 (2.4)		
Elementary occupations	88 (4.7)	3 (2.4)		4 (3.2)	3 (2.4)		
Manager	194 (10.5)	10 (8.0)		11 (8.8)	10 (8.0)		
Plant and machine operator, and assembler	31 (1.7)	3 (2.4)		1 (0.8)	3 (2.4)		
Professional	416 (22.4)	21 (16.8)		36 (28.8)	21 (16.8)		
Service and sales worker	592 (31.9)	50 (40.0)		39 (31.2)	50 (40.0)		

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Characteristic	All participants			Propensity score–matched participants			Standardized mean difference
	Control (n=1856)	Intervention (n=125)	*P* value	Control (n=125)	Intervention (n=125)	*P* value	
Skilled agricultural, forestry, and fishery worker	6 (0.3)	2 (1.6)		0 (0.0)	2 (1.6)		
Technician and associate professional	243 (13.1)	17 (13.6)		14 (11.2)	17 (13.6)		
Unknown	21 (1.1)	0 (0.0)		1 (0.8)	0 (0.0)		
Time to lodge a claim (weeks)			<.01			.48	0.03
Average	27.8	17.8		18.6	17.8		

[a]N/A: not applicable.

Outcomes

Outcomes are listed in Table 2 and illustrated in Figure 1. The median follow-up since cancer diagnosis was 79 weeks (IQR 60-106 weeks). In the matched control group, 22 (17.6%) participants returned to work compared with 38 (30.4%) in the intervention group (*P*=.02). Additionally, 19 (15.2%) matched control participants died prior to claim closure compared with 13 (10.4%) in the intervention group (*P*=.26). When considering survivorship only, the return to work rate was 33.9% (38/112) in the intervention group compared with 20.8% (22/106) in the matched control group (*P*=.03). No difference was identified between the control and intervention groups for the duration or rate of claim closure arising from causes other than return to work or death (Table 2). Expiry of the benefit period and abandonment of a disability claim were the most cited reasons for claim closure in both the control and intervention groups (Table 3).

Table 2. Outcomes.

Characteristic	Propensity score–matched participants		*P* value
	Control (n=125)	Intervention (n=125)	
Return to work			
Value, n (%)	22 (17.6)	38 (30.4)	.02
Duration (weeks), median	60	71	.62
Duration (weeks), IQR	49-88	49-94	
Claim closure (no return to work or death)			
Value, n (%)	20 (16.0)	16 (12.8)	.12
Duration (weeks), median	68	71	.62
Duration (weeks), IQR	55-99	49-94	
Claims open			
Value, n (%)	64 (51.2)	58 (46.4)	.71
Death			
Value, n (%)	19 (15.2)	13 (10.4)	.26

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Figure 1. Cumulative event plot of returning to work (intervention vs matched control group). RTW: return to work.

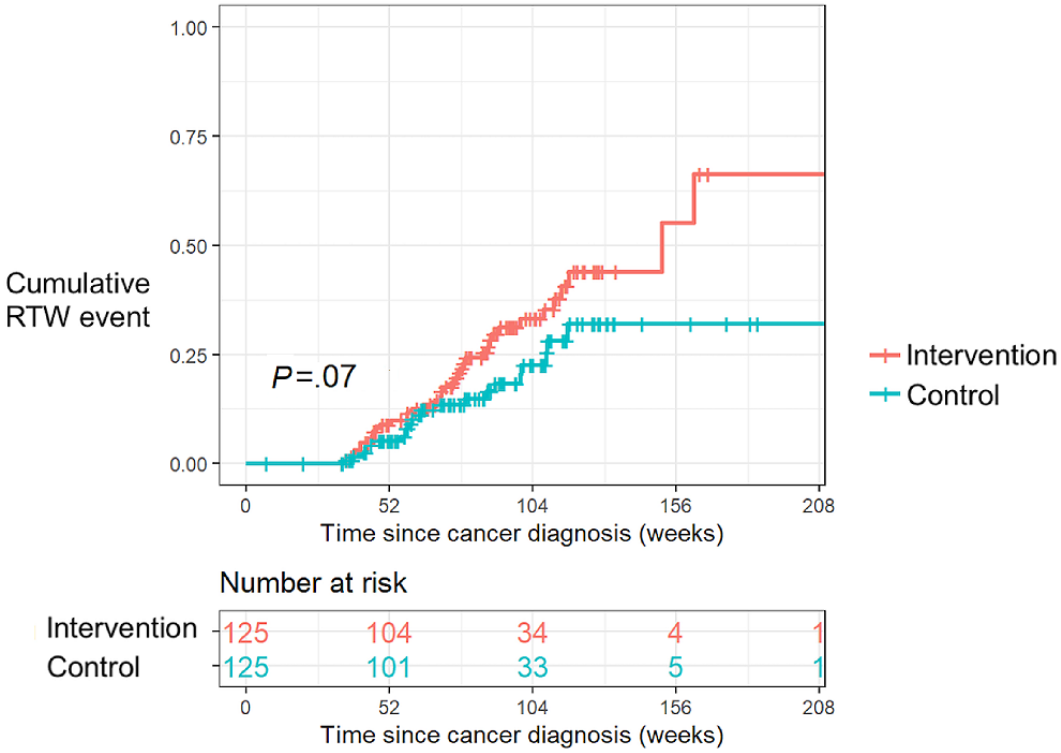

Table 3. Claim closure outcomes (other than return to work or death).

Claim closure reason	Propensity score–matched participants	
	Control (n=125), n	Intervention (n=125), n
Abandoned	8	5
No longer meets the definition of disability	5	1
Expiry of the benefit period	7	9
Lump sum paid	0	1

The cumulative event plot of returning to work for the matched participants is presented in Figure 1. Further analysis showed that the estimated return to work rate at 2 years after a cancer diagnosis was 33.1% (95% CI 22.4-42.3%) for the intervention group compared with 22.6% (95% CI 12.3-31.8%) for the control group. The median time for the first 15% of the cohorts to return to work was 70.6 weeks (95% CI 52.6-79.6 weeks) for the intervention group compared with 87.1 weeks (95% CI 60.0-109.1 weeks) for the matched control group.

Discussion

This study evaluated the impact of a remotely delivered coaching program combined with digital support for patients diagnosed with cancer. An increase of 12.8% in the return to work rate was identified for coach program participants over an 18-month period compared with matched controls. These results are consistent with clinical-based trials of in-person multidisciplinary interventions that have been shown to enhance return to work [14]. Furthermore, this study demonstrates that support programs can be effectively implemented as part of routine employment support and remotely delivered outside of the hospital setting. The median time to return to work showed a nonsignificant trend favoring coach program participants versus matched controls. A maturing data set and greater study numbers may in time reveal the true effect (or not) of the program intervention on median time.

The return to work rates identified in this study are comparable to those in existing literature when factoring a baseline minimum of 3 months of absence from work and a definition of returning to a prediagnosis work capacity at 1.5 years (33.9% for the intervention group and 20.8% for the matched control group). For example, large cohort studies have shown that approximately 60% of cancer survivors successfully return to work at 1 to 2 years after a cancer diagnosis, but noted that the majority will have reduced hours either permanently or over a time limited period [6,7,25-27]. Another important difference between this study and cohort studies that may underestimate the true rate of returning to work among cancer survivors is that some individuals diagnosed with cancer may remain employed or have adequate leave (eg, sick leave and annual leave) that avoids the need for a claim on their disability insurance policy. Finally, this study precluded those with an early claim closure (less than

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34 weeks), to allow for a suitable referral period for the intervention, which would similarly underestimate the true rate of returning to work among working-age cancer survivors.

Returning cancer survivors to the workplace mitigates against financial toxicity for the individual, while reducing the economic burden of cancer on payers and employers [28]. Other studies have demonstrated the cost-effectiveness of coaching interventions delivered remotely and for the routine support of employees diagnosed with chronic diseases, such as diabetes, cardiovascular diseases, and respiratory diseases [29-34]. Notably, cost savings have not been demonstrated with low-intensity coaching (average of 2 calls each) and delivered over 12 months or less [31-33]. For this study, no difference between the intervention and matched controls for returning to work was observed within 12 months of diagnosis (Figure 1). Possible explanations for this include a delay in receiving the intervention, with an average period of 24 weeks between a cancer diagnosis and first receiving the intervention. Additionally, for the present intervention to be successful, the barriers to returning to work must be amenable to the adoption of healthy behaviors and self-management principles. Many patients receiving active cancer treatment have associated toxicities that are known to impair short-term work ability [6,35], and these may not be immediately amenable to improvements in self-management. The results of this study complement other recent studies showing the receptiveness of cancer survivors to digital technology for the support of physical rehabilitation [36,37], along with demonstrated improvements in quality of life through digital support [38].

Employment after a cancer diagnosis is an important social determinant of health [3] and is associated with improved quality of life and the magnitude of the cancer health burden [11,12,39]. Hence, coaching support that is implemented as part of routine care and made accessible to broader populations will typically provide reductions in medical expenditure. Additional cancer rehabilitation that would advance the current intervention while improving function in survivors and decreasing the economic burden of cancer for individuals and the society includes rehabilitation for pain, musculoskeletal issues, deconditioning, balance, and lymphedema [28].

This study has several limitations. Individuals were not randomized to participate; hence, there may be differences in motivation for opting to participate in the program compared with the matched control group, and this could not be balanced out through propensity score matching. Other researchers have shown that the wish to participate in support programs is usually an indicator of the need for greater assistance with health and knowledge [40]. Conversely, high motivation for opting to participate may overestimate the program's effect when applied to a generalized setting. Socioeconomic status, which may substantially differ between coaching participants and controls, was not available for use in the propensity score models. However, program participants and matched controls had comparable rates of occupation. Similarly, propensity scores were used for benefit type, as an indication of the level of insurance and by proxy the level of income, and both factors would likely address socioeconomic status. The type of treatment and stage of disease, both known factors of return-to-work outcomes, were not captured in this insurance data set and therefore were not available for matching. Finally, the overrepresentation of females, likely a result of opting in, and certain occupations, and the inclusion of the top 10 cancer types could somewhat reduce the generalizability of the results.

The study findings indicate that patients diagnosed with cancer and receiving a remotely delivered coaching program in a real-world setting returned to work at a higher frequency than did control participants receiving usual care. The results of this study add to the literature of cancer as a chronic and manageable disease in the workplace.

Authors' Contributions

JL: data curation, investigation, methodology, project administration, validation, visualization, writing–original draft, writing–review, and editing. KB: data curation, formal analysis, investigation, validation, visualization, writing–review, and editing. SF: conceptualization, investigation, methodology, writing–review, and editing. KT: conceptualization, data curation, methodology, writing–review, and editing. NL: data curation, methodology, writing–review, and editing. MB: investigation, methodology, writing–review, and editing. RMG: conceptualization, investigation, methodology, validation, visualization, resources, project administration, writing–review, and editing.

Conflicts of Interest

KB and RMG are shareholders of CancerAid. MB is a clinical advisor of CancerAid. The remaining authors have no disclosures.

Multimedia Appendix 1
Trial design and median times. RTW: return to work.
[PNG File , 78 KB - cancer_v7i4e31966_app1.png]

Multimedia Appendix 2
Screenshot of the CancerAid smartphone application.
[PNG File , 415 KB - cancer_v7i4e31966_app2.png]

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Multimedia Appendix 3
Screenshot of the CancerAid smartphone application.
[PNG File , 974 KB - cancer_v7i4e31966_app3.png]

Multimedia Appendix 4
Patient flow.
[PNG File , 151 KB - cancer_v7i4e31966_app4.png]

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Review

Physical Comorbidities and Their Relationship with Cancer Treatment and Its Outcomes in Older Adult Populations: Systematic Review

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Abstract

Background: Cancer is one of the predominant causes of morbidity and mortality in older adult populations worldwide. Among a range of barriers, comorbidity particularly poses a clinical challenge in cancer diagnosis, prognosis, and treatment owing to its heterogeneous nature. While accurate comorbidity assessments and appropriate treatment administration can result in better patient outcomes, evidence related to older adult cancer populations is limited as these individuals are often excluded from regular clinical trials due to age and comorbid conditions.

Objective: To determine the prevalence of physical comorbidity and the impact of physical comorbidities and rurality on treatment and its outcomes in older adult cancer populations.

Methods: Scientific databases Embase and PubMed were searched for published scientific literature on physical comorbidity and older adult cancer patients. Google Scholar was searched for scholarly literature published in nonindexed journals. Snowballing was utilized to identify research papers missed in the above searches. Included studies : (1) reported on original research involving cancer patients; (2) included patients aged 65 years or older; (3) had patients receiving cancer-related treatment and (4) cancer survivors; (5) reported on physical comorbidity as a variable; (6) were published in English; and (7) conducted from any geographical location.

Results: In total, 29 studies were selected for data extraction, evidence synthesis, and quality assessment. In these, comorbidities ranged from 37.9%-74.3% in colorectal cancer, 74%-81% in head and neck cancer, and 12.6%-49% in breast cancer. Moderate comorbidities ranged from 13%-72.9%, and severe comorbidities from 2.5%-68.2%. Comorbidity increased with age, with comorbidity affecting both treatment choice and process. Physical comorbidities significantly affected treatment initiation, causing delay, toxicity, and discontinuation. Older adult cancer patients were given less vigorous and nonstandard treatments and were also less likely to be offered treatment. Where patients are given more vigorous treatment, several studies showed better survival outcomes. Appropriate treatment in older adult cancer patients increased both overall and disease-related survival rates. None of the studies noted rurality as a distinct variable.

Conclusions: This systematic review concludes that there is evidence to substantiate the adverse effect of comorbidity on treatment and survival outcomes. However, the mechanism by which comorbidity impedes or impacts treatment is unknown in many cases. Some low-quality evidence is available for considering the functional status and biological age in treatment decisions. Future studies that substantiate the value of comprehensive older adult assessments before treatment initiation in cancer patients,

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including assessing the nature and severity of comorbidities, and additional consideration of rurality as a factor, could lessen the effect of comorbidities on the treatment process.

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KEYWORDS

comorbidities; cancer; chemotherapy; geriatric; quality of life; morbidity; treatment; older adults; review

Introduction

Cancer is one of the predominant causes of morbidity and mortality in older adult populations worldwide, particularly in developed countries owing to the proportionately high aging population [1-5]. Frailty, comorbidities, financial burden, treatment-related adverse effects, and lack of social support, transportation, and treatment facilities are some of the hindrances in cancer treatment among older adult populations [6-9]. Of these factors, comorbidity poses a major clinical challenge in cancer diagnosis, prognosis, and treatment owing to its heterogeneous nature in terms of number as well as severity [5,10-13].

Accurate comorbidity assessments and appropriate treatment administration can result in better treatment outcomes in older cancer patients [10-14]. However, evidence related to the impact of comorbidities and their relationship with treatment outcomes in older adult cancer populations is limited as these individuals are often excluded from regular clinical trials due to age and comorbid conditions [15,16]. Recently, there has been an increased interest among researchers to specifically study the treatment of and outcomes in older adult cancer populations. This review focuses on older adult cancer patients and aims to examine the prevalence of comorbidity among the older adult cancer population and to understand the impact of physical comorbidities on (1) treatment (delay in treatment initiation, completion, dose alteration, or treatment-related adverse effects) and (2) outcomes (survival and quality of life [QoL]) in the population.

Methods

Reporting Guidelines Used

This review was undertaken using established criteria for the conduct and reporting of systematic reviews given by the 2009 PRISMA (preferred reporting items for systematic reviews and meta-analysis) [17], including those identified by Moher et al [18].

Search Strategy

Embase and PubMed were searched for peer-reviewed literature published between January 1, 1991, and June 2019. Google Scholar was also searched to identify scholarly publications not identified from the database searches. Searches were undertaken using a combination of medical subject heading terms, Emtree indexed search terms, and specified keywords relating to the target population and subject matter, including “geriatric cancer,” “cancer treatment,” “physical comorbidity,” “survival,” “quality of life,” and “treatment outcomes.” The search strategy and terms used to search the Embase, PubMed, and Google Scholar databases are reported in Multimedia Appendix 1. In addition, snowballing was undertaken to identify scientific literature cited within papers that may have been otherwise missed from the above searches. The searches were limited to literature published in English. Search results were downloaded to Covidence [19] to assist with the review and data extraction. The process and results of the search are presented in the PRISMA flow chart (Figure 1).

Of note, initial searches and subsequent browsing were undertaken for articles within the above parameters that also included “rurality” or related terms in their description of study design, with specific reference to variables for analysis. This process yielded no results, and therefore, the overall scope of the systematic review was necessarily narrowed. However, as discussed later in this review, the absence of literature in this respect highlights a significant gap for further research development. The present systematic review also did not include randomized controlled trials, as the review aimed to understand the impact of comorbidities on treatment outcomes. In addition, this approach reflects the approach and findings of an existing systematic review in the broader field [20].

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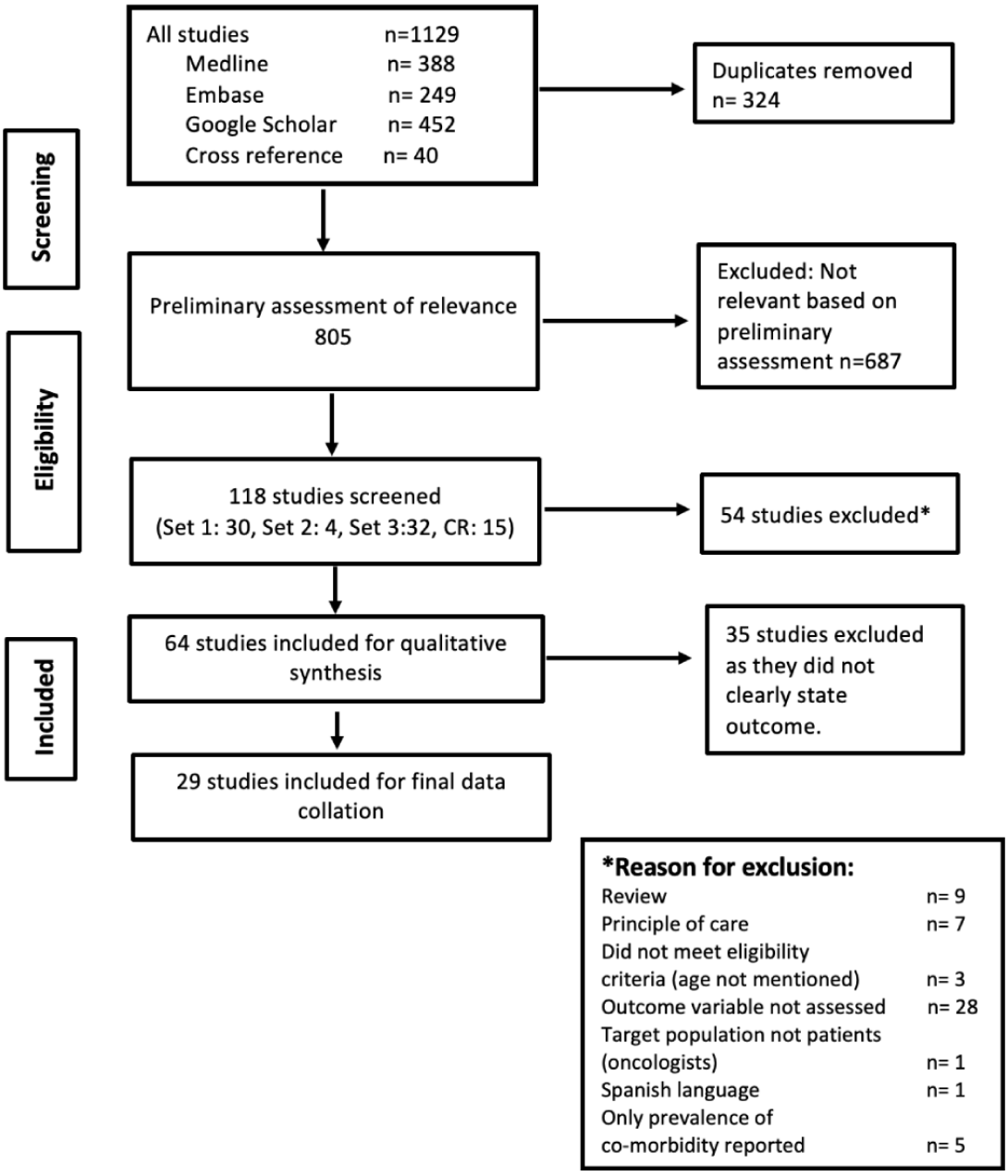
Figure 1. PRISMA flowchart of search results and study selection. PRISMA: preferred reporting items for systematic reviews and meta-analysis.



Selection of Studies

Two independent reviewers, MG and AS, initially reviewed a number of the articles by title and abstract, using specific eligibility criteria mentioned as follows in order to assess the level of agreement. Once this agreement and consistency of eligibility criteria application were reached via agreement on at least 5 of 6 criteria for articles in reviewers' initial screening selections, the reviewers continued to screen the remaining articles for relevance against the criteria. As previously mentioned, only literature published in English was included in this stage.

Eligibility criteria for study inclusion included: (1) reported on original research involving cancer patients; (2) included patients aged 65 years or older; (3) patients were receiving cancer-related treatment; (4) those who are survivors; (5) reported on physical comorbidity as a variable; and (6) were published in English. Research from any geographical location (ie, urban or rural) was included.

Population-based studies that included a subgroup analysis of older adults (ie, 65 years and older) were also included in the present systematic review. This assisted in accounting for the results of participants of younger ages.

The study was chosen for the review if both the reviewers individually approved it, and, in cases of uncertainty, the article was included for full-text screening. Each reviewer then screened the full text of selected studies individually to ensure that the articles met all inclusion criteria. In cases of any discrepancy, consensus was reached after meticulous discussion by the reviewers.

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Data Extraction

After completion of screening, data from included articles were extracted manually by the two reviewers. The reviewers then independently assessed and scored the individual studies using the National Institute of Health quality assessment tool for observational cohort and cross-sectional studies [21]. The tool consists of 14 questions relating to the risk of bias and other indicators of quality. The average scores of the reviewers across these indicators were then calculated to categorize the studies as "high," "moderate," or "low" quality.

Results

In total, 1129 studies were identified from the electronic database searches, and 40 studies were obtained through cross-reference. This was reduced to 805 studies after removing 364 duplicates and reduced further to 118 studies based on the process of title and abstract screening. After excluding 364 duplicates and 686 articles that did not meet eligibility criteria, articles were then identified and agreed upon as potentially relevant.

A total of 118 papers remained following this screening process, with the exclusion of a further 54 papers as per the exclusion criteria. The process and outcomes are illustrated in Figure 1 (PRISMA flowchart). Excluded were book reviews (n=9); studies that did not report the age of participants (n=3); target study population was not comprised of patients but rather was comprised of a general population potentially including both patients and nonpatients (n=1); outcome variable was not assessed (n=28); and only the prevalence of comorbidity, rather than type or other details, was reported (n=5). Studies were also excluded if they did not indicate the principle of care (ie, treatment regimen and treatment modality; n=7). No editorial reports were obtained during the initial search and therefore did not account for any excluded articles. Case reports were excluded at the preliminary assessment of relevance stage, in which 687 articles in total were excluded. Figure 1 illustrates the number of studies identified and included and the reasons for exclusion.

Based on the inclusion and exclusion criteria, a total of 29 studies were selected for data extraction and evidence synthesis and then assessed for quality.

Quality Assessment

Quality assessment of the studies revealed 1 study to be high quality [22], 5 studies of moderate quality [23-27], and 23 studies [28-50] to be of low quality. Those of low quality were those studies in which: sample size justification, power description, or variance and effect estimates were not provided or were lacking; exposures of interest were measured prior to the outcomes being measured; and there were high rates of attrition owing to loss to follow-up after baseline (while this was not mentioned by all studies, approximately 13 studies noted a <20% attrition rate). We did not exclude any study from the final review based on this quality assessment, and its results are presented in Multimedia Appendix 2. The following sections discuss principal findings consolidated from all 29 studies, focusing on identifying research gaps for further elaboration.

Study Characteristics: Summary

A summary of the studies included is reported in Multimedia Appendix 3, and the characteristics and quality of each study are provided in Multimedia Appendix 2. Next, we elaborate on the study characteristics summary, with cited studies specified in the following results sections.

All studies were observational in nature, comprising cross-sectional, prospective, or retrospective studies. Most studies were retrospective (n=27) in nature. Fifteen of the 29 studies obtained their data from data registry reviews, and the remainder were based on data obtained from patient hospital records.

Sample size ranged from 59 in a small study from Portugal [24] to 61,740 in a retrospective study from the United States [33]. Big data drawn from database record reviews and patient hospital records are likely to include patients from various geographic settings. However, the difference between urban and rural settings and their impact on comorbidity were not specifically studied. Only 1 of the 29 studies included in this review examined this difference in comorbidities between urban and rural settings [45].

Studies on colorectal cancers (n=11) were the most common, followed by head and neck cancers (n=5) and breast cancers (n=4). All the studies focused on single-site cancers and none on metastatic cancers. The tumor stage was described in all but 4 of the studies, with a marginal focus on stage III cancers overall. The common covariates examined in the studies were age (100%), sex (56.7%), stage of cancer (50%), and ethnicity (30%).

Different tools of assessment were used in the studies to assess comorbidity. The Charlson Comorbidity Index (CCI), with or without modification, was the most commonly used tool (56.7%) in the studies [22,24,28,29,31,33,35,36,41,46-48,50]. Three studies used the Kaplan-Feinstein Index [3,32,39] and the adult comorbidity evaluation index [25,34]. One study assessed the QoL in participants using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) scale [32], and 1 study used the activities of daily living scale [44] to elucidate daily physical activity capabilities and limitations

Comorbidities were reported based on the severity as either mild, moderate, or severe (n=8) or based on a numerical scale ranging from 0 to ≥8 (n=16), while one study reported on both [46]. Four studies did not mention any categorization of comorbidities. Reported comorbidities were classified under cardiovascular, diabetes, gastrointestinal, pulmonary, renal, neuromuscular, hematopoietic, psychiatric problems, and others (eg, obesity, arthritis, HIV/AIDS, poor vision and hearing), with the specific type of comorbidity not mentioned in 6 studies. Diabetes was most commonly mentioned, being included in about 40% of the studies, followed by hypertension (36.7%) and cardiovascular-pulmonary and cerebrovascular problems (30%).

Chemotherapy was found to be the most commonly used treatment (75.9%), followed by surgery (51.7%) and

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radiotherapy (17.2%). These therapies were either used alone (n=18) or in combination (n=11).

Comorbidities

Prevalence of Comorbidities

The prevalence of the presence of any comorbidities among patients with colorectal cancer ranged from 37.9% to 74.3%, 74% to 81% [33] among those with head and neck cancer, and 12.5% [38] to 49% [29] among those with breast cancer as reported in Multimedia Appendix 4. Moderate comorbidities were reported ranging from 13% [33] to 72.9% [24] and severe comorbidities ranged from 2.5% [49] to 68.2% [41] in the study population of selected studies. The proportion of patients classified under varying severity levels of comorbidity was not mentioned in 3 studies [34,43,44]. Patients with no comorbidities ranged from 0.7% to a maximum of 87.4% [28]. Klepin et al [23] reported the median total number of comorbidities as 2 (range 0-10) and the median comorbidity burden score as 3 (range 0-25) among patients. Tan et al [50] reported the median CCI as 3 (range 2-10) to indicate the severity of comorbidities. Koroukian et al [38] scored multimorbidities which included functional limitations and geriatric syndromes along with comorbidities. About 21.2% of patients had no multimorbidity, and 78.8% had scores of 1-3. Miguel et al [24] categorized 72.9% as fit and 27.1% as vulnerable categories. Sanoff et al [48] elaborately described the prevalence of comorbidities from the surveillance, epidemiology, and end results program, the New York State Cancer Registry, and the National Comprehensive Cancer Network databases individually.

Impact of Comorbidities on Cancer Treatment

Across the selected studies, comorbidities were identified as impacting cancer treatment in a number of ways; however, the causative mechanism of this impact and the degree of impact was neither consistently studied nor reported, making it challenging to draw overall conclusions. The impact of physical comorbidities on cancer treatment and salient findings of each study, as these were statistically analyzed and reported by study authors, is summarized in Tables S3 and S4 of Multimedia Appendix 4 . Major themes included impact of comorbidities on cancer treatment choice, initiation, dose reduction, and other alterations including delay, adverse effects, and discontinuation.

The choice of treatment was noted as affected in some way due to comorbidities in 19 studies [22,24,25,27,28,30-33,36,38,40,42-44,46-48,50]. Nonstandard treatment and less aggressive treatment were given for older geriatric patients during both primary and secondary treatment regimens, the main factors cited in this being age and physical comorbidities. Hoeben et al [25] reported that the type of chemotherapy had to be modified in 3% out of 57% of patients who received chemotherapy.

Comorbidity affecting treatment initiation was reported in 3 studies [22,25,45]. Hu et al [45] revealed that patients aged 75-79 years were 71% less likely than those aged 65-69 years (OR [odds ratio] 0.29, 95% CI 0.25-0.34) to initiate chemotherapy, and patients with >2 on the comorbidity index were 63% less likely (OR 0.37, 95% CI 0.33-0.42) to initiate chemotherapy after surgery. Age, comorbidity, and marital status were significant predictors for chemotherapy initiation, which showed a model variance of 92.6% in the chi square test. Gross et al [22] studied the presence and absence of individual comorbidities and the initiation of adjuvant therapy. Initiation of therapy for patients with and without coronary heart failure was 36.2% vs 64.9% (OR 0.49, 95% CI 0.40-0.60), with and without chronic obstructive pulmonary disease (COPD) was 55.2% vs 61.5% (OR 0.83, 95% CI 0.70-0.99), and with and without diabetes was 58.3% vs 60.7% (OR 0.81, 95% CI 0.68-0.97). Hoeben et al [25] reported that chemotherapy was not initiated in 43% of patients due to age, comorbidity, or performance status, whereas patient preference accounted for only 17% of noninitiation decisions following surgery [25].

Dose alteration was identified and discussed in 7 studies [23-25,27,29,35,42]. An increase in comorbidities was related to dose modification in patients for ≥2 vs <2 comorbidities and was reported as 40% vs 31% (P<.05) by Goede et al [35] and 59% vs 46% (P=.03) by Klepin et al [23]. Dose reduction was also related to adverse effects from treatment (n=19, 9%) in patients [29]. Hoeben et al [25] reported that 18% and 28% of patients who received chemotherapy underwent alterations in dose and number of sessions, respectively, and in 3% of patients, dose reduction was made before the initiation of treatment. This dose reduction was noted as being not significantly related to age or comorbidity. Jørgensen et al [42] observed that dose reductions in the carboplatin and taxane treatment group in ovarian cancer patients were related to toxicity, but in 17%, it was due to comorbidity or age; however, no significant difference was found based on age for the group receiving only the carboplatin treatment regimen. In rectal cancer, 29.8% of patients had dose reductions (34.3% for 0-1 CCI and 16.7% for >2 CCI; P=.22) [24]. On the contrary, Grønberg et al [27] found no significant differences during therapy and posttherapy in patients (without drug modification) with severe comorbidity.

Treatment delay was examined in 3 studies [25,29,43]. Hoeben et al [25] reported that there was modification in time course between successive chemotherapy sessions in 23% of patients, but this was not related to age or comorbidity. Ferrero et al [43] reported no difference in delay between the age groups 70-75 years and >75 years or based on frailty, but this result was not significant. However, O'Connor et al [29] reported an unplanned delay in treatment for more than a week in about 20% of patients due to toxicity which was significantly related to a history of comorbidities, especially diabetes, hypertension, and low creatinine clearance. An anthracycline-based chemotherapy regimen, CCI ≥1, and hypertension were predictors for treatment delay. A CCI ≥1 was a significant predictor for delay in chemotherapy administration. Age was also a risk factor for delayed treatment.

Treatment discontinuation was reported in 9 studies [22,23,27,29,35,41-43,45]. The most common factors cited in treatment discontinuation were disease progression, toxicity, and patient preference [23,41]. Hu [45] reported that older patients (P<.05) and a <2 comorbidity score (OR 0.63, 95% CI 0.52-0.75) were significant predictors for early discontinuation, and age at diagnosis was the strongest predictor of treatment discontinuation. Similar results were reported by O'Connor et al [29] (OR 4.43, 95% CI 1.55-12.69; P=.045 for >75 years and

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<75 years). Gross et al [22] found no significant association between individual comorbid conditions and completion of treatment. According to Grønberg et al [27], 69% of patients completed chemotherapy (*P*=.08); however, the rate was lesser in patients with a severe comorbidity.

The overall response rate for treatment was also found to be lesser in patients with higher comorbidities (75% vs 85% for ≥2 vs <2 comorbidities, respectively; *P*<.05), but no significant variation was found when the results were adjusted for age and treatment, suggesting that patients with high comorbidity were biased to receiving less vigorous treatment [35]. Ferrero et al [43] reported that complete response to treatment was greater among the 70-75 years age group than among the <75 years age group (60% vs 28.9%, respectively; *P*=.005). Also, no significant difference between age groups was found for treatment discontinuation due to toxicity in ovarian cancer patients (*P*=.28) [43]. A similar result was found with respect to the carboplatin-only treatment regimen in a study done by Jørgensen et al [42], whereas in the carboplatin and taxane regimen, performance status and severity of comorbidity were predictors for treatment discontinuation.

Treatment toxicity, adverse effects, or postoperative complications were observed in 14 studies [22-25,27,29,33-35,37,40,41,43]. Goede et al [35] analyzed the individual comorbidities with treatment toxicity and reported no relationship between the variables. However, Grønberg et al [27] observed that the incidence of fever was high in patients with severe comorbidities and also identified that minor comorbidities were not registered in their study, which might have contributed to the result. This suggests the importance of recording the comorbidities, their types, occurrence, and nature in-depth without omitting any details in order to decrease treatment-related adverse effects. In lung cancer, the hematological and nonhematological toxicities were 3% and 24%, respectively [37]. Houterman et al [40] reported no significant difference between treatment complications and comorbidities, irrespective of age. Peters et al [34] reported on recipient site and medical complications out of which the latter was found to be significantly present in head and neck cancer patients with ≥2 comorbidities (OR 2.89, 95% CI 1.71-4.84; *P*<.001). Phaibulvatanapong et al [41] presented a detailed account of treatment-related complications with adverse effects (grade 3-5) in 83.4% and severe toxicity in 42.4% of patients, both of which were related to performance status in a mixed cancer study population (*P*<.05). Ferrero et al [43] reported a higher rate of postoperative complications in high-frailty patients compared with low-frailty patients (23.5% vs 4.3%; *P*=.03). Tan et al [50] similarly reported worse postoperative complications in patients with a CCI >3 or those who had emergency surgery. The study also reported worse perioperative complications and higher death rates among those >85 years old. Hospitalization was not related to congestive heart failure (CHF), COPD, or diabetes, irrespective of whether individuals received treatment [22]. Conversely, Genther and Gourin [33] reported that comorbidities were related to emergency hospital admission (relative risk1.21, 95% CI 1.06-1.38; *P*=.005) but not to postoperative complications.

Treatment-related toxicity (25.4%, 52%, and 9%) [24] was also another reason cited for treatment discontinuation (1.7%, 15%, and 20%) [23] and dose reduction (29.8%, 51%, and 9%)[29]. Adverse effects varied with the type of treatment (52% vs 41% for those receiving vs not receiving adjuvant chemotherapy, respectively) [25]. O'Connor et al [29] found that history of hypertension is a predictor for poor tolerance of chemotherapy causing treatment delay (OR 2.51, 95% CI 1.02-6.20; *P*=.046).

Some of the selected studies have noted patients' personal preference in treatment choice and discontinuation [24,26,32,41,42,50]. For example, Derks et al [32] reported that about 18% of the patients above 80 years of age refused to undergo treatment. Patients diagnosed in more recent years (ie, 2009 or later) were more likely to receive and complete treatment [45,47]. These studies overall show that increased age correlates with an increased likelihood of a patient declining treatment; however, the studies do not identify the specific reasons for this (eg, the impact of comorbidity, impact of function or nonfunction, and so on).

Therefore, several of the selected studies show a strong association between comorbidities and treatment dose alteration, noninitiation of treatment, treatment choice, and early discontinuation of treatment. Due to significant variation in cancer types or sites, patient cohorts, recording of comorbidities, and several other variables, it is, however, difficult to draw clear conclusions regarding the influence of comorbidities in particular on the treatment decisions and the effects among the broader patient population and that of older cancer patients in particular.

Quality of Life and Survival Related Outcomes

Two studies documented health-related QoL of older adult cancer patients [27,41], while 23 studies reported overall progression-free and disease-free survival, and 4 studies did not include a QoL or survival component [31,33,36,45]. Hospital readmission (n=3) [22,29,37] was also investigated in several studies. Of note, while the inclusion criteria included both patients receiving treatment and patients who were survivors of cancer as separate cohorts, all studies reported both on patients currently receiving treatment and who had completed treatment, and none were specific to survivors as a singular cohort only. The following summarizes findings from these 23 studies, with a specific focus on their reporting of survival, comorbidity, age, and treatment relationships.

Comorbidity, especially development of multimorbidities, is a strong prognostic factor for survival in cancer patients. Comorbidity was an independent factor in determining specific and overall survival (OS) [35]. 30-day mortality was greater in individuals aged over 80 years than in those aged 60-79 years (12% vs 3%, respectively; *P*=.02), and OS was greater in the latter group (30.1% vs 50.5%, *P*<.001) [49]. Berglund et al [28] reported that higher cancer-related and noncancer-related mortality was seen in patients with severe comorbidity both in early and advanced stages of cancer. Also, the hazard ratio (HR) was significantly higher with severe comorbidity in early breast cancer patients during the follow-up.

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Moderate comorbidity increased the risk of mortality twice compared to those without comorbidity, even after adjusting for age, functional status, and treatment (adjusted odds ratio [AOR] 1.98, 95% CI 1.37-2.85; *P*<.001 [51]; HR 1.71 95% CI 1.15-2.56; *P*=.007) [26]. It was observed that older patients with pre-existing comorbidities were less likely to be suggested for both primary and secondary treatment (AOR >75 years 8.7, 95% CI 2.3-32.4; AOR <75 years 1.2, 95% CI 0.3-4.5 [46]; 25% vs 38%, respectively [40]; OR 0.63, 95% CI 0.58-0.69) [28]. Age and comorbidity were also independently related to reduced chances of being offered treatment [46]. Houterman et al [40] reported that in patients <70 years, moderate (HR 2.43, 95% CI 1.27-4.66) and severe (HR 2.87, 95% CI 1.40-5.90) comorbidities significantly increased the risk of mortality, while in patients ≥70 years, severe comorbidity (HR 2.97, 95% CI 1.12-7.86) significantly increased the risk of mortality. Treatment was not a significant prognostic factor when the age and severity of comorbidity were adjusted [40]. However, studies have proved that providing treatment or completing the treatment schedule reduces the rate of mortality irrespective of comorbidity (adjusted hazard ratio 1.43, 95% CI 0.57-3.60 [46]; HR 0.70, 95% CI 0.64-0.76 [22]; crude 5-year survival: 51% vs 32%; HR 0.5; *P*<.001 [47]; HR 0.5 [35]; 52% vs 34% *P*<.001; HR 0.73, 95% CI 0.55-0.98) [25]; 92% vs 66%; *P*=.013 [29]).

Falch et al [49] identified that with increased age, there was an increase in complications postsurgery, which led to higher mortality rates (≥80 years vs 60-79 years: 35% vs 17%, respectively; *P*=.009). CHR (HR 1.83, 95% CI 1.14-2.93) and noncerebrovascular neurological conditions (HR 1.96, 95% CI 1.12-3.42) influenced the survival rates of colon cancer patients [46]. One important finding by Koroukian et al [44] and Koroukian et al. [30] is that the association between survival and comorbidity may not be significant in the absence of functional limitations and geriatric syndrome. Poor physical functioning in QoL assessment was observed in the presence of high comorbidity [27], and the performance status of an individual is also a strong predictor for survival [26]. Derks et al. [32] observed poor QoL in patients who did not receive standard treatment, while the prognostic value of comorbidity was retained even after adjusting other variables [35,40].

In line with the above findings, Ferrero et al [43] reported better survival in less-frail patients (56 vs 27 months). There was a trend for a better OS in the low-frailty cohort (median 56 vs 27 months; *P*=.07). Ferrero et al [43] reported that high-frailty patients had poorer performance status (*P*<.001) and a higher incidence of hypertension (*P*=.001), diabetes (*P*=.001), obesity (*P*=.01), and chronic renal failure (*P*=.05) when compared with low-frailty patients. Miguel et al [24] also reported comorbidity as an independent predictor of OS. They also reported no difference in mean disease-free survival, grade 3 to 4 toxicity, and dose reduction between the groups.

Discussion

Principal Findings

The reviewed studies confirmed the association of physical comorbidities and treatment in older adult cancer patients. However, the strength of evidence is lesser as a majority of the studies were of low quality. The studies included in this systematic review had heterogeneous study designs, cancer populations, study settings, measurement scales, and reporting parameters of comorbidities, thus not permitting data pooling for a meta-analysis. Nonetheless, the results obtained do highlight several gaps and factors that, if further investigated and addressed, may contribute to a better understanding of the potential effects of different treatment and management approaches for cancer in older adult patients with comorbidities. In addition to the existing evidence, the review pointed towards clear gaps in research and clinical service provision in this field. Research priorities need to be clearly stated by international agencies to establish the prevalence, patterns, impact, and treatment of comorbidities in older adult cancer patients. There is a need to explore the difference in care patterns of cancer patients in urban and rural settings. Similarly, more evidence from low-income countries needs to be synthesized to investigate the relationship between comorbidity and treatment in cancer patients in those settings.

Regardless, as per the American Society of Clinical Oncology (ASCO) guidelines, older adults are to undergo a comprehensive geriatric assessment (GA) before deciding on their cancer treatment to identify the best option for them. By doing so, vulnerabilities among those aged 65 years and above can be detected because it is recommended that the GA is used as intended to guide treatment decisions in the cohort comprised of older patients with cancer [52].

Many of the selected studies have also supported the association of increased age with increased comorbidity. Studies clearly confirmed that age influences the treatment process and treatment method among older patients. Among patients, higher comorbidity was observed with increasing age [44,49], and an increase in the pace of disease progression in older patients was further observed despite the comorbidity burden being corrected [28]. Age at diagnosis was the strongest predictor for completion of treatment in older adult cancer patients [26]. It was also an independent predictor for the type and aggressiveness of treatment received and discontinuation of treatment [31,32]. The effect of age was observed even after adjusting for the comorbidity factor [34]. It has been observed that less vigorous and nonstandard treatment regimens were suggested to patients based on increasing age, even in cases where the patient may be capable of withstanding more aggressive treatment [33]. Jørgensen et al [42] found that a subgroup of undertreated patients with less aggressive treatment would have been able to endure standard treatment. The outcomes of adjuvant treatment were not affected by advancement in age in the study conducted by Sartafi et al [46]. Hence, studies have recommended considering biological age and functional status for treatment choice and not merely chronological age [29,31,40].

Studies assessed show that comorbidity is a direct confounder rendering competing risks for morbidity and mortality. Higher comorbidity diminished functional status [29], increased the rate of hospitalization [48], resulted in dose modification [44], and is an independent predictor for in-hospital death [25]. Functional limitation and “older adult syndrome” are also related to not receiving treatment [28,31]. Severity of comorbidity was

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a predictor for patients not receiving standard treatments in the ≥70 years age group (P<.05) [26]. Sarfati et al [46] reported that 32 out of 51 patients (63%) of >75 years of age (AOR 8.7, 95% CI 2.3-32.4) and 13 out of 16 patients (81%) with a comorbidity score >3 (AOR 20.1, 95% CI 4.2-95.6) were not offered chemotherapy. With increasing comorbidity, the treatment offered to patients was less vigorous [30,35,42], with age and comorbidity independently affecting the chances of receiving treatment [36]. Comorbidity also affected the disease prognosis negatively [30,31,38,43]. Adjuvant therapy yielded better outcomes in patients who did not suffer from CHF, COPD, or diabetes mellitus, thus showing the association of comorbidity with treatment response [48]. Hypertension also resulted in treatment delay and resulted in greater rates of hospitalization [32]. The effect of comorbidity on survival persisted after adjustment for other variables like age, gender, and cancer site, although combinations of therapies were seen to improve outcomes in patients with high comorbidity [43].

Both age and comorbidity are related to treatment response [29]. In the context of cancer, assessment of comorbidities is an appraisal of the effect of cancer and its treatment on the physical, mental, and social health of patients. Therefore, the use of comprehensive older adult assessments in cancer patients during treatment decisions should be strengthened [31]. Although the CCI is a widely used tool, Phaibulvatanapong et al [41] reported that it would not be suitable for comorbidity assessment, specifically for cancer patients, as cancer is one of the scoring components of CCI and might show an unjustified high score for metastatic patients. As such, significant consideration must be given to the consistent administration of the comprehensive geriatric assessment as per the ASCO guideline for geriatric oncology [52].

Limitations

In this systematic review, contradictory findings on age and survival were reported. OS was significantly better in patients aged less than 75 years (median 98 vs 30 months; P=.02) [28). However, Falch et al [49] reported that tumor stage, complete tumor resection rate, and overall complication rate were not influenced by age, thus challenging the findings of the effect of age on survival. Significant effects of comorbidity and treatment choice were observed on the overall, disease-specific, progression-free survival, and disease-free survival rates. Functional status of patients was a predictor for survival in a study conducted by Sanabria et al [26], which reiterates its importance in treatment choice. No conclusive evidence regarding QoL and comorbidities could be obtained as one study showed significant association [50], and no significant association was identified in another study [22].

The studies from this systematic review indicated that physical comorbidities are extensively prevalent among older cancer patients and impact various treatment stages. However, the exact mechanism by which physical comorbidities impact treatment was not demonstrated by any article other than identifying a relationship between age and physical comorbidity. Therefore, the influence of physical comorbidity on treatment outcomes is still unknown, and this signifies the need for research to conclude how comorbidity impacts treatment and treatment outcomes in older cancer patients.

Conclusions

With a growing population, the number of cancer cases is also on the rise. An increasing older population, as a proportion of the overall population, will also be reflected in a growing older cancer patient population, which contributes a significant proportion of the cancer patient population in general. Future large-scale, multicentered longitudinal randomized trials focused on the older adult population are therefore warranted to measure the effects of comorbidities on physical and psychological variables of interest in addition to QoL. Studies that test self-management interventions, such as exercise, are also needed to assess their impact on the management of comorbidities, and subsequent improvement of symptoms and functional status, thereby improving QoL for older patients with cancer. Additionally, integration of data related to symptoms into routine electronic records and care remains a high priority. These studies should include and stratify older patients by functional status, comorbid conditions, older adult syndromes, and prognosis to better represent the real-world population and improve research validity. Treatment of comorbidity, the severity of comorbidity, and the interaction of comorbidity with cancer treatment have not been discussed in the papers selected for this review. Overall, increased age and increased comorbidities correlate with significantly lesser likelihood of treatment initiation. Some variability in the included comorbidities and comorbidity scoring and the potential for other confounding variables (eg, marital status, as per Hu et al [45]) to complicate reported outcomes impact the statistical and clinical significance of this group of studies.

This systematic review provides evidence to prove the varied impact of physical comorbidities on cancer treatment and outcomes among older adult populations. It is suggested that comorbid older adult patients with better functional status might tolerate this treatment and show better survival and QoL outcomes when provided with standard and more aggressive treatment. Therefore, comprehensive older adult assessments are strongly recommended; they can help analyze the health status of older individuals, which then influences treatment decisions. Unfortunately, the quality of the majority of studies in this review was low, which makes incorporating their recommendations into routine practice less certain. Hence, this study recommends high-quality evidence generation in older adult cancer patients with physical comorbidities to translate research findings to clinical practice.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search Strategy.
[DOCX File , 17 KB - cancer_v7i4e26425_app1.docx]

Multimedia Appendix 2
Supplementary Table 1: Summary of included studies.
[DOCX File , 19 KB - cancer_v7i4e26425_app2.docx]

Multimedia Appendix 3
Supplementary Table 2: Characteristics and quality of studies selected for review on impact of comorbidity in older adult cancer treatment.
[DOCX File , 31 KB - cancer_v7i4e26425_app3.docx]

Multimedia Appendix 4
Supplementary Tables 3 and 4.
[DOCX File , 45 KB - cancer_v7i4e26425_app4.docx]

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Abbreviations

AOR: adjusted odds ratio
ASCO: American Society of Clinical Oncology

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CCI: Charlson Comorbidity Index
CHF: congestive heart failure
COPD: chronic obstructive pulmonary disease
EORTC: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
GA: geriatric assessment
HR: hazard ratio
OR: odds ratio
OS: overall survival
PRISMA: preferred reporting items for systematic reviews and meta-analysis
QoL: quality of life

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Original Paper

Predicting Hepatocellular Carcinoma With Minimal Features From Electronic Health Records: Development of a Deep Learning Model

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Abstract

Background: Hepatocellular carcinoma (HCC), usually known as hepatoma, is the third leading cause of cancer mortality globally. Early detection of HCC helps in its treatment and increases survival rates.

Objective: The aim of this study is to develop a deep learning model, using the trend and severity of each medical event from the electronic health record to accurately predict the patients who will be diagnosed with HCC in 1 year.

Methods: Patients with HCC were screened out from the National Health Insurance Research Database of Taiwan between 1999 and 2013. To be included, the patients with HCC had to register as patients with cancer in the catastrophic illness file and had to be diagnosed as a patient with HCC in an inpatient admission. The control cases (non-HCC patients) were randomly sampled from the same database. We used age, gender, diagnosis code, drug code, and time information as the input variables of a convolution neural network model to predict those patients with HCC. We also inspected the highly weighted variables in the model and compared them to their odds ratio at HCC to understand how the predictive model works

Results: We included 47,945 individuals, 9553 of whom were patients with HCC. The area under the receiver operating curve (AUROC) of the model for predicting HCC risk 1 year in advance was 0.94 (95% CI 0.937-0.943), with a sensitivity of 0.869 and a specificity 0.865. The AUROC for predicting HCC patients 7 days, 6 months, 1 year, 2 years, and 3 years early were 0.96, 0.94, 0.94, 0.91, and 0.91, respectively.

Conclusions: The findings of this study show that the convolutional neural network model has immense potential to predict the risk of HCC 1 year in advance with minimal features available in the electronic health records.

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KEYWORDS

hepatocellular carcinoma; deep learning; risk prediction; convolution neural network; deep learning model; hepatoma

Introduction

Liver cancer is the sixth most cancer in incidence and the fourth leading cause of cancer-related mortality worldwide [1]. The most common type of liver cancer is hepatocellular carcinoma (HCC), accounting for approximately 80% of all liver cancer [1]. The incidence and mortality rate of HCC are higher in Sub-Saharan Africa and Southeast Asia than in the United States [2]. HCC incidence has been increasing globally, including in the USA, and is expected to continue growing over the next 20 years due to the higher number of patients with advanced hepatitis C virus and nonalcoholic steatohepatitis [3,4]. A significant number of studies (epidemiological and clinical) have reported risk factors of HCC that can be used to correctly stratify patients at risk and to implement prevention measures

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[5,6]. Accurate risk stratification tools may contribute to the timely identification of HCC patients and facilitate early detection and diagnosis.

The recent widespread adaption of electronic health records (EHRs) has caused the proliferation of clinical data and offers tremendous potential for predicting different diseases early, including cancer [7,8]. The use of EHRs can also contribute to high-quality treatment, improved patient management, reduced health care costs, and efficient clinical research [9,10]. Multiple studies have demonstrated that risk prediction models can anticipate the future incidence of HCC and ensure early treatment [8,11]. Flemming et al [12] recently developed a model for predicting the 1-year risk of HCC among patients with cirrhosis, but the performance was not satisfactory.

Convolutional neural network (CNN) models have already shown remarkable performance in detecting diseases from digital images and predicting diseases from EHRs [13]. CNN models take advantage of the hierarchical pattern in EHRs and assemble more complex patterns using smaller and simpler patterns. Thus far, however, no study has used deep learning algorithms, including CNN models, to predict HCC. Therefore, we developed a CNN model that analyzes EHRs to accurately predict HCC risk. We presented each patient's EHR data as a matrix which was formed by the medical events versus the temporal continuity and regarded the matrix as a 2D EHR image. With the time information, the EHR image revealed the severity and the trend of the medical events explicitly, which were beneficial to HCC risk classification.

Methods

Data Sources

We collected data from Taiwanese National Health Insurance Research Database, a rich source of data with the medical histories of 23 million people (approximately 99.9% of the total population in Taiwan). The database contains demographic, medication (number of prescriptions, the brand and generic name of the drugs, the date of the prescriptions, the dosage of the medication), and diagnostic information. The database is of excellent quality and completeness, and is used to conduct high-quality research. The Taipei Medical University research ethical board approved this study. Participant consent was not required because all individual's information was deidentified.

Study Population

We screened HCC cases and their information from a subset of 2 million patients from the National Health Insurance Research Database of Taiwan from January 1, 1999, to December 31, 2013. We also randomly sampled non-HCC patients, and there were nearly 4 times the number of non-HCC cases as there were HCC cases from the same database. We chose this multiple because the increase of predictive performance slowed down after a control:case ratio beyond 4 to 5 in our experiment and another study [14]. Moreover, all the participants were between 20 and 90 years old.

HCC Patients

HCC cases were identified by the International Classification of Disease, Ninth Revision, clinical modification (ICD-9-CM) code 155. HCC patients were ascertained only when they also met one of the following criteria: individuals registered as having cancer in catastrophic illness file, individuals with a primary cancer diagnosis in inpatient admission, and individuals that took HCC treatment medications or any specific procedure for HCC.

Variables Employed

The input variables for the predictive model included deidentified patient's ID, gender, age, diagnosis code, visiting date, prescription code, and exposure time of drugs. However, only the first 3 digits of the ICD-9-CM were adopted to represent the disease information. After 88 undefined codes were excluded, 993 ICD-9-CM were considered in this study, including V-code (Multimedia Appendix 1). Drug exposure was reflected by the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. We took the first 5 characters to cover most drugs in the same category; for example, the 5-digit ATC code (C09AA = angiotensin-converting enzyme inhibitors, plain) included all plain angiotensin-converting enzyme inhibitors, such as C09AA01 (captopril), C09AA02 (enalapril), and so forth. Nevertheless, 7 characters (eg, R06AX12) were considered for the other drugs with "X" as the fifth character because usually "X" means other agents in ATC code. There were 699 ATC codes expressed in this manner among these enrolled patients.

Constructing the EHR Image

Three-year (observation time) data of every enrolled patient were extracted from the National Health Insurance Research Database. To predict HCC's risk 1 year in advance, the final day of the extracted data was 1 year (advanced time) before the index day, as shown in Figure 1. For patients with HCC, the index day was the day they were diagnosed with HCC, while that of the non-HCC patients was the last day they had a diagnosis code in the data set. We chose 3 years as the observation time as a trade-off: the longer the observation time, the fewer the number of eligible patients with a sufficient data period there would be; on the other hand, with a shorter time window, the amount of data of each patient would be less. We needed a total 4 years of data for every patient, including 3 years of training and the skipping of the last year. In other words, 3 years of data were used to predict the next year of HCC cancer risk. Another thing to remember is that the duration of the drug exposure was not counted repeatedly if the times of the drug orders overlapped in different prescriptions.

We used these extracted data to construct the matrices which were regarded as the EHR images for each patient and which were afterward used to train and validate the CNN model for HCC risk prediction. The rows of the matrices were the diagnostic codes and the drug codes, and the columns were the temporal information of those events. Once the patient was diagnosed with a certain ICD-9-CM code or given a certain ATC code on a certain day, "1" was assigned to the corresponding coordinate of his or her matrix. At the end, to

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reduce the column size of the matrix, we rounded up the temporal coordinate by a period of 7 days, meaning the unit of the temporal sequence was 1 week instead of 1 day after being aggregated. Furthermore, to normalize the sum value (0 to 7) of the elements in the matrix to 0-1 for the following CNN computation, each element was divided by the maximum value of all the enrolled patients at the same coordinate. Considering it is not reasonable to mix different organ systems with a common CNN filter, we broke the ICD-9-CM down into 19 organ systems. Adding up the drug group, we found a total of 20 images for each patient to develop the deep learning model, as shown in Figure 2.

Figure 1. Preprocess from electronic health record to matrix. Diag: diagnosis: HCC: hepatocellular carcinoma; Indiv: individual.

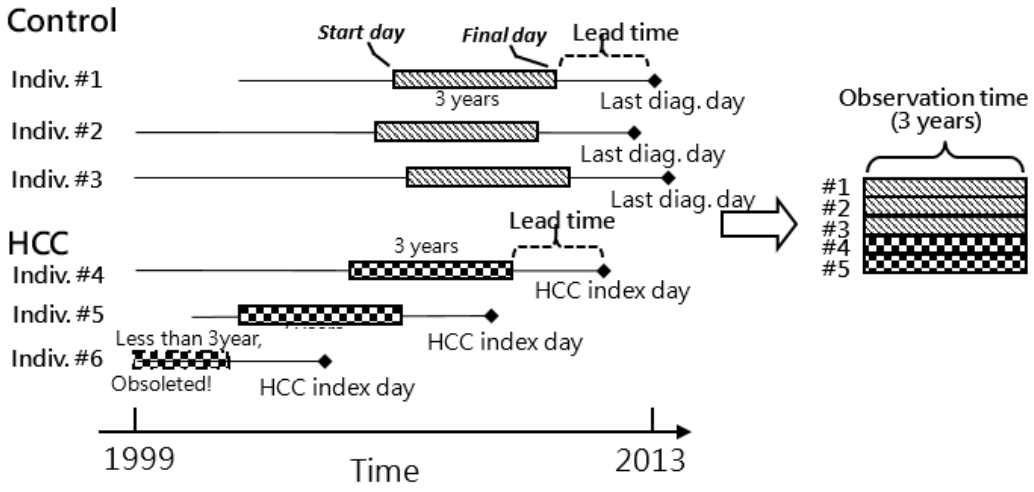
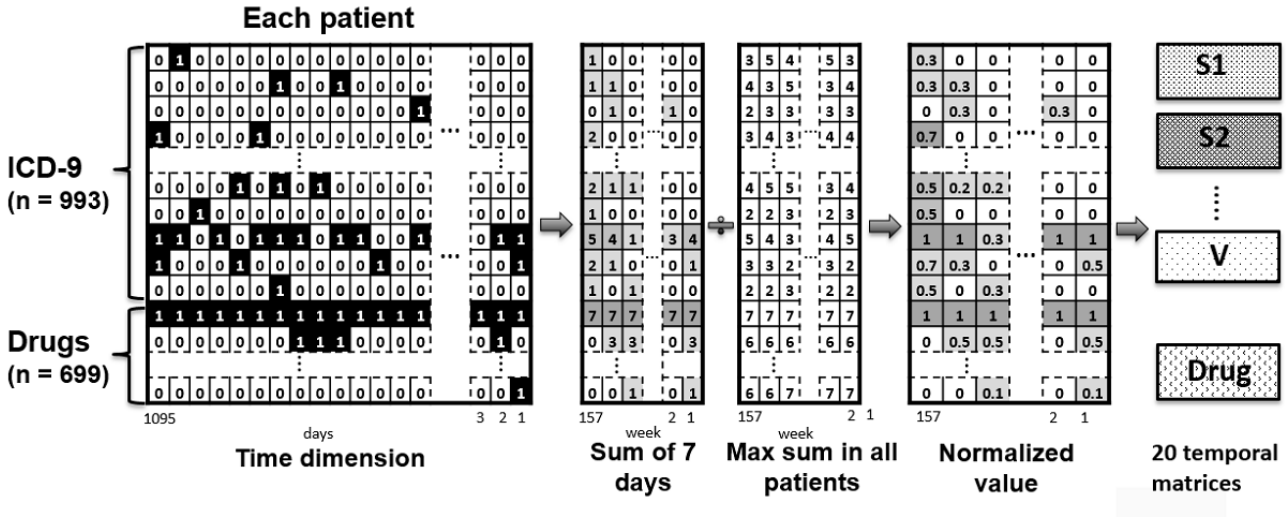


Figure 2. Preprocess from the matrix to 20 electronic health record images. ICD-9: International Classification of Disease, Ninth Revision; S1: subgroup 1 (001-139) of ICD-9; S2: subgroup 2 (140-239) of ICD-9; V: V codes, a supplementary classification in ICD-9.



Architecture of the CNN Model

CNN is a biologically inspired variant of a multi-layer perceptron, which uses filters to extract the features of the input by dot production [15,16]. We applied 5 hidden layers between the input and the output layer. Among them, the first one was a convolution layer with 4 filters in the shape of 1 × 57, where 157 was the number of the weeks in 3 years and the number of columns of the input matrix. The filters were trained to learn the weighting of the temporal sequence of each organ system and the drug group.

The second layer was a max-pooling layer with a size of 1 × 3 to reduce the sparsity of the learned features and was followed by a dropout layer that set 10% of the data to 0 at random to prevent the overfitting of the model. The fourth layer flattened the output of the previous layer and concatenated age and gender information. The fifth layer was a fully connected layer with 400 neurons. Finally, the output layer had 2 neurons, representing high risk and low risk, with the softmax classifiers to indicate the predictive result, as shown in Figure 3.

As for the hyper-parameters of the CNN model, the epoch was set as 2 to obtain the optimal area under the receiver operating curve (AUROC) according to our experimental result. The batch size was 32, and the learning rate was optimized by the AdaDelta method [17]. Moreover, the activation function used in the first 3 layers was the rectified linear unit [16]. To eliminate the bias of data sampling, we introduced 5-fold cross-validation [18] to evaluate the performance of this model. Therefore, each time, 80% of all patients were applied for training and the remaining 20% were used for validation by

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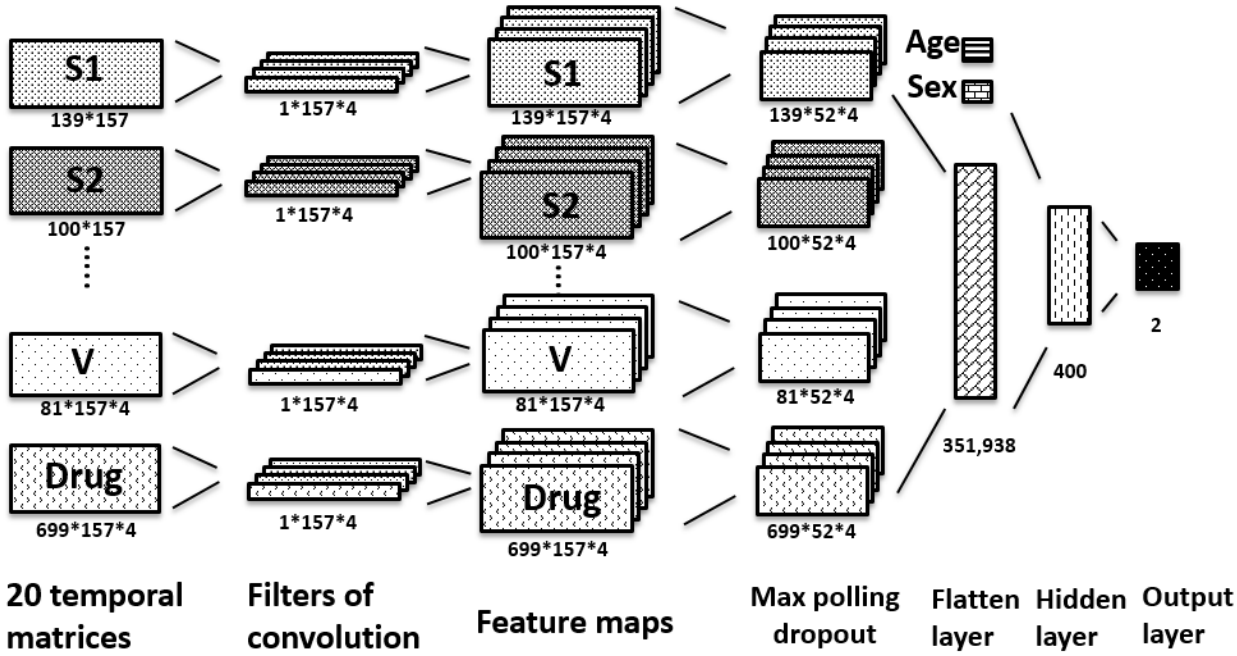
turn. The final performance was assessed by the average of all AUROC of the 5 folds.

Figure 3. Structure of the convolutional neural network. S1: subgroup 1 (001-139) of the International Classification of Disease, Ninth Revision (ICD-9); S2: subgroup 2 (140-239) of ICD-9; V: V codes, a supplementary classification in ICD-9.



Statistical Analysis

In this study, continuous numeric variables are presented by mean and SD, while the categorical variables are described by frequency and percentage. The performance of the model was assessed by the AUROC, sensitivity, and specificity. Moreover, we used odds ratio (OR) as an indicator to compare to the weighting of the variables in the CNN model to check their consistency. OR is a statistic that quantifies the strength of the association between 2 events, which in this study were ICD-9-CM (or ATC code) and HCC. If the OR is greater than 1, then the 2 events are considered to be associated. Conversely, if the OR is less than 1, they are considered to be negatively correlated. For the calculation of the OR, the ICD-9-CM or ATC code was considered as true only when they occurred 3 times or more in the extracted 3 years of EHR data. In stepwise fashion, we set the content of each input variable to 0 and checked the AUROC loss against the result of the full input. The variable would have higher weighting if it underwent more AUROC loss in the testing like the feature selection [19].

All analyses were performed using R language (The R Foundation for Statistical Computing). Keras, a high-level neural network application programming interface was applied as the top of TensorFlow to construct the mentioned CNN model in this study. Running on a computer with Intel i7 CPU, 64GB DRAM, and an Nvidia GTX 1080 GPU with 8GB DRAM, the 5-fold cross-validation took 80 minutes to complete.

Results

A total of 47,945 patients (24,664 males and 23,281 females) were included in this study, with 9553 being diagnosed with HCC and 38,392 being non-HCC patients. The mean age of HCC patients was 59.9 (SD 14) years while that of the control patients was 47.5 (SD 17.3) years. Moreover, the portion of the male patients in the HCC group and the control group was 64.64% (6175/9553) and 48.16% (18,489/38,392), respectively. Table 1 shows the demographic variables of the HCC and control groups.

The overall AUROC of predicting HCC patients 1 year in advance was 0.94 (95% CI 0.93-0.94), with a sensitivity of 0.869 and a specificity of 0.865. The threshold for the output of the CNN model to classify the risk group was 0.11, which was chosen by the maximum sum value of the sensitivity and the specificity. We also evaluated the performance of the model with different advance times. The overall AUROC when predicting HCC patients at 7 days, 6 months, 1 year, 2 years, and 3 years early was 0.96, 0.94, 0.94, 0.91, and 0.91, respectively.

Furthermore, different input groups and their combination were applied separately to assess their value. Our 1-year-in-advance predictive model with training and validating completed with only age and gender information achieved an AUROC of 0.73. The AUROC was 0.86 when only the disease codes were used and 0.88 when age, gender, and the disease codes were used. Meanwhile, the model applying only ATC achieved an AUROC of 0.91, while the application of age, gender, and ATC yielded an AUROC of 0.92.

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Table 1. Demographics of the sampled data set.

Demographic	HCC (n=9553)	Control (n=38,392)	Difference
Age (years), mean (SD)	59.9 (14)	47.5 (17.3)	N/A
Male, n (%)	6175 (64.6)	18489 (48.2)	N/A
ICD-9[a], mean diagnoses per patient in 3 years (ordered by difference)			
Total	126.2	78.1	48.1
571 (Chronic liver disease and cirrhosis)	8.36	0.61	7.75
250 (diabetes mellitus)	6.23	2.27	3.96
070 (viral hepatitis)	3.19	0.3	2.89
401 (essential hypertension)	5.43	2.83	2.59
465 (acute upper respiratory infections)	5.37	3.63	1.73
780 (general symptoms)	4.16	2.43	1.73
533 (peptic ulcer)	1.93	0.55	1.38
372 (disorders of conjunctiva)	2.78	1.59	1.19
724 (disorders of back)	2.38	1.22	1.17
402 (hypertensive heart disease)	1.89	0.76	1.12
ATC[b] code, mean prescribed days per patient in 3 years (ordered by difference)			
Total	2362	1099	1263
A05BA (liver therapy)	97.87	5.8	92.08
A10BB (blood glucose–lowering drugs)	93.51	29.88	63.63
C08CA (selective calcium channel blockers with vascular effects)	119.37	60.93	58.44
A10BA (blood glucose–lowering drugs)	77.87	32.36	45.51
B01AC (platelet aggregation inhibitors)	87.12	45.71	41.42
N05BA (benzodiazepine, for anxiolytics)	71.18	34.29	36.89
A02AX (antacids for acid related disorders)	42.61	14.68	27.93
C07AB (beta=blocking agents, cardiovascular system)	58.82	31.39	27.43
C09AA (ACE[c] inhibitors, cardiovascular system)	42.13	15.36	26.77
A02AF (antacids with antiflatulents)	27.91	2.06	25.84

[a]ICD-9: International Classification of Disease, Ninth Revision.

[b]ATC: Anatomical Therapeutic Chemical (classification system).

[c]ACE: angiotensin-converting enzyme.

Table 2 shows the AUROC impact of age, gender, and some diseases when they were withdrawn from the model, together with their ORs, against HCC. Some high impact variables were chronic liver disease and cirrhosis (AUROC loss 2.52%), viral hepatitis (0.67%), age (0.57%), peptic ulcer (0.41%), gender (0.39%), and screening for malignant neoplasms (0.78%), all of which were negatively associated with HCC due to having an OR of less than 1. Table 2 also shows some variables with extremely high or low ORs, but their AUROC was not high because the number of patients was not large; these variables included varicose veins (OR 22.47), other disorders of the liver (OR 5.34), normal pregnancy (OR 0.16), and others. Table 2 also shows the ORs of a cohort whose age and gender were matched with those of the HCC cohort, and their individual number was also 4 times greater than that of the HCC cohort, which was similar to the random sampled cohort. After the correlation of age and gender with HCC was decoupled, the ORs of the matched cohort did not appear to be as critical as those of the random sampled cohort, but their trends were consistent.

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Table 2. Age, gender, and diseases with AUROC loss greater than 0.01% or OR greater than 4 or less than 0.3.

Characteristic	AUROC[a] loss (%) (95% CI)	OR[b] (95% CI)	Patient number	Age- and gender-matched OR (95% CI)
Age > 50 years	0.57 (0.6-0.54)	4.26 (4.0-4.49)	24,074 (50.2)[c]	N/A[d]
Male	0.39 (0.42-0.36)	1.97 (1.88-2.06)	24,671 (51.4)[c]	N/A
ICD-9[e] (description)				
571 (chronic liver disease and cirrhosis)	2.52 (2.35-2.62)	14.63 (13.75-15.58)	5753	11.08 (10.5-11.7)
070 (viral hepatitis)	0.67 (0.58-0.77)	11.36 (10.48-12.32)	3023	8.98 (8.4-9.6)
533 (peptic ulcer)	0.41 (0.69-0.13)	3.46 (3.22-3.72)	3446	2.92 (2.7-3.1)
456 (varicose veins of other sites)	<0.01	22.47 (15.89-31.78)	246	14.31 (11.3-18.1)
573 (other disorders of liver)	<0.01	5.34 (4.54-6.27)	611	3.93 (3.5-4.4)
794 (nonspecific abnormal results of function studies)	<0.01	4.48 (3.59-5.6)	313	3.03 (2.6-3.6)
574 (cholelithiasis)	<0.01	4.36 (3.75-5.06)	700	3.9 (3.4-4.4)
V76 (screening for malignant neoplasms)	0.78 (1.2-0.36)	0.42 (0.36-0.48)	2445	0.42 (0.4-0.5)
626 (disorders of menstruation and other abnormal bleeding from female genital tract)	0.14 (0.31-0.01)	0.3 (0.27-0.35)	3352	0.66 (0.6-0.7)
625 (pain and other symptoms associated with female genital organs)	0.16 (0.33-0.01)	0.25 (0.18-0.35)	674	0.57 (0.4-0.7)
V22 (normal pregnancy)	<0.01	0.16 (0.12-0.22)	1180	0.44 (0.3-0.6)

[a]AUROC: area under the receiver operating curve.

[b]OR: odds ratio.

[c]These data are presented as numbers and percentages.

[d]N/A: not applicable.

[e]ICD-9: International Classification of Disease, Ninth Revision.

Table 3 displays the AUROC-impacted value and ORs of the drugs. The high impact drugs include liver therapy (AUROC loss 1.35%), antacids with antiflatulents (1.2%), solutions for parenteral nutrition (0.77%), aluminum compounds (0.63%), antihistamines (0.57%), and others. Some drugs appear to be negatively associated with HCC, including the treatment of acne (0.48%) and progestogens (0.36%), but this does not mean that they could reduce the risk of HCC since only an association, and not causation, was discovered between them. Given the age- and gender-matched cohort, the ORs greater than 1 could be considered similar to those of the unmatched cohort, while the ORs less than 1 were not so low.

We referred to this CNN predictive model while testing a special case in which a male patient had only age and gender information but did not have any medical records during the observed 3 years. The estimated HCC risks are listed in Figure 4 according to his age. In this case, the patient was classified into the high-risk group at the age of 52 years. However, if the patient had 1 record of screening for malignant neoplasms (V76 of the ICD-9-CM) a half year before the final day of his EHR and the result was benign, the high-risk alarm would be delayed until the age of 87 years. The reason for this is that the screening for malignant neoplasms was negatively relevant to HCC.

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Table 3. Drugs with high AUROC-impacted value.

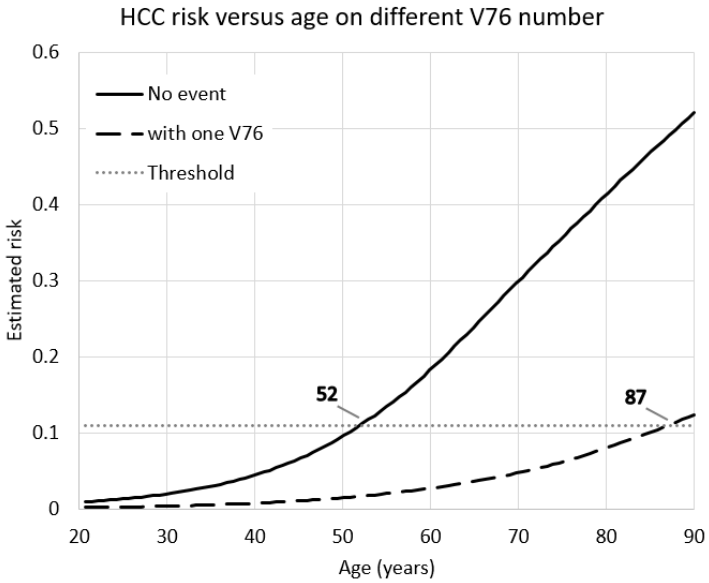
ATC[a]	AUROC[b] loss (%) (95% CI)	OR[c] (95% CI)	Patient number	Age- and gender-matched OR
A05BA (liver therapy)	1.35 (1.27-1.42)	14.26 (13.29-15.31)	4353	12.03 (11.3-12.8)
A02AF (antacids with antiflatulents)	1.2 (1.19-1.21)	10.38 (9.72-11.08)	4707	11.87 (11.1-12.7)
B05BA (solutions for parenteral nutrition)	0.77 (0.67-0.87)	5.18 (4.71-5.69)	1873	6.07 (5.5-6.7)
A02AB (aluminum compounds)	0.63 (0.56-0.76)	3.27 (3.04-3.51)	3335	3.31 (3.1-3.6)
R06AX12 (antihistamine, treatment of allergy)	0.57 (0.42-0.65)	31.78 (26.28-38.43)	1008	37.58 (31-45.6)
B05XC (vitamins)	0.56 (0.52-0.59)	5.92 (5.19-6.76)	942	6.38 (5.6-7.3)
A11JC (vitamins, other combinations)	0.5 (0.09-0.98)	13.68 (11.7-15.98)	890	14.46 (12.4-16.8)
C03DA (antimineralocorticoid)	0.45 (0.44-0.45)	6.42 (5.73-7.19)	1286	7.2 (6.4-8.1)
A05AA (bile therapy)	0.42 (0.27-0.51)	14.13 (12.28-16.25)	1115	11.39 (10.1-12.9)
A11BA (multivitamins)	0.39 (0.21-0.67)	7.47 (5.48-10.18)	176	7.78 (5.8-10.5)
A11AA (multivitamins with minerals)	0.36 (0.03-0.58)	7.7 (6.22-9.52)	379	6.92 (5.7-8.4)
B02BA (vitamin K)	0.25 (0.03-0.6)	7.58 (5.61-10.23)	189	6.53 (5-8.6)
D10AF (treatment of acne)	0.48 (0.15-1)	0.4 (0.36-0.46)	3017	0.72 (0.6-0.8)
G03DC (progestogens)	0.36 (0.08-0.53)	0.39 (0.33-0.46)	1809	0.91 (0.8-1.1)
D10AX03 (azelaic acid, antiacne)	0.31 (0.09-0.57)	0.36 (0.26-0.5)	503	0.72 (0.5-1)

[a]ATC: Anatomical Therapeutic Chemical (classification system).

[b]AUROC: area under the receiver operating curve.

[c]OR: odds ratio.

Figure 4. An example of a male patient. HCC: hepatocellular carcinoma.



Discussion

Main Findings

Accurate stratification of patients at high risk for HCC is the primary step for early detection and treatment. Our predictive model, based on a CNN algorithm and using minimal features from electronic medical records, can correctly stratify HCC risk in patients. The main advantages of our model are that it can predict patients with HCC 6 months, 1 year, and 3 years early with an AUROC as high as 0.96, 0.94, and 0.91, respectively. Furthermore, this model does not require any laboratory data. It is entirely based on age, gender, diseases, and drug data from the EHR as part of routine patient care. Finally, results of the prediction are reliable and can be trusted; this paper presents the highly weighted variables and checked their OR against HCC to gain insight into the black box of the CNN model. HCC risk stratification performed 1 to 3 years in advance could help physicians in identifying the high-risk patients and thus improving treatment and surveillance in an evidence-based fashion, such as by actively treating hepatitis C, instructing

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patients to improve their lifestyle, or screening for malignant neoplasms before normally scheduled.

Comparison With Other Studies

Several groups of researchers have already attempted to improve the identification and risk stratification of HCC patients. Flemming et al [12] showed that the ADRESS-HCC risk model (including 6 variables of age, diabetes, race, etiology of cirrhosis, sex, and severity of liver dysfunction) could identify HCC patients 1 year earlier with an ROC of 0.70. A total of 34,932 patients were included in their model, and the median follow-up was 1.26 years. The traditional statistical regression was used to develop and validate the predictive model for HCC risk. Furthermore, Yang et al [20] developed a predictive model of HCC risk of over 5 or 10 years in advance in patients with chronic hepatitis B. Potential risk factors, including age, sex, alcohol consumption, and serum alanine aminotransferase level, were considered to develop and validate the predictive model. The regression model achieved AUROCs ranging from 82.1% to 88.5%, and the nomograms model achieved AUROCs ranging from 82.1% to 86.6%. In comparison, our model can predict HCC risk 1 year ahead as opposed to a longer 5-10 year period; in this way, patients at high risk are more likely to undergo further medical treatment for the more immediate hazard instead of putting it off.

Clinical Implications

This deep learning–based model works by analyzing the pattern relationships of existing data. The CNN model with multiple hidden layers has already shown remarkable success for image classification [21]. However, there is still no deep learning–based HCC risk predictive model that uses EHR data. As EHRs are a rich source of patient data, CNN models can organize these high-dimensional data sets to provide greater prediction for patients with HCC. Making use of artificial intelligence to facilitate HCC prediction is beneficial because current clinical guidelines indeed have little effect on predicting those patients with HCC 1 year earlier and usually require complementary laboratory data.

Preventing HCC is the main target in the care of a patient with multiple risk factors. A prevention strategy should focus on reducing the development of HCC risk factors or treating them in the early stage [22]. The best approaches in HCC prevention usually include identifying high-risk factors and eliminating these factors if possible. This study presents the diseases and the drugs with high weighting in the model as well as those with higher ORs. These have also been reported in other studies. A significant amount of literature has already indicated that age, gender [7], and diseases like viral hepatitis, peptic ulcer, chronic liver disease, and cirrhosis [23-25] are associated with the development of HCC. Also, some studies found evidence for a relation between vitamins and liver diseases such as fibrosis [26] or nonalcoholic fatty liver disease [27]. Mineralocorticoid receptor activation could play a role in hepatic fibrogenesis, and its modulation could be beneficial for nonalcoholic steatohepatitis [28]. Moreover, a liver drug, silymarin, has been used to good effect in different liver disorders due to its antioxidant, anti-inflammatory, and antifibrotic properties [29]. Previous studies have shown that the use of antacids promotes liver disease [30], and the high impact of antacids (see Table 3) should be further investigated to determine whether a causal relationship exists.

Another noteworthy finding was that some variables had high ORs for HCC but were not in the list of highly weighted variables. This may be because the number of the patients diagnosed with these variables was not large enough to garner heavy weighting. For example, ICD-9 code 456 (varicose veins of other sites) had an OR as high as 22.47, but the AUROC loss for it was less than 0.1% because there were only 246 patients with this code out of the 9553 patients with HCC and the total population of 47,945.

As correlation is not necessarily causation [31], it cannot be concluded that those variables with high ORs induce HCC: they are only positively correlated with it. However, these can still be considered significant variables and be used to predict HCC risk. For example, we cannot claim antacids with antiflatulents induce HCC despite their OR for HCC being as high as 10.38. However, the patients taking these drug do have a higher probability of having HCC due to its relationship with HCC.

On the other hand, OR of screening for malignant neoplasms was less than 0.5, which means it is negatively correlated with HCC. The reason for this correlation is that the neoplasms screening records of the patients with HCC do not increase after day they are diagnosed with HCC, while the non-HCC patients continuously accumulate screening records until the last day of their extracted data. Furthermore, the reason why some diagnoses in Table 2, including endometriosis, symptoms associated with female genital organs, and pregnancy, negatively correlate with HCC is that they are more commonly associated with young females who have the opposing traits to those considered as high-risk factors of HCC: being old and male. The inspection of the ORs corresponding to the highly weighted variables also helps us to understand how the predictive model works.

Strengths and Limitations

Our model has several strengths. First, this is the first study to use a deep learning–based predictive model to stratify patients with HCC 1 year in advance via the claim database. Second, our study achieved a higher performance than did previous studies all while using a minimal number of features from standardized and widely available clinical data of EHRs. Despite the promising results in stratifying HCC patients, our study has several limitations that should be addressed. First, laboratory data inclusion may enable more accurate deep learning models to be trained and validated with higher confidence. Second, several variables such as genetic data, ethnicity, family history, alcohol consumption, smoking, dietary habit, vital signs, and BMI were not considered in our predictive model, the inclusion of which may improve the prediction; nonetheless, our model achieved a high performance with the currently available variables in EHRs. Finally, external validation on other data sets are warranted to the ensure generalizability of our current model.

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Conclusions

Our prediction model achieved high performance with high sensitivity and specificity for predicting HCC risk using standardized and widely available claim data. This predictive model also identified some risk factors and may provide physicians a means to recognizing deteriorating patients in timely fashion. As the model predicts patients with HCC 1 year in advance, it is therefore able to improve patient care and enhance research into best practices to further reduce mortality in patients with HCC.

Acknowledgments

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Authors' Contributions

CWL and YCL conceived the study. CWL and HCY were responsible for the methodology; CWL, PNN, YTF, and ZYH managed the software; YCL, CWH, and MMI were responsible for validation; CWL conducted the formal analysis; YCL conducted the investigation; HCY acquired the resources; CWL, PNN, and YTF were responsible for data curation; MMI and CWL wrote and prepared the original draft; YCL reviewed and edited the draft; HCY was responsible for visualization; and YCL was responsible for supervision, project administration, and funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary files.
[DOCX File , 537 KB - cancer_v7i4e19812_app1.docx]

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Abbreviations

ATC: Anatomical Therapeutic Chemical (classification system)
AUROC: area under the receiver operating curve
CNN: convolutional neural network
EHR: electronic health record
HCC: hepatocellular carcinoma
ICD-9-CM: International Classification of Disease, Ninth Revision, clinical modification
OR: odds ratio

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Original Paper

Characteristics of Participants and Nonparticipants in a Blended Internet-Based Physical Activity Trial for Breast and Prostate Cancer Survivors: Cross-sectional Study

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Abstract

Background: As the number of cancer survivors is increasing, it is important to be able to offer exercise and physical activity (PA)–promoting interventions that are both effective and reasonably accessible. Internet-based interventions are typically less expensive and more accessible alternatives to on-site supervised interventions. Currently, little is known about the characteristics of nonparticipants in PA promotion trials in the cancer survivorship setting, both in general and specifically in trials using internet-supported interventions.

Objective: This study aims to gain insight into the characteristics associated with nonparticipation in a blended internet-based supported intervention trial to promote PA.

Methods: Breast and prostate cancer survivors, 3-36 months after primary curative treatment, were invited to participate in the PABLO trial; this trial compared an internet-based intervention to enhance PA levels, with or without additional support from a physical therapist, to usual care. Participants and nonparticipants were asked to complete a comprehensive questionnaire assessing sociodemographics, fatigue, and health-related quality of life. Baseline data for participants and nonparticipants were compared using the independent Student *t* test and chi-square test.

Results: The inclusion rate in the trial was 11.03% (137/1242). Of the nonparticipants, 13.95% (154/1104) completed the questionnaire. Participants were more highly educated (P=.04), had a paid job less often (P=.03), and were on sick leave more often (P=.03). They reported less PA per week, both moderate (P=.03) and vigorous (P<.01), before diagnosis and during leisure time (P<.01, effect size [ES]=0.44). They reported a significantly lower stage of change (P≤.01), lower self-efficacy (P<.01, ES=0.61), perceived barriers to PA (P<.01, ES=0.54), and more general fatigue (P<.01, ES=0.60). Participants reported lower health-related quality of life for most domains (ES ranging from 0.34 for mental health to 0.48 for social functioning). No significant differences were found for other sociodemographics, mood state, or attitudes toward or perceived social support for PA.

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Conclusions: The participants who self-selected for trial participation reported lower PA levels before diagnosis and a stronger need for support compared with nonparticipants. The trial thus included those patients who might benefit the most from internet-based supportive PA interventions.

Trial Registration: Netherlands trial register NTR6911; https://www.trialregister.nl/trial/6733

(JMIR Cancer 2021;7(4):e25464) doi:10.2196/25464

KEYWORDS

internet-based intervention; physical activity; nonparticipants; breast cancer survivors; prostate cancer survivors; RCT

Introduction

Background

Long-term side effects of cancer treatment commonly lead to a decrease in psychosocial and physical functioning [1]. Multiple systematic reviews have demonstrated the positive effects of physical exercise interventions on various outcomes in cancer patients and survivors, including fatigue, physical functioning, and health-related quality of life (HRQoL) [2-5]. There is also some evidence that exercise can have a positive effect on survival in several cancer population (eg, breast and prostate cancer) [6]. For these reasons, physical exercise programs are becoming an increasingly important component of cancer care, both during and after primary treatment [7].

As the number of cancer survivors is increasing, it is important to be able to offer exercise- and physical activity (PA)-promoting interventions that are both effective and reasonably accessible. Supervised interventions have proven to be superior to unsupervised interventions in increasing PA levels [2]. Nevertheless, previous studies have reported that approximately half of eligible patients declined to participate in supervised exercise and PA-promoting interventions [8,9]. Moreover, offering supervised exercise to all patients would represent a significant burden to the health care system in terms of financial and human resources [10]. Internet-based interventions are typically less expensive and more accessible alternatives for those who cannot or do not want to participate in on-site supervised interventions or who have limited exercise support needs. At the same time, internet-based interventions may not be suitable for every patient. An increased understanding of reasons for nonparticipation in exercise interventions, especially those that are internet-based, is required to improve selection for and referral to such programs.

Given that participation in exercise and PA promotion trials for people living with and beyond cancer could be improved, such trials also offer opportunities to study factors associated with nonparticipation. Currently, little is known about the characteristics of nonparticipants in PA promotion trials in cancer survivorship in general, and specifically in trials using internet-based interventions. Two previous studies compared the characteristics of patients with breast cancer who took part in a randomized controlled trial (RCT) of supervised exercise during radiotherapy and chemotherapy with those did not participate in the trial. Both studies reported significantly higher fatigue levels at baseline for nonparticipants [11,12]. Travel distance and time investment (eg, fixed training schedules) were also noted as reasons for nonparticipation. During chemotherapy, nonparticipants differed in attitudes toward PA; they perceived fewer benefits and more barriers and had a lower sense of self-efficacy with regard to exercising [11]. In a supervised RCT among cancer survivors [13], nonparticipants reported a lower educational level, were more likely to smoke, had higher levels of psychological distress and lower outcome expectations, and experienced fewer barriers compared with the participants.

Objectives

To inform clinical practice and to achieve higher inclusion rates in future internet-based intervention studies, it is of interest to know more about potential patient- and tumor-specific participant and nonparticipant characteristics. It is also of interest to know whether reasons for nonparticipation in supervised programs differ from those presented with an internet-based approach in which barriers such as travel distance and strict time management are no longer relevant [14]. The aim of this study is to gain insight into the characteristics of participants and nonparticipants of an internet-based intervention promoting PA among breast and prostate cancer survivors whose primary oncological treatment had been completed between 3 months and 3 years earlier.

Methods

Design and Study Population

For this cross-sectional investigation, we used baseline data from the PABLO study, an RCT in which a web-based intervention is being evaluated as a means of improving PA levels in cancer survivors. Patients were recruited from 3 Dutch hospitals: the Netherlands Cancer Institute, Amsterdam, Rijnstate Hospital, Arnhem, and the University Medical Centre, Utrecht. Breast and prostate cancer survivors were randomized into 3 groups: (1) internet-based physical activity support program (IPAS), (2) IPAS + additional telephone support from a physical therapist, or (3) control group (usual care) A detailed description of the trial protocol and internet-based intervention has been published previously [15]. This protocol followed the CONSORT-EHEALTH guidelines [16].

Breast and prostate cancer survivors who had completed primary curative treatment 3-36 months earlier, but who could still be receiving adjuvant endocrine treatment or trastuzumab, were invited to participate. Patients were excluded if they lacked basic proficiency in Dutch, had serious cognitive or psychiatric problems that would preclude following the intervention, complete the study questionnaires, or lacked access to the internet. Those without a digital ID, the Dutch digital authentication system on the basis of one's social security

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number (used primarily for governmental services), were also excluded, as this was required to log on to the IPAS. Patients participating in concurrent studies or rehabilitation programs containing psychosocial or exercise interventions were excluded, as were those who were unable to perform unsupervised exercise at the recommended levels or who could not safely perform such exercise according to the pre-exercise screening recommendations of the American College of Sports Medicine [17]. Patients with cardiovascular, metabolic, or renal diseases could only participate after receiving approval from their treating physician. Finally, to ensure that the trial targeted those who could potentially benefit from PA, we excluded patients who reported already engaging regularly in >200 minutes per week of moderate-to-vigorous PA for more than 6 months, as determined via a brief interview.

For this study, eligible patients who declined to participate in the PABLO trial were asked to complete a web-based questionnaire. Participants completed the same questionnaire as part of the baseline measurement. The questionnaire was administered using the web-based program *Exploratio* (Newcom Research & Consultancy). Patients who did not wish to complete the full questionnaire were offered the opportunity to voluntarily report reasons for nonparticipation on the response card that was attached to the trial invitation.

Procedure

Patients' medical records were screened for inclusion and exclusion criteria, except for prescreening PA levels. Potentially eligible participants for the trial were approached by mail or in person when their treating health care worker (nurse practitioner or physician [assistant]) considered the patient to be eligible for the trial. All participants and nonparticipants in this study provided written informed consent and completed the web-based questionnaire. Ethical approval was obtained from the institutional review board of the Netherlands Cancer Institute, Amsterdam (NL62269.031.17).

Outcome Measures

Self-reported Reasons for Nonparticipation in the PABLO Trial

Reasons for nonparticipation for those who were willing to complete the nonparticipants' questionnaire were assessed by five preset options: (1) participation in another trial, (2) no time, (3) the study is not applicable to me or no interest, (4) participation is too burdensome for me, and (5) other.

Those who declined to complete the full nonparticipants' questionnaire were asked if they were willing to provide the reasons for nonparticipation, using five slightly different response options: (1) I am already sufficiently physically active, (2) no time, (3) my physical state is not good enough, (4) I do not think I will benefit from it, (5) other.

Clinical Characteristics

Clinical data, including tumor type and staging, type of treatment, and time between diagnosis and the end of treatment, were obtained from the medical records.

Sociodemographics and Health Behavior

Sociodemographic information about age, sex, educational level, living and work situation, as well as lifestyle data, such as smoking behavior, alcohol consumption, and PA behavior, before the diagnosis of cancer was assessed via a questionnaire. The questionnaire also included study-specific questions about patients' use of the internet and their level of computer skills.

Self-reported PA, Fatigue, Mood, and Health-Related Quality of Life

Self-reported PA behavior was assessed using the International Physical Activity Questionnaire (IPAQ). The IPAQ contains 4 domains: PA at work, during transport, at home, and during leisure time. Scores were calculated according to the IPAQ manual, resulting in metabolic equivalent of task minutes per week, as the total score per domain [18].

Fatigue was assessed using the Multidimensional Fatigue Inventory Questionnaire (MFI) [19]. The MFI consisted of 20 items organized into five dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Scores ranged from 4 to 20 per subscale. Higher scores indicate higher levels of fatigue.

Mood was assessed using the Profile of Mood States (POMS) [20]. This 32-item questionnaire consisted of five mood scales: anger, depression, fatigue, tension, and vitality. For anger, depression, fatigue, and tension, higher scores indicate higher mood expression of a specific item (ranging from 0 to 20). Vitality was reverse coded so that higher scores indicated less vitality (ranging from 0 to 20). Items' scores ranged from 0 to 4. The total score was calculated as the sum of the means of the 4 mood scales minus the vitality score. Higher scores indicate higher levels of anger, tension, depression, fatigue, and lower vitality.

HRQoL was assessed using the 36-Item Short Form Health Survey (SF-36) [21]. The SF-36 includes eight scales assessing physical functioning, vitality, role functioning limitations due to physical problems, role functioning limitations due to emotional problems, social functioning, physical pain, mental health, and general health. Scores range from 0 to 100 per subscale. Higher scores indicated higher levels of functioning and HRQoL.

Behavioral and Attitudinal Variables Toward PA

The current exercise behavior stage was assessed by a single item, on the basis of the transtheoretical model [22]. Patients were asked to choose from five statements, each of which corresponded to one of the stages of change, the one statement that best described their current situation. In the transtheoretical model, five behavioral change stages are identified: (1) precontemplation (ie, not sufficiently active and not intending to change; (2) contemplation (ie, not sufficiently active but willing to change within the next 6 months); (3) preparation (ie, not sufficiently active but planning to change within 1 month; (4) action (ie, sufficiently active but for <6 months); and (5) maintenance (ie, sufficiently active for >6 months) [22].

Questions on the basis of the theory of planned behavior were used to assess self-efficacy, barriers to and benefits of PA, and

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perceived social support [11,23]. Five items assessed self-efficacy regarding PA. Respondents rated on a 0-10 response scale, how likely they thought it was that they would exercise when tired, in a bad mood, when feeling pressed for time, when on holiday, or with bad weather [24]. The overall self-efficacy score was obtained by calculating the average of all items, ranging from 0 to 10. A higher score indicates a stronger sense of self-efficacy. Cronbach α for this scale in our sample was .85.

Items on perceived barriers to and benefits of PA were selected from 2 existing questionnaires [23,24], as previously used by Van Waart et al [11]. Potential barriers were assessed using 18 items assessing motivation, money, time, energy, other obligations, transportation, support for exercise, counseling about exercise, limited possibilities in the environment, pleasure, family obligations, fear of injuries, discipline, health conditions, nausea, fatigue, pain, and work responsibilities. Responses were on a 5-point Likert-type scale (*never a barrier* to *very often a barrier*). The barrier score was calculated as the average of the item scores, ranging from 0 to 5 per item. Higher scores indicate a higher perceived level of barriers. Cronbach α for the total scale was .87.

The perceived benefits of PA were assessed using 11 items, including improved health leading to a reduced risk of disease, feeling better about oneself, improved fitness, improved daily functioning, weight loss, meeting new people, getting one's mind off cancer and its treatment, improving overall well-being, coping with the stress of cancer and treatment, gaining control over cancer and life, and recovering from treatment. Items were scored on a 5-point Likert scale (*completely disagree* to *completely agree*). The perceived benefit score was obtained by averaging item scores, ranging from 0 to 5 per item. A higher score indicated a higher sense of benefit. Cronbach α for this scale was .91.

Attitudes toward PA were assessed using 7-point adjective rating scales. Two dimensions were measured: (1) instrumental attitude (useful–useless, harmful–beneficial, wise–foolish, and bad–good) and (2) affective attitude (enjoyable–unenjoyable, boring–interesting, pleasant–unpleasant, and easy–hard) [23]. The overall score for attitude was similarly calculated as the average score of the combined 8 items, ranging from 0 to 7 per item. Cronbach α for this scale was .95. Higher scores indicate more positive attitudes toward exercise [11].

Finally, perceived social support from partners, family, friends, colleagues, general practitioners, treating physicians, and other patients with cancer for PA was assessed. These items were scored on a 5-point Likert-type response scale, with an overall Cronbach α of .9. The overall perceived support score was calculated by summing the items [11,25]. The higher the score, the more perceived social support.

Statistical Analysis

We report descriptive statistics using means, SDs, medians, and IQRs for continuous variables, and frequencies and percentages for categorical variables.

We compared baseline data between participants and nonparticipants using an independent Student *t* test for continuous variables. For ordinal variables, a linear-by-linear association was used. For dichotomous variables, we used Fisher exact test.

On the basis of the literature, we hypothesized that there might be an interaction between tumor type and the following variables—age, work situation, PA levels before diagnosis, IPAQ-scores, and stage of change. Interaction tests were performed using regression analysis. In case of a statistically significant interaction, the descriptive statistics and group comparisons were stratified by tumor type. Two-sided *P* values <.05 were considered statistically significant. Effect sizes were calculated as the group mean differences divided by pooled SD. Given the exploratory nature of this study, we did not correct for multiple tests. All analyses were performed using SPSS version 25 (SPSS Inc).

Results

Participation of Respondents

Of the 1242 invited individuals, 137 participated in the PABLO trial (participation rate: 137/1242, 11.03%). Of all nonparticipants (n=1105), 206 indicated a willingness to complete the questionnaire, of whom 154 actually did so (154/1105, 13.94% response rate). More than half of the patients (722/1242, 58.13%) did not respond. Another 12.32% (153/1242) of the invited patients sent back a response card, including reasons for not participating in the trial, but did not complete the web-based questionnaire (Figure 1).

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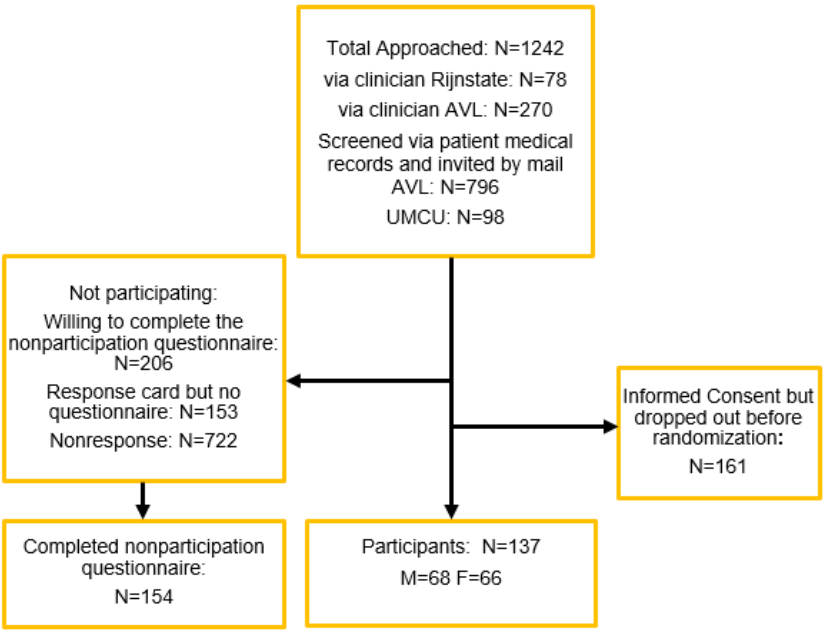
Figure 1. Diagram of nonparticipants of the PABLO trial. AVL: Antoni van Leeuwenhoek; F: Female; M: Male; UMCU: University Medical Centre Utrecht.



Self-reported Reasons of Nonparticipation

The most often reported reason for nonparticipation was the perceived adequate level of PA. This was reported by 40.3% (62/154) of those who completed the questionnaire and 82.5% (127/154) of those who provided their reason on the response card. Additional reasons reported by the questionnaire respondents were (multiple options possible): “I don’t have time to participate” (33/154, 21.4%), “Participation is too burdensome for me” (6/154, 3.9%), “The study is not applicable to me/no interest” (4/154, 2.6%), “Participation in another trial” (3/154, 1.9%) and “Other” (46/154, 29.9%). Other reasons stated on the response card by those who did not complete the questionnaire were “I don’t think I will benefit from it” (16/198, 8.1%), “No time” (15/198, 7.6%) “My physical state is not good enough” (8/198, 4%) and “Other” (41/198, 20.7%), of which 3 reported “The online approach.”

Clinical Characteristics

Statistically significant interactions with tumor type were observed for age, retirement, and self-rating of a vigorous level of PA on the IPAQ. For these variables, stratified results were reported, in addition to the total group results.

The percentage of nonparticipants did not differ significantly between breast and prostate cancer survivors (82/154, 53.3% and 72/154, 46.7%, respectively). In breast cancer survivors, nonparticipants were less likely to have undergone a mastectomy and were more likely to have undergone breast-conserving surgery. No significant differences in any treatment-related variables were observed within the prostate cancer survivor group (Table 1).

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Table 1. Baseline clinical characteristics of 154 individuals who filled out the nonparticipants questionnaire and 137 participants.

Clinical characteristic	Nonparticipants breast cancer (n=82)	Participants breast cancer (n=67)	Nonparticipants vs participants breast cancer, *P* value	Nonparticipants prostate cancer (n=72)	Participants prostate cancer (n=70)	Nonparticipants vs participants prostate cancer, *P* value
Tumor type or sex, n (%)	82 (53.2)	67 (51.1)	N/A[a]	72 (46.8)	70 (48.9)	N/A
Treatment, n (%)[b]						
Chemotherapy	32 (39.0)	28 (44.4)	.52	0 (0)	0 (0)	N/A
Radiotherapy	64 (78.0)	48 (71.6)	.46	24 (33.3)	20 (28.6)	.58
Chemo and radiotherapy	26 (31.7)	22 (34.9)	.69	0 (0)	0 (0)	N/A
Endocrine therapy	51 (62.2)	32 (47.8)	.44	6 (8.3)	6 (8.8)	.92
Breast-conserving surgery	65 (79.3)	41 (61.2)	.02	N/A	N/A	N/A
Mastectomy	16 (19.5)	24 (35.8)	.03	N/A	N/A	N/A
Breast reconstruction	24 (29.3)	24 (35.8)	.40	N/A	N/A	N/A
Prostatectomy	N/A	N/A	N/A	48 (66.7)	52 (75.4)	.26
Brachytherapy	N/A	N/A	N/A	3 (4.2)	2 (3.0)	.71
Treatment duration (months), mean (SD)	6.8 (4.8)	6.7 (4.1)	.92	4.1 (3.6)	4.5 (5.3)	.61

[a]N/A: not applicable.

[b]Combination of treatments possible per patient, total percentages reach above 100%.

Sociodemographics and Health Behavior at Baseline

The mean age of the participants was 60.1 years (SD 14.1). The mean age of the nonparticipants was 63 years (SD 11.1). In breast cancer survivors, nonparticipants were significantly older than participants (mean 57.35 vs 52.66%; *P*=.01). For the total group, nonparticipants had significantly lower education levels than did the participants (*P*=.04). No significant differences between nonparticipants and participants were found in living situations. Nonparticipants more often had paid jobs (*P*=.03) and were less on sick leave (*P*=.03). Nonparticipating prostate cancer survivors were more often retired (*P*=.03) than the participants. No significant differences were found between the groups in terms of smoking or alcohol consumption. Self-reported computer skills and frequency of internet use did not differ significantly between groups. Nonparticipants more often reported being moderately (*P*<.001) and vigorously (*P*<.001) physically active per week in the period before diagnosis than the participants (Table 2).

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Table 2. Sociodemographics at baseline of 154 individuals who filled out the nonparticipants questionnaire and 137 participants.

Sociodemographic	Nonparticipants (n=154)	Participants (n=137)	Nonparticipants vs participants, *P* value
Age (years), mean (SD)	63 (11.1)	60.1 (14.1)	.05
Living situation, n (%)			.53
Single	19 (12.3)	23 (16.8)	
Living together	128 (83.1)	108 (78.8)	
With partner, not living together	6 (3.9)	5 (3.6)	
Missing	1 (0.6)	1 (0.7)	
Education level (%)			.04
Primary school	2 (1.3)	2 (1.5)	
High School	68 (44.1)	46 (33.6)	
College or university	80 (52.0)	88 (64.2)	
Missing	4 (2.6%	1 (0.7)	
Work situation, n (%)[a]			
Paid job	76 (49.4)	56 (42.4)	.03
Retired	67 (45.6)	45 (33.1)	.03
Sick leave	8 (5.2)	16 (11.7)	.03
Other[b]	42 (27.3)	40 (30.1)	.95
Smoking behavior, n (%)			.10
Never	56 (36.4)	62 (45.3)	
Quit	82 (53.2)	64 (45.9)	
Current	16 (10.4)	10 (6.8)	
Missing	N/A[c]	1 (0.7)	
Alcohol consumption, n (%)			.09
No	27 (17.5)	35 (27.1)	
Yes	127 (82.5)	101 (72.9)	
Missing	N/A	1 (0.7)	
Computer use, n (%)			.81
Sometimes	7 (4.5)	7 (5.1)	
Often	146 (94.8)	128 (93.4)	
Missing	1 (0.6)	2 (1.5)	
Computer skills, n (%)			.66
Bad	14 (9.1)	11 (8.0)	
Moderate	43 (27.9)	36 (26.3)	
Good	96 (62.3)	88 (64.2)	
Missing	1 (0.6)	2 (1.5)	
Physical activity levels before diagnosis[d] (in days per week), mean (SD)			
Moderate[e]	6.4 (1.9)	5.7 (2.4)	<.001
Vigorous[f]	4.0 (2.2)	2.9 (2.1)	<.001

[q]Multi-answer options, total percentage reaches above 100%; Missings: paid job, Nonparticipants n=17, participants n=5; Retired, nonparticipants n=7, participants n=1; At home because of illness: nonparticipants n=13, participants n=5; Other, nonparticipants n=16, participants n=1.

[b]Student, voluntarily unemployed, involuntarily employed, volunteer work.

[c]N/A: not applicable.

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[d]Effect size for physical activity levels before diagnosis: moderate, 0.32; vigorous, 0.51.

[e]Question: How many days of the week were you moderate physical active for at least 30 minutes?

[f]Question: How many days of the week were you vigorous physical active for at least 20 minutes?

Self-reported PA, Fatigue, Mood, and Health-Related Quality of Life

As shown in Table 3, we did not observe a significant difference between participants and nonparticipants for PA intensities, as measured by the IPAQ (ie, walking, moderate, or vigorous). For the IPAQ domain leisure time, participants were significantly less active (metabolic equivalent of task minutes per week) than nonparticipants (P<.01, ES=0.44). No significant differences were found for the other 3 IPAQ domains (ie, at work, home, and during transport). In the stratified analysis (data not shown in the table), we observed significantly lower levels of vigorous PA in participating breast cancer survivors (P=.01, ES=0.45). This difference was not observed in prostate cancer survivors. No significant differences were observed between participants and nonparticipants in any of the five domains of mood states. Trial participants reported significantly more fatigue than nonparticipants on all five dimensions of the MFI: general fatigue (P<.01, ES=0.60), physical fatigue (P<.01, ES=0.77), reduced activity (P<.01, ES=0.61), mental fatigue (P<.01, ES=0.45), and reduced motivation (P=.02, ES=0.30). For HRQoL, participants reported significantly worse scores for nearly all domains of the SF-36, with effect sizes ranging from 0.34 for mental health to 0.48 for social functioning. Emotional role functioning was the only domain in which no significant group differences were found (Table 3).

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Table 3. Group differences in descriptive statistics for the outcome measures of fatigue, quality of life, mood status, PA levels, and PA attitude of 154 individuals who filled out the nonparticipants questionnaire and 137 participants.

Measure	Nonparticipants (n=154)	Participants (n=137)	Mean difference (95% CI)	Effect size	Nonparticipants vs participants, *P* value
IPAQ[a]—intensity, mean (SD)					
Walking	1630.9 (1758.9)	1278.9 (1800.1)	–343.0 (–755.7 to 69.6)	0.20	.10
Moderate physical activity	4190.4 (3898.5)	3522.25 (4225.4)	–668.1 (1609.0 to 272.7)	0.15	.16
Vigorous physical activity	1699.7 (3063.1)	1091.8 (2882.9)	–607.9 (–1299.6 to 83.7)	0.21	.09
IPAQ[a]—per domain, mean (SD)					
Work	1443.6 (3890.1)	1611.9 (4454.1)	168.3 (–797.9 to 1134.4)	0.05	.68
At home	2427.0 (2752.4)	1984.6 (3200.5)	–442.4 (–1131.7 to 246.8)	0.15	.20
Leisure time	2260.8 (2686.5)	1148.4 (2300.5)	–1112.3 (–1646.8 to 577.9)	0.44	<.01
During transport	1430.2 (1505.0)	1187.1 (1493.0)	–243.2 (–591.0 to 104.6)	0.16	.17
MFI[b], mean (SD)					
General fatigue	9.7 (4.2)	12.3 (4.5)	2.7 (1.7 to 3.7)	0.60	<.01
Physical fatigue	8.8 (4.3)	12.1 (4.3)	3.4 (2.4 to 4.4)	0.77	<.01
Reduced activity	9.0 (3.9)	11.3 (4.0)	2.3 (1.4 to 3.3)	0.61	<.01
Mental fatigue	8.3 (3.6)	10.0 (4.0)	1.7 (0.8 to 2.5)	0.45	<.01
Reduced motivation	8.8 (3.4)	9.8 (3.2)	1.0 (0.2 to 1.7)	0.30	.02
POMS[c], mean (SD)					
Fatigue	0.6 (1.6)	1.0 (2.3)	0.4 (0.2 to –0.04)	0.20	.08
Tension	0.5 (1.5)	0.7 (1.7)	0.3 (–0.1 to 0.6)	0.13	.19
Depression	0.6 (2.1)	0.6 (1.8)	–0.01 (–0.5 to 0.4)0.0	0.00	.96
Anger	0.5 (1.8)	0.6 (1.7)	(–0.4 to 0.4)	0.06	.99
Vitality	15.9 (2.9)	16.5 (3.0)	0.4 (–0.3 to 0.9)	0.09	.07
Total	18.2 (7.5)	19.4 (7.2)	1.24 (–0.47 to 2.9)	0.16	.16
SF-36[d], mean (SD)					
Physical functioning	88.5 (15.9)	82.6 (16.1)	–6.0 (–9.7 to –2.2)	0.37	<.01
Social functioning	87.0 (17.5)	77.3 (22.7)	–9.7 (–144 to –5.1)	0.48	<.01
Physical role	77.4 (36.2)	58.9 (43.0)	–18.5 (–27.7 to –9.4)	0.47	<.01
Vitality	70.7 (19.0)	59.7 (20.4)	–11.0 (–15.61 to –6.5)	0.56	<.01
Emotional role	84.4 (32.2)	78.5 (33.7)	–5.9 (–13.5 to 1.7)	0.19	.13
Mental health	80.7 (15.3)	74.8 (19.1)	–5.9 (–9.8 to -1.9)	0.34	<.01
General health	67.9 (17.7)	60.9 (20.8)	–7.0 (–11.5 to –2.6)	0.36	<.01
Bodily pain	85.9 (16.7)	78.9 (20.4)	–7.0 (–11.5 to –2.6)	0.38	<.01
Stage of change, n (%)					<.01
Precontemplation	1 (0.6)	2 (1.5)	N/A[e]	N/A	N/A
Contemplation	5 (3.2)	19 (13.9)	N/A	N/A	N/A
Preparation	20 (13.0)	43 (31.4)	N/A	N/A	N/A
Action	10 (6.5)	20 (14.6)	N/A	N/A	N/A
Maintenance	115 (74.7)	51 (37.2)	N/A	N/A	N/A
N/A	0 (0)	2 (1.5)	N/A	N/A	N/A
Self-efficacy, mean (SD)	8.0 (1.8)	6.8 (2.1)	–1.1 (–1.6 to –0.7)	0.61	<.01

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Measure	Nonparticipants (n=154)	Participants (n=137)	Mean difference (95% CI)	Effect size	Nonparticipants vs participants, *P* value
Barriers, mean (SD)	1.7 (0.5)	2.0 (0.6)	0.3 (0.2 to 0.4)	0.54	<.01
Benefits, mean (SD)	3.9 (0.8)	3.8 (0.7)	–0.1 (–0.2 to 0.1)	0.13	.46
Attitude, mean (SD)	5.8 (1.1)	5.6 (1.0)	–0.2 (–0.4 to 0.1)	0.19	.15
Social support, mean (SD)	4.7 (0.9)	4.6 (0.9)	–0.2 (–0.4 to 0.1)	0.11	.14

[a]IPAQ: International Physical Activity Questionnaire scores represent total metabolic equivalent of task minutes per week.

[b]MFI: Multidimensional Fatigue Inventory Questionnaire scores range from 4 to 20, high scores indicate high fatigue.

[c]POMS: Profile of Mood States scores; see *Methods*.

[d]SF-36: 36-Item Short Form scores range 0-100, high scores indicate a better experienced quality of life.

[e]N/A: not applicable.

PA-Related Behavioral and Attitudinal Variables

Participants reported a significantly lower stage of change (*P*<.01), lower level of self-efficacy (*P*<.01, ES=0.61), and more perceived barriers to starting with or continuing PA (*P*<.01, ES=0.54) than trial nonparticipants. We did not observe any significant group differences in attitudes toward PA or perceived social support for PA (Table 3).

Discussion

Principal Findings

In this study, we examined in detail the differences in characteristics between participants and nonparticipants in an internet-based PA promotion trial for breast and prostate cancer survivors. The results suggest that trial participants were a self-selected group of survivors who experienced a stronger need for support to become more physically active. Trial participants generally reported significantly lower levels of PA behavior before diagnoses and were more often in the lower stage of the behavioral stage of PA change. At the same time, they reported a higher level of symptom burden, lower HRQoL, lower self-efficacy, and more barriers to PA than nonparticipants.

Our findings are in contrast with the results of earlier studies of nonparticipants in (supervised) exercise trials during and shortly after cancer treatment, which indicated that patients with more perceived barriers to PA were more prone to decline participation [8,11,13,26]. This discrepancy could indicate that symptoms such as fatigue and experienced barriers to becoming or staying physically active during and shortly after treatment may initially contribute to lower participation rates but may result in a greater willingness to participate when a trial is introduced longer after the oncological treatment has been completed. Self-selection for participation appears to result in a study population of cancer survivors with relatively higher levels of symptom burden, lower PA levels, and more barriers to PA. Factors that might explain this self-selection within our group of survivors could be (1) the unsupervised and internet-based nature of the intervention, (2) the timing of the intervention, (3) the method of providing information during recruitment, and (4) a more general awareness of the benefits of PA. In the following paragraphs, we discuss each of these issues separately.

The Internet-Based and Unsupervised Nature of the Trial Intervention

Use of (blended) internet-based interventions without the need for formal, hands-on supervision may have had a positive impact on trial participation by increasing the accessibility and convenience of the intervention. This might be particularly important for survivors with higher symptom burden, lower HRQoL, and more practical barriers to participation (eg, travel distance and fixed time schedules that characterize supervised exercise programs) [11,13]. Conversely, the web-based nature of the intervention was mentioned only three times as a reason for not participating in the trial. Importantly, we did not observe any significant differences in self-reported computer skills or frequency of weekly internet use between participants and nonparticipants.

Timing of the Intervention

Eligible patients were invited to participate in the trial 3-36 months after completion of their primary treatment. In trials during treatment, patients who experienced direct side effects and distress because of treatment planning may have declined to participate in an exercise trial, those who have completed their treatment may feel that the timing is appropriate for participating in an exercise trial. In contrast, it is conceivable that because, for a substantial number of survivors, the program was offered relatively late in their survivorship trajectory, many no longer perceived a need for a PA intervention. This could indicate that many survivors are able to regain satisfactory levels of PA without the support of a formal program.

Type of Trial Information

To obtain sufficient contrast, the trial specifically focused on survivors with insufficient self-reported levels of PA at the start of the trial. Therefore, we provided extensive information about the intervention to the target group during the recruitment process. This strategy of information provision during accrual could have generated a self-selection of survivors with relatively low levels of PA.

General Awareness of the Benefits of PA

Information available about the potential benefits of PA has increased over the last few years. Such information is available both as part of routine hospital care and through public communications about specified exercise guidelines for cancer

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survivors [27]. This may have led to more awareness among cancer survivors about the importance of being physically active. As a result, some survivors may have increased their levels of PA, whereas others may have become more acutely aware of their inability to do so. In line with this, participants reported lower levels of self-efficacy related to PA and experienced more barriers, lower PA levels during leisure time, and a lower HRQoL. Therefore, participants may have felt a stronger need for external support to attain sufficient levels of PA, and thus, had a greater willingness to participate in the trial.

Regarding sociodemographic characteristics, our results are similar to those observed in supervised, noninternet-based exercise trials during and after treatment of prostate, breast, lymphoma, colon, and ovarian cancer [7,11,13]. In line with these studies, participants in our trial were more highly educated than nonparticipants. The relatively high educational level of our total sample may also reflect the fact that the majority of the recruited participants came from the Netherlands Cancer Institute, a specialized oncological treatment center that tends to attract more highly educated patients [28].

A notable finding at baseline was that more than one-third of trial participants reported being in the *maintenance stage* of PA. This was an unexpected finding, as being in this stage (as defined by a short telephone interview) was one of our exclusion criteria. The high number of patients who reported being in the *maintenance stage* could reflect socially desirable responses or overestimation of PA levels, as assessed by the questionnaire. Additional research with objectively measured PA and comprehensive interviews beforehand could be used to investigate whether these biases that apply to the questionnaire or the telephone interview could explain the contradictory results that we observed.

This study has some limitations. First, it is important to place the inclusion rate in the context. First, we invited patients via their treating physicians based on medical record information. Therefore, we were unable to screen survivors on PA levels before sending the invitation. This, in turn, led to approaching many survivors who, in fact, were not eligible for participation because they had sufficient PA levels. This makes it difficult to compare our inclusion rate with that of other semisupervised exercise oncology trials that reported uptake rates of approximately 40% [8,9,11,29]. Second, our findings may, to a certain extent, be subject to recall or social desirability bias. This could have affected the patient-reported outcomes; in particular, some of the nonparticipants may have overreported their levels of PA to justify not participating. Third, selective nonresponses could have occurred where those who were least active also tended not to respond to the nonparticipant questionnaire.

Further research is required that includes survivors with lower educational levels [30]. This group of survivors is expected to be less physically active and thus might benefit more from supportive PA interventions. In addition, the majority of our trial sample was selected from an urbanized region in the Netherlands. A broader multicenter trial could provide results that are more generalizable to breast and prostate cancer survivors living in nonurban areas. Our findings point to a subgroup of patients with an apparent need for support that was self-selected for participation in the trial. Providing appropriate educational materials, timing the offer of interventions to meet the needs of survivors, and having a range of PA interventions (internet-based and supervised) are likely to increase the interest of cancer survivors in such interventions. This holds not only for recruiting survivors into PA intervention studies but also for maximizing the likelihood that they will take up the offer to engage in PA programs offered as a routine element of clinical practice. Finally, efforts should be made to encourage clinicians to follow the recommendations of the American College of Sports Medicine's *Exercise Is Medicine* initiative to assess, advise, and refer patients to exercise or rehabilitation programs [10].

In summary, participants of the PABLO trial showed lower levels of PA before treatment, lower stages of behavioral change, greater symptom burden (most notably fatigue), and a lower level of HRQoL than nonparticipants. These differences between participants and nonparticipants are not reflected in the findings of semisupervised exercise trials that take place during or shortly after treatment. This suggests that the PABLO trial was successful in recruiting cancer survivors who may benefit the most from internet-based supportive PA interventions.

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Authors' Contributions

WGG, WHH, MMS, AMM, NKA, and HGP were involved in the study design. HJW and MFAB were involved in drafting the manuscript. SG coordinated the study at Rijnstate hospital. All authors have read and provided feedback on earlier versions of this manuscript and gave permission for the submission of the final version.

Conflicts of Interest

None declared.

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Abbreviations

HRQoL: health-Related Quality of Life
IPAQ: International Physical Activity Questionnaire
IPAS: Internet-based Physical Activity Support
MFI: Multidimensional Fatigue Inventory
PA: Physical Activity
POMS: Profile of Mood States
RCT: Randomized Controlled Trial
SF-36: Medical Outcomes Study Short Form-36

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Original Paper

Features That Middle-aged and Older Cancer Survivors Want in Web-Based Healthy Lifestyle Interventions: Qualitative Descriptive Study

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Abstract

Background: With the increasing number of older cancer survivors, it is imperative to optimize the reach of interventions that promote healthy lifestyles. Web-based delivery holds promise for increasing the reach of such interventions with the rapid increase in internet use among older adults. However, few studies have explored the views of middle-aged and older cancer survivors on this approach and potential variations in these views by gender or rural and urban residence.

Objective: The aim of this study was to explore the views of middle-aged and older cancer survivors regarding the features of web-based healthy lifestyle programs to inform the development of a web-based diet and exercise intervention.

Methods: Using a qualitative descriptive approach, we conducted 10 focus groups with 57 cancer survivors recruited from hospital cancer registries in 1 southeastern US state. Data were analyzed using inductive thematic and content analyses with NVivo (version 12.5, QSR International).

Results: A total of 29 male and 28 female urban and rural dwelling Black and White survivors, with a mean age of 65 (SD 8.27) years, shared their views about a web-based healthy lifestyle program for cancer survivors. Five themes emerged related to program content, design, delivery, participation, technology training, and receiving feedback. Cancer survivors felt that web-based healthy lifestyle programs for cancer survivors must deliver credible, high-quality, and individually tailored information, as recommended by health care professionals or content experts. Urban survivors were more concerned about information reliability, whereas women were more likely to trust physicians' recommendations. Male and rural survivors wanted information to be tailored to the cancer type and age group. Privacy, usability, interaction frequency, and session length were important factors for engaging cancer survivors with a web-based program. Female and rural participants liked the interactive nature and visual appeal of the e-learning sessions. Learning from experts, an attractive design, flexible schedule, and opportunity to interact with other cancer survivors in Facebook closed groups emerged as factors promoting program participation. Low computer literacy, lack

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of experience with web program features, and concerns about Facebook group privacy were important concerns influencing cancer survivors' potential participation. Participants noted the importance of technology training, preferring individualized help to standardized computer classes. More rural cancer survivors acknowledged the need to learn how to use computers. The receipt of regular feedback about progress was noted as encouragement toward goal achievement, whereas women were particularly interested in receiving immediate feedback to stay motivated.

Conclusions: Important considerations for designing web-based healthy lifestyle interventions for middle-aged and older cancer survivors include program quality, participants' privacy, ease of use, attractive design, and the prominent role of health care providers and content experts. Cancer survivors' preferences based on gender and residence should be considered to promote program participation.

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KEYWORDS

cancer survivors; diet; physical activity; lifestyle; internet; interventions; qualitative; eHealth; mobile phone

Introduction

Background

Over 16 million individuals in the United States are living with a history of cancer, a prevalence expected to grow to over 22 million by 2030 [1]. The risk of cancer increases with age; thus, cancer survivors aged ≥65 years are anticipated to comprise approximately 73% and aged 50 to 64 years approximately 18% of the survivors by 2040 [2]. Cancer survivors are at a greater risk of cancer recurrence or second malignancy [3], and accelerated aging [4], which increases mortality risk [5]. Healthy eating, physical activity, and weight management can attenuate these health risks and functional decline [6,7]; however, only 29% of cancer survivors have normal weight, 27% eat at least 5 daily servings of vegetables and fruit, and 47% engage in at least 150 minutes per week of aerobic physical activity (only 34% for older cancer survivors) [8,9].

Technology offers several important advantages for health behavior change interventions, such as increased access, greater user convenience, lower user cost, and personalized tailoring [10-13]. Internet use is rapidly increasing among adults aged ≥50 years, who represent the majority of cancer survivors [1,2]. About 88% of US adults aged 50 to 64 years and 73% aged ≥65 years are internet users, with the most rapid increase in use among adults aged ≥65 years (ie, from 57% in 2014 to 73% in 2019) [14]. Identifying features that promote participation in technology-based lifestyle interventions may support the realization of these potential advantages. Prior research indicates that cancer survivors prefer web-based health care technology and interventions (known as eHealth) [15], if the intervention provides tailored survivorship care plans, education to prevent cancer recurrence, and communication with fellow cancer survivors [16,17]. Although many middle-aged and older adults perceive the electronic exchange of health information as important [18], few studies have included middle-aged and older cancer survivors—a subgroup not often targeted specifically in eHealth literature. Moreover, studies rarely report variations in survivors' preferences based on gender and geographic location (rural and urban) [19].

Objective

The aim of this study was to explore the views of middle-aged and older cancer survivors regarding features of web-based healthy lifestyle programs to inform the development of a web-based diet and exercise intervention. We included cancer survivors aged ≥65 years while also reflecting the perspectives of cancer survivors who are aging into the group within the next 10 to 15 years. In addition, we wanted to capture potential variations in these views by gender and rural and urban status.

Methods

Design

We used a qualitative descriptive approach [20] to explore the perspectives of a diverse sample of cancer survivors on the design of a web-based healthy lifestyle intervention. According to the Rogers' Diffusion of Innovation (DOI) Theory, the characteristics of innovation are crucial to its adoption and use [21]. Therefore, we considered it important to use a pragmatic perspective to explore the characteristics of innovation through the views of its potential users. A qualitative descriptive approach allows data interpretation that closely reflects participants' views and aims to uncover individuals' perspectives on the studied phenomenon [22]. It also allows the research results to emerge from the data without undue restraints of a structured approach [23]. The study protocol was approved by the University of Alabama at Birmingham and the University of Tennessee Health Science Center Institutional Review Boards.

Participants

Using a purposeful sampling strategy [24], cancer survivors were recruited from a hospital tumor registry in a southeastern US state using recruitment letters followed by a screening telephone call. The goal was to recruit the best informants [24], who would provide insightful views related to design and participation in the internet program based on their cancer survivor experience. Eligibility criteria included adults who (1) were aged ≥45 years; (2) were diagnosed within 1 to 5 years with a localized cancer of the breast, colorectum, endometrium, ovary, genitourinary (prostate), kidney, or multiple myeloma; (3) were English-speaking; (4) were community dwelling; (5) completed eighth grade or higher; (6) had BMI of at least 25 kg/m^2 but less than 50 kg/m^2; (7) do not engage in regular exercise; and (8) eat <2.5 servings of fruits and vegetables per day. In addition, the opportunity was advertised through cancer support groups and cancer types other than those in (2) were

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allowed if participants were from rural areas or Black survivors to maximize their representation. Potential participants were not screened for computer, smartphone, or mobile phone access at the time of recruitment.

Data Collection

A total of 10 focus groups were conducted with 57 cancer survivors, with persons per focus group ranging from 2 to 12. Focus groups are effective for exploring potential users' perspectives to inform intervention development [25,26]. To capture variations in survivors' views, focus groups were both gender homogenous and mixed and were conducted in rural and urban areas [27] (Table 1). Rural and urban status was defined based on participants' zip codes and the 2010 Urban Area to ZIP Code Tabulation Area Relationship File [28]. At the beginning of each focus group, we obtained informed consent; then participants completed a survey about their use of the internet, computers, and cell phones. To protect cancer survivors' anonymity, each participant selected an alias to use during the discussion.

Table 1. Focus group composition.

Gender	Urban		Rural		Total focus groups (n=10), n (%)	Total participants (n=57), n (%)
	Focus groups, N	Participants, n (%)	Focus groups, N	Participants, n (%)		
Women	1	8 (21)	1	2 (11)	2 (20)	10 (18)
Men	3	12 (32)	1	4 (21)	4 (40)	16 (28)
Mixed	2	18 (47; n=9 women; n=9 men)	2	13 (68; n=9 women; n=4 men)	4 (40)	31 (54)

Considering one of the premises of Rogers' DOI Theory that the characteristics of innovation are essential for its potential adoption [21], the research team developed a focus group guide aimed to inductively generate information [20,23] related to cancer survivors' use of eHealth: familiarity and use of healthy lifestyle websites providing information on diet and physical activity, cancer survivors' preferences for learning and using technology, and type and frequency of feedback for participation in the program activities (Textbox 1). We also demonstrated and asked feedback on 3 web-based program features that were under consideration for a web-based program at that time: live web chat, Facebook discussion group, and Articulate Storyline interactive e-learning sessions. We chose these features because of their potential to facilitate engagement with a program, provision of social support, and easy access via multiple devices (smartphones and computers) [29-32]. Each feature was explained and demonstrated for focus group participants, followed by probing questions about the feature's perceived effectiveness for delivering program content and promoting cancer survivors' program participation. We also explored comfort levels with sharing information using these features (particularly Facebook discussion groups) and participants' preferences for the duration and frequency of using these features.

Textbox 1. Sample focus group questions.

Sample focus group questions

1. What health websites have you used for information on eating healthy and physical activity? What features did you like and dislike and find helpful and less helpful and why?
2. Introduction, demonstration, and discussion of 3 internet program features (see probing questions below).
   - *Live web chat* involves watching an informational video on a health-related topic, such as healthy eating, which is delivered via a website. With a live web chat, cancer survivors can watch the video, type questions, and receive answers from a staff member after the video is over.
   - *The Facebook discussion group* is dedicated to a specific community or membership or subjects, such as health, diet, lifestyle, cooking, social issues, and more. For example, cancer survivors can use the discussion group to talk about losing weight and other health-related issues with other members.
   - Articulate Storyline (interactive, e-learning sessions) allows cancer survivors to interact with the information in a video. For example, the Storyline can ask the survivor about the type of cancer and treatment and then provide advice about exercise or healthy eating that is personalized to the survivors' needs.

     Probing questions for every feature: What would cancer survivors like about this feature? Why?; What would cancer survivors not like about this feature? Why?; Why would cancer survivors find this feature engaging?; Why would cancer survivors not find this feature engaging?; How often would cancer survivors use this feature?; How comfortable would cancer survivors be to use this feature?; What other comments do you have about this feature?
3. How would cancer survivors prefer to learn about how to use the internet program and technology?
4. What feedback and how often would cancer survivors like to receive about their progress in an internet healthy lifestyle program? How can cancer survivors use this feedback?

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The focus group guide was pilot-tested using a mock focus group of volunteer cancer survivors and research staff. The guide was further refined through an iterative approach to data collection and analysis [33] when transcripts were reviewed and analyzed soon after the focus group completion to inform and adapt probing questions. Focus groups were facilitated by 2 experienced moderators and lasted approximately 2 hours. All sessions were audio recorded. Participants were provided with light refreshments and US $25 compensation for their time and travel.

Data Analysis

Focus group recordings were transcribed verbatim by a professional transcription company. Verified transcripts were independently analyzed by 3 researchers (NVI, IIH, and LT) using inductive thematic [34] and content analyses [35] with NVivo (version 12.5 Plus, QSR International). The analytical process involved several steps. First, the researchers independently coded the original transcripts by identifying key points and recurring subthemes and themes that were central to the areas of discussion within and across the focus groups. A constant comparative method [36] that involves iterative comparison of new information with coded data was used to guide the analysis. This inductive analytical process allowed us to identify common themes and subthemes that transcended all focus groups while capturing variations in cancer survivors' perspectives on the discussed topics. The researchers reviewed the merged coding results after the analysis of each transcript to resolve coding discrepancies. They also regularly met with the rest of the research team to discuss emergent themes and refine the codebook. An intercoder agreement was established at a recommended 90% [37].

When the thematic analysis of all focus groups was completed and saturation in the data was achieved, the researchers performed content analysis on the generated themes and codes using the counts of text references in NVivo to systematically represent consistencies and variations in viewpoints across the focus groups based on participants' gender and residence. This analysis also helped identify how the themes were interrelated and interconnected to describe cancer survivors' varied views on a web-based healthy lifestyle program. Demographic and survey data were analyzed using descriptive statistics with SAS (version 9.4, SAS Institute).

Results

Description of the Participants

A total of 57 survivors of 6 different cancer types participated in the focus groups (Table 2). The mean age was 65 (SD 8.27) years, and both genders were evenly represented (29/57, 51% men and 28/57, 49% women). About two-thirds were urban dwelling (37/57, 65%) and more than half were White (32/57, 56%) survivors. Most of the participants had cell phones (56/57, 98%) or smartphones (46/57, 81%) and a computer with internet access (35/57, 61%). More than half of the participants used email (33/57, 58%) and text messaging (39/57, 68%) at least once a day (Table 3).

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Table 2. Demographic characteristics of focus group participants (N=57).

Characteristics	Participants, n (%)
Gender	
Male	29 (51)
Female	28 (49)
Age (years)	
47-64	25 (44)
65-74	24 (42)
≥75	8 (14)
Race	
Black	23 (40)
White	32 (56)
Other	2 (4)
Cancer type	
Breast	17 (30)
Prostate	18 (32)
Multiple myeloma	7 (12)
Colorectal	5 (9)
Gynecologic (ovarian or endometrium)	7 (12)
Other	3 (5)
Residency status	
Rural	19 (33)
Urban	37 (65)
Missing	1 (2)
Marital status	
Married or lives with partner	38 (67)
Divorced, separated, or widowed	19 (33)
Education	
High school or less	19 (33)
Some college	16 (28)
College graduate	22 (39)
Employment	
Employed	13 (23)
Retired	28 (49)
Homemaker	2 (4)
Unable to work	7 (12)
Other	7 (12)
Household income level (US $)	
<25,000	16 (28)
25,000-<50,000	10 (18)
50,000-<75,000	8 (14)
≥75,000	11 (19)
Unknown	12 (21)

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Table 3. Technological characteristics of focus group participants (N=57).

Characteristic	Participants, n (%)
Has the following	
Cell phone	56 (98)
Smartphone	46 (81)
Desktop or laptop computer with internet access	35 (61)
Tablet (eg, iPad [Apple Inc] or Kindle [Amazon])	26 (46)
Sends or receives email	
At least once a day	33 (58)
At least once a week	6 (11)
At least once a month	5 (9)
Less often	9 (16)
Missing	4 (7)
Sends or receives text messages	
At least once a day	39 (68)
At least once a week	14 (25)
At least once a month	1 (2)
Less often	1 (2)
Missing	2 (4)
Accesses internet	
At least once a day	36 (63)
At least once a week	7 (12)
At least once a month	2 (4)
Less often	9 (16)
Missing	3 (5)
Visits social networking sites	
At least once a day	24 (42)
At least once a week	7 (12)
At least once a month	2 (4)
Less often	20 (35)
Missing	4 (7)
Uses instant messaging	
At least once a day	15 (26)
At least once a week	5 (9)
At least once a month	4 (7)
Less often	26 (46)
Missing	7 (12)

Themes

The analysis of the focus group discussions revealed 5 major themes that reflected cancer survivors' views on a web-based healthy lifestyle program related to (1) program content, (2) program design and delivery, (3) program participation, (4) technology training, and (5) receiving feedback. These themes, with related subthemes and illustrative quotes, are presented in Table 4.

Using content analysis, we summarized cancer survivors' dominant perspectives on the 3 program features (live web chat, Facebook discussion group, and e-learning sessions) by program content, design, delivery, and participation in Table 5. We also captured variations in survivors' views by gender and rural and urban status, as shown in Figure 1.

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Table 4. Themes, subthemes, and illustrative quotes.

Themes and subthemes	Quotes
Program content	
Credibility	"I think that, you know, all the information tools that's out there, all the resources even the live web chat that I really like, uh, because I like Facebook. So, I think all of them play a role that cancer survivors can use. If the resources and the information that's given is valid, then I don't have a problem with it." [female, urban]
Source of information	"I don't think any media person or, but the person should be expert in nutrition as well as the expert should have some expertise or knowledge in the disease, for example cancer. That person can give a good answer which is passing through cancer, or treatment, or maybe physician, as well as have knowledge of nutrition science." [male, urban]
Information type and format	"But to have the, the video there of how certain things that would be done in exercise and uh, if you've got a disability here, what type of exercises I can do. I believe that it'd be very helpful for the viewer and the people that's having discussion...people that's uh, are cancer survivors they need to know and see examples of specific exercises they might be able to do with their various limitations, you know, because many of them are limited in this area, and that area." [female, urban]
Program design and delivery	
Security	"I mean with privacy now in the medical field you have to be so careful. And a lot of people really are very private about their health issues. I would hate to see them miss out on this because they, everybody can see exactly who they are. I mean I know on Facebook you can create all different kinds of accounts and things. I can't. But with something like this I think it would be kind of important maybe for it to the privacy issues to be considered in setting it up." [female, rural]
Usability	"It should be easy to use. -- If you could drill down through it pretty quick, and you could just get to what you're looking for. You know, I mean it could be this exercise side or the diet side or you know, certain based on where you're located, something like that, and make it quickly narrow." [female, urban]
Frequency	"Is that important to you that this a scheduled time thing?...Probably so. It might be a variation of times during the day at a certain time because you could plan. You know, things happen and if you miss 1 and 2 o'clock, catch one at 6 or whatever." [male, rural]
Length	"So, I would say what you consider the attention span. The sense, to me, if it's live and it's 10 to 15 minutes, you're going to get me 100%." [male, rural]
Program participation	
Pros	"But the fact of the support group in discussion in a sense is that it's...there's other people like me that are going through what I went through or that could take advantage of what I went through and what I'm doing." [male, rural]
Cons	"I probably need this program we're talking now. I'm just illiterate with, as far as, computer illiterate, okay." [female, urban]
Technology training	
Computer skills	"I mean if we're trying to reach people that's not, only knows how, that's the only way to do it, that they might be...I mean if they already know how to navigate, all you got to do is say, 'Here's your program. Here's your website' and you'll do it. If that's not the case, you're going to have to visualize it, show them. Not tell them, show them. Like you said, show me how to do it." [female, rural]
Venue	"...you should be able to direct them to a class—where they are teaching people about the computer no matter what their age is, because I know there are people that are doing that at the hospital. So, if you get them on the front end and they can start then taking computer classes, then they can help themselves by knowing how to go on the internet." [female, urban]
Motivation	"...as soon as a newly diagnosed person comes in, if they [doctors] know that they can follow up on the internet with certain programs, and they tell you that they are not computer literate, then you should be able to direct them to a class."[female, urban]
Receiving feedback	
Feedback type	"You get your answer if you have a question about a certain food or type of food. You could incorporate it right away instead of having to wait." [female, rural]
Occurrence	"I have to have every day here otherwise I won't walk. Yea, I have to get on my app every day and, 'oh my lord, I got to go walk' kind of thing." [female, urban]
Mode	"I think feedback is, is great and, and if it was me, you know, social media is, is, is, is great." [male, urban]
Tracking	"It probably be usually online. Cause I've tried to track it on paper. Uh, cause I, I'd gotten, uh, diabetes**,** trying to figure out, keep up with what you eat." [female, urban]

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Table 5. Dominant perspectives on internet program features[a].

Themes and subthemes	Internet program features		
	Live Web Chat	Facebook discussion group	e-Learning sessions (Articulate Storyline)
Program content			
Credibility	• Reliable information • Credible source of information	• Reliable information	• Relevant information
Source of information	• Physician • Certified nutritionist	• Health care professional	• Competent person
Information type and format	• Being able to choose a topic • Opportunity to generate further questions • Communicate with others	• Healthy eating and physical activity • Facilitated discussion • Get answers to questions • Health information videos	• Personalized information • Interactive • Using video and pictures • Links to website
Program design and delivery			
Security	• Anonymity	• Closed group • Different names	N/A[b]
Usability	• Easily accessible	• Easy to use	• Simple to use • Animation
Frequency	• Every day • Weekly	• On a regular basis	• Once a week
Length	• 15-30 minutes • Up to 60 minutes	• 5-10 minutes • 15-30 minutes	• 15-30 minutes
Program participation			
Pros	• Expert response • Flexibility and choice	• Facilitated discussions • Communicating with others	• Customized • Motivational • Flexible schedule
Cons	• Unreliable and irrelevant information • Unaddressed questions • Lack of experience with web chat • Lack of computer skills	• Not using Facebook • No anonymity • Lack of time • Questionable quality of information	• Lack of computer skills • Time consuming

[a]This table summarizes the frequent perspectives based on content analysis. See text for more perspectives.

[b]N/A: not applicable.

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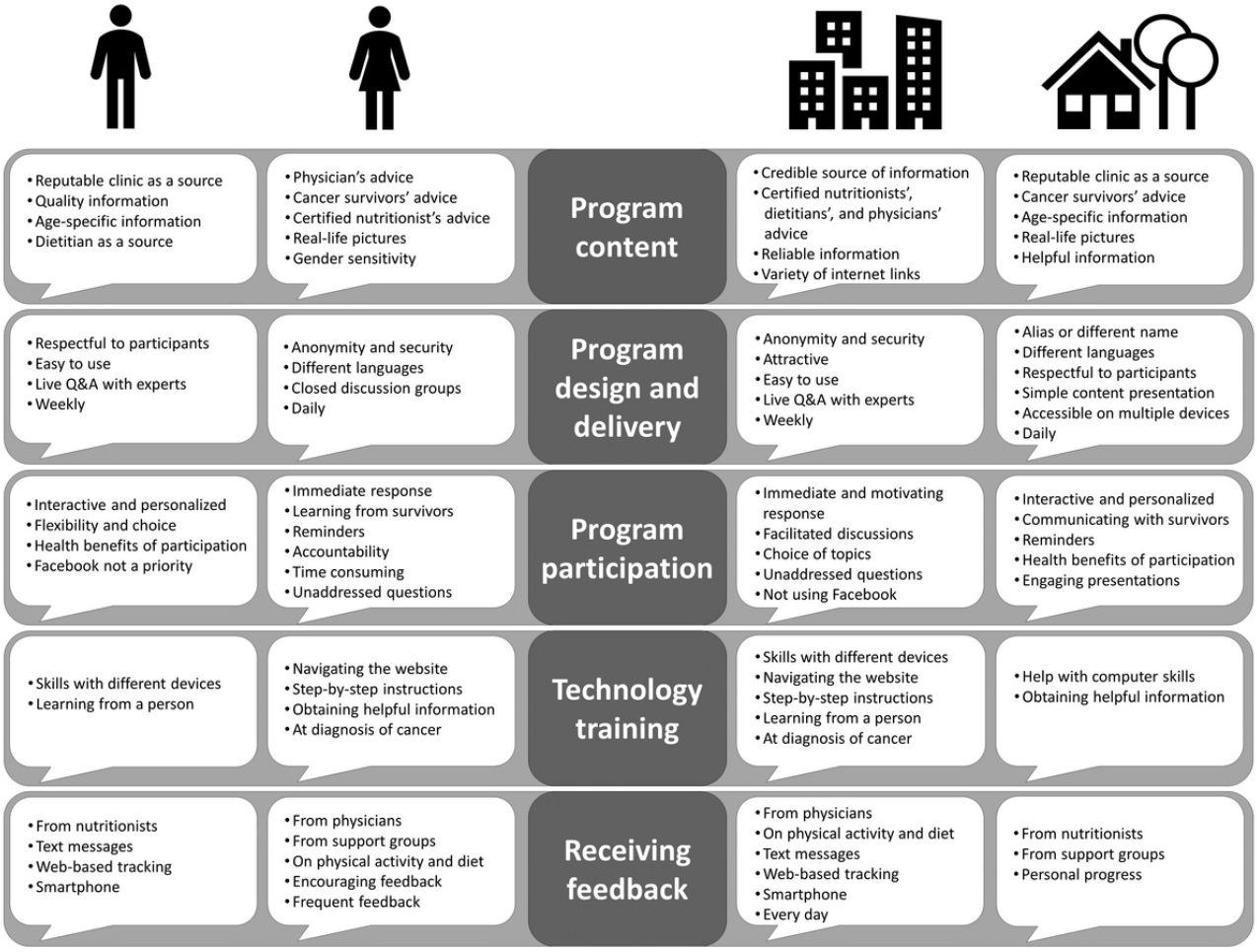
Figure 1. Perspectives by gender (male and female) and residence (urban and rural). Q&A: question and answer.



Program Content

Focus group participants noted that a web-based healthy lifestyle program for cancer survivors must contain credible, high-quality, and individually tailored information developed or recommended by content experts or health care professionals. Three subthemes emerged related to program credibility, source of information, and its type and format (Table 4). All survivors were equally concerned about receiving conflicting information or information of questionable quality. A male participant observed, "...it should have information that's credible that you trust." Overall, urban survivors expressed more concerns about the credibility of web-based health-related information than rural survivors. The desire to receive relevant and credible information was particularly prominent in the discussion of the web-based program features (Table 5). For example, when reacting to a demonstration of the live web chat, an urban male participant stated, "I think it would be very important to make sure whoever the cancer survivor sees offering advice or providing feedback has credibility." Both rural and male survivors were more reluctant to receive information via a Facebook discussion group because of its questionable quality:

> *It's like if somebody says, "That might not be such a good idea if you try that for your health." Or, something to guide the information that other people get because people enjoy messing up people or something.*

With respect to the source of the information, survivors expressed trust in physicians, registered dietitians, and other health care professionals to guide them in the choice of healthy behaviors (Table 5). A female participant commented as follows when discussing a live web chat:

> *Well, first of all, you have someone that's very knowledgeable because she's a doctor, right? And so, we can pretty much believe what she's gonna tell us. And she's speaking about some very important things for all of us to know, cancer-fighting foods and how we can incorporate that into our meals every day.*

Women and urban survivors were more likely to see physicians as a trustworthy information source, "I would like for it to be a physician, and I would like for it to be reputable." Women noted that they preferred physicians' recommendations because they had knowledge and understanding of the survivorship process:

> *...if there was a health care provider, someone who...knows all about cancer and knows what's procedure and they know everything that is going on with a person in that cancer field.*

Female and rural participants were also receptive to guidance from other cancer survivors in a live web chat or Facebook discussion group:

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> *I would love to have internet live chat there with a cancer survivor. That way I can learn how to eat healthy.*

Regarding healthy eating, male and urban participants were more inclined to get advice from a certified expert:

> *There's so much on food out there and so many times that somebody with their plan...for healthy food that you don't know. I would want somebody who has medical and nutritional expertise so that I could put my trust.*

Cancer survivors wanted to receive information that was tailored to their needs, health conditions, and age. They particularly liked personalized health education delivered through e-learning sessions, which also allowed private interaction with the content (Table 5). A male survivor observed as follows:

> *It's customized to each individual person and looks private, right? It's just you and the interactive tool here. You plug in the information that gives it directly to you. There's no onlookers, there's no chat room. And you get a customized individual answer to your specific situation and the type of cancer you have, your age, all that is, like I said, is confidential, it's private. That's perfectly fine.*

More male and urban participants talked about the need to receive information adapted to their cancer, whereas more rural survivors were interested in the information tailored to a specific age group, "...it would be satisfying that you can get right to the information for your particular age and other factors." Women liked a program that used health information videos and pictures as visual reinforcement, particularly when introducing types of physical activity (Table 5). One woman noted when discussing e-learning sessions, "And then give maybe video, real person videos of those 5 exercises, and personalize it to a much higher degree..." Female survivors also noted the importance of being sensitive to the information presented to them, "Don't let it tell us that we're fat."

Thus, a web-based healthy lifestyle program should contain information that cancer survivors find trustworthy, reliable, and tailored to their health needs, cancer type, and age. Urban survivors tended to be more concerned about information credibility and were more likely to see physicians as trustworthy information sources. Women were more inclined to receive information from a physician, whereas men preferred obtaining advice from a broader spectrum of certified experts. Women also preferred more visual reinforcements for health information and were more open to participate in Facebook discussion groups.

Program Design and Delivery

Security, usability, frequency, and length emerged as important subthemes in the discussions of the internet program features (Table 4). Focus group participants expressed concerns about privacy issues related to participation in live web chats and Facebook discussion groups (Table 5). Regarding Facebook, a female survivor explained as follows:

> *I wouldn't like it for the reason there's no anonymity. I might not want everyone to know who I am when I am asking these questions because some people don't want the world to know that they have cancer.*

Rural participants were less concerned about privacy and suggested using different names or aliases for anonymity:

> *I'm very open about my cancer and a lot of people aren't though. They're more private and so I'm thinking they might...can they log in and do they create their own name when they log into something like this? So, like use an alias?*

Although lack of anonymity was a common concern, interactions with other survivors in closed and password-protected groups were considered acceptable. Female participants particularly noted the advantages of small groups where members knew each other and could interact more freely:

> *Well, it's probably better with a closed group with invitation only; that's a small group, and then you get used to that group. And you're familiar with everyone in that group, it will be better that way to me.*

Program usability was another important consideration for cancer survivors. They wanted a web-based program to be simple, easy to use, and accessible via different devices. A male participant emphasized these features combined with the quality of the information as a condition for joining the program:

> *...it should be easily accessible. It should be easy to use. And it should have information that's credible that you trust. And, I think if you have all those three,...you're fairly likely to use it...*

Female and rural participants particularly wanted the program to be simple enough for cancer survivors who had to deal with health issues on a daily basis:

> *You got to remember whoever is in on this going to that site, we're dealing with the cancer and that's a load. So, you need it simple, not because we're ignorant on that particular stuff. We need it easy where we can just go in...*

Participants noted the benefits of e-learning sessions, which use visuals and animations to make it easier for cancer survivors to understand and use the information:

> *...it would have to be animated if it was talking about physical exercise. If you wanted to tell them what to do that's one thing, but it has to be animated to actually show them how to do it correctly.*

In addition, the ability to ask questions and get answers emerged as an important design feature, particularly for male and urban survivors, "...a site where you can ask questions and get answers, I think all that's wonderful, once again, I would be open to the idea." Female participants were more interested in receiving immediate feedback so that they could use the information for their needs:

> *You get your answer if you have a question about a certain food or type of food. You could incorporate it right away instead of having to wait.*

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Although some participants did not use Facebook, they acknowledged the opportunities it offered for facilitated discussions about cancer-related issues.

The focus group participants offered varied perspectives on the frequency and duration of the program activities. Many participants believed that the weekly use of a live web chat and e-learning sessions would meet cancer survivors' expectations. However, more rural participants wanted to engage with the program features daily, "I'd be there every day almost probably." In general, women were willing to spend more time on program activities than men. Participants believed that spending 15 to 30 minutes on average in a live web chat and e-learning session would be ideal; however, they wanted to devote less time to participate in a Facebook discussion group, except for rural survivors, who were eager to interact with group members longer. An urban participant observed as follows:

> *It depends on the questions of the person, and depends on the time, availability of time with the expert who is responding, but at least five to 10 minutes are more than sufficient for any patient survivor...So, not more than 10 minutes.*

Therefore, a web-based healthy lifestyle program should guarantee cancer survivors' privacy and security, particularly in Facebook discussion groups. Rural survivors were more accepting of group interactions using aliases, whereas women saw the advantages of small closed groups. The program should be easy to use and accessible from different devices and use visuals and animations to reinforce information understanding. Participants had varied views on the frequency and length of each program feature, with women being willing to spend more time on program activities and rural survivors wanting to engage in group discussions longer.

Program Participation

The focus group participants shared their views regarding the pros and cons of the discussed program features and their potential influence on cancer survivors' participation in a web-based healthy lifestyle program (Table 4). Learning from experts, attractive design, flexibility, and opportunities to interact with other survivors were cited as important factors in promoting program participation. Participants liked the e-learning session feature for its flexible schedule and ability to return to the session at any time (Table 5). A male survivor observed, "One thing about the program such as this, you can go to it any time you want to." The interactive and personalized nature of e-learning sessions was also noted as a strong appealing feature, particularly by male survivors, "Well, it's interactive and more like a guided tour."

At the same time, survivors appreciated the opportunity to receive an expert response to their questions in a live web chat, but noted the constraints of real-time streaming. A female participant shared, "...it would be nice that you had several choices and not miss it because you can't be there at that time at that moment, but then would it be live?" Participation in facilitated discussions in Facebook closed groups and learning about other survivors' experiences was also considered an appealing feature, particularly by women and rural participants:

> *...hearing from other people that might have had, you know, say they were taking a treatment, or they, while they were recovering,...went through similar to what I went through and certain foods helped them. It would help me, I think, to try even if I haven't tried that food because I know that somebody has already been there.*

Computer literacy was perceived as an important consideration for cancer survivors' participation in web-based programs. While acknowledging the advantages of internet programs, participants expressed concerns about limited computer skills. Urban participants were particularly concerned about lack of experience with a live web chat:

> *I'm not really a computer person. So, I know I wouldn't do that.*

Similarly, survivors had little experience participating in Facebook discussion forums and felt that Facebook was "not a priority." A male participant observed, "I wouldn't do the group discussion on there because I don't do Facebook and I don't do chats." In addition, privacy issues and lack of anonymity were perceived as barriers to participation in a Facebook group. Some women felt uncomfortable participating in a live web chat because they were afraid that their questions would not be answered:

> *When you are on a live chat, there is a delay. When you're typing your question, there is a delay before it actually gets to that person. If somebody else's question gets ahead of you, sometimes they can get caught up in the explanation for that particular person and then your question might get skipped over because somebody else is typing in also and they just, they might overlook it...I don't like to be overlooked even though there is a delay, I still want my question answered.*

Women also felt that using an e-learning session might be time consuming, despite its obvious advantages:

> *...I don't have time to just be looking at that all the time...But I think it's great. It keeps you on your toes.*

Therefore, to promote cancer survivors' participation, a web-based healthy lifestyle program should have an attractive design, provide opportunities to learn from experts, and facilitate interactions among program participants. Preference was given to e-learning sessions for their interactive and personalized nature and the ability to participate in nonreal time; however, women perceived them to be more time consuming than live interactions. Women and rural survivors tended to value Facebook closed-group discussions to learn from other cancer survivors. Computer literacy and privacy issues were perceived as barriers to program participation.

Technology Training

Focus group participants shared their views on receiving training in computer skills and what might motivate them to consider such training (Table 4). More rural survivors acknowledged the need to learn how to use a computer, "...some of them may not know how to get on a computer, so they going to need to know that." Moreover, this training should begin early on, that is,

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simultaneously with cancer diagnosis. A female participant observed as follows:

> *Like, once a person is diagnosed, tell me, okay we've got this wonderful tool, and this is how you use it. At least give me the option of using it whether I accept it or not, but at least put it as part of the basic plan when I am first diagnosed.*

Female participants also indicated the importance of educating cancer survivors on how to navigate the website and how to use its features:

> *None of the tools will work if people are not educated, okay. So, we can talk about all these great things and these great ideas but until we sit people down and say, Okay, this is how you do this, this, this.*

Participants suggested several venues to provide computer training for cancer survivors, including offering computer classes at a clinic for groups of newly diagnosed patients. A male survivor explained as follows:

> *You can set up some classes at a particular location like the... Clinic...where they would periodically teach you...how to handle access the computer. And I think that would have some merit.*

Many participants preferred individualized help to standardized computer classes and recommended using support from family members and librarians. An urban survivor observed as follows:

> *The smartest people I ever met in life is at the library...They'll sit down with you and show you how to go through the computer whatever.*

Participants also agreed that health care providers and patients could play an important role in motivating survivors to learn computer skills:

> *...how do you think cancer survivors would prefer to learn about how to use internet programs and technology?...The doctors can get us started, I think for most of us.*

Thus, a web-based healthy lifestyle program requires basic computer literacy, particularly among rural cancer survivors. Women were more interested in learning how to navigate the program features. Urban and male survivors preferred individualized assistance to standardized computer classes. Training should start at cancer diagnosis and be endorsed by physicians and other cancer survivors.

Receiving Feedback

The participants acknowledged the importance of feedback to encourage cancer survivors' participation. They provided suggestions about the feedback type, frequency, mode of delivery, and methods of diet and activity tracking (Table 4). There were variations in the frequency and type of feedback about goal achievement. Women and urban participants mentioned an interest in obtaining more specific feedback about their physical activity and healthy eating:

> *If you could click through to, here's the exercises, did you do any of these? And you could just click it, boom, boom and be done. Or I ate these things and click, click and then it could send you, you came three times this week and you did these many exercises. That'd be kinda cool.*

Rural participants valued feedback about their personal progress to improve accountability:

> *...you need something to keep you accountable,...something like this that shows you that you are overweight,...you need to exercise and...you need to eat right.*

Women were more likely to use feedback as a form of encouragement to reach the goals:

> *I want them to continue giving me some encouragement words and say, okay, you're doing good, you're doing great. Keep it up.*

Women were also interested in receiving immediate or frequent feedback to stay motivated:

> *It should be immediate response. It's important to me to have some.*

However, when speaking about losing weight, participants preferred to check their progress on a weekly basis. An urban participant explained the following:

> *So, I already know what I weighed before I started but at the end of the week, I need you to tell me, okay you've accomplished your goal, or you missed the mark. So, but only once a week for me because I can't accomplish everything,...it takes time and with our bodies, to lose weight it's going to take more time. So, I want to know my results by the week.*

Women were more inclined to receive feedback via Facebook support groups, where members can discuss their progress:

> *...you had someone kind of cheering you on, but you are getting some feedback.*

Men preferred text messaging to group discussions because it was simpler and convenient:

> *Text messages would be good because most phones now you can...they ask you what you want to do. They're going to read the message to you. They will make it easier.*

Participants noted that tracking progress could be done via internet, phone, and journaling, depending on survivors' preferences:

> *...you have both options: you can write down all those foods you eat, or you can just key it into the system. So, that keying in worked for me better. I just like the computer so that works better for me.*

Hence, regular feedback about cancer survivors' progress is an important feature of a web-based healthy lifestyle program. Women and urban participants valued more specific feedback related to program activities, whereas rural survivors wanted feedback for accountability. Women were more interested in receiving immediate or frequent feedback for motivation and were more inclined to receive feedback via Facebook support groups. Men preferred text messaging and smartphones as a means to deliver feedback.

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Discussion

Principal Findings

This qualitative study is one of the first to explore the perspectives of middle-aged and older cancer survivors on the design of a web-based healthy lifestyle intervention. Using focus group discussions with a diverse sample of 57 male and female cancer survivors from rural and urban settings, we captured a variety of perspectives related to program content, design, delivery, participation, technology training, and feedback. Participants emphasized the quality of information, participants' privacy, ease of use, attractive design, timely feedback, and importance of considering the role of health care providers and content experts when designing web-based healthy lifestyle interventions for middle-aged and older cancer survivors. Although these themes were common across all survivors, we noted variations in views on internet program features across male and female and urban and rural participants, which may influence cancer survivors' participation in web-based healthy lifestyle programs.

Participants reported mixed perspectives on the features requiring more staff contact (ie, live web chat and Facebook moderation by an expert) rather than interactive e-learning sessions. Although e-learning sessions are not able to provide answers to open-ended questions or allow direct, bidirectional communication with other cancer survivors or an expert, the e-learning sessions were viewed positively by our participants and can provide several additional preferred qualities (eg, tailoring, interactive, private, and more participant control of time and frequency). Once developed, such computer-based approaches require less ongoing staff contact and may be more sustainable.

Our results also emphasize the importance of a trusted, reliable source (eg, physicians); however, physicians often do not have the required training to provide the detailed diet and exercise information needed by cancer survivors [38,39]. This suggests that content experts (eg, kinesiologists, registered dietitians, etc) along with health care providers should contribute to content development when using internet technologies to promote healthy lifestyles. Finally, physicians could motivate and connect middle-aged and older cancer survivors to these resources.

In addition, lack of technology expertise is a major barrier to participating in and, thus, benefiting from internet programs that promote healthy lifestyles. Although our participants requested more staff-intensive training options, low-cost and distributable approaches to increasing technology use comfort and competence are needed.

Strengths and Limitations

In a recent systematic review of studies on eHealth views in populations other than cancer survivors, similar themes to those that emerged in this study were reported (eg, usability, privacy, information reliability, etc) [19], thereby corroborating our results. Moreover, consistent with Rogers' DOI Theory [21], our qualitative results provide insights into important characteristics of eHealth innovations that are likely to increase diffusion (or adoption and use) of a web-based healthy lifestyle intervention by middle-aged and older cancer survivors, namely, receiving reliable and motivational information from an expert (relative advantage), personalized and relevant information, timely and frequent feedback (compatibility), ease of use, interactive and visual (complexity), computer skills training and website navigation (triability), and experiencing health benefits (observability). Future research is needed to examine other aspects of Rogers' DOI Theory that influence the adoption of an innovation, such as the characteristics of the adopter, social system, individual adoption process, and diffusion system.

Importantly, our findings extend the published literature in several ways. The majority of our participants are older cancer survivors who are rarely been studied but have reported different perspectives on eHealth when compared with older individuals without a history of cancer [18,19]. Further, we add to the gap in the literature by showing how cancer survivors' perspectives may differ based on gender and rural and urban status [19]. In addition, technology-based interventions have been evaluated in cancer survivors as a whole, but less is known about how older cancer survivors view specific features used in developing internet approaches to promote healthy behavior change [40-43]. These strengths combined with our diverse sample (ie, 29/57, 51% women; 23/57, 40% Black survivors; 22/57, 39% without a computer with internet access; 19/57, 33% rural; 19/57, 33% with ≤12 years of education; and 16/57, 28% reporting annual household income <US $25,000 per year) and rigorous qualitative analysis have yielded unique, varied, and important insights into eHealth perspectives that are useful for others planning to use internet technologies to promote healthy lifestyles among middle-aged and older cancer survivors.

Despite its merits, our study has potential limitations. First, we did not assess other potentially important features, such as noninteractive videos and social media approaches other than Facebook. Our findings also suggest gender and urban and rural variations in views on eHealth; however, further research is needed to confirm and quantify possible differences. Moreover, it was not feasible to recruit enough cancer survivors based on age distribution without losing our rural and urban focus group stratification; therefore, we were not able to differentiate participants' perspectives based on age groups. In contrast, our inclusion of participants regardless of their use or ownership of a computer or smartphone yielded helpful perspectives about technology training that may support middle-aged and older cancer survivors less likely to feel comfortable with technology. Owing to our study criteria, our sample included cancer survivors who were overweight or obese, were not regular exercisers, and did not eat at least 2.5 cups of fruits and vegetables daily. A recent analysis of 3367 racially and ethnically diverse cancer survivors identified through the National Health Interview Survey indicated that approximately 70% of survivors were overweight or obese and over 80% did not meet the guidelines for physical activity or fruit and vegetable consumption. Thus, our sample is likely representative of the majority of cancer survivors in the general population [44]. However, the perspectives expressed here may not be applicable to cancer survivors with advanced cancer or a cancer type with poorer prognosis nor to individuals who are non-English speaking or have at least an eighth-grade education.

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Finally, our participants were limited to the southeastern US state, thereby potentially reducing generalizability to other regions. Notably, this is offset by the significance of targeting a region (ie, southeastern United States) with the highest cancer mortality and comorbidity (eg, diabetes) rates in the United States [45,46].

Conclusions

This study highlights the value of designing web-based approaches that individualize information and allow users more flexibility regarding the timing and frequency of participation. In addition, our results have several important implications. Our findings can be used to enhance the design of web-based features and educational materials used as part of providing blended care for oncology patients, an increasingly prevalent patient care paradigm that combines in-person with technology-based approaches [47-49]. Further research is needed to determine how to best connect health care providers to the information, tools, and workflows needed to encourage cancer survivor intervention participation [50]. Similarly, developing and testing strategies that increase technology comfort and competence are critical for ensuring that as many middle-aged and older cancer survivors as possible can experience the health and well-being benefits of web-based healthy lifestyle interventions now and as they age into this age category.

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Conflicts of Interest

None declared.

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Abbreviations

DOI: Diffusion of Innovation

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Original Paper

Remote Monitoring of the Performance Status and Burden of Symptoms of Patients With Gastrointestinal Cancer Via a Consumer-Based Activity Tracker: Quantitative Cohort Study

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Abstract

Background: The number of older patients with gastrointestinal cancer is increasing due to an aging global population. Minimizing reliance on an in-clinic patient performance status test to determine a patient's prognosis and course of treatment can improve resource utilization. Further, current performance status measurements cannot capture patients' constant changes. These measurements also rely on self-reports, which are subjective and subject to bias. Real-time monitoring of patients' activities may allow for a more accurate assessment of patients' performance status while minimizing resource utilization.

Objective: This study investigates the validity of consumer-based activity trackers for monitoring the performance status of patients with gastrointestinal cancer.

Methods: A total of 27 consenting patients (63% male, median age 58 years) wore a consumer-based activity tracker 7 days before chemotherapy and 14 days after receiving their first treatment. The provider assessed patients using the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale and Memorial Symptom Assessment Scale-Short Form (MSAS-SF) before and after chemotherapy visits. The statistical correlations between ECOG-PS and MSAS-SF scores and patients' daily step counts were assessed.

Results: The daily step counts yielded the highest correlation with the patients' ECOG-PS scores after chemotherapy (P<.001). The patients with higher ECOG-PS scores experienced a higher fluctuation in their step counts. The patients who walked more prechemotherapy (mean 6071 steps per day) and postchemotherapy (mean 5930 steps per day) had a lower MSAS-SF score (lower burden of symptoms) compared to patients who walked less prechemotherapy (mean 5205 steps per day) and postchemotherapy (mean 4437 steps per day).

Conclusions: This study demonstrates the feasibility of using inexpensive, consumer-based activity trackers for the remote monitoring of performance status in the gastrointestinal cancer population. The findings need to be validated in a larger population for generalizability.

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KEYWORDS

step count; performance status; symptom; wearable; activity tracker; gastrointestinal cancer; monitoring; cancer; gastrointestinal; burden

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Introduction

The number of gastrointestinal cancer cases is predicted to increase due to the aging population [1]. Moreover, patients in geographical areas with fewer services already experience health care disparities, while pandemic-related government restrictions such as stay-at-home orders resulted in fewer checkups [2,3]. A remote monitoring system can provide personalized care to larger populations without any geographical limitations. This study investigates the use of wearable activity trackers as an alternative to standard, in-person tests. In oncology, patients' performance status is a crucial factor in treatment decision-making and their prognosis. Tests such as the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale [4,5] and the Memorial Symptom Assessment Scale-Short Form (MSAS-SF) [6] have been used to assess patients' status. Although there is abundant evidence that patients' ECOG-PS and MSAS-SF scores correlate with cancer-related outcomes such as chemotherapy toxicity and response to treatment [7], both tests have limitations. The use of activity trackers to monitor patients can mitigate these limitations and provide a more accurate picture of patients' status.

Although patients spend most of their time between cancer treatments at home, tests such as the ECOG-PS and MSAS-SF are conducted at clinic visits and do not provide a daily view of patients' performance status [8]. As a result, the tests' reliability and validity may be diminished due to the low agreement between clinicians, nurses, and patients on performance status ratings. A study by Ando et al [9], which included 206 patients with lung cancer, revealed that patients rate their ECOG-PS lower than oncologists and nurses. Similarly, Blagden et al [10] observed that oncologists and patients agreed about patients' ECOG-PS in only 50% of cases for 98 patients with lung cancer. Moreover, similar studies illustrate that interrater reliability decreases as patients' functional activity declines. Although interrater reliability was high between a clinical oncologist, a ward resident, and a medical officer for highly active patients [10], Mayer et al [11] found only 53%-61% agreement in ECOG-PS of patients with cancer in the palliative care setting.

Incorporating patient-generated health data can reduce bias and improve the accuracy of the patients' performance status tests. Electronic mobile activity trackers provide new methods for collecting and monitoring patients' daily activities and function in real settings. The feasibility of commercially available activity trackers has already been demonstrated for patients with other types of cancer [12]. As surveyed by Purswani et al [13], tracking the number of steps patients take is a key component of the evaluation of patients' health status in oncology. Perez et al [14] observed that a decrease in the number of daily steps among older patients with cancer is an indicator of chemotherapy toxicity. Gresham et al [15] demonstrated a strong correlation between average daily steps and ECOG-PS for patients with cancer. Although Soh et al [16] validated the use of a mobile care system for self-monitoring in patients with advanced gastrointestinal cancer, the utility of activity trackers in patients with gastrointestinal cancer is less explored. In this pilot study, we evaluate the correlations between patients' ECOG-PS and MSAS-SF scores and their step counts. Further, we explore the best way to visualize the data to track daily fluctuations and monitor patients' health status.

Methods

Overview

The development phase of this study began in February 2019. The Memorial Sloan Kettering Cancer Center Institutional Review Board authorized the conduct of this study in August 2019. Medical professionals were recruited from Memorial Sloan Kettering Cancer Center in New York, and the resulting team included oncologists, an oncology nurse specialist, oncology rehabilitation physicians, and a customer relationship management expert.

Recruitment

Patients were eligible to participate in the study if they were aged ≥18 years, had gastrointestinal cancer, and started a new line of chemotherapy. Patients were excluded if they were using assistive devices such as a walker or a cane or were receiving concomitant radiation and chemotherapy. Additionally, patients needed to be enrolled in the study for at least seven days before starting the new chemotherapy line to allow for a proper baseline activity assessment. All patients gave their written consent to participate in the study.

Technologies and Technique

Each participant was given a Misfit Shine AT fitness tracker (Misfit) after institutional review board approval and written informed consent. This particular model was selected after assessing various consumer-based activity trackers based on the following four characteristics:

1. No feedback provided. Patients should not receive any feedback regarding their step count, nor any positive or negative reinforcement in response to a high or low number of steps [17,18].
2. Long battery life. Patients should not need to remove the device to recharge it, which would potentially result in forgetting to put it back on again [19].
3. Waterproof. The activity tracker should be waterproof to allow patients to continue wearing it while showering.
4. Ability to act as an independent device. The activity tracker should be able to act as an independent device and not require synchronization with a cell phone.

The Misfit Shine exhibits all these characteristics and best fit our needs for this study. Misfit Shine has been validated for clinical use in prior studies [13,20,21]. For example, Ferguson et al [21] demonstrated a strong correlation between measurements obtained by the Misfit Shine and research-grade activity monitors. Furthermore, Mercer et al [22] observed a high acceptance rate of the Misfit Shine device among adults aged >50 years.

Data Collection

A Misfit account was created for each patient and patients were instructed to wear the Misfit Shine on their nondominant wrist. The number of daily steps was recorded automatically in the

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app via Wi-Fi. Clinicians had access to the patients' data on the administrator web page. An unidentified code was applied to each patient for security. It is important to mention that patients did not have access to their accounts in order to prevent them from reviewing their step count. Step count data were collected for each patient for 7 days prechemotherapy and 14 days postchemotherapy. A day with a step count >100 was referred to as a "full day of data collection," a day with a step count <100 was referred to as a "partial day of data collection," and a day with no step count recording was referred to as "no data collection." Only patients with at least three full days of data collection during both the prechemotherapy and postchemotherapy periods were included in the final study.

Step Count Assessment

A research study assistant collected patient data in two phases. C1D1 (cycle 1, day 1) indicates that the data were collected before the first cycle of chemotherapy ("prechemotherapy"). C2D1 (cycle 2, day 1) indicates that the data were collected after the first cycle of chemotherapy and before the second cycle ("postchemotherapy"). Patient data were collected 7 days before C1D1 and 14 days after C1D1. There was no intervention involved in the activity monitoring, and the data were collected after the completion of each cycle, not in real-time.

Symptom Burden Assessments

Data on the presence and severity of symptoms were collected at baseline and at C2D1 by administering the MSAS-SF [6]. The MSAS-SF is a patient-rated instrument that evaluates 26 physical symptoms and the frequency of 4 psychological symptoms. Patients' physical symptoms were assessed using a Likert scale ranging from 0 (not present) to 4 (very much). The frequency of psychological symptoms was rated from 1 (rarely) to 4 (almost constantly). The MSAS-SF comprises three subscales: the global distress index (GDI), physical symptom subscale (PHYS), and psychological symptom subscale (PSYCH). The MSAS-GDI assesses the average frequency of 4 psychological symptoms (sadness, irritability, nervousness, and anxiety) and 6 physical symptoms (lack of appetite, lack of energy, drowsiness, pain, constipation, and dry mouth). MSAS-PHYS is the average score of 12 physical symptoms: lack of appetite, pain, constipation, lack of energy, drowsiness, nausea, vomiting, dry mouth, change in taste, feeling bloated, dizziness, and weight loss. The MSAS-PSYCH assesses the average frequency of 6 psychological symptoms: anxiety, nervousness, sadness, difficulty sleeping, difficulty concentrating, and irritability. Finally, the total MSAS (TMSAS) score is the average score of all 32 physical and psychological symptoms.

Results

Patient Characteristics

A total of 41 patients consented to the study, but one patient dropped out of the study because they decided to receive treatment at another institution. Only 27 patients (68%) had adequate activity tracker data, as shown in Figure 1. There were 17 males and 10 females, with a median age of 58 years (range 38-81 years). At baseline, patients had ECOG-PS scores of 0 (n=17, 63%) and 1 (n=10, 37%). The majority of patients were diagnosed with colon cancer (n=17) and were receiving metastatic chemotherapy (n=13). In this study, patients had lower TMSAS scores (mean 0.63, SD 0.37) compared to the broader cancer population (mean 0.77, SD 0.53) [16]. Patients also had lower scores on the MSAS-GDI, MSAS-PHYS, and MSAS-PSYCH compared to the broader cancer population. A lower MSAS score is an indicator of a low ECOG-PS score [23,24]. Additional information about patient characteristics is provided in Table 1. The patients' step counts with and without adequate data at baseline are shown in Table 2 and Table 3.

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Figure 1. Completeness of patient data collection.

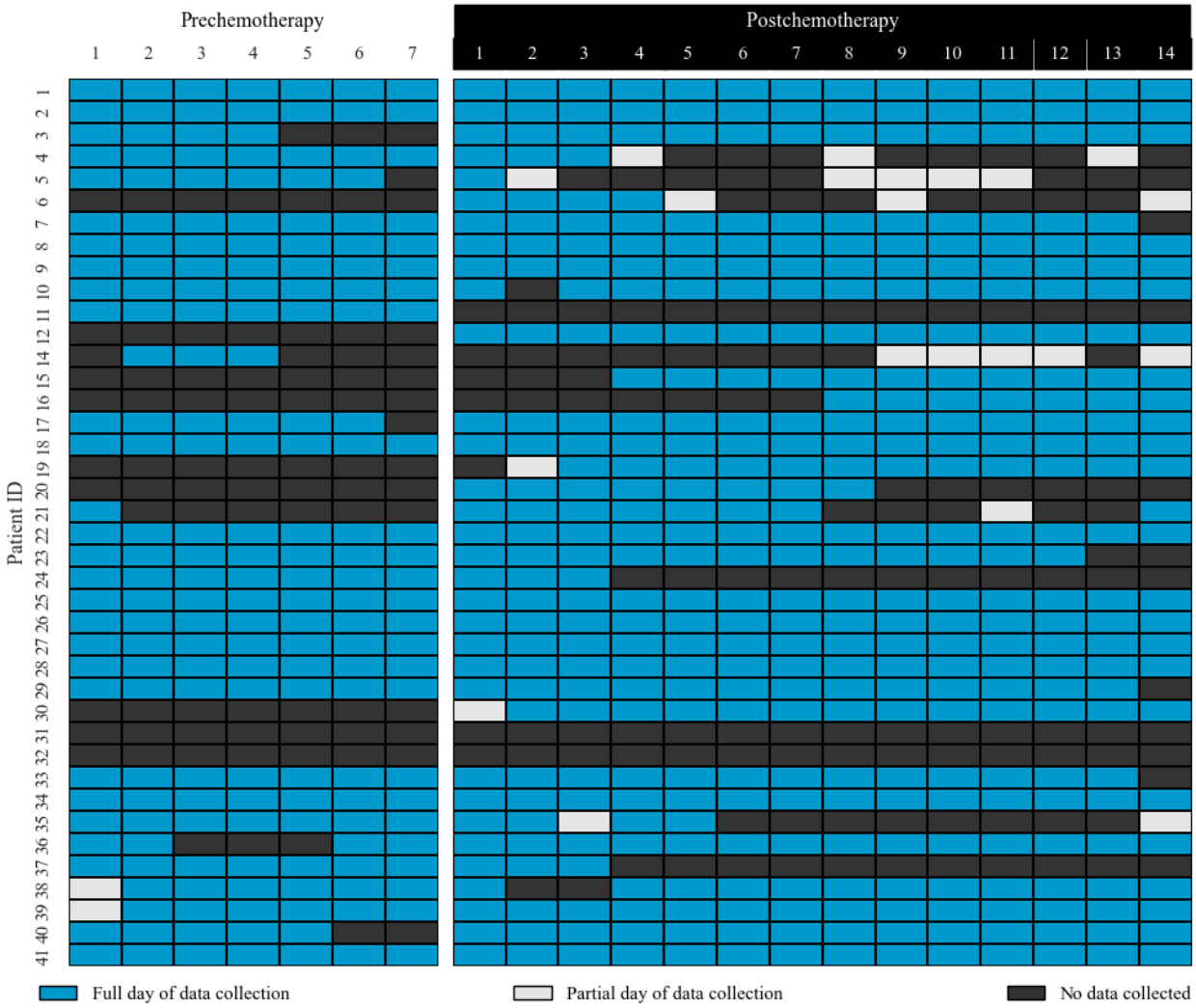

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Table 1. Demographic and clinical characteristics at baseline visit.

Demographics and characteristics	Values
Gender, n (%)	
Male	17 (63)
Female	10 (37)
Age (years), median (range)	58 (37-83)
Marital status, n (%)	
Married	18 (66)
Single	9 (34)
Education, n (%)	
College graduate or higher	15 (55)
Lower than college degree	12 (45)
Chemotherapy types, n (%)	
Adjuvant	8 (30)
Neoadjuvant	6 (22)
Metastatic	13 (48)
Smoking status, n (%)	
Ever	10 (27)
Never	17 (63)
Eastern Cooperative Oncology Group Performance Status score, n (%)	
0	17 (63)
1	10 (37)
>1	0 (0)
Memorial Symptom Assessment Scale score, mean (SD)	
Global distress index subscale	0.63 (0.37)
Physical symptom subscale	0.69 (0.52)
Psychological symptom subscale	1.28 (0.75)
Total Memorial Symptom Assessment Scale	0.63 (0.37)

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Table 2. The daily mean, median, maximum, and minimum activity level pre- and postchemotherapy.

Treatment phases and days	Mean activity level	Median activity level	Maximum activity level	Minimum activity level
Prechemotherapy				
Day 1	0.713[a]	0.724[a]	0.269	0.572[a]
Day 2	0.729[a]	0.779[a]	0.350	0.540[a]
Day 3	0.857[a]	0.782[a]	0.773[a]	0.776[a]
Day 4	0.820[a]	0.720[a]	0.875[a]	0.895[a]
Day 5	0.842[a]	0.785[a]	0.558[a]	0.798[a]
Day 6	0.720[a]	0.724[a]	0.372	0.632[a]
Day 7	0.729[a]	0.692[a]	0.585[a]	0.584[a]
Postchemotherapy				
Day 1	0.193	0.096	0.296	0.091
Day 2	0.625[a]	0.556[a]	0.596[a]	0.563[b]
Day 3	0.676[a]	0.591[a]	0.709[a]	0.406[b]
Day 4	0.858[a]	0.793[a]	0.923[a]	0.361
Day 5	0.894[a]	0.900[a]	0.805[a]	0.569[b]
Day 6	0.913[a]	0.929[a]	0.817[a]	0.550[b]
Day 7	0.885[a]	0.897[a]	0.835[a]	0.439[b]
Day 8	0.716[a]	0.738[a]	0.630[a]	0.566[b]
Day 9	0.549[a]	0.591[a]	0.421[b]	0.584[b]
Day 10	0.862[a]	0.892[a]	0.738[a]	0.609[b]
Day 11	0.829[a]	0.807[a]	0.822[a]	0.442[b]
Day 12	0.863[a]	0.870[a]	0.744[a]	0.563[b]
Day 13	0.858[a]	0.862[a]	0.776[a]	0.507[b]
Day 14	0.725[a]	0.764[a]	0.642[a]	0.351

[a]$P<.05$.

[b]$P<.001$.

Table 3. The correlation of mean, median, maximum, and minimum activity levels pre- and postchemotherapy.

Activity levels	Prechemotherapy mean activity level	Prechemotherapy median activity level	Prechemotherapy maximum activity level	Prechemotherapy minimum activity level
Postchemotherapy mean activity level	0.839[a]	0.763[a]	0.794[a]	0.644[a]
Postchemotherapy median activity level	0.823[a]	0.774[a]	0.762[a]	0.695[a]
Postchemotherapy maximum activity level	0.792[a]	0.648[a]	0.838[a]	0.509[b]
Postchemotherapy minimum activity level	0.501[b]	0.605[b]	0.293	0.412[b]

[a]$P<.05$.

[b]$P<.001$.

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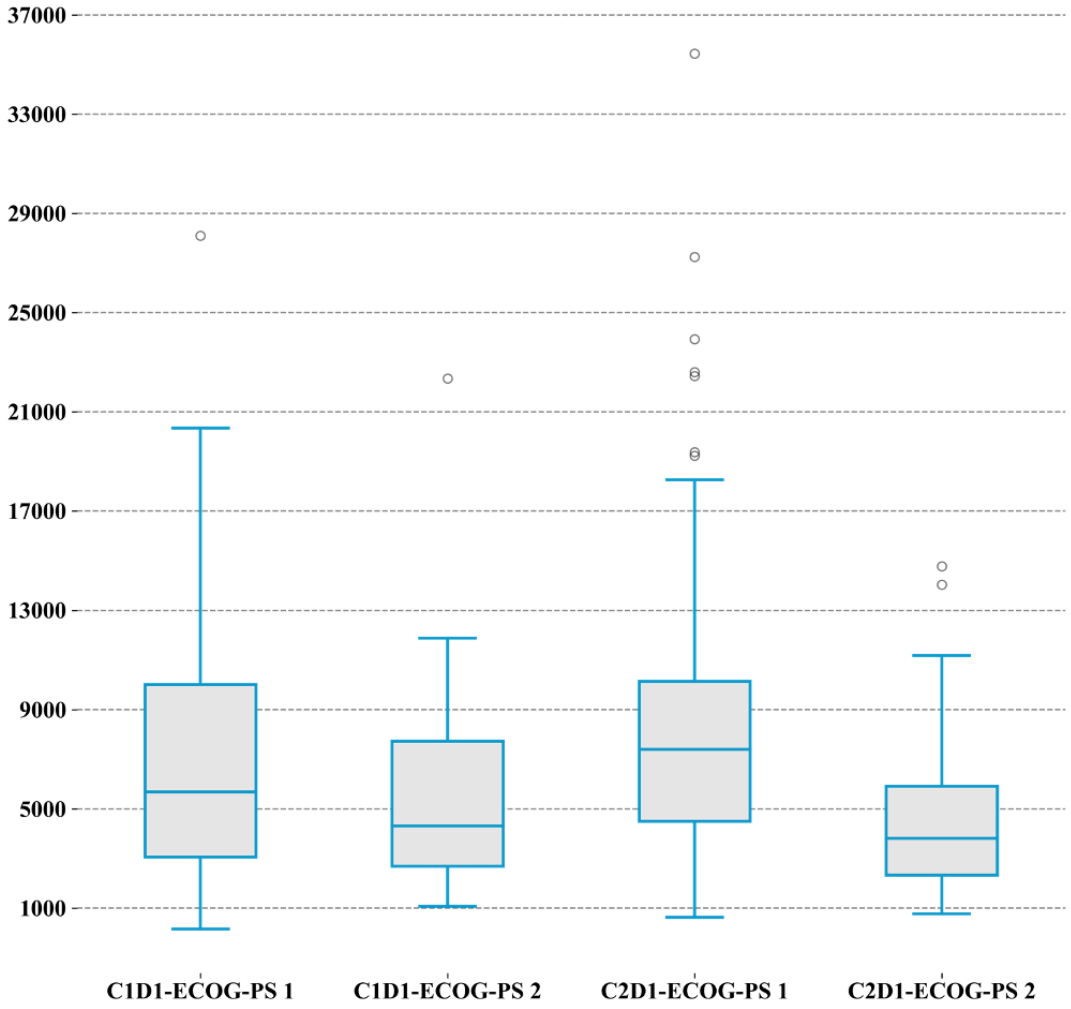
Step Count and Its Correlation With Performance Status

The overall average number of steps per day for all patients was 6290 before chemotherapy and 6325 after chemotherapy. The average step count prechemotherapy for patients with an ECOG-PS of 1 was 7023 steps per day, while patients with an ECOG-PS of 2 had an average step count of 5405 steps per day (Figure 2). The average step count at postchemotherapy for patients with an ECOG-PS of 1 was 8020 steps, while the average step count at C2D2 for patients with an ECOG-PS of 2 was 4448 steps. Although the correlation between both ECOG-PS categories at C1D1 was not significant (P=.06), there was a significant correlation at C2D1 (P<.001). The patients with an ECOG-PS of 0 had a higher median step count after chemotherapy. Conversely, the median step count for patients with an ECOG-PS of 2 decreases after chemotherapy. It is notable to mention that we did not find a significant correlation between either cancer type and number of steps or type of chemotherapy and number of steps.

Figure 2. The step count per day by ECOG-PS score. C1D1 indicates that the data were collected before chemotherapy, and C2D1 indicates that the data were collected after chemotherapy. ECOG-PS: Eastern Cooperative Oncology Group Performance Status.



Effect of Chemotherapy on Patients' Step Count

The overall median number of steps walked by patients pre- and postchemotherapy was 4983 and 5480, respectively. Overall, the step count decreases after chemotherapy; the median difference between pre- and postchemotherapy for the cohort was 497 steps, and the IQR decreased from 5916 steps to 5119 steps postchemotherapy. Prechemotherapy, patients younger than 60 years of age walked more than patients older than 60 years of age (median number of steps 5618 versus 4738, P=1.4). This difference persisted postchemotherapy as well (median number of steps 5860 versus 4534, P=.002). Figure 3 illustrates the daily step count of patients before and after chemotherapy.

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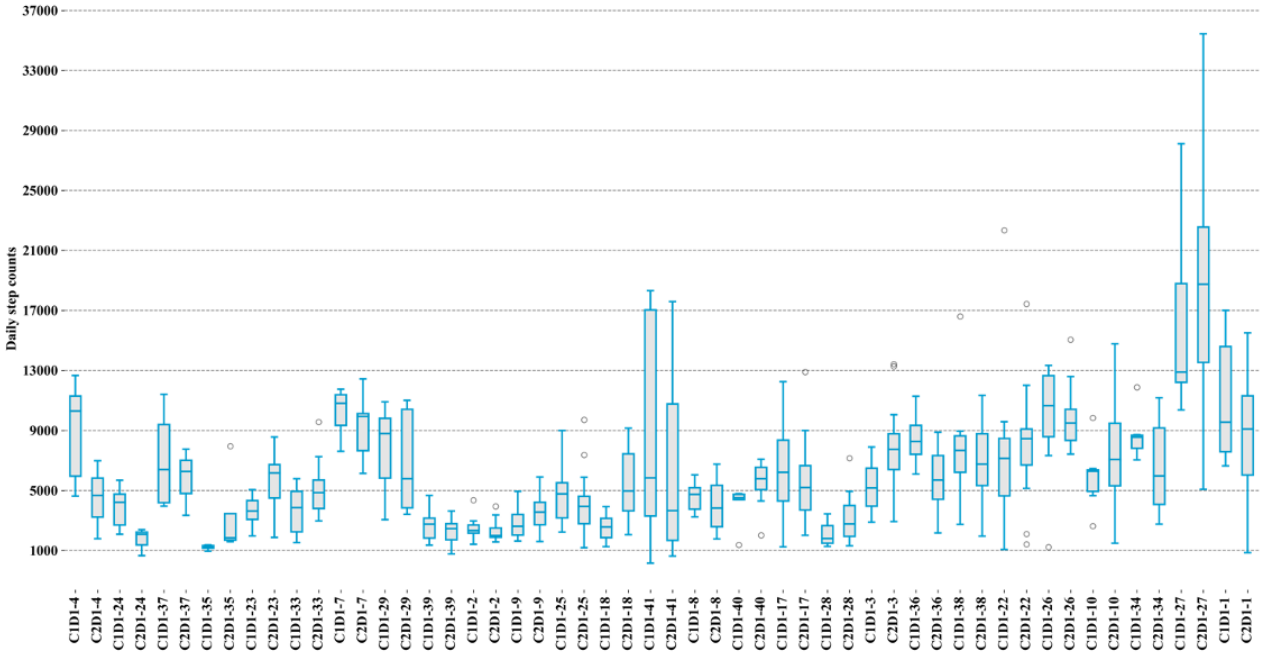
Figure 3. The daily step count of each patient before the first cycle of chemotherapy (labeled as C1D1) and after the first cycle of chemotherapy (labeled as C2D1).



We calculated the volatility of step counts pre- and postchemotherapy to illustrate the degree of behavior change, as follows:

where $S(t)$ is the number of steps at time t. A positive $\sigma(t)$ shows an increase in step count compared to the previous day and a negative $\sigma(t)$ indicates a decrease in step count compared to the previous day. Prechemotherapy, there were 120 days for which the step count increased compared to the previous day and 56 days for which the step count decreased compared to the previous day. Postchemotherapy, there were 222 days for which the step count increased compared to the previous day and 102 days for which the step count decreased compared to the previous day. Figure 4 displays the daily changes in step count for all patients. The annualized volatility of the step counts of each patient was calculated to explain the volatility of behavior change before and after chemotherapy, as follows:

where n is the number of days with available data. The annualized variance in step count increased for 16 patients postchemotherapy, and decreased for 11 patients. Of the patients who experienced an increase in their annualized variance step count, 9 of them were patients with an ECOG-PS of 0 and 7 of them were patients with an ECOG-PS of 1. Among patients with an ECOG-PS of 1, 70% experienced an increase in the annualized variance step count compared to patients with an ECOG-PS of 0 (52%). Figure 5 illustrates the annualized variance step count of patients before and after chemotherapy.

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Figure 4. Step count volatility for each patient.

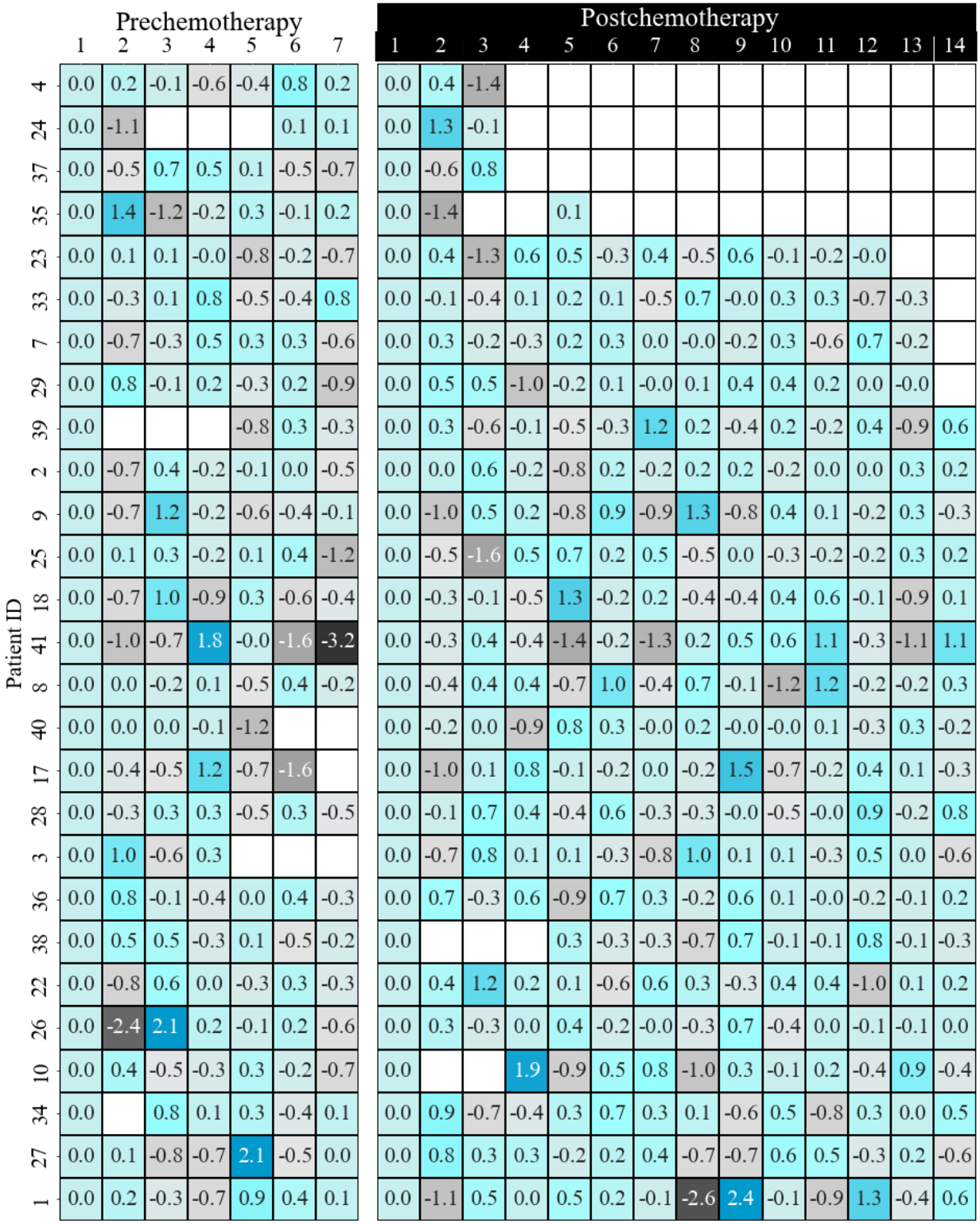

Figure 5. The annualized variance of the step counts of patients before (labeled as C1D1) and after (C2D1) the first cycle of chemotherapy.

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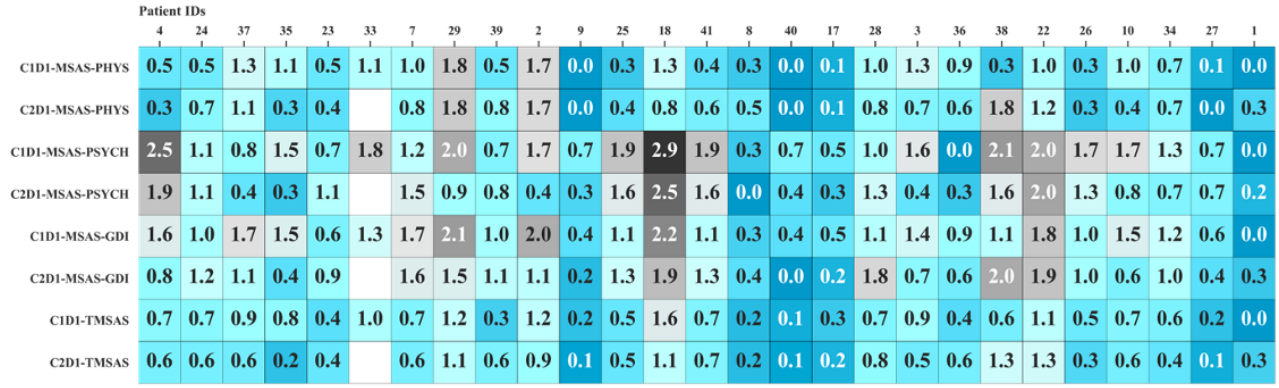
Step Count and Its Correlation With Burden of Symptoms

The median physical and psychological scores prechemotherapy were 0.53 (IQR 0.26-1.06) and 1.26 (IQR 0.66-1.86), respectively. The median GDI and TMSAS scores were 1.12 (IQR 0.64-1.56) and 0.66 (IQR 0.30-0.88), respectively. Patients' symptom burden changed after chemotherapy. Patients had a median improvement of 0.18 for their GDI score, 0.09 on the TMSAS, and 0.26 for the psychological score, while the physical score did not change. In addition, 59% (16/27) had an improvement in their GDI and 62% (17/27) had an improvement in their TMSAS during the postchemotherapy phase. The rate of improvement for the cohort was 46% and 65% for the physical and psychological domains, respectively.

Those with an improvement in their GDI, TMSAS, and physical scores took more daily steps before and after chemotherapy compared to those with no improvement in these scores. The three patients who experienced an improvement in their GDI, physical, and TMSAS scores walked 6205, 5769, and 6239 steps before chemotherapy and 5788, 6216, and 5788 steps daily after chemotherapy. However, those with no improvement in their GDI, physical, and TMSAS scores walked 5032, 5436, and 5148 steps per day before chemotherapy, and 3934, 4562, and 4816 steps per day after chemotherapy. All MSAS scores of patients before and after chemotherapy are shown in Figure 6. Given the small sample size, the *P* value was not significant for any of these assessments.

Figure 6. Patients' MSAS scores before and after the first day of the first cycle of chemotherapy (labelled as C1D1 and C2D1, respectively). GDI: global distress index; MSAS-SF: Memorial Symptom Assessment Scale-Short Form; PHYS: physical symptom subscale; PSYCH: psychological symptom subscale; TMSAS: total MSAS.



Feasibility and Acceptance of Activity Tracker

Only 13 of 40 patients did not have adequate data. There were 8 patients without adequate data prechemotherapy, 3 patients without adequate data postchemotherapy, and 2 patients with inadequate data both pre- and postchemotherapy. Of the collective 280 prechemotherapy days of the study cohort, there were 195 days (69%) with a "full day of data collection," 2 days (1%) with a "partial day of data collection," and 83 days (30%) with "no data." Of the collective 560 postchemotherapy days of the study cohort, there were 405 days (72%) with a "full day of data collection," 21 days (3%) with a "partial day of data collection," and 134 days (25%) with "no data." During the 7-day prechemotherapy phase, on average, patients had 5 days with a "full day of data collection." During the 14-day postchemotherapy phase, patients had an average of 10 days with a "full day of data collection." Patients with adequate activity tracker data were younger compared to those with inadequate data (median age 58 years versus 60 years, *P*=.59).

Out of 27 participants, only one participant had discomfort when wearing the activity tracker prechemotherapy; however, this person found it comfortable to wear the device postchemotherapy. In addition, two patients found it uncomfortable to wear the activity tracker postchemotherapy. The patient who experienced discomfort when wearing the activity tracker prechemotherapy had an increase in the number of steps taken postchemotherapy. In contrast, for the patients who had trouble with the device postchemotherapy, the number of steps decreased. The median satisfaction score pre- and postchemotherapy remained the same at 80.

Discussion

This study investigated the feasibility of employing consumer-based activity trackers to monitor patients with gastrointestinal cancer undergoing chemotherapy. As shown in Figure 1, most patients wore their activity trackers during the 21-day study period. However, there was a drop-off in wearing the activity trackers at the end of each cycle. Previous studies illustrated a similar drop-off in the number of patients wearing their wearable devices [12,25]. As these results indicate, the length of study duration affects the amount of missing data. Thus, this increase in the amount of missing data and solutions to mitigate this problem need to be studied.

The study results indicate statically significant correlations between the number of steps patients take daily and two common performance status tests (ECOG-PS and MSAS-SF), which is consistent with earlier research findings [15]. These observations provide preliminary evidence supporting the clinical validity of using activity trackers in the care of patients with gastrointestinal cancer. As reported, patients with higher ECOG-PS scores experienced a higher volatility in their step count. Moreover, patients with a higher step count also had lower MSAS-GDI and TMSAS scores; this indicates that more active patients experience a lower burden of symptoms. These results suggest that physical activity could improve patients'

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symptoms. Correspondingly, clinicians should promote physical activity in patients undergoing chemotherapy to keep patients' symptoms under control.

We developed a steps volatility chart as a remote activity monitoring tool, as shown in Figure 4. Clinicians can easily track patients' daily activity levels by looking at the chart. The graph of patients' step volatility may be employed for interventions in a manner similar to other monitoring systems [26-28]. Use of the step volatility chart for cancer prevention and control and survivorship of patients should be studied in the future.

We believe patients' step counts, coupled with ECOG and MSAS scores, can help clinicians better understand patients' conditions. Activity tracker data provide a dynamic view of patients and could decrease the bias in patients' assessment tests. Although our study was limited by patient sample size, the number of monitored days, and our patients' performance status, we studied our patients in an uncontrolled environment outside clinical settings. In doing so, we illustrated the functionality of using wearable activity trackers to collect data in real life. The patients in this study tend to be healthier, with lower ECOG-PS scores, than the broader cancer population. Although this may limit the generalizability of our findings to a broader population, our results are in line with other studies on patients with severe conditions [12,13]. Our study's relatively healthy population demonstrates the usability of the wrist-worn activity tracker for this particular population.

In conclusion, the remote monitoring of patients' physical activity could decrease the cost of health care and provide a higher quality of health care to a broader population. Remote monitoring could revolutionize how we treat patients and help to provide health care for patients who live in remote areas without direct access to health care clinics or at times when doctors cannot see their patients in person. As a next step, we will collect data from a larger sample of patients with cancer with a broader range of ECOG-PS scores and find an approach that will encourage patients to use wearable activity trackers more regularly.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

C1D1: cycle 1, day 1
C2D1: cycle 2, day 1
ECOG-PS: Eastern Cooperative Oncology Group Performance Status
GDI: global distress index
MSAS-SF: Memorial Symptom Assessment Scale-Short Form

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PHYS: physical symptom subscale
PSYCH: psychological symptom subscale
TMSAS: total MSAS

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Original Paper

Emerging Trends and Thematic Evolution of Breast Cancer: Knowledge Mapping and Co-Word Analysis

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Abstract

Background: One of the requirements for scientists and researchers to enter any field of science is to have a comprehensive and accurate understanding of that discipline.

Objective: This study aims to draw a science map, provide structural analysis, explore the evolution, and determine new trends in research articles published in the field of breast cancer.

Methods: This study comprised a descriptive survey with a scientometric approach. Data were collected from MEDLINE using a search strategy based on Medical Subject Heading (MeSH) terms. This study used science mapping, which provides a visual representation and a longitudinal evolution of possible interrelations between scientific areas, documents, or authors, thus reflecting the cognitive architecture of science mapping. For this scientometric evaluation of the topic of breast cancer research, a very long period was considered for data collection. Moreover, due to the availability of numerous publications in the database, the assessment was divided into three different periods ranging from 1988 to 2020.

Results: A total of 12,577 records related to scientometric studies were extracted. The field of breast cancer research demonstrated three diagrams containing the most relevant themes for the three chronological periods evaluated. Each diagram was plotted based on the centrality and density linked to each research topic. The research output in the field was observed to revolve around 8 areas or themes: *radiation injury*, *cardiovascular disease*, *fibroadenoma*, *antineoplastic agent*, *estrogen antagonistic*, *immunohistochemistry*, *soybean*, and *epitopes*, each represented with different colors.

Conclusions: In the strategic diagrams, the themes were both well developed and important for the structuring of a research field. The first quadrant comprised motor themes of the specialty, which present strong centrality and high density (eg, corticosteroid antineoplastic age, stem cell, T-lymphocyte, protein tyrosine kinase, dietary, and phosphatidyl inositol-3-kinase). In the second quadrant of diagram, themes have well-developed internal ties but unimportant external ties, as they are of only marginal importance for the field. These themes are very specialized and peripheral (eg, DNA-binding). In the third quadrant, themes are both weakly developed and marginal. The themes in this quadrant have low density and centrality and mainly represent either emerging or declining themes (eg, ovarian neoplasm). Themes in the fourth quadrant of the strategic diagram are considered important for a research field but are not fully developed. This quadrant contains transversal and general, basic themes (eg, immunohistochemistry).

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Scientometric analysis of breast cancer research can be regarded as a roadmap for future research and policymaking for this important field.

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KEYWORDS

scientometrics; breast cancer; co-word analysis; Scimat; science mapping

Introduction

One of the requirements for scientists and researchers to enter any field of science is to have a comprehensive and accurate understanding of that discipline [1]. Accordingly, knowledge of the concepts, history, framework, scope, components, and functions of each discipline of science, as well as analyzing and examining how these are linked in the intertwined chain of human sciences and demonstrating these links with the fields on which they are more dependent, is of key importance [2]. In general, this knowledge should facilitate the best assay to gain a comprehensive picture of the fields of activity and applications of that discipline, which should be used as a guide by those who have not yet determined their future research passageway [3].

Science mapping is the analysis of publications within a scientific field from different viewpoints; it helps visualize a general assessment of a given field [4]. By using this map, the course of changes and developments in the field can be plotted to differentiate the fields with the most and the least proximity. Science mapping is undertaken to identify points of knowledge that follow "hot topics" and current trends in a given field [5]. A science map drawn based on the scientific research outputs of a field makes it possible to study the emergence of new fields and the cessation of some saturated scientific fields [6,7]. Simply put, the purpose of a science map is to depict the results of the analysis of publications of a scientific field from different angles and to provide an overview of that field [8]. Science maps attempt to showcase the processes of growth, integration, and disintegration of different fields of science over time. Scientific domains in these maps are determined in proportion to the level of activity of scientists, and the empty spaces in the illustrative map indicate unworked or unknown domains of science. This illustration thus showcases the growth, integration, or disintegration of different scientific fields over time [9,10]. In recent times, scientometrics—as a branch of information science and a bibliometric subfield—has been used in a plethora of studies to quantitatively examine emerging research patterns in the literature [11].

One of the most widely used methods for analyzing the structure of knowledge in various fields and drawing science maps is *co-word analysis* that examines the co-occurrence of keywords in the title, abstract, or text of articles. Therefore, co-word analysis is done on a set of published articles in a specific subject area [12]. By analyzing keywords used in articles of a specific research field, we can better understand the content of the common topics in that field [13,14]. Moreover, by measuring the relative intensity of these co-occurrences, simplified representations of concept networks in a given field can be illustrated [15].

Co-word analysis can reveal the main topics of the field under study, semantic structures, and the evolution of those works over time. In a co-word analysis, it is assumed that the most frequent words have a greater impact in a field of study than words that appear less frequently. Moreover, co-word analysis allows us to reveal emerging trends and changes in paradigms to facilitate predicting the direction of future research [13]. Co-word analysis can be used as a powerful tool to enable the follow-up of structural changes and the development of the sociocognitive network. This method also helps us identify emerging topics in scientific fields and draw a clear path for future research [16]. Furthermore, these networks were mapped by running network analyses using cosine link reduction and pathfinder networking scaling techniques [17].

One of the most important topics in medical research is breast cancer. Breast cancer is the most frequent type of cancer among women, affecting approximately 2.1 million women each year. It also causes the highest number of cancer-related deaths among women [18]. A total of 268,600 new cases of invasive breast cancer were estimated to be diagnosed among women and approximately 2670 cases among men in the year 2019 [19]. In addition, an estimated 48,100 cases of ductal carcinoma in situ were estimated to be diagnosed among women. Approximately 41,760 women and 500 men were expected to die from breast cancer in 2019 [20,21].

As in other fields of science, new research studies continually emerge in the field of breast cancer, leading to advancements in the field. Many of these studies often have some similarities and overlaps. For a variety of reasons, the volume of research suddenly sees a surge in some subfields, and with such increments, thematic overlaps can occur. However, in other areas, little research may be done over months and years. Given the importance of research in the field of medicine, in general, and breast cancer, in particular, it is necessary to provide a broad picture of the status of research conducted in this field. In other words, the structure of knowledge in this field should be revealed using techniques such as co-word analysis to demonstrate how this field has developed over time, and more importantly, to better understand the emerging topics, issues, and themes that have developed in this field.

This study uses co-word analysis to examine articles published in the field of breast cancer and improve or continue the necessary context for correction, continuation, or promotion of the pattern of their scientific behavior by gaining an understanding of the interests and tendencies of researchers in the field over time. Accordingly, this study aims to draw a science map, provide structural analysis, explore the evolution, and find new trends in articles published in the field of breast cancer by addressing the following research questions:

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1. What are the most important research areas in the field of breast cancer?
2. Under which of the 4 themes (ie, motor themes, specialized and peripheral themes, emerging or disappearing themes, and general and basic themes) are breast cancer thematic areas classified in the strategic diagram?
3. What are the most important issues in terms of frequency and intensity?
4. How have breast cancer thematic areas been developed across different periods?

Methods

Search Strategy

We used the MEDLINE database to retrieve and extract bibliographic information from breast cancer-related research articles. MEDLINE is the premier bibliographic database of the US National Library of Medicine (NLM) that contains more than 25 million references to journal articles in the field of life sciences with a concentration on biomedicine [22]. A distinctive feature of MEDLINE is that the records are indexed with NLM Medical Subject Headings (MeSH) [23,24]. With regard to subject areas, MEDLINE includes biomedicine and health care research, broadly defined to encompass those areas of life sciences, behavioral sciences, chemical sciences, and bioengineering that are needed by health professionals and others engaged in basic research and clinical care, public health, health policy development, or related educational activities. MEDLINE also covers life sciences fields vital to biomedical practitioners, researchers, and educators, including aspects of biology, environmental science, marine biology, plant and animal science, as well as biophysics and chemistry [24].

To further validate the retrieved results, the search strategy used in this study was limited to research papers published in core clinical journals. The period covered in this study included all the years covered by this database (from 1950 to March 24, 2020). In other words, this study evaluated a total sample of 12,577 research articles published across 70 years. The retrieved records were saved as full records in plain text using tab-delimited and RIS (research information systems) formats. Finally, after saving the retried data, the related files were integrated and saved as a single file for subsequent use.

Data Acquisition and Processing

Overview

This study has been written on the basis of co-word analysis. Bibliometric methods explore the impact of a research field, a group of researchers, or a particular paper [25]. In this study, we used science mapping, which provides a visual representation and a longitudinal evolution of the interrelations between scientific areas, documents, or authors, reflecting the cognitive architecture of science mapping [26].

We used SciMAT [22,27], which is a powerful open-source science mapping [28] software. The tool allowed us to analyze the evolution and relevance of the literature focused on breast cancer. This tool was designed according to the science mapping analysis approach, which allows researchers to analyze a research field; detect and visualize its conceptual subdomains (particular topics or themes or general thematic areas); and develop a longitudinal framework to analyze and track the conceptual, intellectual, or social evolutions of e-government through the course of consecutive periods [29]. Different bibliometric tools are available to perform this kind of study [29], but SciMAT has some characteristics that distinguish it from other science mapping analysis tools.

SciMAT divides the analysis into four phases. A detailed explanation of these phases can be found elsewhere [7,30], although a brief description is provided below.

Detection of Research Themes

The first phase involves detection of research themes. This phase summarizes the first five steps of the workflow of science mapping analysis. In each period studied, the corresponding research themes are detected by applying a co-word analysis [31] to the raw data of from the published documents in the research field, followed by clustering of keywords to topics or themes by using the simple centers algorithm [32]. Formally, the methodological foundation of co-word analysis is based on the idea that the co-occurrence of keywords describes the content of the documents in a corpus [33]. These co-occurrences of keywords can be used to build co-word networks [34], and these networks can be associated with research themes using clustering tools. The co-occurrence frequency of two keywords is extracted from the corpus by counting the number of documents in which the two keywords appear together. Once the co-word network is built, each arc or edge will have in its weight the co-occurrence value of the linked terms. Next, the weight of each edge is transformed to normalize it (extracting the similarity relations between terms) using their keyword and co-occurrence frequencies [35].

Data Visualization

In this phase, the detected research themes are visualized using two different visualization instruments: a strategic diagram [22,36-38] and a thematic network. Each theme can be characterized by two measures [12,13]—centrality and density.

Centrality measures the degree of interaction of a network with other networks and shows the strength of external ties to other themes [39]. This value can be considered as the measure of the importance of a theme in the development of the entire research field analyzed. Density measures the internal strength of the network and reflects the strength of internal ties among all the keywords that describe the research theme. This value can be considered as a measure of the theme's development [40]. Once the centrality and density rankings are calculated, the themes can be laid out in a strategic diagram. Given both measurements, a research field can be visualized as a set of research themes, mapped in a 2D strategic diagram (Figure 1), and classified into the following four groups:

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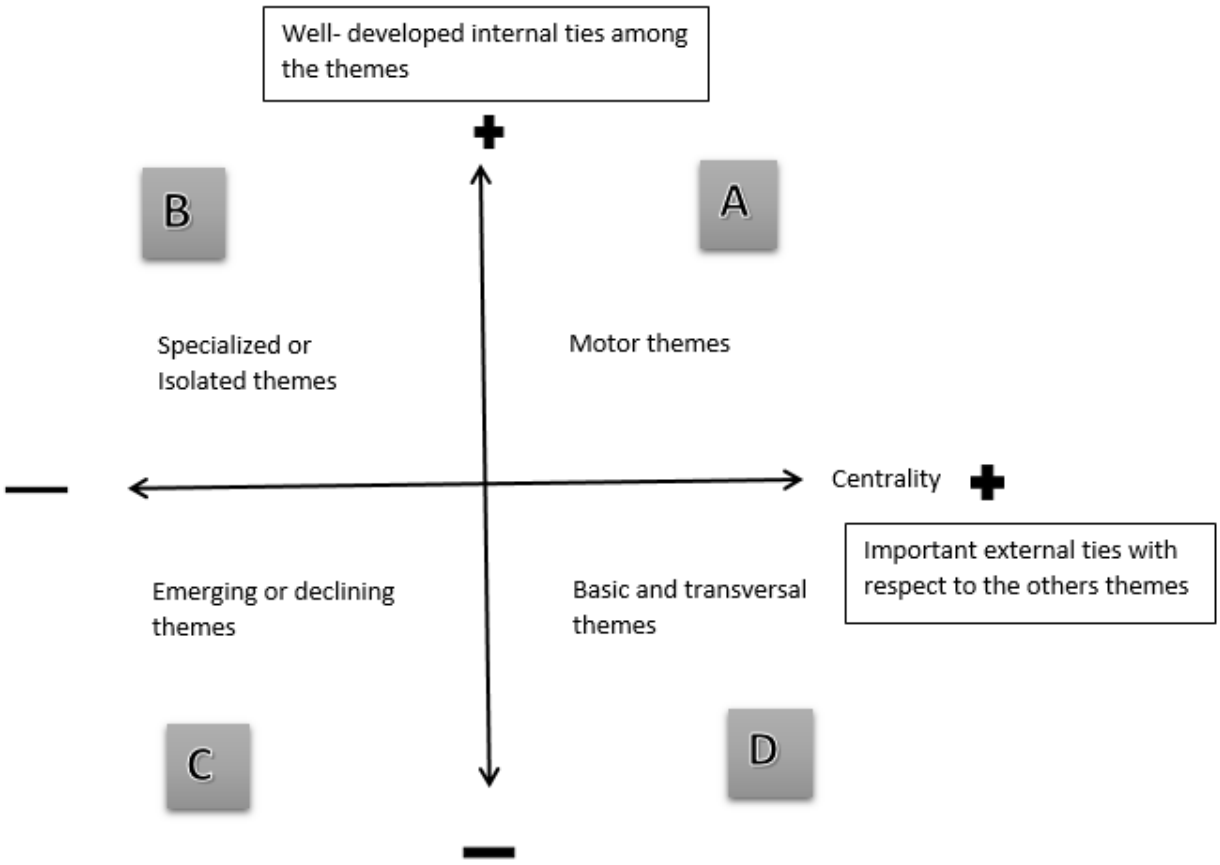
Figure 1. Strategic diagram in 2D and the 4-group classification: (A) motor themes, (B) specialized or isolated themes, (C) emerging or declining themes, (D) basic and transversal themes.



1. Motor themes
   that are both well developed and important for the structuring of a research field; these themes present strong centrality and high density.
2. Specialized and peripheral themes
   that have well-developed internal ties but unimportant external ties, as they are of only marginal importance for the field.
3. Emerging or declining themes
   that are both weakly developed and marginal; the themes in this quadrant have low density and low centrality.
4. Basic and transversal themes
   that are important for a research field but are not developed (eg, notes in computer science) [26].

Discovery of Thematic Areas

The next phase involved temporal or longitudinal analysis. In this phase, the evolution of the research themes over a set of periods is first detected and then analyzed to identify the main general areas of evolution in the research field, their origins, and their interrelationships. This allows the discovery of the conceptual, social, or intellectual evolution of the field. SciMAT can build an evolution map [29] and an overlapping items graph (Figure 2) [41] to detect the evolution areas (see Figure 3).

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Figure 2. The overlapping graph. The horizontal arrow represents the number of items shared by both periods. The upper incoming arrow represents the number of new items in the second period, and the upper outgoing arrow represents the items that are presented in the first period, but not in the second period [28,41].

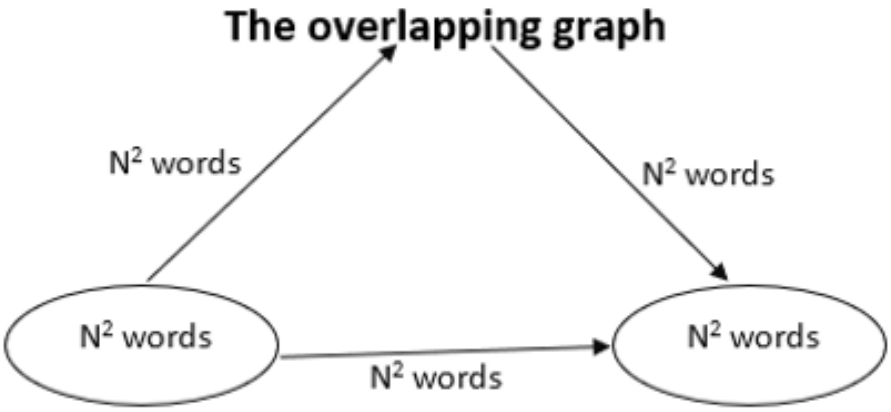
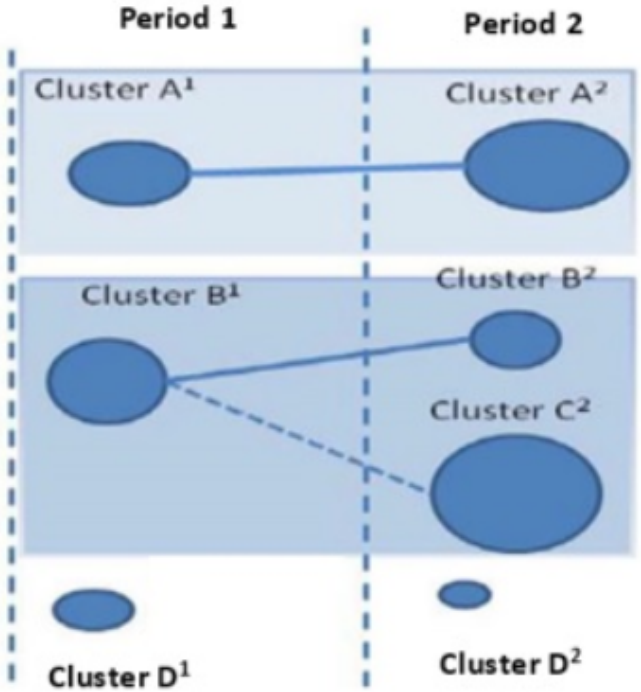


Figure 3. The evolution map: cluster D1 is discontinued, and cluster D2 is considered to be a new cluster.



For this purpose, an inclusion index is used to detect conceptual nexuses between research themes in different periods and thus identify the thematic areas in a research field. In addition, as each theme is associated with a set of documents, each thematic area can also have an associated collection of documents, obtained by combining the documents associated with its set of themes. Thus, the evolution map shows the temporal evolution of research themes of e-government, and the overlapping graph represents the number of associated keywords (Figure 2) [42].

Performance Analysis

In this phase, the relative contribution of research themes and thematic areas to the whole research field is measured (quantitatively and qualitatively) and used to establish the most prominent, most productive, and highest impact subfields. This performance analysis is developed as a complement to the analysis step of the science mapping workflow. Some bibliometric indicators in this phase used include the number of published documents, number of citations, and the different types of h index [43,44].

Eventually, three diagrams were represented based on the three temporal visualization phases. Following the science mapping workflow, visualization techniques were used to represent a science map and the results of different analyses. In this sense, the network results from the mapping step were represented in the form a strategic map, evolution map, and overlapping graph. Finally, when the science mapping analysis was completed, experts analyzed the results and maps, using their experience and knowledge.

Ethics Approval

Since this was a metadata analysis of published work, approval from an ethics committee was not required.

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Results

Overview

After retrieving a total of 12,577 records related to scientometric research, the importance of keywords (Table 1) and various journals was demonstrated (Table 2).

Table 1. Most frequently used terms in the selected articles (N=12,577).

Sr. no.	Source titles	Records, n (%)
1	Breast neoplasms	11,855 (97.9)
2	Prognosis	1919 (15.8)
3	Lymphatic metastasis	1735 (14.3)
4	Mastectomy	1520 (12.6)
5	Mammography	1435 (11.8)
6	Neoplasm staging	1420 (11.7)
7	Neoplasm recurrence local	1208 (10)
8	Neoplasm metastasis	1154 (9.5)
9	Risk factors	1115 (9.2)
10	Estrogen receptors	1113 (9.2)
11	Time factors	1014 (8.4)
12	Age factors	955 (7.9)
13	Carcinoma	889 (7.3)
14	Carcinoma ductal breast	814 (6.7)
15	Combined modality therapy	781 (6.4)
16	Axilla	779 (6.4)
17	Carcinoma intraductal noninfiltrating	753 (6.2)
18	Antineoplastic combined chemotherapy protocols	720 (5.9)
19	Lymph nodes	686 (5.7)
20	Mass screening	677 (5.6)
21	Antineoplastic agents	674 (5.6)
22	Biomarker tumor	655 (5.4)
23	Immunohistochemistry	640 (5.3)
24	Chemotherapy adjuvant	594 (4.9)
25	Neoplasm invasiveness	591 (4.9)
26	Lymph node excision	590 (4.9)
27	Tamoxifen	581 (4.8)
28	Receptor progesterone	563 (4.6)
29	Mastectomy segmental	543 (4.5)
30	Menopause	526 (4.3)

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Table 2. The top 30 journals with the highest number of articles published on breast cancer (N=12,577).

Row	Source title	Records, n (%)
1	Cancer	3321 (27.4)
2	Lancet London England	567 (4.7)
3	American Journal of Surgery	523 (4.3)
4	British Journal of Surgery	454 (3.7)
5	Radiology	453 (3.7)
6	Journal of Clinical Pathology	376 (3.2)
7	American Journal of Roentgenology	347 (2.9)
8	The New England Journal of Medicine	331 (2.7)
9	JAMA[a]	330 (2.7)
10	American Journal of Clinical Pathology	320 (2.6)
11	Annals of Surgery	295 (2.4)
12	The American Journal of Pathology	289 (2.4)
13	Medicine	256 (2.1)
14	Archives of Surgery (Chicago, Illinois) 1960	232 (1.9)
15	Archives of Pathology Laboratory Medicine	199 (1.6)
16	British Journal of Radiology	199 (1.6)
17	Endocrinology	194 (1.6)
18	Surgery	193 (1.6)
19	British Medical Journal (Clinical Research Ed.)	192 (1.6)
20	Surgery Gynecology Obstetrics	186 (1.5)
21	Journal of the American College of Surgeons	177 (1.5)
22	Journal of Clinical Endocrinology and Metabolism	153 (1.3)
23	Plastic and Reconstructive Surgery	152 (1.3)
24	British Medical Journal	145 (1.2)
25	Journal of Clinical Investigation	126 (1)
26	Southern Medical Journal	118 (1)
27	American Journal of Public Health	106 (0.9)
28	Annals of Internal Medicine	102 (0.8)
29	Surgical Clinics of North America	96 (0.8)
30	The American Journal of Clinical Nutrition	94 (0.8)

[a]JAMA: Journal of the American Medical Association.

Result for the Thematic Period (1987-2020)

Figure 4 shows the number of concepts related to the thematic area of breast cancer in the three 11-year periods spanning from 1988 to March 31, 2020.

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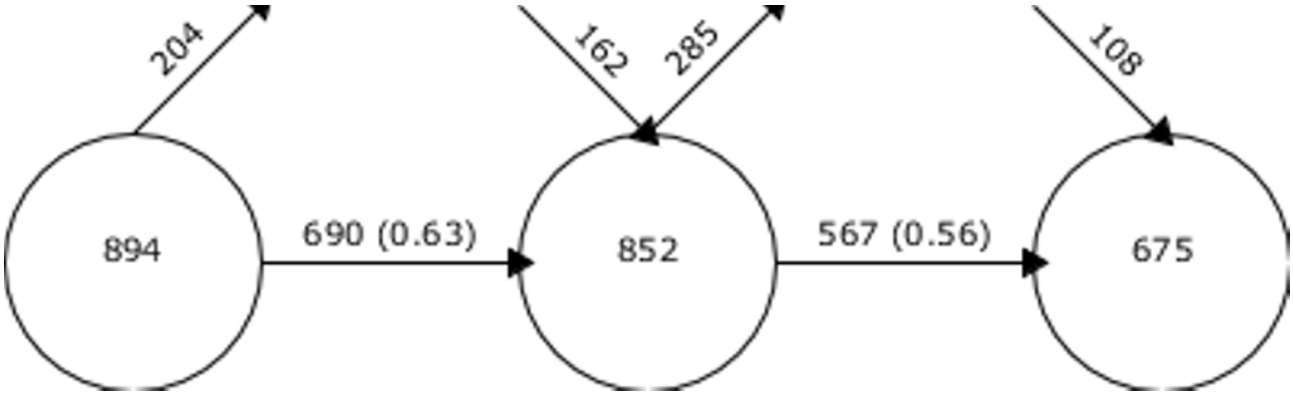
Figure 4. Thematic areas in the three evaluation periods based on centrality and density. The horizontal output arrows represent the number of concepts that served as the input for the next period; the vertical output arrows represent the number of concepts that exited a given period and were considered less important; and the vertical input arrow represents the number of concepts that received attention. In the second period, 852 new concepts appeared in the articles and 690 concepts were considered from the previous period. Of these 567 concepts entered the third evaluation period, and 675 new concepts appeared in the articles.



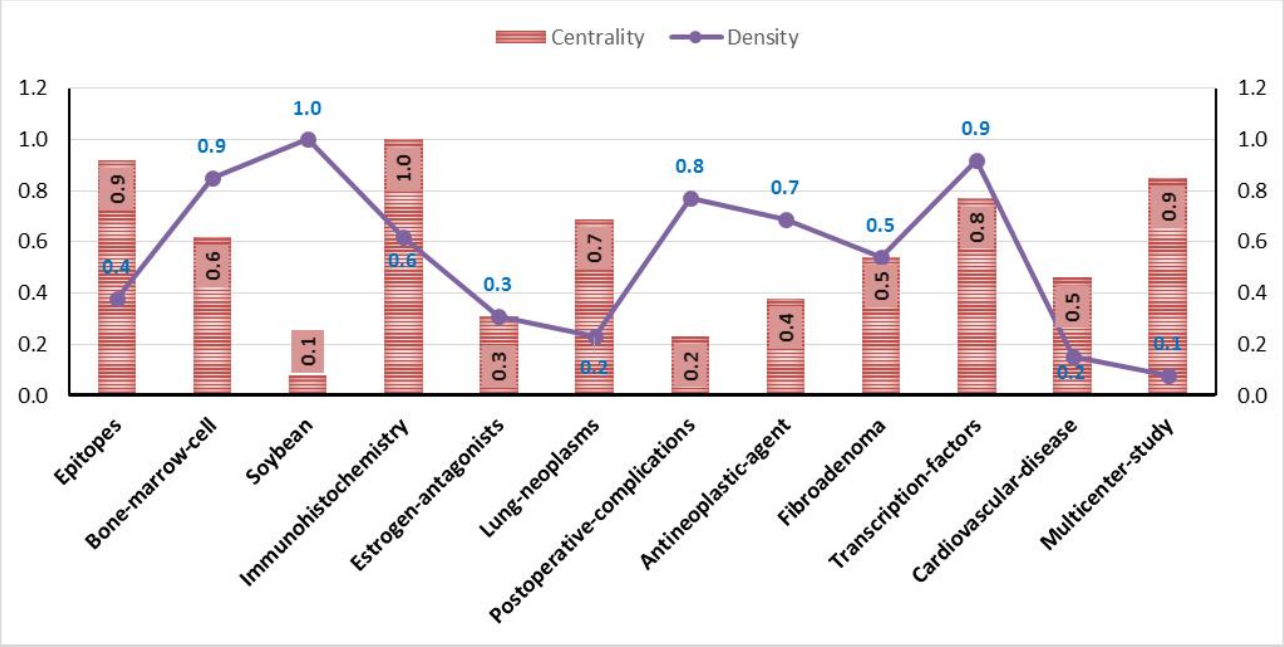
In the first period, the highest centrality was found for immunohistochemistry (IHC), and the highest density was related to the soybean theme. In the second period, the highest centrality was found in the antineoplastic themes, and the highest density was detected for the themes isoflavones and enzyme inhibitors. In the third period, the highest centrality was found for the antineoplastic agent theme, and the highest density was detected for the vegetable theme.

The strategic diagram of breast cancer was drawn based on the abundance of articles in the 4 thematic areas, including motor cluster, basic and transversal cluster, highly developed cluster, and emerging and declining cluster. The most important topics were found in the motor cluster, which are displayed in 10-year periods.

First Evaluation Period (1989-1998)

In the first period, the upper-right quadrant (ie, motor cluster) comprised transcription factors, bone marrow cell, immunohistochemistry, and fibroadenoma, indicating the important role of these concepts in the field of breast cancer from 1989 to 1998 (see Figure 5). A transcription factor is a protein that controls the rate of transcription by binding to a specific DNA sequence. Immunohistochemistry is one of the best ways to detect these factors (Multimedia Appendix 1).

Figure 5. Breast cancer–related concepts identified in the first evaluation period based on density and centrality from 1988 to 1998. Date adopted from global statistics retrieved from the Web of Sciences.



Second Evaluation Period (1999-2009)

The concepts related to the motor theme included isoflavones, enzyme inhibitors, immunohistochemistry, estrogen, proportional hazard model, and steroid. Soy isoflavones are enzyme inhibitors similar to lipoxygenase. Moreover, there is a close relation between suppression of dendritic cell maturation and functions by isoflavones (phytoestrogen; see Figure 6). Therefore, soy isoflavones can bind to estrogen receptors and act as an estrogen antagonist (Multimedia Appendix 2).

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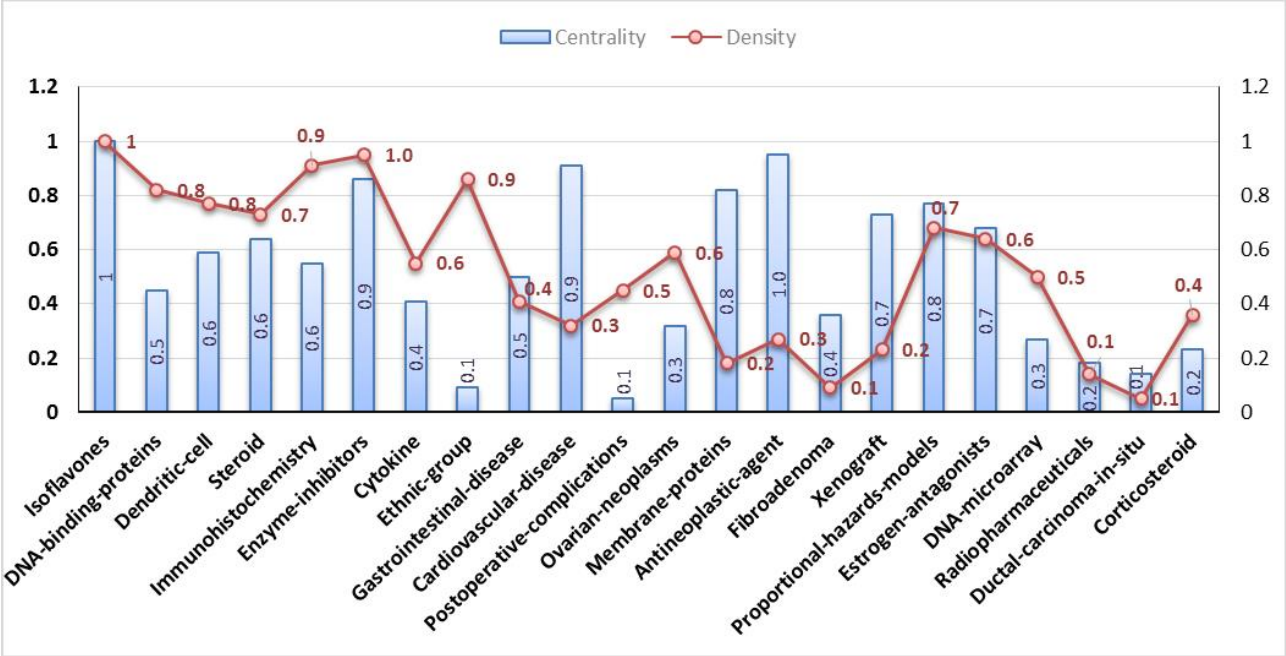
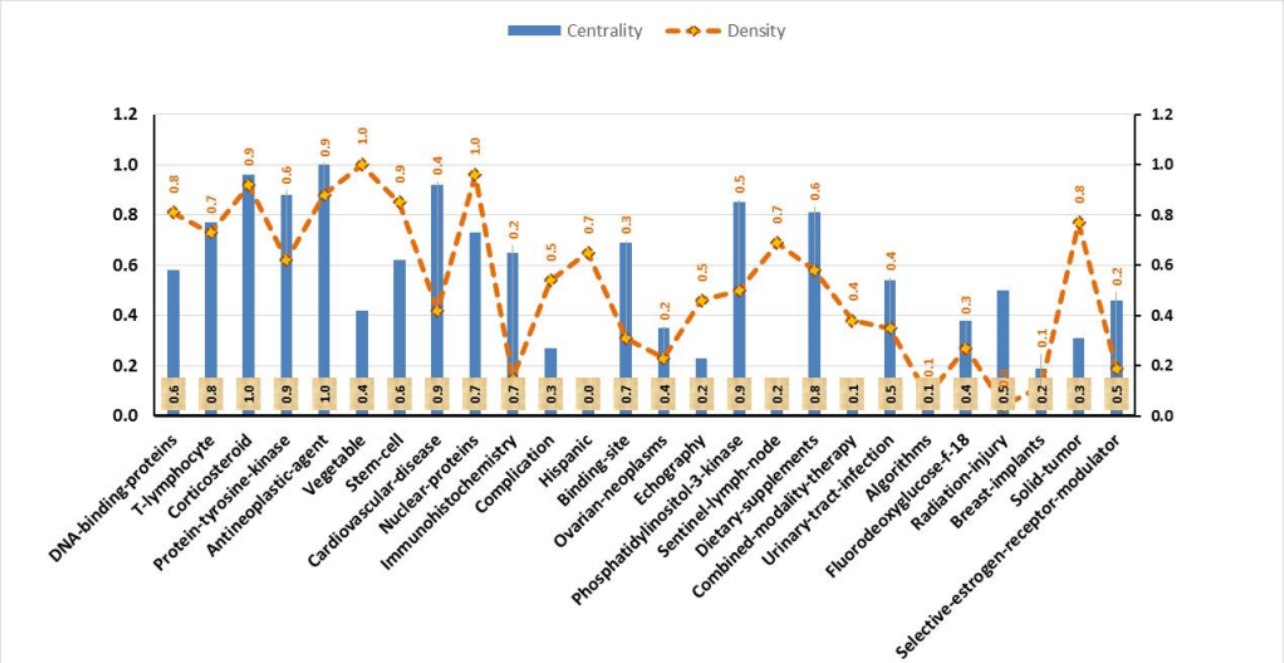
Figure 6. Breast cancer–related concepts identified in the second evaluation period based on density and centrality from 1999 to 2009. Date adopted from global statistics retrieved from the Web of Sciences.



Third Evaluation Period (2010-2020)

The concepts of the motor theme in the third evaluation period included revealing corticosteroid antineoplastic age, stem cell, T-lymphocyte, protein tyrosine kinase, dietary, and phosphatidylinositol-3-kinase, indicating the importance of these topics in this period (Figure 7).

Figure 7. Breast cancer–related concepts identified in the third evaluation period based on density and centrality from 2010 to 2020. Date adopted from global statistics retrieved from the Web of Sciences.



Steroids are important biodynamic agents and can be used as a particular agent for receptor-mediated diseases just like for breast cancer. Furthermore, infiltrative T-lymphocytes are related to invasive breast cancer.

Protein tyrosine phosphatases have a crucial role in the regulation of stem cell renewal and differentiation. Some studies have shown relations between DNA-binding protein oxidation and dietary supplements that contain plant extracts and vitamins (Multimedia Appendix 3).

Discussion

Principal Findings

After retrieving a total of 12,577 records related to scientometric studies, we were able to demonstrate important keywords,

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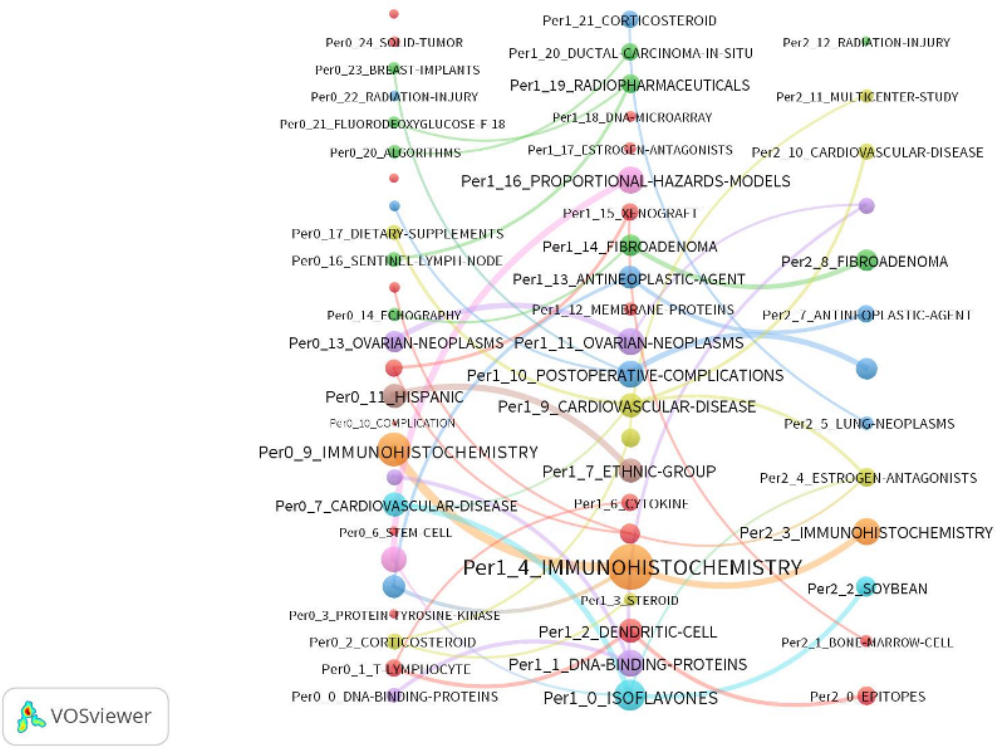
including *breast neoplasms*, *prognosis*, *lymphatic*, *metastasis*, *mastectomy*, *mammography*, and *neoplasm staging*. Indeed, examples of 30 journals with the highest number of articles published on breast cancer were *Cancer*, *Lancet (London, England)*, *The American Journal of Surgery*, *British Journal of Surgery*, *Radiology*, *Journal of Clinical Pathology*, *American Journal of Roentgenology*, *The New England Journal of Medicine*, *JAMA (Journal of the American Medical Association)*, and *TheAmerican Journal of Clinical Pathology*. Moreover, across the three evaluation periods, the themes with the highest density and centrality were observed in the first period, with the highest centrality was related to immunohistochemistry and the highest density related to the soybean theme. In the second evaluation period, the highest centrality was associated with the antineoplastic themes, and the highest density was observed in the isoflavones and enzyme inhibitor themes. In the third evaluation period, the highest centrality was related to the antineoplastic agent theme, and the highest density was observed in the vegetable theme.

As in this scientometric evaluation of breast cancer topic, a very long period was considered for data collection. Moreover, due to the multiplicity of the publications, this assessment was divided into 3 decades from 1989 to 2020. The results of this study confirmed the progression of studies in recent decades and different concentrations of assessments completed in different years. Moreover, communications between these themes were also shown (Figure 8).

Figure 8. Thematic trends in the field of breast cancer from 1988 to 2020. Date adopted from global statistics retrieved from the Web of Sciences.



Emerging Themes from the Three Evaluation Periods

Using SciMAT [22] and Vos-viewer [45], the research output in the field was observed to revolve around 8 areas. As shown in Multimedia Appendix 3, the themes in the rightmost column included *radiation injury*, *cardiovascular disease*, *fibroadenoma*, *antineoplastic agent*, *estrogen antagonistic*, *immunohistochemistry*, *soybean*, and *epitopes*, as indicated with different colors. Thematic links are demonstrated by a solid line. The size of these nodes is proportionate to the number of documents under each theme. In addition, the color of the nodes indicates different areas.

As seen in Figure 4, the analyzed research output is categorized by solid cohesion. Most of the identified topics have been gathered via thematic nodes. They arise from a topic appearing in the previous period and show a continuous evolution with almost no jumps or gaps.

Regarding the starting period, thematic areas started in the first period (Figure 5, Figure 7, right panel). Thus, they can be considered as the primary subjects in breast cancer. Furthermore, in the second period, a new thematic area emerged: *ethnic group*, *proportional hazards*, *corticosteroids*, *postoperative*, *ovarian neoplasm*, *ethnic group*, and *cytokine*. Indeed, the emerged thematic areas play an essential role in the development of the field. Regarding the theme composition, the thematic areas of *immunohistochemistry* are mainly composed of motor themes across all three periods. Furthermore, in the third period, *ethnicity* evolved to *Hispanic*. In addition, topics such as stem cell, solid tumor, breast implant, echography, and protein tyrosine kinase emerged in this field with some of them evolving from the second period.

The relationship between IHC and cancer biology, which is now better known, has influenced axillary lymph node dissection (ALND). Tumor biological factors are different in each tumor

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if tumor tend to metastasize to visceral or lymph nodes depends on tumor biological features. With advanced knowledge and understanding of tumor biology, systemic therapy and targeted therapy policies have changed. At present, the decision to initiate and prescribe chemotherapy (ie, systemic therapy) is influenced by the tumor stage and tumor biological factors, as well as the patient's lymphatic status. For example, in some cases, a tumor is diagnosed by screening mammography in the early stages, and there is no lymphatic involvement. Decisions to continue adjuvant treatments depends on the biological factors of the tumor. Biological factors play a key role on the decision to start neoadjuvant therapy. For example, triple-negative, and Her2neu-positive tumors have a dermatological response to neoadjuvant therapy.

In patients with a positive sentinel lymph node biopsy (SLNB), tumor biological factors such as ER/PR/Her2neu are prognostic factors, and it is of interest to know whether ALND changes the patient's cervix. According to the AMAROS trial [46], axillary radiotherapy was comparable to axillary dissection for local axillary control and even had fewer side effects. In patients with T1 and T2 masses, who had a positive SLNB and received axillary radiotherapy, overall survival and disease-free survival were similar to those who underwent axillary dissection. Therefore, SLNB is currently recommended for many patients with breast cancer. Currently, based on the IBCSG23-01 study, the National Comprehensive Cancer Network guidelines recommend only radiotherapy for patients with a positive SLNB (micrometastasis), without axillary dissection. Thus, SLNB has currently replaced ALND in many cases.

The false-negative rate is low in cases where a dual agent is used and at least more than two SLNs are found in patients with clinical lymph nodes (N1). Lymph node biopsy can be performed for patients undergoing neoadjuvant therapy. However, dual-agent therapy is preferably used when finding at least two lymph nodes in patients with preneoadjuvant clinical lymph node N1.

According to the AJCC (American Joint Committee on Cancer) staging, biomarkers such as ER/PR/Her2neu are recommended to be effective.

Pathological Analysis

Currently, the basis of breast cancer treatment is complete knowledge of its progression and biological factors (ER/PR/Her2neu). These factors affect the stage of the disease and also indicate the likelihood of tumor recurrence. They can also assist in response to selected treatments.

Conclusion

Eventually, scientometric analysis can showcase the current state of the science. Similarly, co-word analysis determines the frequency of words and thus indicates the most important research topics of a field. Using these methods, the characteristics and challenges of research fields and scientific disciplines can be determined. In addition, scientometric analysis of breast cancer research can be regarded as a roadmap for future research and policymaking in this important field of study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Strategic diagram for the second evaluation period (1999 to 2009).
[PNG File , 102 KB - cancer_v7i4e26691_app1.png]

Multimedia Appendix 2
Strategic diagram for the second evaluation period (1999 to 2009).
[PNG File , 180 KB - cancer_v7i4e26691_app2.png]

Multimedia Appendix 3
Strategic diagram for the third evaluation period (2010 to 2020).
[PNG File , 166 KB - cancer_v7i4e26691_app3.png]

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Abbreviations

AJCC: American Joint Committee on Cancer
ALND: axillary lymph node dissection
IHC: immunohistochemistry
JAMA: Journal of American Medical Association
MeSH: Medical Subject Headings
NLM: National Library of Medicine
SLNB: sentinel lymph node biopsy
RIS: research information system

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Original Paper

Medical Needs Extraction for Breast Cancer Patients from Question and Answer Services: Natural Language Processing-Based Approach

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Abstract

Background: A large number of patient narratives are available on various web services. As for web question and answer services, patient questions often relate to medical needs, and we expect these questions to provide clues for a better understanding of patients' medical needs.

Objective: This study aimed to extract patients' needs and classify them into thematic categories. Clarifying patient needs is the first step in solving social issues that patients with cancer encounter.

Methods: For this study, we used patient question texts containing the key phrase "breast cancer," available at the Yahoo! Japan question and answer service, Yahoo! Chiebukuro, which contains over 60,000 questions on cancer. First, we converted the question text into a vector representation. Next, the relevance between patient needs and existing cancer needs categories was calculated based on cosine similarity.

Results: The proportion of correct classifications in our proposed method was approximately 70%. Considering the results of classifying questions, we found the variation and the number of needs.

Conclusions: We created 3 corpora to classify the problems of patients with cancer. The proposed method was able to classify the problems considering the question text. Moreover, as an application example, the question text that included the side effect signaling of drugs and the unmet needs of cancer patients could be extracted. Revealing these needs is important to fulfill the medical needs of patients with cancer.

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KEYWORDS

natural language processing; internet use; patient generated health data; neoplasms

Introduction

Background

Patients with cancer have many medical needs. These needs are diverse and not necessarily communicated to doctors, nurses, and other medical staff. A database of their problems is needed to determine which patients experience problems or have unmet needs and to what extent.

Such a database does exist in Japan, the "cancer problem classification" (CPC), and is maintained by the Shizuoka Cancer Center. It was created by collecting and categorizing the claims of cancer survivors through a nationwide survey into 4

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categories. The CPC has systematized the worries and burdens of patients with cancer surveyed through telephone consultations and other means, with 7855 participants in 2003 and 4054 in 2013 [1]. However, this process was conducted manually by experts, and making a new one would be costly and time-consuming. With the recent exponential growth of the internet, a vast number of illness-related problems have already been accumulated in Japan [2], where blogs are actively written. As of July 2021, TOBYO [3] has the largest collection of diaries and blogs in Japan dedicated to battling diseases (approximately 63,000 of such diaries and blogs), covering some 1500 conditions. Among them, the number of blogs on breast cancer, the treatment of which tends to be prolonged, is particularly large, accounting for over 10% (approximately 6900) of blogs. Furthermore, Yahoo! Japan's question and answer (YJQA) service, commonly called Chiebukuro [4], is one of Japan's leading question and answer (QA) services, containing approximately 60,000 questions that include the key phrase "breast cancer." Thus, a vast archive of patient claims has already been created on the internet.

In this context, many recent studies have utilized accumulated information [5-9]. For example, Rosenblum and Yom-Tov [5] investigated how people search for information related to attention-deficit/hyperactivity disorder using the Microsoft Bing search engine [10] and Yahoo! Answers, a web QA site. Park et al [6] investigated the use of medical concepts regarding diabetes from the textual data of blogs and QA sites, whereas Yom-Tov and Gabrilovich [7] investigated the side effects of medications from web search queries. Tsuya et al [8] demonstrated that cancer patients share information about their diseases, including diagnosis, symptoms, and treatments via Twitter [11], and Hong [9] explored whether patients could accurately and adequately express their information needs on Chinese health QA websites. Thus, using patients' claims on the web can provide a qualitative and timely understanding of needs from the patient's perspective and be considered a type of patient-reported outcome, which may help transform health care in terms of patient-centered care [12,13].

However, there are some limitations to using the accumulated information, the biggest problem being the difficulty in examining a large amount of data. Because there is no existing classification, similar to the CPC, we can only gather a limited amount of information on side effects, for example, by manually processing the data. Therefore, the automatic classification of text data is essential.

Objectives

This study aimed to extract the needs of patients with breast cancer from the YJQA data and classify them into CPC categories. We adopted the fourth-level CPC categories described above for the classification of patient needs. In the CPC's first-level categories, the problem granularity is coarse, and it is difficult to understand specific issues. For example, while the CPC's first-level category is outpatient, the corresponding fourth-level categories are "1.1.1.1. Difficulty in obtaining information to select a hospital or doctor" and "1.1.1.2. Difficulty in hospital selection." Therefore, this study attempted to classify the fourth-level categories to grasp patients' problems more concretely.

Methods

Materials

This study built a data set of 7993 questions submitted to the YJQA between January 1, 2018, and July 31, 2020. The CPC has been systematized to use the problems and burdens of cancer patients, consisting of 16 first-level categories and 631 fourth-level categories. This study utilized 2 corpora: the CPC corpus and the YJQA corpus, for training.

The CPC corpus is a large collection of pairs of cancer survivors' worries and their labels. The label consists of the CPC category code and the CPC category name (hereafter, both are collectively referred to as CPC categories), obtained from the CPC database [1]. Unless otherwise noted, the CPC categories represent fourth-level categories. An example from the CPC corpus is presented in Textbox 1.

The YJQA corpus is a labeled corpus of 1000 randomly selected questions on breast cancer posted to the YJQA from January 1, 2018, to June 9, 2020. Because multiple different worries are possible, each question is assigned manually to up to 3 different CPC categories. An example from the YJQA corpus is presented in Textbox 2.

Textbox 1. CPC category code, name, and cancer survivors' worries.

CPC category code: 1.1.1.1

CPC category name: Difficulty in obtaining information for selecting hospitals and doctors.

Cancer survivors' worries: I was worried because I had to make decisions based on my limited knowledge and emotions, without any information or indicators to judge whether the hospital's policies and techniques were accurate, especially whether my doctor was trustworthy.

Note: CPC refers to the "cancer problem classification."

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Textbox 2. CPC category code, name, and questions in YJQA.

CPC category code: 1.1.1.1.

CPC category name: Difficulty in obtaining information for selecting hospitals and doctors.

Question in YJQA: Choosing a hospital for breast cancer treatment. I'm wondering if I'm making a mistake in choosing the first hospital. Is there any problem in choosing the university hospital that is closest to my house?

CPC category code: 3.2.2.1./16.3.2.1.

CPC category name: I'm worried about finding out the test results/concerns regarding suspicion of cancer (other)

Question in YJQA: I had a breast cancer screening and had to be retested for a suspected breast mass. My mother had breast cancer. I will have a mammogram next month. Is the chance of getting breast cancer high? I am very scared and worried.

Note: CPC refers to the "cancer problem classification," and YJQA refers to Yahoo! Japan's question and answer service.

We assigned CPC categories to 456 of the 1000 cases, while the remaining 546 cases had no corresponding CPC categories. Thus, the total number of cumulatively classified questions was 661, which were assigned to 133 CPC categories. Table 1 summarizes the most frequent categories, up to the 10th (top 10), regarding the number of questions classified. For example, the most frequent category was "worrying about cancer with subjective symptoms," with 24.2% of the labeled data falling into this category. Moreover, the category "difficulty in expressing questions and concerns to doctors" was included in the top 10 categories, suggesting that people submitted questions to the YJQA because they had difficulty expressing their concerns to their doctors.

Of the 7993 questions submitted to the YJQA, 6993 were used as the YJQA corpus data classified using CPC categories, excluding the 1000 labeled questions (training data).

Table 1. Results of manual classification of YJQA questions (top 10 categories).

CPC category code	CPC category name	n, %
16.3.1.1.	Worrying about cancer with subjective symptoms	160 (24.2)
16.2.1.1.	Matters related to cancer screening	85 (24.2)
12.2.4.1.	Anxiety due to lack of knowledge about cancer	42 (12.9)
16.3.2.1.	Concerns regarding suspicion of cancer (other)	39 (6.4)
9.1.2.2.	Difficulty in asking questions or expressing concerns to the doctor	17 (2.6)
3.2.2.2.	Worrying about the results and their trends	17 (2.6)
12.1.1.1.	Anxiety about the possibility of recurrence or metastasis	14 (2.1)
3.2.1.6.	Concerns about undergoing tests (other)	11 (1.7)
3.1.1.1.	Uncertainty about treatment options	10 (1.5)
3.2.2.3.	Issues related to receiving tests (other)	9 (1.4)

Classification Algorithm

Our classification algorithm consists of the following steps:

1. Preprocessing: Convert the 2 corpora (CPC corpus and YJQA corpus) into term frequency (TF)-inverse document frequency (IDF)-weighted word vectors.
2. STEP1: Given an unknown problem, convert the problem into TF-IDF-weighted word vectors.
3. STEP2: Classify the target problem into the most relevant CPC category based on cosine similarity between the target problem's vector from STEP1 and vectors from the 2 corpora.

Here, we extract nouns, verbs, and adjectives using the morphological dictionary mecab–ipadic–NEologd [14] while excluding symbols and numbers. For the TF–IDF calculation, we utilized the TfidfVectorizer under the default parameters in the sklearn.feature_extraction.text module.

Thereafter, we constructed three classification methods using the CPC corpus, the YJQA corpus, and their combined corpus, referred to as the description-based (D-based) method, example-based (E-based) method, and description and example combination-based (D+E-based) methods, respectively.

Evaluation Methods

We evaluate the accuracy of each method by calculating the proportion of correct classifications.

The proportion of correct classifications for the D-based method is calculated as follows. First, we find the categories with the highest cosine similarity between the word vectors of the CPC corpus and the manually labeled YJQA corpus (top 1-10). Next, we calculate the proportion of correct categories from 1. Here, it is counted as a correct category if at least 1 of the 3 (maximum) categories is included. Based on the highest cosine similarity, the calculated percentage is referred to as the top 1 accuracy (Acc@1). Similarly, using the top 10 cosine similarities, the top 10 accuracies (Acc@10) are calculated. The

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proportion of correct classifications is calculated using 5-fold cross-validation to evaluate the E-based method [15]. Using the cosine similarity between the training and validation data sets, the proportion of correct classifications is the mean and median of the rate, as in the above calculation. For the evaluation of the D+E-based method, the proportion of correct classifications is calculated by employing the same evaluation method as for the E-based method using both the CPC and YJQA corpora.

Results

Evaluation Results

Table 2 shows the proportions of correct classifications calculated using the above evaluation methods. The Acc@1 and Acc@10 of the D-based method were approximately 10% and 30%, respectively. Furthermore, for both the E-based and D+E-based methods, they were approximately 50% and 70%, respectively. The E-based method is an optimized classification method used to classify YJQA questions. However, it does not cover all CPC categories, whereas the D+E-based method covers all CPC categories, and the rate of correct answers is not significantly different from that of the E-based method. Therefore, in this study, we interpret the results of the D+E-based method.

Table 2. Accuracy for each method.

Accuracy	D-based[a]	E-based[b]	D+E-based[c]
Acc@1			
Mean	0.1096	0.4891	0.4781
SD[d]	–[e]	0.017	0.018
Median	–	0.4835	0.4725
Acc@10			
Mean	0.2946	0.6960	0.7062
SD[d]	–	0.030	0.201
Median	–	0.7015	0.7106

[a]D-based: description-based method.

[b]E-based: example-based method.

[c]D+E-based: description and example combination-based method.

[d]SD: unbiased sample standard deviation.

[e]For the D-based method, there are missing values because 5-fold cross-validation is not utilized as described in the evaluation method section.

Classification Results

We present the classification results of the D+E-based method for the target data to be classified. Table 3 lists the top frequency categories. The top 10 categories accounted for 61.9% of the total. The category with the most frequent questions was “worrying about cancer with subjective symptoms” (1661 questions), which accounted for 23.8% of the total. There were 448 categories classified by the D+E-based method, and the distribution of the top 30 categories is shown in Figure 1. The rate of change from the top 1 to the top 2 categories was the largest at 57.7%. Moreover, the rate of change from the top 20 categories was 20% to 40%, after which it was approximately 10%. As a result, the frequency distribution has a long tail.

Table 3. Results obtained using the description and example combination-based method (top 10 categories).

CPC category code	CPC category name	Frequency (%)
16.3.1.1.	Worrying about cancer with subjective symptoms	1661 (23.8)
16.2.1.1.	Matters related to cancer screening	702 (10)
16.3.2.1.	Concerns regarding suspicion of cancer (other)	494 (7.1)
12.2.4.1.	Anxiety due to lack of knowledge about cancer	419 (6)
3.1.3.5.	The received treatment (choice), whether it is correct	255 (3.6)
3.2.2.2.	Worrying about the results and its trend	234 (3.3)
12.1.1.1.	Anxiety about the possibility of recurrence or metastasis	225 (3.2)
9.1.2.2.	Difficulty in asking questions or expressing concerns to the doctor	137 (2)
12.3.2.3.	I can’t stop thinking about cancer	111 (1.6)
9.1.1.1.	Doctor's words and attitude	93 (1.3)

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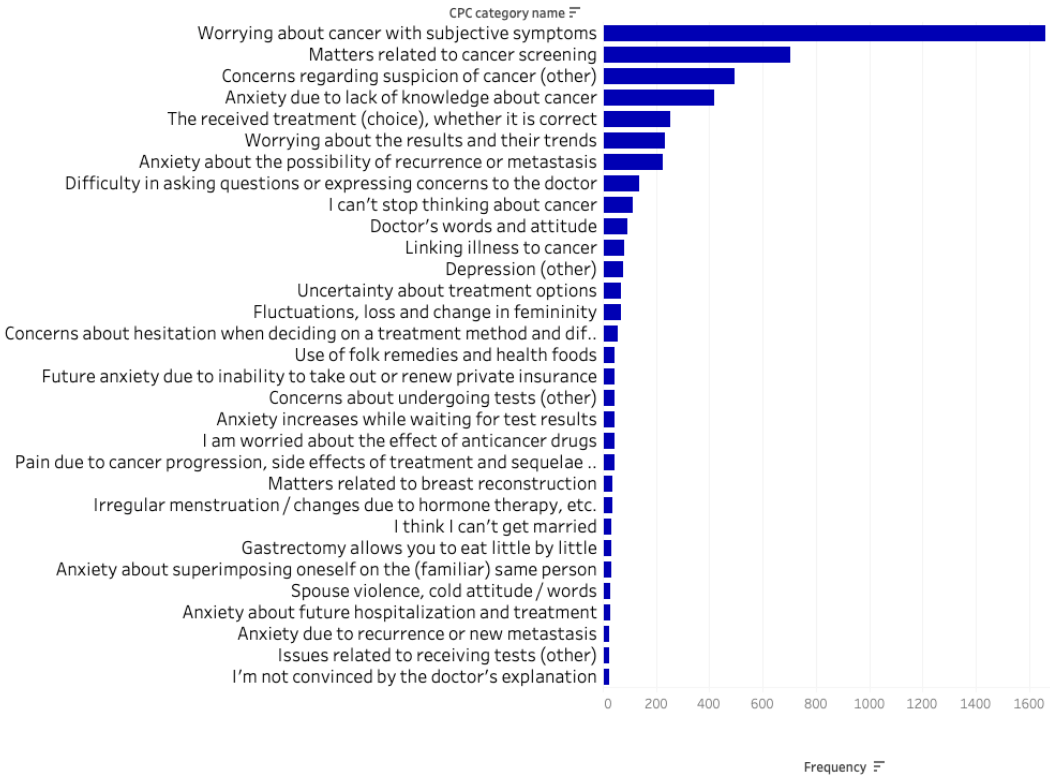
Figure 1. Classification using the D+E-based method (X-axis) and its frequency (Y-axis; top 30 categories). D+E: description and example combination-based method.



Similarity of Distribution Between Manual Classification and Our Method

We evaluated whether the frequency distribution of the proposed method was close to that of the real method. Comparing the classification results with the manual classification results (Table 1), we found that 7 out of 10 categories with high frequency were the same, and the first and the second category in both cases were "worrying about cancer with subjective symptoms" and "cancer screening."

The frequency distribution of the CPC, including the low-frequency part, was compared between the proposed and manual methods. The top 30 categories' frequency distributions in the D+E-based method were used for visual and numerical evaluation of all categories. Figure 2 shows the distribution of the classification results using the D+E-based method and manual classification. The distributions were similar. In addition, we calculated the Jensen-Shannon divergence [16] for all categories to measure the distance between these distributions. Values closer to zero indicated higher degrees of similarity in distribution.

The value of the Jensen-Shannon divergence for the distribution of the manual classification and D+E-based classification result is 0.105, which shows that the 2 distributions are similar. Even though the individual accuracy was low, the CPC distribution obtained by the proposed method was closer to the correct one.

Therefore, it is possible that the proposed method can be used to conduct a large-scale survey of patient concerns automatically.

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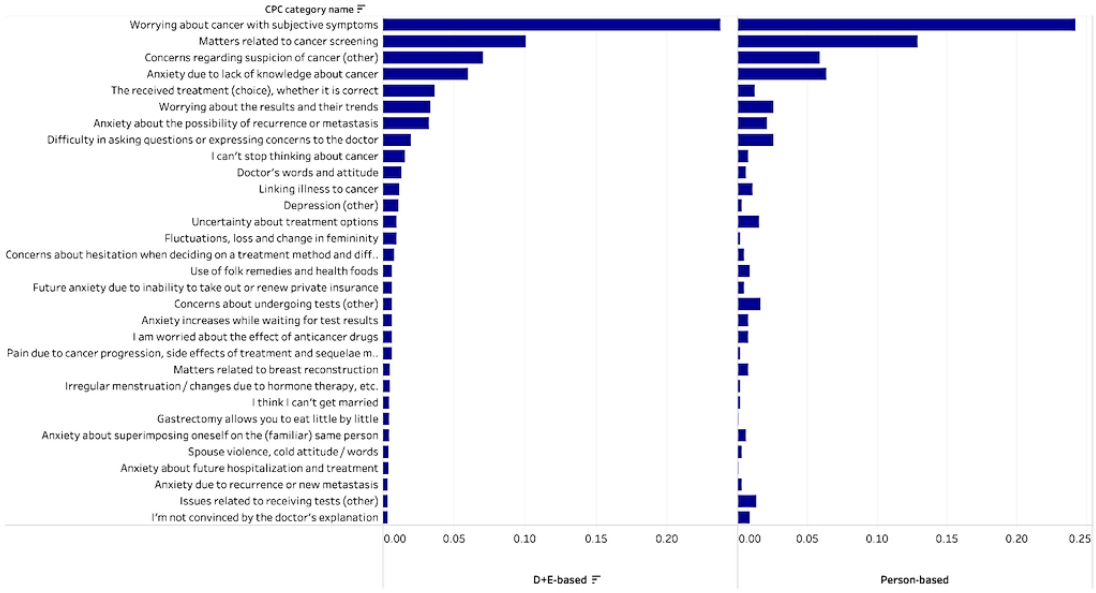
Figure 2. Distribution of the classification results using the D+E-based method and manual classification.



Examples

The 3 examples in this section show how the consistency of actual questions and results was confirmed and how the side effects of drugs and unmet needs were extracted.

Table 4 shows the questions estimated to have high cosine similarity. Table 5 shows the questions classified into category 11 (extracted with high cosine similarity) to extract side-effect signaling. In Table 5, we included the code and name of categories classified by our model, drug name, and side effects that could be read from the text of the questions. Table 6 shows some of the questions and their categorization for the low-frequency categories and "COVID" search to extract unmet needs. In Table 6, we included the code and name of categories classified by our model and unmet needs that could be read from the text of the questions.

Table 4. Questions estimated to have high cosine similarity.

Questions (translated to English from Japanese)	Cosine similarity	Code and name of categories
Please tell me what makes you susceptible to breast cancer!	0.714	15.1.1.5. I was told that I have cancer
	0.206	12.2.5.1. Suspecting or worrying about another type of cancer
	0.204	11.3.1.1. Current health condition
I had one of my breasts removed due to breast cancer. I did not have simultaneous reconstruction. My breasts are small, to begin with, so when I was asked about simultaneous reconstruction, I didn't think much about it and told my doctor that I would think about it after the surgery. In my 40s, I was admitted to the hospital, but most people my age had simultaneous reconstruction and expanders. I wondered if I had made the wrong choice. Since If I have to do it later, I'll have to have one more surgery, I think it's okay as is. I heard that it takes quite a few days to reconstruct. It needs one year at the earliest. Moreover, I heard that nipple and areola surgeries are different. That's a long time. But I still think I want to have reconstruction. If you have reconstructed, if you haven't reconstructed, if you have reconstructed in another way, if it's not covered by insurance, etc, please give me some advice! I'd like to hear about your experiences. It will be two months until my next visit to the hospital. I want to ask my doctor many questions, so if you could tell me anything, I would be very happy. Please give me some advice. Moreover, it seems that the implants and expanders for reconstruction have been discontinued because they are carcinogenic. I don't think I will be able to have reconstruction for a while, but please advise me.	0.682	13.3.1.6. Matters related to breast reconstruction
	0.264	3.1.1.1. Uncertainty about treatment options
	0.255	3.1.3.5. The received treatment (choice), whether it is correct
I am undergoing treatment for breast cancer, and my white blood cell count has dropped due to side effects, so my immune system is not high. I don't want to go to the birthday party at my parents-in-law's because I'm worried that I might get infected with the coronavirus. My mother-in-law and father-in-law know that I am undergoing treatment and my immunity is low, but they don't want to cancel the party because it's their adorable grandchild's birthday. It's hard for me to tell them. I don't want my husband to go either, but he doesn't seem to mind at all. Is there any way to avoid attending the party?	0.657	11.1.2.3. Persistent side effects of anticancer drugs (other)
	0.515	11.1.1.8. Symptoms of side effects from anticancer drugs (other)
	0.417	15.2.16.1. Relationship with family (Other)

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Table 5. Questions that were classified into the categories of category 11.

Questions (translated to English from Japanese)	CPC[a] category code and name	Drug name	Side effects
I am undergoing treatment for breast cancer, and my white blood cell count has dropped due to side effects, so my immune system is not high. I don't want to go to the birthday party at my parents-in-law's because I'm worried that I might get infected with the coronavirus. My mother-in-law and father-in-law know that I am undergoing treatment and my immunity is low, but they don't want to cancel the party because it's their adorable grandchild's birthday. It's hard for me to tell them. I don't want my husband to go either, but he doesn't seem to mind at all. Is there any way to avoid attending the party?	11.1.2.3. Persistent side effects of anticancer drugs (other)	Anticancer drug for breast cancer	Leukopenia
Can I improve the numbness caused by the side effects of anticancer drug treatment? My sister is undergoing anticancer treatment for breast cancer, and she is suffering from numbness in her hands and feet. Is there anything she can do to relieve the numbness? Does she have to stop the anticancer treatment?	11.1.1.2. Nerve damage such as numbness and discomfort caused by anticancer drugs	Breast cancer drug	Numbness
I am undergoing anticancer treatment, FEC[b] treatment with infusions every 3 weeks, breast cancer. I have completed four courses, and I am about to start another one, and I have a question about hair loss. My hair still looks like a baby's, so I can say that I am losing hair. Although I have heard that other parts of my body, such as the eyelashes, eyebrows, shins, and lower hair, I am not losing other than my hair. My doctor said that you lose when I asked my doctor about it the second time. I'm worried that the medication might not be working correctly. If you have any experience with this or know anything about it, please advise me.	11.1.1.1. Hair loss due to anticancer drug treatment	FEC treatment	Hair loss
I would like to know about mouth ulcers during anticancer treatment. I have breast cancer and will start anticancer treatment, but before that, I went to a dentist and was told that I should have my teeth treated. She told me that I would probably get many mouth ulcers from the anticancer treatment but that I should just go and see her. She told me that I should go in. If it's a common mouth ulcer, I'm sure they can treat it with ointment, but I'm not sure if the mouth ulcer will begin to heal before the anticancer drugs are finished? The side effects of the anticancer medicines make it hard to go to the dentist, and the thought of having to go stresses me out. If I can heal my mouth ulcers faster by going to the dentist, I'll do my best. However, if it doesn't make much difference, I don't want to push myself as much as possible because of the hair loss, fatigue, side effects, and other things. If I go to the hospital because of mouth ulcer, will it heal faster? If you have any experience or know of anyone who had mouth ulcers, please let me know.	11.1.1.6. Mucosal damage caused by anticancer drugs (stomatitis, etc)	Breast cancer anticancer drug	Stomatitis
My 66-year-old mother is undergoing anticancer treatment for the lung's adenocarcinoma. She is taking Docetaxel plus Cyramza once every four weeks. She had numbness after the second dose and reduced the dose for the third dose, but the numbness keeps getting worse…She's been taking the maximum daily dose of Lyrica to reduce the numbness, but she says it's not helping at all. She can't walk anymore, and it has become mentally painful for her, so we are hoping that we can alleviate her numbness. Can you tell me anything about how to deal with the numbness, herbal medicine, or anything else that might help reduce the numbness a bit? Thank you very much.	11.1.1.2. Nerve damage such as numbness and discomfort caused by anticancer drugs	Docetaxel + Thyramza	Numbness

[a]CPC: Cancer Program Classification.

[b]FEC: fluorouracil, epirubicin, and cyclophosphamide.

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Table 6. Questions and their classification categories considered as unmet needs.

Questions (translated to English from Japanese)	CPC[a] category code and name	Unmet needs
My mother has breast cancer with bone metastasis. I heard that bone metastasis has a high risk of fracture, so should I prevent her from driving a car in the future? Moreover, my 80-year-old grandmother is still driving. However, there are many accidents involving the elderly, and the risk of having an accident is probably higher than for younger people. If I assume the worst-case scenario, should I stop her from driving instead of saying, "It's a pity to take away her car?" If I ask her to quit driving, in what situation/venue should I tell her? Moreover, I have a driver's license, but I'm a driver on paper only. Should I go back to school to drive for my mother and grandmother when we go out with the family? I don't think I'll be able to drive on public roads since I have not driven for a long time…	8.2.1.1. Traffic conditions are bad	Driving a car with a displaced bone cancer patient
Please tell me if I can sue for cancer misdiagnosis. Two years ago, I went to a hospital because a retest was required by mammography. Since there was something suspicious on the echo, I had cytology done on the spot. The cytology didn't give me any results due to a bad specimen, so I asked for histology. The doctor told me that I would have to stay overnight at another hospital for a mammotome biopsy, etc. I didn't want to spend a lot of time figuring out what was black and white, so I had a surgical biopsy, a definitive diagnosis that could be done at that hospital. As a result, I was diagnosed with "breast adenopathy" and told to visit the hospital regularly. But some of the results of the tissue examination were not convincing, so I had the examination done at another hospital. The result was breast cancer…how could they remove it from the definitive diagnosis…I would be horrified if they were convinced it was mammary gland disease and discovered it too late. I want to sue the doctor who is still examining and treating me as usual, but I heard that medical lawsuit are difficult. Is it possible to sue him? Do I have a chance to win?	5.3.1.3. Should I get a second opinion?	Lawsuits against misdiagnosis
I had breast cancer sparing surgery in early February and will start radiation treatment in April. However, I am going through a tough time with corona right now, and I feel anxious about going to the hospital every day. Is there anything else I can do except taking personal measures?	8.2.1.3. Frequent visits to the hospital are difficult	Worried about corona infection due to hospital
I had a breast cancer sparing surgery in February this year and was scheduled for radiation therapy, but it has been postponed due to the coronavirus. It will still take some time for the situation to improve, but should I avoid starting radiation therapy at this time? I am on hormone therapy, but I am getting anxious about not undergoing radiation therapy.	11.1.3.6. Symptoms of radiation-related side effects (other)	Treatment postponed due to coronavirus
My 88-year-old mother is in a special care facility and has a fever of 37.5. She has breast cancer, so I don't know if the fever is caused by breast cancer, corona, or a cold. What are the symptoms of a fever caused by breast cancer? Do I need to see my family doctor? If it is not caused by breast cancer, does the fact that I have a high fever in a special care facility mean that I have contracted the virus from a staff member?	11.2.1.5. Fever	I can't tell if it's cancer symptoms or corona symptoms
About 18 years ago, my mother was diagnosed with breast cancer. She had an operation and has been living a normal and healthy life since then. However, 2 years ago, she was told that the cancer had spread to her lungs. At present, she has difficulty breathing even when she moves a little, probably due to the accumulation of pleural effusion. When she was told that the cancer had spread, the doctor did not give her a life expectancy, but when she looked it up on the internet, she found all sorts of information that made her feel uneasy. Can you tell me whether she will live much longer or whether she may be able to live longer while coping with her illness? I'm getting married soon, and I was planning to show her my wedding dress next year. However, with the corona epidemic, that plan is now undecided. I want to show her my wedding dress at least. I'm not sure if this is practically possible.	12.1.1.1. Anxiety about the possibility of recurrence or metastasis	I want my mother to see me in my wedding dress, but she has been diagnosed with cancer
When I distrusted the female surgeon at the [omitted][b] Hospital and applied for a second opinion (a letter of introduction was required), I was pressured to go to the hospital for a second opinion. The doctor there is a surgeon famous for his breast-conservation therapy, but he didn't listen to me very carefully and told me that he agreed with Dr. [omitted] (the doctor in charge at [omitted] Hospital) and that I should tell her that he agreed with her because doctors have a difficult relationship with each other. Is there such a thing? The book on breast cancer published by the [omitted] Hospital, famous for cancer treatment, claims it to be the "standard treatment," even though the treatment policy is different. Is there anyone who was notified that they had cancer and went for a second opinion and then were offered a different treatment plan? Do doctors always protect their doctors? I was amazed at the lecturers' pride in the national university hospital (even though they are quacks).	5.3.1.6. Matters related to second opinions (other)	Not fulfilling the role of a second opinion

[a]CPC: Cancer Program Classification.

[b]We blinded the proper noun because it is not relevant to extract the unmet needs.

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Discussion

Consistency of the Actual Questions and Results

Here we discuss the consistency of the actual questions and results with high and low cosine similarity, respectively. In Table 4, it is unclear whether a cancer patient asked the first question, but it appears to express concern about the possibility of developing cancer. The second question was about breast reconstruction, and the third was a concern about coronavirus (COVID-19).

We also discuss questions that could not be correctly classified in Table 4. The reason for the inability to classify the questions with the highest cosine similarity correctly can be the use of the cosine similarity between the word vectors in the bag of words, and the context could not be taken into account. More specifically, since the question included the word "constitution," it was considered to be classified in the category that included the word "constitution." Similarly, the top 2 worries about breast reconstruction could be classified in the CPC category, which includes the phrase "breast reconstruction." The top 3 problems are related to COVID-19, which is not included in the current CPC category, and therefore must be newly defined.

As for the results with the cosine similarity from the lowest to third-lowest, the question was a request for Japanese translation from English and was not in itself a question about breast cancer. This is because questions including the phrase "breast cancer" were also extracted when searching for "breast cancer," and the data acquisition method must be improved in the future.

Clinical Application

In the previous section, we noted that this research was effective for statistical surveys. In addition, we believe that there are other possible applications. In particular, we will examine the extraction of adverse drug events (signal detection) and the extraction of unmet needs.

Potential Application to Side Effect Signaling

Extracting side effects from the submitted questions would be very beneficial for pharmaceutical companies and patients because it would allow them to collect significant information on drug safety. Specifically, since some questions classified under the overarching category of "symptoms, side effects, and sequelae" (category 11) of the CPC are considered to contain information on side effects, we can extract such information by applying intrinsic expression extraction to the question text.

In Table 5, the first question contained information about the drop in white blood cells, and the second contained information about numbness in the hands and feet; however, we could not identify the drug that caused the side effect because there was no information about the drug, and the third contained information about the side effects of hair loss due to fluorouracil, epirubicin, and cyclophosphamide (FEC) treatment, a type of chemotherapy. However, the third question simply indicated that FEC treatment caused a side effect called hair loss. Thus, although side effects can be extracted, the granularity of the drug information may be insufficient. Of the 6993 cases, 470 (6.7%) were classified under category 11 using the D+E-based method, of which 100 (21.3%) cases were randomly sampled, and 15 (3.2%) had specific drug names.

Potential Application for Unmet Needs

Patients' unmet needs are becoming a major societal issue. In particular, the unmet needs of those who should answer have not yet been sufficiently addressed. Except for a few fee-based QA sites [17,18], QA sites are generally answered by nonexperts, but some questions should be answered by physicians.

Unmet needs are needs that are not addressed due to a lack of services or resources or that have never existed before. The former may be found by discussing the high-frequency categories with medical workers, which may help identify needs that have been insufficiently addressed in the past, although many patients complain about them. The latter can be extracted by searching for low-frequency categories or words that have become popular in recent years (eg, "COVID").

In Table 6, the first example is an unmet need (car driving) of a cancer patient with bone metastasis, the second is a misdiagnosis lawsuit, and the third is an unmet need related to COVID-19. In this study, unmet needs were extracted by reading the questionnaire; however, constructing an automatic classification model for unmet needs is a future task.

Limitations and Future Work

Since we used the Japanese text of questions found by the search phrase "breast cancer" as the training data of the method in this study, the method may not apply to other cancer types and other countries. However, our method can be expanded to different cancer types and countries in cases where problem data are available. Here, the cancer problem categories specific for other countries are needed because they were defined for Japanese people in this study. When expanding our method to other cancer types and countries, future work will have to focus on reproducibility. Therefore, it is necessary to reconstruct the training data from the questions found by searching for each cancer word to apply the method to other cancer types.

In addition, COVID-19 infections in Japan appeared in February 2020, and patients with cancer might experience COVID-19-related problems. Therefore, it is possible that the current CPC categories may not be able to ensure proper classification. Thus, it is necessary to define new problem classification categories for patients with cancer after February 2020. In addition, since new topics, not limited to COVID-19, are always likely to occur, it is necessary to construct a model that could extract such uncommon topics.

The target of this study was question texts posted on QA services, and it may not be possible to classify other texts correctly. The fact that the accuracy of the D-based method was extremely poor among the 3 methods may be due to the difference between the questionnaire text used in the CPC and the text posted on the YJQA. We also found that cancer patients' problems are not limited to questions posted on the QA website but also Twitter and blogs. It is necessary to broaden the training data of the classification method for these texts to classify the worries of cancer patients. In addition, there are many posts in

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which the content is unrelated to worries or contains too many emojis. Therefore, it is necessary to build a model to determine whether a post contains worries. Subsequently, 2 schemes are needed to classify the blogs containing worries into CPC categories.

Conclusions

This paper proposed a method to classify questions submitted to the YJQA into the CPC with a correct answer rate of approximately 70%. Although classification alone does not solve patients' problems, a comprehensive understanding of the type and number of problems can help prioritize services to solve problems from the patients' point of view. We would like to examine the services that could be provided in the future based on this information.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary table containing all the Cancer Problem Clarification (CPC) categories obtained using the D+E-based method.
[XLSX File (Microsoft Excel File), 28 KB - cancer_v7i4e32005_app1.xlsx]

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Abbreviations

CPC: cancer problem classification
FEC: fluorouracil, epirubicin, cyclophosphamide
QA: questions and answers

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TF–IDF: term frequency-inverse document frequency
YJQA: Yahoo! Japan questions and answers

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Original Paper

Suggested Modifications to the Management of Patients With Breast Cancer During the COVID-19 Pandemic: Web-Based Survey Study

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Abstract

Background: Management of patients with cancer in the current era of the COVID-19 pandemic poses a significant challenge to health care systems. Breast cancer is the most common cancer internationally. Breast cancer is a disease that involves surgery, chemotherapy, hormonal therapy, targeted therapy, radiotherapy, and, more recently, immunotherapy in its management plan. The immune system requires months to recover from these medications, and this condition is even worse in patients with metastatic breast cancer who need ongoing treatment with these drugs. Some of these drugs, such as inhibitors of cyclin-dependent kinases 4 and 6, can cause rare but life-threating lung inflammation. Patients with breast cancer who have metastatic disease to the lungs can experience deterioration of disease symptoms with COVID-19 infection. Oncologists treating patients with breast cancer are facing a difficult situation regarding treatment choice. The impact that COVID-19 has had on breast cancer care is unknown, including how to provide the best care possible without compromising patient and community safety.

Objective: The aim of this study was to explore the views of oncologists regarding the management of patients with breast cancer during the COVID-19 pandemic.

Methods: A web-based SurveyMonkey questionnaire was submitted to licensed oncologists involved in breast cancer management in Saudi Arabia, Egypt, and United Arab Emirates. The survey focused on characteristics of the participants, infection risk among patients with cancer, and possible treatment modifications related to different types of breast cancer.

Results: The survey was completed by 82 participants. For early hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer, 61 of the 82 participants (74%) supported using neoadjuvant hormonal therapy in selected patients, and 58% (48/82) preferred giving 6 over 8 cycles of adjuvant chemotherapy when indicated. Only 43% (35/82) preferred inhibitors of cyclin-dependent kinases 4 and 6 with hormonal therapy as the first-line treatment in all patients

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with metastatic HR-positive disease. A total of 55 of the 82 participants (67%) supported using adjuvant trastuzumab for 6 instead of 12 months in selected patients with HER2-positive breast cancer. For metastatic HER2-positive, HR-positive breast cancer, 80% of participants (66/82) supported the use of hormonal therapy with dual anti-HER2 blockade in selected patients. The preferred choice of first-line treatment in metastatic triple negative patients with *BRCA* mutation and programmed cell death 1 ligand 1 (*PD-L1*) <1% was poly(adenosine diphosphate–ribose) polymerase inhibitor according to 41% (34/82) of the participants, and atezolizumab with nab-paclitaxel was preferred for *PD-L1* >1% according to 71% (58/82) of the participants.

Conclusions: Several modifications in breast cancer management were supported by the survey participants. These modifications need to be discussed on a local basis, taking into account the local infrastructure and available resources.

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KEYWORDS

breast cancer; COVID-19; pandemic; web-based survey; treatment modification; oncology; treatment; modification; risk; infection

Introduction

Management of patients with cancer in the current era of the COVID-19 pandemic poses a significant challenge to health care systems [1]. However, it is mandatory to maintain the required level of care of patients with cancer while taking the necessary precautions to maintain the safety of both patients and health care professionals (HCPs) [2-4]. Nevertheless, certain modifications of medical management of patients with cancer, including surgical approaches, locoregional therapies, and systemic therapies, in addition to changes in treatment and follow-up schedules are required to maintain the balance between the care and safety of patients. In addition, setting priorities for medical care may be required when the available health services are insufficient for the number of patients who need care [1]. Patients with cancer can be considered a heterogeneous group of patients with different presentations, stages at diagnosis, tumor burdens, and therapeutic modalities with associated adverse events and related immune suppression. Thus, patients with cancer may have variable risk of COVID-19–related complications [5].

Patients with breast cancer, at least in part, are more vulnerable to COVID-19 infection due to a variety of reasons, including myelosuppression produced by chemotherapy given in (neo)adjuvant or metastatic settings [6], inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) [7-9], and palliative radiotherapy to the spine or pelvis. In addition, myelosuppression can be secondary to bone marrow infiltration by metastatic tumor cells. Different scientific and medical societies have released suggestions and recommendations that address possible treatment modifications and precautions in the management of patients with cancer in the era of the COVID-19 pandemic, such as the European Society of Medical Oncology (ESMO) [10], American College of Surgeons [11], and National Comprehensive Cancer Network [12].

The main theme of these expert opinion–based recommendations focuses on reducing the probability or duration of neutropenia, reducing the frequency of hospital visits and stays, and avoiding medications that may be dangerous to use during the current COVID-19 pandemic. For example, the ESMO recommendations dissect the priority of the management of patients with breast cancer into low, medium, and high priorities for medical care [10]. Similarly, Cancer Care Ontario reported different priorities for medical care of patients with cancer using variable therapeutic modalities, including surgery, radiotherapy, systemic therapy, and palliative care [13]. Furthermore, the American College of Surgeons provided pragmatic suggestions for triaging patients for surgical management based on the volume of COVID-19 cases, available intensive care unit (ICU) capacity, available hospital resources, and degree of urgency of surgical management [11].

Therefore, during the COVID-19 pandemic, it may be necessary to reconsider the risk to benefit ratio of different treatment modalities to select the best therapeutic strategy for each patient. Therefore, discussion in multidisciplinary tumor boards and assessment of available hospital facilities are critically important. Moreover, it is crucial to check the response of practicing oncologists to these recommendations of therapeutic modifications and determine whether they are being adopted in real practice. In this survey study, we will explore the views of oncologists treating patients with breast cancer on possible modifications in breast cancer management in the current period of the COVID-19 pandemic. This survey will include suggested modifications by key medical societies in different subtypes of breast cancer, focusing mainly on systemic therapy. In addition, the survey may help fill the gap between guidelines recommended by scientific societies in the COVID-19 era and what is actually occurring in everyday clinical practice in three Middle Eastern countries. These countries have different health care systems, economic resources, and patient volumes. This study will shed light on how these potential modifications can actually guide oncology practice in the current era.

Methods

Development of the Instrument

We generated our survey instrument using rigorous survey development and testing methods [14]. Items were selected based on a literature review, emails, and telephone correspondence. Three experts in the field of breast cancer from King Abdullah Medical City, Saudi Arabia, extensively discussed the topic and reviewed items until no further questions were raised. Items were nominated and then ranked by expert breast oncologists to reach a consensus on the selected items. Further review was performed to eliminate redundant items using binary responses (exclude and include). Fuzzy logic was applied to check the consensus among the experts in a more robust way than in the traditional method [14].

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During construction of the survey, we grouped the items into the domains we wanted to explore and then refined the questions [15]. The self-administered survey consisted of 25 items that focused on 5 domains: characteristics of participants; COVID-19 infection risk among patients with cancer/need for treatment modifications; and possible modifications related to patients with hormonal receptor (HR)–positive, human epidermal receptor 2 (HER2)–negative breast cancer, as well as patients with HER2-positive and triple negative breast cancer. The structured response formats used in this survey included binary (yes/no), nominal, and ordinal responses. Other options were also allowed, such as "I don't know."

Testing of the Instrument

During pretesting and pilot testing, questions were reviewed by three breast cancer experts to check the consistency and appropriateness of the survey questions [16]. Then, the questions were reviewed by a nonexpert colleague to assess the dynamics, flow, and accessibility. Three medical oncologists performed pilot testing of the instrument.

We also conducted a clinical sensibility assessment to evaluate the comprehensiveness, clarity, and face validity of our instrument on a scale of 1 to 5. We invited 4 colleagues with methodologic and oncology expertise. The results of the clinical sensibility testing using mean scores on a 5-point scale suggested that the instrument had face validity (4.3), content validity (4.2), clarity (4.3), and discriminability (4.5). This survey was approved by the Institutional Review Board of King Abdullah Medical City, Makkah, Saudi Arabia (20-634).

Study Procedures

We used a nonprobability snowball sampling design [17]. This web-based questionnaire was submitted to licensed medical oncologists involved in breast cancer management in Saudi Arabia, Egypt, and United Arab Emirates. We identified breast oncologists who are members of national oncology societies in the abovementioned countries through the databases of these societies. The oncologists were contacted by email to request their participation in the survey and were asked to send the survey link by email to other experienced breast oncologists. Two reminders were sent, 1 week apart, by email to the invited participants.

Participants received electronic links accompanied with concise instructions, the background and objectives of the survey, the target population, the expected time to finish the survey, and a request to participate voluntarily. They were required to register on the first page of the survey and provide their professional and academic degrees. Fellows or trainees were excluded, and only those respondents who had at least three years of experience in the management of breast cancer after completion of their specialist training were included. Participants consented to join the survey and to keep records of their professional details, institutes, and countries of clinical practice.

Each page of the survey contained 4 to 5 items, giving a total of 6 pages. The completeness of the survey was checked using JavaScript. To avoid duplicate entries, the survey could not be displayed again to the same user after their response was submitted. The anonymity of the answers was maintained using SurveyMonkey. The data were protected from unauthorized access. Only the authors and data analyst had access to the data.

Outcome Assessment

The survey was conducted between July 10 and 30, 2020. We assessed the percentages of the responses of the breast oncologists. Descriptive statistics were used to summarize the data and report the views of the participants. We followed the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines for conducting and reporting the results of the survey [18].

Results

The survey was distributed to 100 people in Saudi Arabia, Egypt, and United Arab Emirates. A total of 82 people responded and agreed to participate in the survey. The completeness rate (completing all items of the survey) among the respondents was 100%.

Characteristics of the Survey Participants

Of the 82 respondents, 62 (76%) were medical oncologists, while clinical oncologists and hematooncologists constituted 13 (16%) and 7 (9%) of the participants, respectively. The majority of respondents (72/82, 88%) worked in governmental hospitals, and 62% of the participants (51/82) had more than 10 years of work experience (Table 1).

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Table 1. Characteristics of the survey participants (N=82).

Characteristic	Value, n (%)
Country of practice	
Saudi Arabia	31 (38)
Egypt	39 (48)
United Arab Emirates	12 (15)
Subspecialty	
Medical oncologist	62 (76)
Clinical oncologist	13 (16)
Hematooncologist	7 (9)
Duration of experience	
Less than 5 years	15 (18)
5-10 years	16 (20)
More than 10 years	51 (62)
Type of institute of main practice	
Governmental hospital	72 (88)
Academic institute	7 (9)
Private hospital	3 (4)

COVID-19 Prevalence and Requirement for Treatment Modifications

The majority of the participants (75/82, 92%) reported that they had patients diagnosed with COVID-19 in their hospitals. Meanwhile, 67% (55/82) reported that HCPs had been diagnosed with COVID-19 in their institutes (Figure 1). Most of the respondents (72/82, 88%) agreed or strongly agreed that patients with cancer are at increased risk of COVID-19–related complications (Figure 2) and that the risk of these complications is different among patients with cancer (66/82, 81%) (Table 2). Noteworthily, the majority (70/82, 85%) supported modifications in breast cancer management during the COVID-19 pandemic (Figure 3). Similarly, the majority (76/82, 93%) endorsed the use of virtual multidisciplinary tumor boards for patients with breast cancer during the COVID-19 pandemic (Table 2).

Figure 1. Responses to survey questions asking if the participants (A) have patients diagnosed with COVID-19 at their institute and (B) have health care professionals diagnosed with COVID-19 at their institute.

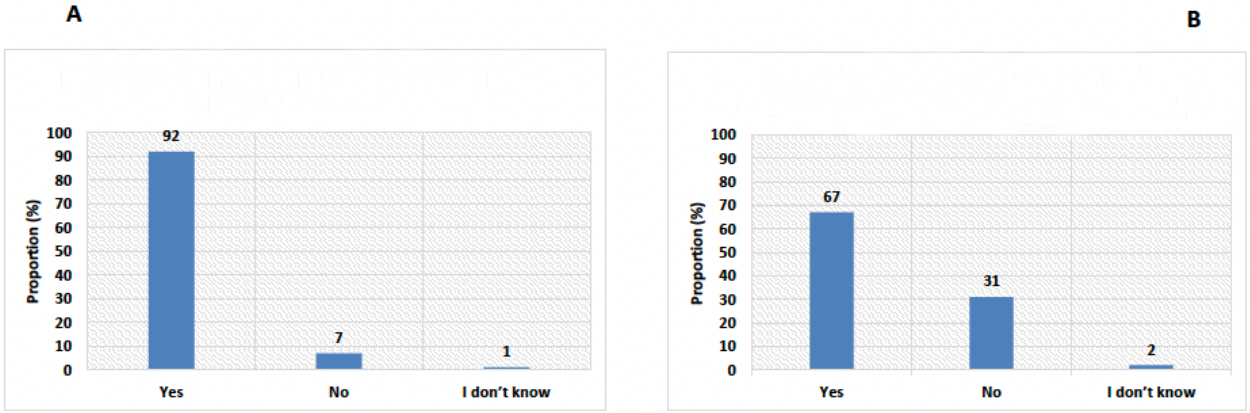

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Figure 2. Participants' answers to the question of whether patients with cancer are at greater risk of COVID-19–related complications.

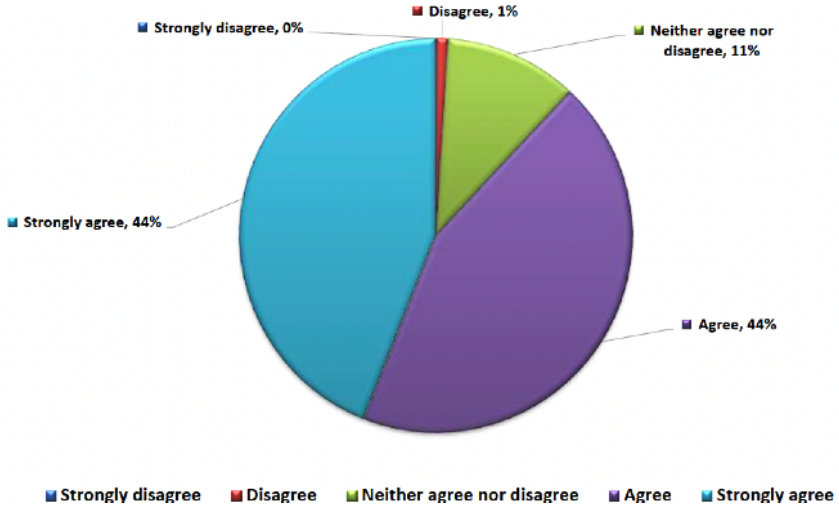
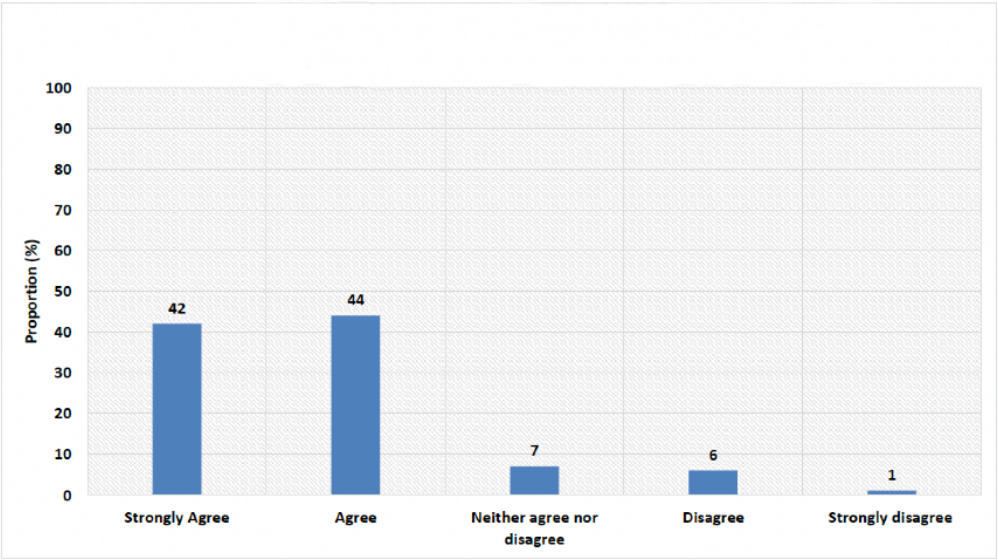


Table 2. Responses to questions related to the risk of infection during the COVID-19 pandemic and required treatment modifications.

Question	Responses (N=82), n (%)				
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Are patients with cancer at increased COVID-19 infection–related complications, such as respiratory failure?	36 (44)	36 (44)	9 (11)	1 (1)	0 (0)
Is the risk of serious complications of COVID-19 infection, such as respiratory failure, different among patients with cancer?	17 (21)	49 (60)	13 (16)	3 (4)	0 (0)
Are treatment modifications required for patients with breast cancer during the COVID-19 pandemic?	34 (42)	36 (44)	6 (7)	5 (6)	1 (1)
Is a virtual multidisciplinary approach for the management of patients with breast cancer mandatory in the current situation?	45 (55)	31 (38)	2 (2)	3 (4)	1 (1)

Figure 3. Participants' answers to the question of whether treatment modifications are required for patients with breast cancer during the COVID-19 pandemic.



Patients With HR-Positive Breast Cancer

Neoadjuvant Therapy

When neoadjuvant therapy is indicated, the majority of participants (61/82, 74%) supported using neoadjuvant hormonal therapy in selected patients (strong ER-positive, low Ki-67), while 11% (9/82) endorsed using neoadjuvant hormonal therapy in all patients. In T1/T2 tumors, when no downsizing is required, participants were divided over the use of neoadjuvant hormonal therapy as a bridge until the pandemic is over (Table 3).

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Table 3. Suggested modifications to HR-positive, HER2-negative breast cancer practice for inpatient physicians.

Question and answer options	Responses (N=82), n (%)
When neoadjuvant therapy is indicated (downsizing is required), what is the treatment of choice?	
Neoadjuvant chemotherapy	12 (15)
Neoadjuvant hormonal therapy	9 (11)
Neoadjuvant hormonal therapy in selected cases (strong estrogen receptor+, low Ki-67)	61 (74)
Will neoadjuvant hormonal therapy be considered in T1 and T2 tumors (when no downsizing is required) as a bridge until the pandemic is over?	
Strongly agree	13 (16)
Strongly agree	34 (42)
Neither agree nor disagree	15 (18)
Disagree	19 (23)
Strongly disagree	1 (1)
Can adjuvant radiotherapy be given before adjuvant chemotherapy to avoid chemotherapy-induced neutropenia until the COVID-19 pandemic is over?	
Strongly agree	0 (0)
Agree	21 (26)
Neither agree nor disagree	16 (20)
Disagree	37 (45)
Strongly disagree	8 (10)
Using CDK 4/6[a] inhibitors for new patients with metastatic HR[b]-positive, HER2[c]-negative breast cancer:	
CDK4/6 inhibitor+aromatase inhibitor is the treatment of choice	35 (43)
Defer CDK 4/6 inhibitor to the second line until the pandemic is over in all cases	18 (22)
Defer CDK 4/6 inhibitor to the second line until the pandemic is over in selected cases	29 (35)
For new patients with nonvisceral metastasis, what is the treatment of choice in the first line during the COVID-19 pandemic ?	
Fulvestrant	9 (11)
Aromatase inhibitor	45 (55)
CDK 4/6 inhibitor+aromatase inhibitor	28 (34)
For patients who have already started a CDK4/6 inhibitor+aromatase inhibitor, will the CDK4/6 inhibitor be held until the pandemic is over?	
Strongly agree	3 (4)
Agree	23 (28)
Neither agree nor disagree	20 (24)
Disagree	30 (37)
Strongly disagree	6 (7)
For patients with metastatic HR-positive, HER2-negative breast cancer, will you give everolimus or alpelisib in the second line?	
Strongly agree	3 (4)
Agree	23 (28)
Neither agree nor disagree	27 (33)
Disagree	27 (33)
Strongly disagree	2 (2)
For patients who have already started everolimus or alpelisib, will these medications be held until the pandemic is over?	
Strongly agree	4 (5)
Agree	18 (22)
Neither agree nor disagree	26 (32)

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Question and answer options	Responses (N=82), n (%)
Disagree	33 (40)
Strongly disagree	1 (1)

[a]CDK 4/6: cyclin-dependent kinases 4 and 6.

[b]HR: hormone receptor.

[c]HER2: human epidermal growth factor receptor 2.

Adjuvant Chemotherapy

When chemotherapy is indicated in early HR-positive, HER2-negative breast cancer, 58% (48/82) and 21% (17/82) of participants preferred giving 6 and 8 cycles, respectively, while 21% (17/82) reported that the number of chemotherapy cycles does not matter. Noteworthily, 55% (45/82) of the participants disagreed or strongly disagreed with delaying adjuvant chemotherapy until after finishing adjuvant radiotherapy, while only 26% (21/82) agreed with this approach (Table 3).

Therapy for Patients With Metastasis

For metastatic patients, 43% of the participants (35/82) preferred using a CDK4/6 inhibitor with hormonal therapy in all patients, while 35% (29/82) preferred deferring CDK4/6 inhibitors to the second line in selected patients (Table 3). The treatments of choice of the survey participants for patients with nonvisceral metastasis were aromatase inhibitors (45/82, 55%), CDK4/6 inhibitor with aromatase inhibitor (28/82, 34%), and fulvestrant (9/82, 11%). For patients who had already started therapy with a CDK4/6 inhibitor, 44% of participants (36/82) disagreed or strongly disagreed with holding the CDK4/6 inhibitor until the pandemic is over, while only 32% (26/82) agreed or strongly agreed with that approach. Additionally, the participants were divided over the use of everolimus or alpelisib in second-line therapy. For patients who had already started therapy with everolimus, only 27% of participants (22/82) agreed or strongly agreed that everolimus should be held until the pandemic is over (Table 3).

Patients With HER2-Positive Breast Cancer

Of the 82 participants, two-thirds (n=55, 67%) supported using adjuvant trastuzumab for 6 instead of 12 months in selected patients with HER2-positive breast cancer, such as low-risk patients, older patients, or patients with logistic barriers to receiving the medication during the COVID-19 pandemic.

For first-line treatment of metastatic HER2-positive, HR-positive breast cancer, 80% (66/82) of the participants supported the use of hormonal therapy with dual anti-HER2 blockade in selected patients (older persons, those with low tumor burden) (Table 4).

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Table 4. Suggested treatment modifications in HER2-positive and triple-negative breast cancer.

Question and answer options	Responses (N=82), n (%)
Can adjuvant trastuzumab for 6 instead of 12 months can be considered in selected patients with HER2[a]-positive breast cancer (low-risk patients, older patients, or those with logistic barriers)?	
Strongly agree	17 (21)
Agree	38 (46)
Neither agree nor disagree	7 (9)
Disagree	17 (21)
Strongly disagree	3 (4)
For first line treatment of metastatic HER2-positive, HR[b]-positive breast cancer, will hormonal therapy with dual anti-HER2 blockade be considered in selected patients (older patients, those with low tumor burden)?	
Strongly agree	13 (16)
Agree	53 (65)
Neither agree nor disagree	7 (9)
Disagree	8 (10)
Strongly disagree	1 (1)
In metastatic triple negative breast cancer with *BRCA* mutation and *PD-L1*[c] <1%, what is the first-line treatment of choice?	
PARP[d] inhibitor	34 (41)
Platinum-based chemotherapy	30 (37)
Taxanes	11 (13)
Other	7 (9)
In metastatic triple negative breast cancer with *BRCA* mutation and *PD-L1* >1%, what is the first-line treatment of choice?	
PARP[d] inhibitor	14 (17)
Atezolizumab+nab-paclitaxel	58 (71)
Taxanes	5 (6)
Other	5 (6)
When chemotherapy is indicated for patients with metastatic breast cancer, if intravenous chemotherapy is chosen, what is the preferred regimen?	
Taxane: 3-weekly regimen	49 (60)
Taxane: weekly regimen	17 (21)
Anthracycline	9 (11)
Gemcitabine	4 (5)
Vinorelbine	3 (4)

[a]HER2: human epidermal growth factor receptor 2.

[b]HR: hormone receptor.

[c]*PD-L1*: programmed cell death 1 ligand 1.

[d]PARP: poly–(adenosine diphosphate–ripose) polymerase.

Patients With Triple-Negative Breast Cancer

Regarding the choice of first-line treatment in metastatic patients with *BRCA* mutation and programmed cell death 1 ligand 1 (*PD-L1*) <1%, the preferred treatment choices were poly–(adenosine diphosphate–ripose) polymerase (PARP) inhibitors (34/82, 41%), platinum-based chemotherapy (30/82, 37%), and taxanes (11/82, 13%). Meanwhile, in metastatic triple-negative breast cancer with *BRCA* mutation and *PD-L1* >1%, atezolizumab with nab-paclitaxel was the preferred choice for 71% (58/82) of the participants. When chemotherapy is indicated for patients with metastatic breast cancer, participants were divided between oral (39/82, 48%) and intravenous (IV) (43/82, 52%) chemotherapy. If IV chemotherapy was chosen, the preferred choices of the survey participants were 3-weekly taxane (49/82, 60%) and weekly taxane (17/82, 21%) (Table 4). During the COVID-19 pandemic, 52% (43/82) of participants supported lowering the threshold of prescription of granulocyte colony-stimulating factor following chemotherapy.

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Discussion

Principal Findings

In this survey, we explored the views of breast cancer oncologists practicing in three Middle Eastern countries regarding modifications in breast cancer management during the COVID-19 pandemic. The majority of the participants reported having COVID-19 cases in their institutes and believed that treatment modifications were required during the pandemic. We focused on modifications related to systemic therapy of patients with breast cancer, and these were categorized according to different breast cancer subtypes. The majority of participants supported using treatment strategies that decreased the risk of COVID-19 infection–related complications, such as using neoadjuvant hormonal therapy in patients with HR-positive/HER2 negative breast cancer, using 6 months of adjuvant trastuzumab in selected patients with HER2-positive disease, and using hormonal therapy with dual anti-HER2 blockade in metastatic HR-positive/HER2-positive patients. Meanwhile, participants were divided over some suggested modifications, such as using IV versus oral chemotherapy in metastatic patients when indicated.

Patients with cancer are at increased risk for severe disease and increased mortality due to COVID-19 infection [19]. In hospitalized patients with COVID-19, case fatality rates reported among patients with cancer are higher compared to those of other patients (29.4% vs 10.2%, respectively; $P<.001$) [20]. Large cohort studies have consistently demonstrated that all-cause mortality and the likelihood of ICU admission are higher in patients with cancer, even after adjustment for age, sex, diabetes, smoking, cardiovascular and pulmonary disease, and other common risk factors for COVID-19 severity [20-22]. These data highlight the critical need to decrease the risk of COVID-19 infection among patients with cancer.

Therefore, management of patients with breast cancer is challenging during the COVID-19 pandemic given the limitations of access to care, maintaining the level of patient care, travel restrictions, and immune suppression secondary to therapeutic modalities or the disease itself. This highlights the importance of the abovementioned modifications to breast cancer management to decrease the risk of myelosuppression/immune suppression and decrease the frequency of hospital visits and need of laboratory monitoring in addition to adopting alternative strategies when standard treatment approaches cannot be provided. Here, we will explore the scientific evidence for the different survey items supported by the participating oncologists.

CDK 4/6 Inhibitors in HR-Positive, HER2-Negative Breast Cancer

CDK 4/6 inhibitors with an aromatase inhibitor are currently the standard first-line therapy in HR-positive, HER2-negative patients without visceral crisis. Several clinical trials have established the survival benefit of these medications [7-9]. Neutropenia is the most frequent side effect encountered with this class of medications [7-9]. This may pose a particular risk in the era of the COVID-19 pandemic, particularly in older patients and those with low baseline neutrophil count. Moreover, in September 2019, the US Food and Drug Administration released a warning of rare but serious drug-induced interstitial pneumonitis with CDK 4/6 inhibitors [23]. Therefore, delaying CDK 4/6 inhibitors to second-line therapy until the pandemic is over may be an appropriate strategy, given that they demonstrated survival benefit in the second line when added to fulvestrant [24,25]. Noteworthily, ESMO recommendations reported that postponing the incorporation of a CDK4/6 inhibitor in the first line for patients presenting with special patterns of disease (eg, bone only, low burden, de novo metastatic disease) could be an option, especially in the older population [10].

Interestingly, in the FALCON study, progression-free survival (PFS) was significantly improved with fulvestrant monotherapy compared to anastrozole as a first-line therapy in patients with nonvisceral metastasis (22.3 vs 13.8 months, respectively), which makes fulvestrant an attractive first-line option that is recommended for this category of patients [26].

mTOR and PIK3 Inhibitors

Everolimus and alpelisib improved PFS when added to hormonal therapy in the BOLERO2 and SOLAR1 studies, respectively [10,11]. However, these medications are associated with adverse events such as hyperglycemia and noninfectious pneumonitis; therefore, their use may be problematic in the current era [27,28]. Patients with noninfectious pneumonitis may have similar manifestations to those of COVID-19 infection, such as dyspnea, cough, hypoxia, and fever, thereby complicating the diagnosis, and they may exacerbate potential respiratory drawbacks of COVID-19 infection. Noteworthily, treatment with steroids is required in patients with grade ≥2 noninfectious pneumonitis, which may put patients at increased risk of COVID-19 infection [29]. ESMO advises that the addition of mTOR or *PI3KCA* inhibitors is not of immediate priority and should be avoided [10].

Neoadjuvant Hormonal Therapy in HR-Positive, HER2-Negative Breast Cancer

Several trials have investigated the use of neoadjuvant hormonal therapy in postmenopausal patients with bulky HR-positive, HER2-negative disease to achieve better surgical outcomes. Several studies and meta-analyses demonstrated improved rates of breast conservative surgery with aromatase inhibitors compared to tamoxifen [30-33]. Data from randomized trials in postmenopausal patients displayed that higher ER and lower Ki-67 levels were significantly correlated with a higher probability of response [31,34]. Therefore, neoadjuvant hormonal therapy can be a good strategy to postpone breast surgery without compromising patients' outcome, with the current limitations in health services with limited surgical slots. Noteworthily, neoadjuvant endocrine therapy is recommended by ESMO as an option for patients with ER-positive/HER2-negative breast cancer to enable deferral of surgery by 6 to 12 months in clinical stage I or II breast cancers [10].

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Choice of Systemic Chemotherapy in Metastatic Breast Cancer in the COVID-19 Era

Oral chemotherapeutic agents, including capecitabine and vinorelbine, display activity in heavily pretreated patients; they have demonstrated overall response rates of up to 35% to 40%, which may be comparable to those of anthracyclines and taxanes [35-39]. Oral chemotherapy may be more convenient in the COVID-19 era. Generally, these agents are well tolerated and can be dispensed for several cycles and delivered to patients via medication delivery services. This approach can limit hospital visits and exposure to infection.

HR-Positive, HER2-Positive Breast Cancer: Chemotherapy-Free Regimens

Treatment with hormonal therapy combined with dual anti-HER2 therapy in HER2–positive/HR-positive MBC was assessed in several trials with encouraging results [40-42]. This strategy can be considered in selected patients, such as older patients, patients with borderline performance status, and patients with limited tumor burden. This chemotherapy-free approach can avoid neutropenia and other chemotherapy-related adverse events to minimize possible COVID-19–associated sequelae.

Duration of Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Several studies assessed adjuvant trastuzumab for 6 versus 12 months, including the Hellenic Oncology Research Group, PHARE, and PERSEPHONE studies [43-45]. All studies, except for the PERSEPHONE study, failed to demonstrate noninferiority of shorter versus longer duration of adjuvant trastuzumab. Meanwhile, the absolute difference in survival was 2% on average [46]. These data may be reassuring because in certain groups of patients, particularly those with low risk of relapse and logistic limitations, the survival outcome will not be greatly compromised if the adjuvant trastuzumab duration is limited to 6 months. Noteworthily, for selected patients with HER2-positive breast cancer, such as low-risk patients or older patients with cardiovascular or other comorbidities, adjuvant anti-HER2 therapy may reasonably be discontinued after 6 months instead of 12 months of treatment according to ESMO recommendations during the COVID-19 pandemic [10].

However, our study has some limitations. This survey was conducted in 3 Middle Eastern countries, which may not reflect current practice in other parts of the world. Furthermore, the sample size is relatively small, which is mostly related to the fact that many oncologists in the region are general oncologists without specific practice in breast cancer. In addition, differences in economic status, availability of medications and medication delivery services, and health system infrastructure may affect the application of the abovementioned modification strategies.

Finally, these modifications need to be discussed on a local basis, taking into account the local infrastructure and available resources. In addition, virtual tumor board discussion is critically important in this context to choose the most convenient therapeutic strategy without compromising treatment efficacy or patient safety.

Conflicts of Interest

SE has received honoraria for lectures and served on advisory boards at Roche, Novartis, Pfizer, Bristol Myers Squibb, and MSD. He has received a research grant and honoraria for lectures from Amgen and has served on their advisory board. He has received honoraria for lectures from Merck Serono. The other authors have no conflicts to declare.

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Abbreviations

CDK4/6: cyclin-dependent kinases 4 and 6
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
ESMO: European Society of Medical Oncology
HCP: health care professional
HER2: human epidermal growth factor receptor 2

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HR: hormone receptor
ICU: intensive care unit
IV: intravenous
PARP: poly–(adenosine diphosphate–ripose) polymerase
PFS: progression-free survival
***PD-L1*:** programmed cell death 1 ligand 1

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Original Paper

Digital Technical and Informal Resources of Breast Cancer Patients From 2012 to 2020: Questionnaire-Based Longitudinal Trend Study

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Abstract

Background: Digitalization offers enormous potential in medicine. In the era of digitalization, the development of the use of digital, technical, and informal resources of breast cancer patients and factors influencing the degree of digitization of patients has been insufficiently researched.

Objective: The aim of this study was to assess the development of the use of digital technical and informal resources in a well-defined patient cohort.

Methods: A longitudinal study on 513 breast cancer patients from 2012 to 2020 was conducted using a questionnaire that included the main aspects of the degree of digitalization, including digital device availability and use, stationary and mobile internet access and use, and communication and information seeking regarding breast cancer diagnosis and treatment.

Results: The majority of patients (421/513, 82.1%) owned the technical resources to benefit from eHealth, used the internet to obtain information (292/509, 57.4%), and were willing to use new eHealth solutions (379/426, 89%). Two-thirds of the patients discussed information about their cancer on the internet with their doctor, one-third found additional treatment options on the internet, and 15.3% (44/287) of the patients stated that this had changed their cancer therapy. The degree of digitization is increasing yet still significantly depends on 3 factors: (1) age (whereas 100% [39/39] of the <59-year-old group used the internet in 2020, 92% of the 60 to 69-year-old group [11/12] and only 47% [6/13] of the >70-year-old group used the internet), (2) education (internet use significantly depended on education, as only 51.8% [59/114] of patients with primary school education used the internet, but 82.4% [126/153] with middle school education and 90.3% [213/236] with high school education used the internet; P<.001), and (3) household size (67.7% [111/164] of patients living alone used the internet, whereas 84.7% [287/339] of patients living in a house with ≥2 people used the internet; P<.001).

Conclusions: To implement digital solutions in health care, knowledge of the composition and degree of the use of digital technical and informal resources of the patient group for which the respective solution is developed is crucial for success.

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Trial Registration: German Register of Clinical Studies DRKS00012364; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00012364

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KEYWORDS

digitalization; eHealth; breast cancer; internet

Introduction

Catalyzed by the development of the internet, changes in digitalization are occurring more rapidly in both public and private life. Digitalization with its influence on information seeking, decision-making properties of patients, therapy monitoring, and patient-physician interaction will likely change the health sector in both developed and developing countries [1-3]. Concepts of digitalization such as digital patient diaries and digital side-effect management have become part of many clinical trials [4-8]. The majority of these digitalization efforts pertain to hardware and software solutions that particularly emphasize digitalization on the side of the medical professional and the health care system. Patient access to adequate hardware, the internet, and patient acceptance of digital solutions are mostly assumed to be present in most model projects although it is known that digitalization is largely dependent on factors of age, income, gender, and education [9-13]. The basic requirement for the success of eHealth solutions is not only the "offer" on the side of the health care professionals but also the "demand" on the side of the patient. When implementing a digitalization strategy for a specific question or patient group, it can be assumed that aspects of the degree of the use of digital technical and informal resources of the respective patient cohorts—for example a below-average degree of the use of digital technical and informal resources in the case of an above-average–aged patient cohort—must be paid special attention to [4,12].

The additional benefits of digitalization and the internet are manifold: first, internet use might result in better information concerning breast cancer diagnosis. Li and colleagues [11] showed that patients who used the internet and were satisfied with the internet information concerning their breast cancer diagnosis were significantly more likely to receive breast-conserving therapy and showed significantly improved disease-free survival. Second, the use of online patient-provider communication has increased significantly and might be further developed in order to reach those previously unreached patients [14]. Third, the use of internet-based social community channels might influence patients' experienced degree of satisfaction with therapy decisions and psychosocial well-being. However, although there is no evidence for a negative impact, the positive effects of online communities have not yet been found to significantly impact patient-reported outcomes, likely because of a large number of influencing factors [15]. One more important secondary result of digitalization may be improved shared decision-making as, for example, communication and contact with other patients is strengthened. Recent studies have evaluated the impact of new technologies on the engagement of patients in shared decision-making and found increased empowerment of patients [16] and the potential for collaborative decision-making [17].

With this paper on patients with breast cancer, we present the first long-term study on the development of the degree of digitalization, including digital device availability and use, stationary and mobile internet access and use, and communication and information seeking regarding the breast cancer diagnosis and treatment of a defined patient group in detail. Using a longitudinal trend study design, we aimed to analyze the development of the most important aspects of digitalization in a well-defined patient cohort. To guide the development of digital study concepts, we aimed to identify subgroups of patients with reduced access to digitalization over the study period spanning 2012 to 2020 who would be excluded from digital patient-physician communication due to their low degree of digitalization.

Methods

From January 2012 to April 2020 women with a diagnosis of breast cancer were invited to participate in this longitudinal trend study. After a detailed literature search, we developed a questionnaire that included all aspects of the degree of digitalization and the internet use of the patients (Multimedia Appendix 1). In order to make the extent of digitalization more comparable, we summarized the core figures for dealing with digital media into a patient digitalization index (Multimedia Appendix 2).

Statistical analysis was performed using SPSS 25.0 statistical software (IBM Corporation). A P value of <.05 was considered significant. Multivariate analysis of age; education; household size; country of origin; and factors of the place of residence including size, rurality, community type, and broadband internet coverage was conducted. This revealed the factors of age, education, and household to be significantly associated with multiple factors of internet ownership and usage. As a consequence, only data concerning these 3 factors are shown.

The study was positively evaluated by the ethics committees of the Universities of Bonn and Cologne and registered in the German Register of Clinical Studies (DRKS00012364).

Results

A total of 1129 breast cancer patients were interviewed at the breast cancer centers of the University Hospitals of Cologne and Bonn (Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf) in the study period from 2012 to 2020. Of these, 513 patients participated in the study (Multimedia Appendix 3).

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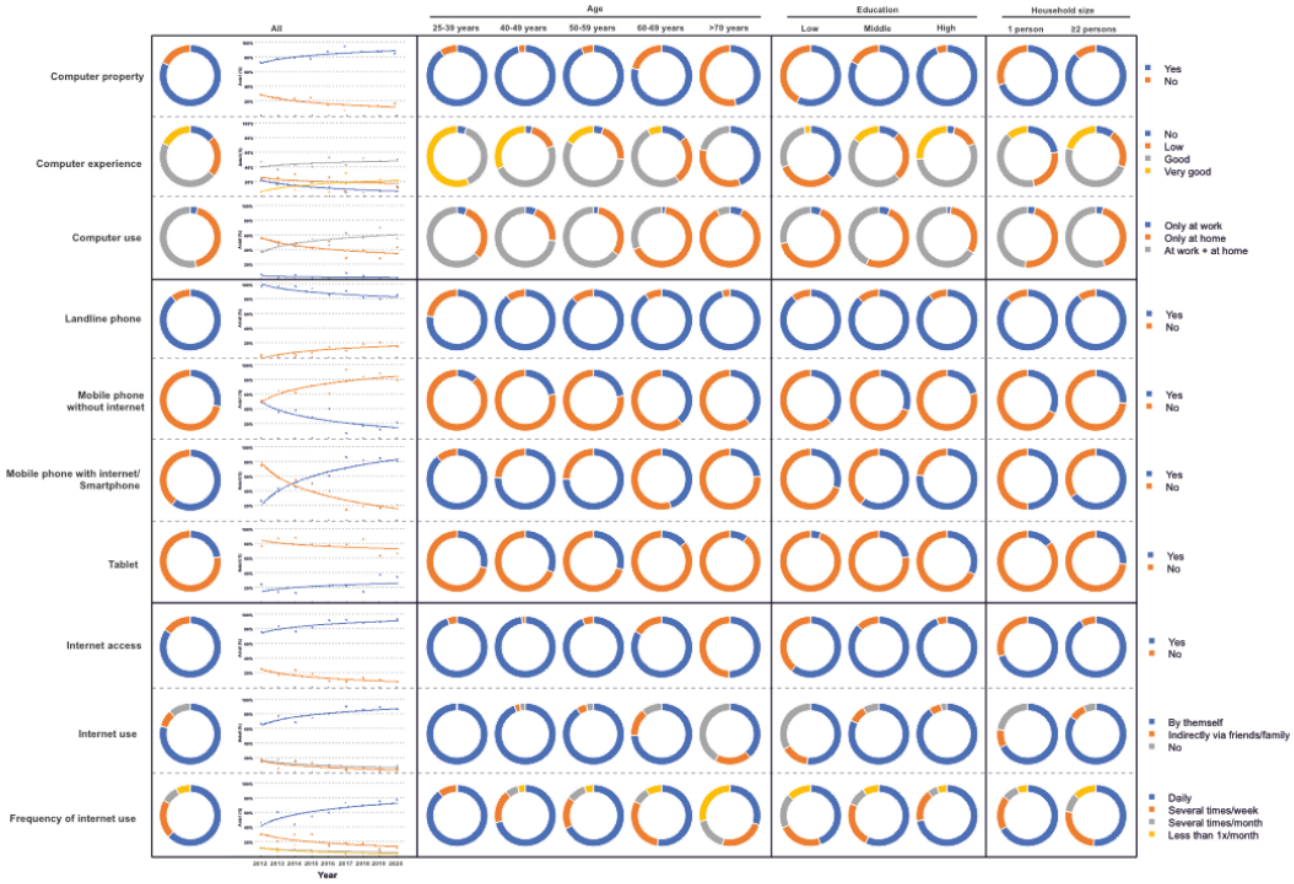
Stationary Device Availability and Use

The basic requirement for access to the internet and the use of eHealth was considered to be the availability of hardware with internet access. Overall, 82.1% (421/513) of patients owned a computer in the study period (Figure 1). The 25 to 59-year-old group showed full computer coverage beginning in 2014 with 94.6% owning computers (279/295). The 60 to 69-year-old group showed a steady increase during the study period, with 83% (10/12) owning a computer in 2020. Only the group of those older than 70 years old showed a smaller increase over the study period, with only half of this patient cohort owning a computer in 2020 (7/13). In addition to age, education was associated with significant differences in computer use: >90% of patients with a high educational background (223/237) had a computer compared to <80% of patients with an educational background lower than high school (198/276; *P*<.001). In addition, a significantly lower portion of patients living alone owned a computer (116/166, 69.9%) compared to patients who lived in a household with at least 2 people (305/347, 87.9%; *P*<.001). We did not observe differences in computer ownership between patients of different origin, place of residence, or broadband coverage.

Figure 1. Presence and development of technical and informal resources over the course of the study from 2012 to 2020 in terms of device availability and competence in use, differentiated by age, level of education, and household size. For a higher-resolution version of this figure, see Multimedia Appendix 4.



Furthermore, 64.1% (323/504) of the patients qualified their computer experience as good or very good. Again, patients with a higher education, those under 60 years old, and patients from a household with at least 2 people showed significantly higher computer experience (*P*<.001). Most reported using computers at home (181/422, 42.9%) and/or at work (224/422, 53.1%). Again, younger patients and those with a higher level of education used the computer significantly more both at work and at home (*P*<.001).

Internet Access and Internet Use

A *conditio sine qua non* for the use of eHealth is access to the internet. Access to the internet at home increased since the beginning of the study and was 84.6% (430/508) at the end of the 9-year study period (Figure 1). Patients <50 years of age showed full coverage of internet access at home since the beginning of the study. A strong increase could be seen in patients aged 50 to 59 years old who had complete access to the internet since 2019. Continuous growth was also evident among those 60 to 69 years old and those older than 70 years, 75% (9/12) and 50% (6/12) of whom were online in 2020, respectively. Patients with different levels of education (primary school education: 71/117, 60.7%; middle school education 135/154, 87.7%; high school education: 224/237, 94.5%) and different household sizes (living alone: 116/166, 69.9%; household size ≥2 people: 314/342, 91.8%) showed significant differences in internet coverage (*P*<.001). Not only the did the availability of the internet at home continuously increase since the beginning of the study, but so did the use of the internet. Moreover, all respondents <40 years old used the internet by themselves since the beginning of the study in 2012, while those 40 to 49 years old and those 50 to 59 years old did so beginning

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2016 and 2018, respectively. Continuous growth of internet usage was evident among the 60 to 69-year-old patients and the >70-year-old patients, 63% (5/8) and 50% (6/12) of whom used the internet by 2020, respectively. In addition, significant differences in the use of the internet were observed between patients with different educational backgrounds (primary school education: 59/114, 51.8%; middle school education: 126/153, 82.4%; high school education: 213/236, 90.3%; *P*<.001) and different household sizes (living alone: 111/164, 67.7%; household size ≥2 people: 287/339, 84.7%; *P*<.001). Interestingly, those who were older, had a lower level of education, and who were single used the internet significantly more often indirectly via friends or family, but even more significantly did not use it at all.

Mobile Internet Access

Although the stationary coverage internet was > 90%, mobile internet access still showed high growth rates. The 25 to 39-year-old group demonstrated full coverage beginning in 2014, while the 40 to 49-year and 50 to 59-year age groups did so beginning in 2016 and 2020, respectively. However, distinct groups still showed a lower access to mobile internet: the 60 to 69-year-old patients (9/12, 75%), the over 70-year-old patients (5/12, 40%), and the patients with little (4/8, 50%) or no education 86% (12/14); meanwhile, in the group of patients with a high school diploma or higher education, this proportion was 100% (13/13). However, a steady increase in mobile internet access was also evident in these patients. As the proportion of patients with mobile or stationary internet access increased, the proportion of patients with either a mobile phone without internet access or landline phone decreased continuously.

General Information Gathering on Breast Cancer

Digitalization is changing the information resources in cancer and the manner in which this information is accessed. The amount of health-related information on the internet has increased, and the internet has become important for many patients for finding health information. Which sources of information do breast cancer patients generally use to learn about their disease? Which information source is the most important for information? Which source of information influences therapy decision-making (Multimedia Appendix 5)? Over the study period, 74.7% (378/513) of patients saw the treating physicians as the most important information source for their cancer and as the most important information source for therapy decision-making. This did not change over the 9-year study period. For 29.8% (153/513) of patients, the internet was the most important source of information. The proportion of those who use the internet as a source of information increased significantly over the study period in 2012 from 36% (22/61) to 62.5% (40/64). Again, for younger patients with higher education and a partner, the internet was significantly more important as an information resource (*P*<.001). It is important to mention that patients in the year 2020 still considered treating physicians to be the most important source of information on disease and therapy (disease: 45/64, 70%; therapy: 45/60, 75%) as compared to the internet (disease: 30/64, 47%; therapy: 24/60, 40%). Patients without internet access hardly used the internet at all to find information on disease or therapy.

The Internet as a Source of Information on Breast Cancer

The majority of patients indicated using the internet as a source of information on their disease (Multimedia Appendix 6a and b). In order to determine more precisely how internet use is related to cancer, we asked the patients in detail about their cancer-specific internet use. We found that the internet was used primarily for general information about cancer, for questions about conventional and alternative cancer therapies, for cancer research, and for nutrition in relation to cancer (Multimedia Appendix 6c). In addition, participants indicated using websites of the German Cancer Society (183/286, 62.7%), the German Cancer Aid (174/286, 59.6%), and specialist journals (87/286, 29.8%) to a large extent, while websites of pharmaceutical companies, gynecologists, and patient associations were used much less frequently (each <28/286, <10%). Despite the abundance of information that can be obtained on the internet, 64% (183/286) of patients used the internet only as a source of information in addition to their doctor, and almost no patients (2/286, 0.7%) stated that they did not need any additional information from their doctor besides the internet (Multimedia Appendix 6d). Two-thirds (193/285) of the patients indicated that they had already discussed information about their cancer on the internet with their doctor, 27.1% (79/285) found additional treatment options on the internet, and 15.3% (44/287) stated that this had changed their cancer therapy (Multimedia Appendix 6f). Interestingly, it appears that as soon as a patient uses the internet as a source of information, there exists no differences in search items between patients of different ages, levels of education, or household sizes.

Reasons Not to Use the Internet to Obtain Information About Cancer

Overall, the proportion of patients that did not use the internet to obtain information decreased continuously beginning from 2012. Those who did not use the internet to obtain information about their illness were significantly older, showed a significantly lower educational background, and significantly more often lived alone. Reasons not to use the internet to find information on their illness mainly included a fear of the information being inaccurate (50/117, 42.7%) or incorrect (62/117, 53%; Multimedia Appendix 6e).

Association of Internet Access and Therapy Decision

The overwhelming majority of the patients indicated that the decision regarding cancer therapy should either be made by the doctor with knowledge of their preferences (218/483, 45.1%) or on an equal basis within the framework of shared decision-making (154/483, 31.9%; Multimedia Appendix 6g). Only a very small proportion indicated they would like the doctor to decide on cancer therapy alone (25/483, 5.2%). Almost one-fifth of patients indicated that they would like to make this decision themselves, knowing their doctor's recommendation. Overall, these preferences showed no differences across patients of different age groups, different educational levels, different household sizes, or different types of residence. However, patients with internet access and who used the internet wanted to be included significantly more often in the therapy decision-making process (141/218, 64.7%) than did patients

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without internet access and who did not use the internet (77/218, 35.3%; *P*=.045)

Communication

Communication over the internet is a basic requirement for many eHealth solutions. In our study, 72.4% (351/485) of patients indicated using the internet for communication (Multimedia Appendix 7a), with the vast majority (340/365, 93.2%) indicating they used it themselves (Multimedia Appendix 7b). Again, those 25 to 49 years old communicated almost completely via the internet, while only 79.7% (118/148) of those 50 to 59 years old, 67.8% (78/115) of those 60 to 69 years old, and 34% (28/82) of those older than 70 years communicated via the internet. Significant differences were observed between patients with high and low levels of education, whereas household size was not associated with differences in communication over the internet.

The vast majority of patients communicated with the oncological outpatient clinics using landline telephones (Multimedia Appendix 7c) although the majority of patients said they would be willing to communicate with their treating physicians by phone (306/415, 73.7%) or email (156/402, 38.8%; Multimedia Appendix 7e and 6f). Additionally, 49.6% (122/246) of patients under 60 years of age compared to 21.8% (34/156) of those over 60 years of age indicated using email as a contact option for oncological outpatient clinics (*P*<.001). Patients with a high level of education used email as a contact option for the oncological outpatient clinics significantly more often (55/226, 24.3%) than did patients with a medium (26/145, 17.9%) or low level of education (7/112, 6.3%; *P*<.001). Access to the internet (access to internet: 88/412, 21.4%; no access to internet:: 0/0, 0%; *P*<.001) and the active use of the internet for information gathering (active use: 75/283, 26.5%; no active use: 12/198, 6.1%; *P*<.001) were significantly associated with the probability of communicating with the oncological outpatient clinics by email.

At the beginning of this study in 2012, few people were able to predict the importance that services such as WhatsApp, Snapchat, or Instagram would have, and it is similarly difficult to predict today the options that will be used in 5 or 10 years. Consequently, openness to new communication options was found to be another important factor in affinity to digitalization of our patients. Importantly, the vast majority of patients (395/430, 91.9%) were willing to use these new communication options (Multimedia Appendix 7g).

Shopping on the Internet

Even if shopping on the internet does not seem to have a direct connection to the degree of digitalization of breast cancer patients, the diversity of services, in addition to gathering information and communication, including shopping, culture, travel, and delivery and driving services, represents an important aspect of depth in internet offering use (Multimedia Appendix 7d). For instance, 63.6% (300/472) of the participants in the study indicated that they would use the internet themselves for shopping in 2020. Compared to those over 60 years of age (66/189, 34.9%), those under 60 years (234/283, 82.7%) showed significantly higher usage (*P*<.001). Patients with a high level of educational (173/226, 76.5%) also showed a significantly higher usage compared to those with a low level (35/102, 34.3%; *P*<.001) and medium level of communication (92/144, 63.9%; *P*<.001). However, older and less educated patients used the internet for shopping significantly more often indirectly via friends or family. Specifically, 9.2% (26/282) of those under 60 years indicated doing so, while 15.9% (30/185) of those over 60 indicated doing so (*P*=.03). Furthermore, 19.6% (20/102) of patients with a low level of education and 11.1% (16/144) of patients with a medium level of education indicated shopping in this manner, respectively, as compared to 8.9% (20/205) of those with a high educational background (*P*=.02).

Digitalization Index

The digitalization of breast cancer patients increases every year. This was reflected in the digitalization index of breast cancer patients, which increased from 45 to 55 from 2012 to 2020.

Overall, about 60.4% (310/513) of the patients showed a degree of digitalization of 70 (Figure 2a), and the degree of digitalization decreased significantly with age. In contrast to the high degree of digitalization in the younger age groups, those older than 70 years old, those living alone, and those with less education still showed, despite an increase over the study period, a much lower digitalization index (Figure 2b).

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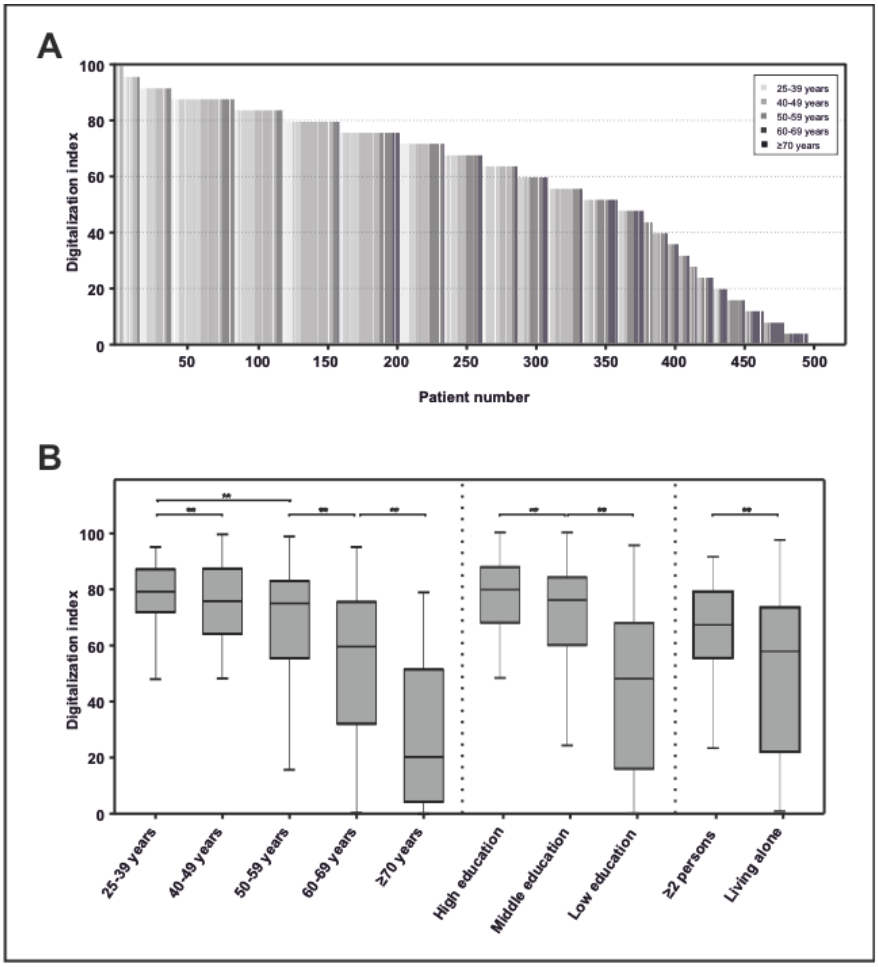
Figure 2. Digitalization index. (A) Waterfall plot of the digitalization index of all participating patients, with the grayscale bar representing age. (B) Digitalization index according to age, level of education, and household size. (**: *P*<.05).



Discussion

With this longitudinal trend study, we present data on the increase of all aspects of electronic device ownership, internet usage, internet communication, and the influence of the internet on disease information and therapy decision-making in a large cohort of breast cancer patients over a 9-year period.

Digital solutions open up a wide range of possibilities for preventive care, information on disease and therapies, follow-up, and trial support. To succeed, digitalization strategies for distinct clinical questions or patient groups must pay particular attention to specific aspects of the degree of digitalization of the particular patient groups they are designed for.

Our study shows that the availability of electronic devices in breast cancer patients has increased steadily from 2012 to 2020. The same applies to the presence of internet access, internet use, and the availability of mobile devices for internet use. There still are significant differences in terms of both access to and the use of the internet between patients of different ages, educational backgrounds, and household sizes. Patients from a low socioeconomic background, including those older adults living alone and with a low level of education, are significantly less well supplied with internet-enabled devices and with access to the internet. The proportion of patients who do not have internet access and who do not use the internet has decreased steadily since 2012, especially in the group of those older than 70 years old and in the group of those with a low level of educational [9,18].

The internet has become an important source of information for patients [1,9,11,19]. As individual reasons for searching for medical information can vary, for example preparing for a medical consultation, looking up medical information, answering open questions after visiting a doctor, or looking for alternative therapies, understanding how and where patients consume information on cancer on the internet is important to identifying patient needs and offering reputable digital information [9]. Although the proportion of patients that used the internet for information increased in our study, physicians continued to be the most important source of information about disease and therapy throughout the course of the study. In contrast to other countries, the proportion of patients that visit the websites of pharmaceutical companies to search for information is low in Germany [11]. Contrary to our expectations that doctors would be replaced as the most important source of information, it seems that the information seeking on the internet occurs in addition to the physician. The use of information resources others than physicians and the internet seem to decrease over time. Another important result of this study was that there is no difference in the search content among those patients who used the internet as an information resource for understanding their cancer, which suggests that, although the factors age, level of

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education, and household size are significantly associated with access to the internet and the degree of digitalization, there exist no relevant differences in the type of information being searched for. The increase in knowledge on the side of patients may lead to a more active participation in the decision-making process [19,20]. In our study, the majority of patients had already discussed information from the internet with their doctor, even if this only changed the therapy to a small extent. Access to health-related information can potentially empower patients to be involved in therapy decision-making as compared to the past. In line with other reports on this topic, we observed a difference in therapy decision-making between patients with and without internet use [1-3].

In addition to information acquisition, communication plays a key role in most digitalization solutions. Although the majority of patients in private or professional settings already communicate via the internet, most patients continue to use the phone to contact their doctors. Regardless of the current form of communication with the oncological outpatient clinics, our study showed a steady increase in willingness to communicate with the treating physicians via new communication channels such as email, which has also been shown to be the case in other countries [20].

Some limitations to our study include the relatively small number of patients in the youngest group of people under the age of 40 years that could be recruited for the study in some years. This resulted in a larger SE in this age cohort than in the other age cohorts. In addition, our study recorded the presence of mobile phones and smartphones but did not differentiate between stationary and mobile internet use. However, we do not consider the latter to be a serious drawback since the use of most eHealth applications can be used independently of the device via a browser. As we used a questionnaire to obtain information from the patients, self-reported digital skills could not be assessed objectively and might have been subjectively reported as too high or too low by the patients. In addition, we cannot rule out a potential selection bias in patients that answered the questionnaire compared to those who did not.

Our study offers several insights. Many trials in oncology implement digital solutions, such as electronic patient diaries, video chat functions, or electronic documentation of side effects. Our study identified those patients that would be excluded from such study concepts due to their low degree of digitalization. The planners of trials should keep an eye on the degree of digitalization of their patient population when planning the study in order to ensure that all patient groups have equal access to new trials. Contrary to the fears of some, the internet has not replaced the doctor as an information resource. Our study shows how important it is to provide adequate information on oncological diagnoses on the internet and how wide the scope of information on oncological topics is for the affected patients. However, since a substantial proportion of patients continues to fear incorrect or inaccurate information, the respective physician should guide the patient's search for information, for example by recommending websites with reliable information. The potential benefit of the internet for physician-patient communication in improving clinical care and workflow is likely the largest but also the most underexploited.

We encourage our colleagues to clarify the digitalization status of their patients at the beginning of therapy to optimize digital patient-physician communication.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[DOCX File , 37 KB - cancer_v7i4e20964_app1.docx]

Multimedia Appendix 2
Digitalization index.
[DOCX File , 13 KB - cancer_v7i4e20964_app2.docx]

Multimedia Appendix 3
Characteristics of 513 patients with breast cancer.
[DOCX File , 19 KB - cancer_v7i4e20964_app3.docx]

Multimedia Appendix 4
Presence and development of technical and informal resources over the course of the study from 2012 to 2020 in terms of device availability and competence in use, differentiated by age, level of education, and household size.
[PNG File , 928 KB - cancer_v7i4e20964_app4.png]

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Multimedia Appendix 5
Most important sources of information and most important sources of information for the treatment of breast cancer.
[DOCX File , 17 KB - cancer_v7i4e20964_app5.docx]

Multimedia Appendix 6
Use of the internet as source of information.
[DOCX File , 21 KB - cancer_v7i4e20964_app6.docx]

Multimedia Appendix 7
Use of the internet for communication.
[DOCX File , 20 KB - cancer_v7i4e20964_app7.docx]

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Original Paper

Assessing the Quality of Online Health Information About Breast Cancer from Chinese Language Websites: Quality Assessment Survey

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Abstract

Background: In China, the internet has become one of the most important ways to obtain information about breast cancer. However, quantitative evaluations of the quality of Chinese health websites and the breast cancer treatment information they publish are lacking.

Objective: This study aimed to evaluate the quality of Chinese breast cancer websites and the value, suitability, and accuracy of the breast cancer treatment information they publish.

Methods: Chinese breast cancer health websites were searched and manually screened according to their Alexa and Baidu search engine rankings. For each website included in the survey, which was conducted on April 8, 2019, the three most recently published papers on the website that met the inclusion criteria were included for evaluation. Three raters assessed all materials using the LIDA, DISCERN, and Suitability Assessment of Materials (SAM) tools and the Michigan Checklist. Data analysis was completed with the Statistical Package for Social Sciences (SPSS) version 20.0 and Microsoft Excel 2010.

Results: This survey included 20 Chinese breast cancer websites and 60 papers on breast cancer treatment. The LIDA tool was used to evaluate the quality of the 20 websites. The LIDA's scores of the websites (mean=54.85, SD 3.498; total possible score=81) were low. In terms of the layout, color scheme, search facility, browsing facility, integration of nontextual media, submission of comments, declaration of objectives, content production method, and robust method, more than half of the websites scored 0 (never) or 1 (sometimes). For the online breast cancer treatment papers, the scores were generally low. Regarding suitability, 32 (53.33%) papers were evaluated as presenting unsuitable material. Regarding accuracy, the problems were that the papers were largely not original (44/60, 73%) and lacked references (46/60, 77%).

Conclusions: The quality of Chinese breast cancer websites is poor. The color schemes, text settings, user comment submission functions, and language designs should be improved. The quality of Chinese online breast cancer treatment information is poor; the information has little value to users, and pictorial information is scarcely used. The online breast cancer treatment information is accurate but lacks originality and references. Website developers, governments, and medical professionals should play a full role in the design of health websites, the regulation of online health information, and the use of online health information.

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KEYWORDS

online health information; breast cancer; Chinese language websites; quantitative evaluations

Introduction

Breast cancer is a malignant tumor of the breast epithelium. Since 1980, the incidence of breast cancer has been increasing worldwide. The age-standardized mortality rate based on the world standard population was 182.6 per million in 2018, and breast cancer is the leading cause of death due to cancer in women (15.0%) [1]. In the past decade, the incidence of breast cancer in China has also been rapidly growing, with a prevalence of 1%-2%, higher than that in other countries [2]. According to the latest national cancer statistics released by the National Cancer Centre of China in January 2019, breast cancer is the fourth-leading cause of death due to cancer among women in China and is one of the malignant tumors threatening the health of Chinese women [3].

For cancer-related information, the majority of the public is more likely to search the internet first. Because cancer is a major disease that is associated with strong privacy and sensitivity, breast cancer patients tend to first seek relevant health information from the internet to deepen their understanding of the disease and assist them in making decisions on health behavior [4]. The process of searching for health information about breast cancer is influenced by subjective and objective factors. The subjective factors include the users' information literacy level. Some research results have shown that the educational level of internet users [5], their attitude toward online health information [6], and their ability to acquire [7] and evaluate [8] online health information have positive effects on their rational utilization of this type of information. The objective factors mainly include the quality of online health information.

In Europe and North America, there is much research on online cancer health information [9,10]. The quality assessment of online health information about cancer has attracted extensive attention from scholars worldwide. Garfinkle [11] evaluated the readability, quality, and accuracy of online health information for patients with low anterior resection syndrome following surgery for rectal cancer and found that online health information is lacking and too complex for patients to understand. Another study [12] assessed the availability and quality of information about female oncofertility on the websites of (inter)national oncology, fertility, and oncofertility organizations and suggested that the availability and quality of online health information be improved and that high-quality resources be recommended by physicians. The quality of online health information is a complex concept involving more than 20 dimensions, as perceived by consumers. The most widely reported criteria used by consumers were trustworthiness, expertise, and objectivity, and the most widely reported indicators were website owner/sponsor, consensus among multiple sources, the characteristics of writing and language, advertisements, content authorship, and interface design [13].

In China, according to the 43rd China Internet Network Development Statistics report released by the China Internet Network Information Centre, as of December 2018, China had 829 million internet users [14]. Online health information services have become an important way for people to obtain health information [15]. The quality of health information service platforms is affected by the quality of the websites and the information they publish [16]. However, due to the imbalance between the rapid development of informatization and the regulation of online information, the quality of online health information service websites and their information has been uneven [17]. According to the results of a recent study [18], Baidu is the most popular online information source for breast cancer; however, more than half (55.1%) of those surveyed were dissatisfied with the online information. To date, China's domestic research on online health information has focused on discussing online health information evaluation indexes [19] and evaluation tools [20] and on theoretical research on online health information service platforms [21]. However, there is still a lack of in-depth research on the quantitative assessment of health information websites and the information they publish.

Currently, there are many tools for online information quality evaluation. Some evaluation tools are highly targeted. For example, the Suitability Assessment of Materials (SAM) tool can be used to evaluate the applicability of information [22]. The Simplified Measure of Gobbledygook (SMOG) tool can be used to evaluate the readability of information [23], while the Health on the Net Foundation Code of Conduct (HONcode) has proposed a special code of ethics for the release of online health information for health websites [24]. Other tools focus on evaluating the quality of online health information from multiple dimensions; for example, the Michigan Checklist includes an evaluation of online health information quality and website design [25]. In addition to assessing the information quality of online treatment schemes, the DISCERN tool uses several items to evaluate the reliability of websites and has been used to evaluate the readability, suitability, and quality of online health information [22] In this study, we carefully examined relevant online health information quality evaluation tools and assessed the effectiveness of these tools and the independence between subdimensions, finding that some subdimensions of these evaluation tools are repeated. To evaluate the quality of online breast cancer health information as comprehensively as possible and to avoid duplication of the subdimensions of the evaluation tools, we chose to conduct our study based on the two dimensions of website quality (usability and reliability) and three dimensions of information quality (value, suitability, and accuracy).

The purpose of this study was to evaluate the quality of Chinese health breast cancer websites and to evaluate the quality of online breast cancer treatment information in terms of value, suitability, and accuracy. This study aims to provide support for breast cancer patients and caregivers to make effective use of online health information services and to make reasonable

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health decisions by analyzing the quality of and the problems with online health information in China.

Methods

Sample

The evaluation of the quality of online health information about breast cancer was divided into two parts: First, the quality of Chinese websites that publish breast cancer health information was evaluated; second, the quality of Chinese online papers on breast cancer treatment was evaluated. The quality of websites mainly depends on their functionality. The quality of papers mainly depends on the health-related content.

The initial screening of Chinese breast cancer websites was completed in two steps. The first step consisted of selecting the top 100 websites as research samples based on the results of Chinese medical and health websites provided by Webmaster's House and the Alexa ranking. The second step consisted of using the Baidu search engine to select the results of the first 20 pages from the list of search results, with "breast cancer" or "breast tumor" used as the search keyword. In all, 38 breast cancer–related health websites were manually screened. ChinaZ^{TM} is the most well-known basic web service provider in China, providing users with Alexa ranking queries, website traffic queries, and other services on Chinese websites. Alexa has the largest number of Uniform Resource Locators (URLs) and detailed ranking information [26]. Alexa China provides free official data queries of Chinese website rankings, which can reflect the traffic and popularity of a website to some extent [27]. Baidu is the most visited Chinese search engine in the world [28,29]. Based on the search results of these two platforms and after eliminating 26 duplicate websites, 112 websites were included in the research sample pool of this study. The inclusion criteria for the health websites were as follows: (1) the websites were Chinese websites, (2) the information released by the websites was obviously relevant to breast cancer health, (3) the websites were not intended to sell merchandise, and (4) the websites were not official hospital websites. We excluded hospital websites because official websites provide basic information about the hospital, such as an introduction to the hospital and departments. Moreover, there is little detailed health information about breast cancer on hospital websites. Based on the inclusion criteria, 20 breast cancer health websites were finally included in the survey.

The inclusion criteria for Chinese online papers on breast cancer were as follows: (1) the papers were written in Chinese, (2) the papers were related to breast cancer treatment information, (3) the papers were not for advertising, and (4) the papers included text and pictures. According to the date of publication of the papers, three recently published papers on each website that met the inclusion criteria were selected as samples to evaluate the quality of online treatment information about breast cancer.

The samples were was collected on April 8, 2019. The sample collection process is shown in Multimedia Appendix 1.

Tools

Quality Assessment Tool for Websites

LIDA was used to evaluate the usability and reliability of health websites on breast cancer. This tool was developed by Minervation, a British consulting company in the health care field, in 2007 and was designed for professionals to evaluate all aspects of health websites, focusing on the degree of recognition of health websites by professionals [30]. The evaluation of usability included four dimensions: clarity, consistency, functionality, and engageability. The evaluation of reliability included three dimensions: currency, conflicts of interest, and content production. In this study, a total of 27 items were used to evaluate the websites. Each question was scored on a scale of 0 to 3, where 0 indicated never, 1 indicated sometimes, 2 indicated mostly, and 3 indicated always.

Quality Assessment Tool for Papers

The quality of the papers was assessed based on three key parameters: value, suitability, and accuracy.

Value Assessment Tool

The value of online papers on breast cancer was assessed using a 7-item scale selected from the DISCERN tool. DISCERN is a tool for judging the quality of written consumer health information about treatment choices; it was developed by the British Library in 1999 [31]. DISCERN consists of a total of 16 questions, and it was the first tool in the world for evaluating the information quality of health websites. It includes three dimensions: the evaluation of websites, the evaluation of the value of therapeutic papers, and overall evaluation. DISCERN is a validated tool that has adequate internal consistency (α=.78) and satisfactory interrater reliability [32]. To assess the value of papers on breast cancer treatment, we selected only the second dimension of the DISCERN scale. It includes 7 questions, each rated on a 5-point Likert scale ranging from 1=no (ie, the criterion is not fulfilled by the publication) to 5=yes (ie, the criterion is fulfilled by the publication).

Suitability Assessment Tool

The SAM tool was used to evaluate the suitability of online health information about breast cancer. SAM, developed and designed by Doak, is an objective assessment tool for evaluating the availability and reliability of health materials [33]. SAM includes 6 dimensions: content (4 items), literacy demand (5 items), graphics (5 items), layout and typography (3 items), learning stimulation and motivation (3 items), and cultural appropriateness (2 items). Each item is scored on a scale of 0 to 2 points, where 0 indicates not suitable, 1 indicates adequate, and 2 indicates superior. In this study, considering that there was no front cover with online health information, we removed one item (cover graphic) that did not apply. The higher the final score of a paper is, the better its suitability.

Accuracy Assessment Tool

Six items in the Michigan Checklist were selected to evaluate the accuracy of the papers. The Michigan Checklist was created by the University of Michigan in 1999, and it focuses on evaluating health websites and their content. The scale included two aspects: content and usability. Because this study mainly

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evaluated the accuracy of papers published on breast cancer websites, the content of the scale (items 18-23) was selected to evaluate the accuracy of the papers:

- #18. Are sources cited or credited?
- #19. Is a bibliography or resource list available?
- #20. Can you identify errors or significant omissions in information presented?
- #21. Are opinions or misleading/biased information presented as fact?
- #22. Does information presented as factual appear to be accurate to the best of your knowledge?
- #23. Is there an identifiable conflict of interest?

Rating Process

The evaluation was performed by three assessors. Assessor 1 (author SWW) holds a master's degree in medical informatics and has 7 years of experience in medical information analysis and research. Assessor 2 (author WFZ) holds a master's degree in computer science and a doctorate in social medicine and has 8 years of experience in computer software development. Assessor 3 (author BZW) holds a doctor of medicine degree and a clinical physician qualification certificate. Two websites (six papers) were used for experimental evaluation. Before the test, the three researchers (assessors) carefully read the scales and usage instructions of the four assessment tools (the LIDA, DISCERN, and SAM tools and the Michigan Checklist) to understand the purpose and significance of the evaluation items. The evaluation was divided into two steps. First, assessors 1 and 2 used LIDA to evaluate the quality of the websites. Then, assessors 1 and 3 used the other three scales to evaluate the quality of the selected papers. To ensure the consistency of the evaluation results, the subdimension was adopted as the evaluation unit; that is, the N-th+1 dimension was evaluated after the evaluation of the N-th dimension of all samples was completed. The evaluation process adopted a parallel mode. Two assessors independently evaluated a given sample simultaneously. In the case of diverging evaluation results, the final results were determined through real-time negotiation.

Ethical Approval

Ethical approval for the study was obtained from the Medical Ethics Committee of the BengBu Medical College (BBMC; reference no. 2017054).

Statistical Analysis

Analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2010 (Microsoft Inc., Washington DC, USA). All values are expressed as the mean ± SD.

Results

Characteristics of the Breast Cancer Websites

The characteristics of the breast cancer websites are shown in Table 1. All 20 websites had internet content provider (ICP) registration numbers. Of the 20 websites, 17 (85%) were corporate websites and 3 (15%) were personal websites. There were 3 (15%) websites with Baidu weights of 7-9, 10 (50%) websites with Baidu weights of 4-6, and 7 (35%) websites with Baidu weights of less than 3. Regarding the number of years since website registration, there were 4 (20%) websites that had been registered for more than 15 years, 8 (40%) websites that had been registered for 5-10 years, and only 1 (5%) website that had been registered for less than 5 years. In terms of regional distribution, 17 (85%) websites were registered in eastern China, 1 (5%) was registered in central China, and 2 (10%) were registered in western China.

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Table 1. Characteristics of the breast cancer websites (N=20).

Characteristic	Group	n (%)
Nature	Enterprise	17 (85)
	Personal	3 (15)
Global ranking	Less than 10,000	4 (20)
	10,000-30,000	5 (25)
	30,000-60,000	2 (10)
	More than 60,000	6 (30)
	—[a]	3 (15)
Traffic ranking	10,000	4 (20)
	10,000-30,000	5 (25)
	30,000-60,000	3 (15)
	More 60,000	5 (25)
	—	3 (15)
Week of Alexa ranking	5000	2 (10)
	5000-10,000	2 (10)
	10,000-30,000	6 (30)
	More than 30,000	4 (20)
	—	6 (30)
ICP[b] certified	Yes	20 (100)
	No	0 (0)
Baidu weight[c]	7-9	3 (15)
	4-6	10 (50)
	Less than 3	7 (35)
Years since registration	More than 15	4 (20)
	10-15	8 (40)
	5-10	7 (35)
	Less than 5	1 (5)
Region	Eastern part	17 (85)
	Central part	1 (5)
	Western part	2 (10)

[a]—: not available.

[b]ICP: internet content provider. ICPs are telecom operators providing comprehensive internet information services and value-added services to a vast number of users. The required certificate is the ICP certificate. Profit-making websites must handle ICP certificates; otherwise, they are illegal businesses.

[c]Baidu weight: Baidu weights are evaluated data that are used to estimate search engine traffic by the webmaster tool through an analysis of the ranking of a website's keywords. The evaluated data are divided into 0-9 for a total of 10 grades. Baidu weights are related to the number of keywords and traffic. The more keywords there are, the higher the weight of accumulation. The higher the keyword flow is, the higher the cumulative weight will be.

Quality of Breast Cancer Websites

We used LIDA to evaluate the quality (usability and reliability) of the 20 breast cancer websites. The evaluation results are shown in Table 2. The evaluation results showed that the overall score of the quality evaluation of the breast cancer websites was 54.85±3.498 (81 points). With regard to the layout, color scheme, search facility, browsing facility, integration of nontextual media, submission of comments, declaration of objectives, content production method, and robust method, the scores of the websites were low. The results showed that the quality of the websites needs to be improved.

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Table 2. Descriptive statistics of LIDA items.

Item	Score=0	Score=1	Score=2	Score=3	Mean (SD)
2.1 Clarity, n (%)					
2.1.1 User scope	0 (0)	1 (5)	19 (95)	0 (0)	1.950 (0.224)
2.1.2 Knowledge level	0 (0)	3 (15)	16 (80)	1 (5)	1.900 (0.447)
2.1.3 Layout	0 (0)	13 (65)	6 (30)	1 (5)	1.400 (0.598)
2.1.4 Navigation	0 (0)	3 (15)	10 (50)	7 (35)	2.200 (0.696)
2.1.5 Location in the website	0 (0)	0 (0)	9 (45)	11 (55)	2.550 (0.510)
2.1.6 Color scheme	0 (0)	10 (50)	6 (30)	4 (20)	1.700 (0.801)
2.2 Consistency, n (%)					
2.2.1 Page layout	0 (0)	0 (0)	13 (65)	7 (35)	2.350 (0.489)
2.2.2 Navigation links	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)
2.2.3 Website structure	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)
2.3 Functionality, n (%)					
2.3.1 Search facility	0 (0)	7 (35)	13 (65)	0 (0)	1.650 (0.489)
2.3.2 Browsing facility	0 (0)	5 (25)	11 (55)	4 (20)	1.950 (0.686)
2.3.3 Cognitive overhead	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)
2.3.4 Navigation tools	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)
2.3.5 Third-party plug-ins	0 (0)	0 (0)	20 (100)	0 (0)	3.000 (0.000)
2.4 Engageability, n (%)					
2.4.1 Effective judgement	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)
2.4.2 Interactivity	0 (0)	3 (15)	17 (85)	0 (0)	1.850 (0.366)
2.4.3 Personalized experience	0 (0)	2 (10)	14 (70)	4 (20)	2.100 (0.553)
2.4.4 Integration of nontextual media	0 (0)	12 (60)	8 (40)	0 (0)	1.400 (0.503)
3.1 Currency, n (%)					
3.1.1 Recent events	0 (0)	3 (15)	17 (85)	0 (0)	1.850 (0.366)
3.1.2 Submit comments	0 (0)	14 (70)	6 (30)	0 (0)	1.600 (0.940)
3.1.3 Updated	1 (5)	1 (5)	1 (5)	17 (85)	2.700 (0.801)
3.2 Conflicts of interest, n (%)					
3.2.1 Who runs the website?	0 (0)	0 (0)	0 (0)	20 (100)	3.000 (0.000)
3.2.2 Pay for the website	0 (0)	2 (10)	18 (90)	0 (0)	1.900 (0.308)
3.2.3 Declaration of objectives	0 (0)	5 (25)	4 (20)	11 (55)	2.300 (0.865)
3.3 Content production, n (%)					
3.3.1 Content production method	0 (0)	1 (5)	19 (95)	0 (0)	1.950 (0.224)
3.3.2 Robust method	0 (0)	9 (45)	11 (55)	0 (0)	1.550 (0.510)
3.3.3 Original sources	0 (0)	0 (0)	20 (100)	0 (0)	2.000 (0.000)

Quality of Breast Cancer Papers

Value

The evaluation of the value of the papers was mainly based on seven questions. The questions were used to evaluate the treatment (or treatments) described in the publication. The overall rating of the value of the papers on breast cancer was low. The highest scores were for items on whether the description indicated that there may be more than one possible treatment choice (item 14) and on whether the paper supports shared decision making (item 15). The items with low scores included information about the risks of each treatment (item 11), what would happen without treatment (item 12), and how the treatment choices affect the overall quality of life (item 13). The specific results are shown in Table 3.

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Table 3. Descriptive statistics of the DISCERN items.

Item	Score=1, n (%)	Score=2, n (%)	Score=3, n (%)	Score=4, n (%)	Score=5, n (%)	Mean (SD)
#9. Does it describe how each treatment works?	16 (27)	20 (34)	14 (23)	8 (13)	2 (3)	2.333 (1.115)
#10. Does it describe the benefits of each treatment?	7 (11)	16 (27)	28 (47)	6 (10)	3 (5)	2.700 (0.979)
#11. Does it describe the risks of each treatment?	24 (40)	18 (30)	12(20)	4 (7)	2 (3)	2.033 (1.089)
#12. Does it describe what would happen if no treatment were used?	44 (73)	11 (18)	3 (5)	1 (2)	1 (2)	1.400 (0.807)
#13. Does it describe how the treatment choices affect overall quality of life?	25 (42)	16 (27)	12(20)	4 (6)	3 (5)	2.067 (1.163)
#14. Is it clear that there may be more than one possible treatment choice?	2 (3)	15 (25)	9 (15)	9 (15)	25 (42)	3.667 (1.336)
#15. Does it provide support for shared decision making?	3 (5)	14 (23)	14 (23)	13 (22)	16 (27)	3.417 (1.253)

Suitability

The suitability evaluation results of the papers are shown in Table 4. In this study, after evaluation, the highest SAM score was 42 points (100%). Of 60 papers, only 1 (1.67%) met the criteria for superior suitability, as established by SAM, 27 (45%) papers met the criteria for adequate suitability, and 32 (53.33%) papers were evaluated as not suitable material. The graphics (0.85/8 points), literacy demand (4.18/10 points), and layout and typography (2.53/6 points) scores were low, and the graphics score was the lowest. Three other aspects were also evaluated: content (3.82/6 points), cultural appropriateness (1.85/4 points), and learning stimulation (2.63/6 points).

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Table 4. Descriptive statistics of SAM[a] items.

Factor	Score=0[b]	Score=1[c]	Score=2[d]	Mean (SD)
Content, n (%)				
1) It is important that readers understand the purpose of the materials. If they do not, they may miss the main point.	4 (6)	28 (47)	28 (47)	1.400 (0.616)
2) Adult learners usually want to solve their problems rather than learn facts. The content of most interest and use is likely to be behavior information to help solve their problems.	1 (2)	57 (95)	2 (3)	1.017 (0.225)
3) Scope should be limited to the purpose/objectives of the material and to what can reasonably be learned in the time typically allocated to reading the information.	11 (18)	39 (65)	10 (17)	0.983 (0.596)
4) A summary offers readers a chance to see the key points in other words or examples. They are important; readers often miss the key points when they first read them.	36 (60)	23 (38)	1 (2)	0.417 (0.530)
Literacy demand, n (%)				
1) The text reading level is an important factor in whether your target group understands your document.	26 (43)	32 (54)	2 (3)	0.600 (0.558)
2) A conversational style and active voice lead to easy-to understand text. Simple sentences are used extensively.	3 (22)	46 (76)	1 (2)	0.800 (0.443)
3) It is best to use common, explicit words and avoid words that express general terms.	0 (0)	59 (98)	1 (2)	1.017 (0.129)
4) We learn new facts/behaviors more quickly when told the context first.	16 (27)	43 (71)	1 (2)	0.750 (0.474)
5) Headers or topic captions tell briefly what is coming up next. These “road signs” make the text look less formidable, and prepare the reader’s thought process to expect the next topic.	7 (12)	45 (75)	8 (13)	1.017 (0.504)
Graphics, n (%)				
1) Simple line drawings can promote realism without including distracting details. Visuals are accepted and remembered better when they portray what is familiar and easily recognized.	44 (73)	14 (24)	2 (3)	0.300 (0.530)
2) Non-essential details, such as room background, elaborate borders, and unneeded color, can distract the reader, whose eyes may be “captured” by these details. The illustrations should visually represent the key points.	44 (73)	12 (20)	4 (7)	0.333 (0.601)
3) Many readers do not understand the purpose of lists, charts, and graphs. Explanations and directions are essential.	55 (92)	2 (3)	3 (5)	0.133 (0.468)
4) Captions can quickly tell the reader what the graphic is all about and where to focus within the graphic. A graphic without a caption is usually an inferior instruction and a missed learning opportunity.	55 (92)	5 (8)	0 (0)	0.083 (0.279)
Layout and typography, n (%)				
1) Layout has a substantial influence on the suitability of materials.	23 (38)	34 (57)	3 (5)	0.667 (0.572)
2) Type size and fonts can make text easy or difficult for readers at all skill levels.	0 (0)	60 (100)	0 (0)	1.000 (0.000)
3) Few people can remember more than seven independent items. For adults with low literacy skills, the limit may be three- to five-item lists. Longer lists need to be broken into smaller chunks.	17 (28)	34 (57)	9 (15)	0.867 (0.650)
Learning stimulation and motivation, n (%)				
1) When a reader responds to an instruction, chemical changes take place in the brain that enhance retention in long-term memory. Readers should be asked to solve problems, to make choices, to demonstrate, etc.	36 (60)	19 (32)	5 (8)	0.483 (0.651)
2) People often learn more readily by observation, by doing something for themselves rather than by reading or being told, and when specific, familiar instances are used rather than the abstract or general.	8 (13)	36 (60)	16 (27)	1.133 (0.632)
3) People are more motivated to learn when they believe the tasks/behaviors are doable by them.	2 (3)	55 (92)	3 (5)	1.017 (0.291)
Cultural appropriateness, n (%)				
1) A valid measure of cultural appropriateness of material is how well its logic, language, and experience (inherent in the instruction) match the logic, language, and experience of the intended audience.	12 (20)	41 (68)	7 (12)	0.917 (0.561)

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Factor	Score=0[b]	Score=1[c]	Score=2[d]	Mean (SD)
2) To be accepted, an instruction must present cultural images and examples in realistic and positive ways.	6 (10)	52 (87)	2 (3)	0.933 (0.362)

[a]SAM: Suitability Assessment of Materials.

[b]Score 0: not suitable.

[c]Score 1: adequate.

[d]Score 2: superior.

Accuracy

For originality and for listing references, the scores were generally low. Of the 60 papers, 44 (73%) were unoriginal and 46 (77%) did not have a bibliography or resource list available. The top three items were "whether the paper contains errors or omissions", "whether the paper is misleading or biased," and "whether the paper is accurate." More than 97% (n=58) of the papers were correct in their content descriptions, with no errors, omissions, or misleading hints. The evaluation results are shown in Table 5.

Table 5. Descriptive statistics of the Michigan Checklist items.

Item	Score=–2, n (%)	Score=+2, n (%)	Score=–3, n (%)	Score=+3, n (%)
#18. Are sources cited or credited?	—[a]	—	44 (73)	16 (27)
#19. Is a bibliography or resource list available?	46 (77)	14 (23)	—	—
#20. Can you identify errors or significant omissions in information presented?	—	—	2 (3)	58 (97)
#21. Are opinions or misleading/biased information presented as fact?			1 (2)	59 (98)
#22. Does information presented as factual appear to be accurate to the best of your knowledge?	1 (2)	59 (98)	—	—
#23. Is there an identifiable conflict of interest?	14 (23)	46 (77)	—	—

[a]N/A: not applicable.

Discussion

Principal Findings

Generally, the quality of Chinese breast cancer websites is poor. The quality of the online papers on breast cancer is also poor. The quality of online information service platforms, which are an important medium for the dissemination of health information in the new media environment [34], affects the public's health decisions [35].

Similar to the results of previous research, this study found that the format (updated and who runs the website) of Chinese breast cancer websites is good [36], but the color scheme, text setting, function of user comment submission, and language design should be improved. For example, using colors to mark the title can make the paper clearer, but this setting is not effective for people with color cognitive impairment. Another similar issue is font size; rather than fancy colors, older users want to be able to read information with a larger font size and higher contrast than younger users. For user groups such as the elderly, special services and personalized layout options can be provided, which requires further thinking by health website owners. Another prominent problem is that the user comment submission function is poor. Pang's study [37] showed that health websites should provide functions for story sharing and memorials for women. These functions provide an outlet for women to share their feelings of grief and loss [37]. Therefore, website designers should focus on personalization and provide a comment section to allow users to submit comments and share experiences on specific content. In addition, China is a multiethnic country, and many ethnic groups have their own languages. Given that health websites are for users nationwide, almost all the websites in this study fail to support multiple languages, which greatly limits the effective dissemination of health information on the websites.

The quality of online breast cancer treatment information is poor. Online treatment information is of little value to users making breast cancer treatment decisions. Although the evaluation of the value of treatment options presents a "modest" result, the assessment of the benefits and risks of treatment is low, and online papers on breast cancer treatment tend to give compromised and biased advice. Although patients with breast cancer have a clear and urgent need for treatment information [38], the results of this study suggest that doctors are still the most valuable source of information for patients who want to know more about breast cancer treatment. Therefore, breast cancer website developers should provide easy-to-understand online health information that meets the needs of breast cancer patients and is useful for treatment.

Regarding the suitability of papers on breast cancer treatment, most of the papers have easy-to-understand titles that clearly describe the purpose of the papers. The layout and cultural appropriateness are also good. However, regarding the use of pictures, some papers use pictures with little relevance and that lack explanatory descriptions. Tables are rarely used, and table captions are lacking. Especially with regard to some professional medical knowledge, the lack of descriptions often makes it

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difficult for users to understand the desired health information on a deeper level. Another important problem we found was that many websites do not give proper explanations of medical terms, which increases the users' difficulty in reading and increases the level of literacy required to understand the text. Certainly, a few health websites in China have realized this problem, such as 39 Health Network™ [39], which provides hyperlinks to detailed explanations of medical terms to help users better understand the health information disseminated. However, most websites fail to do this. Therefore, to better enable users to understand the online health information they seek, health websites should cooperate with professional doctors, nurses, and health care providers, making full use of the professional advantages of medical personnel and providing effective guidance to internet users consuming the online health information.

Although the results of the manual evaluation of the accuracy of the papers by tumor surgeons indicated that the papers are not obviously wrong, biased, or misleading, most papers quoted others (44/60, 73%) and did not provide references or a resource list (46/60, 77%). We randomly selected eight papers and tried to search them using the Baidu search engine. The results showed that these eight papers exist on a large number of websites at the same time. For papers, indifference to copyright is an urgent problem in the dissemination of online health information in China that must be solved. Website operators should strengthen the copyright awareness of online information and regulate their own information publishing behavior. The problem of protecting the copyright of online health information may also be an important research topic in the future.

In addition, there are extensive recessive advertisements (the headline or image often contains attractive health-related information, but when you click the link, it turns out to be a page designed to sell products) on all the large health websites, and they are usually embedded in a page as a picture or video. We assessed the accuracy of health knowledge disseminated in several papers that contained recessive advertisements and found no significant errors. However, the existence of such recessive advertisements still leads users to have negative subjective feelings, reduces trust in the content of the papers, and may mislead users with regard to their health behaviors. Once misled by such information, users may choose less mature treatment methods, even leading to the delay of standard treatment [40]. In this regard, we are reminded of the Wei Zexi incident, which was a tragic case of a young man who died because he trusted false medical information on the internet and chose inappropriate treatment for a disease [41]. Although the *Technical Manual for the Generation and Dissemination of Health Science Information (Media Edition)* and *Recommendations for Public Recognition and Utilization of Online Health Information (2017 Edition)* were published in 2017, monitoring the reliability and accuracy of online health information remains an important task in China [42]. The Chinese government, however, needs to strengthen the monitoring of the quality of online health information to prevent such information from misleading the public with regard to diagnosis and treatment behavior.

Limitations

This study had some limitations. First, we chose influential websites as the research objects of this paper according to their traffic rankings and excluded some websites with low traffic, which caused selection bias. Second, although there are some assessment tools for the readability of written materials (eg, SMOG), to the best of our knowledge, there is no assessment tool for the readability of Chinese written materials. Therefore, an evaluation of the readability of written materials in this study was lacking. Third, video and animation are more important than textual information for users to understand health information. However, due to the lack of relevant evaluation tools, we could not evaluate the quality of these types of multimedia information. Finally, all evaluations were performed by researchers, and their perceptions may differ from those of users. Despite these limitations, the results of this study are still highly valuable for improving the quality of Chinese online health information about breast cancer.

Conclusion

In this study, we found that the quality of Chinese breast cancer websites is poor and that the quality of online health information is not ideal. Most websites can provide users with a convenient and easy-to-use breast cancer information retrieval platform, but the breast cancer–related health information they publish is of little value for users making decisions about breast cancer treatment. At the same time, there are also some problems, such as difficulty in tracing the source of information, a lack of copyright awareness, and a lack of advertising supervision. Therefore, developers should design health websites that meet the needs of breast cancer users [43]. Breast cancer users should choose trustworthy health websites that provide accurate information. The government should strengthen the standardized management of health websites to ensure that the health information published on the websites is accurate, up to date, and effective. In addition, the government should strengthen cooperation between websites and medical professional organizations, such as by establishing professional medical customer services and official WeChat accounts, to ensure that users can obtain effective guidance and suggestions from medical professionals when using online health information.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Searching and screening flow for breast cancer websites and papers.
[PNG File , 83 KB - cancer_v7i4e25783_app1.png]

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Abbreviations

BBMC: BengBu Medical College
HONcode: Health on the Net Foundation Code of Conduct
ICP: internet content provider

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SAM: Suitability Assessment of Materials
SMOG: Simplified Measure of Gobbledygook
SPSS: Statistical Package for Social Sciences
URL: Uniform Resource Locator

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Original Paper

The Effect of Foot Reflexology on Chemotherapy-Induced Nausea and Vomiting in Patients With Digestive or Lung Cancer: Randomized Controlled Trial

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Abstract

Background: Cancer is a chronic disease with an incidence of 24.5 million and 9.6 million deaths worldwide in 2017. Lung and colorectal cancer are the most common cancers for both sexes and, according to national and international recommendations, platinum-based chemotherapy is the reference adjuvant treatment. This chemotherapy can be moderately to highly emetogenic. Despite antiemetic therapy, chemotherapy-induced nausea and vomiting (CINV) may persist. Moreover, cancer patients are increasingly interested in alternative and complementary medicines and have expressed the desire that nonpharmacological treatments be used in hospitals. Among alternative and complementary medicines, foot reflexology significantly decreases the severity of CINV in patients with breast cancer.

Objective: The primary aim of this study was to assess the benefits of foot reflexology as a complement therapy to conventional treatments regarding the severity of acute CINV in patients with digestive or lung cancer. The secondary objectives assessed were the frequency and severity of delayed CINV, quality of life, anxiety, and self-esteem.

Methods: This study was conducted between April 2018 and April 2020 in the Hospices Civils de Lyon, France. This was an open-label randomized controlled trial. Participants were randomized into two groups: the intervention group (ie, conventional care with foot reflexology; n=40) and the control group (ie, conventional care without foot reflexology; n=40). Foot reflexology sessions (30 minutes each) were performed on outpatients or inpatients. Eligible participants were patients with lung or digestive cancer with an indication for platinum-based chemotherapy.

Results: The severity of acute nausea and vomiting was assessed with a visual analog scale during the second cycle of chemotherapy. A significant increase of at least 2 points was observed for the control group (7/34, 21%; *P*=.001). Across all cycles, the foot reflexology group showed a trend toward less frequent delayed nausea (*P*=.28), a significantly less frequent consumption of antiemetic drugs (*P*=.04), and no significant difference for vomiting (*P*=.99); there was a trend toward a perception of stronger severity for delayed nausea in the control group (*P*=.39). Regarding quality of life and anxiety, there was no significant difference between the intervention group and the control group (*P*=.32 and *P*=.53, respectively).

Conclusions: This study's results indicate that foot reflexology provides significantly better management of acute nausea severity and decreased consumption of antiemetic drugs in patients with lung or digestive cancer. In order to fulfill patients'

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desires to use nonpharmacological treatments and complementary and alternative medicines in hospitals, foot reflexology could be provided as a complementary intervention to conventional antiemetic drugs. Foot reflexology did not result in adverse effects. To assess the benefits of foot reflexology in routine practice, a larger study with several health care centers would be needed with a cluster randomized controlled trial.

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International Registered Report Identifier (IRRID): RR2-10.2196/17232

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KEYWORDS

cancer; randomized controlled trial; foot reflexology; nausea and vomiting; chemotherapy; complementary and alternative medicine

Introduction

According to estimates made by the Global Cancer Observatory, lung cancer was the most common cancer for both sexes in 2018 (11.6% of the total number of cancers), followed closely by breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%); the leading cause of cancer death was lung cancer (18.4% of total cancer deaths), followed by colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) [1]. Platinum-based chemotherapy is the adjuvant treatment for lung and digestive cancers according to national and international recommendations [2-7]. Cisplatin is a highly emetogenic chemotherapy (ie, the occurrence of chemotherapy-induced nausea and vomiting [CINV] >90%), while carboplatin and oxaliplatin are moderately emetogenic chemotherapies (ie, incidence of CINV ranges from 30% to 90%) [8]. CINV can either be acute (ie, occurring within 24 hours of receiving chemotherapy) or delayed (ie, occurring between 2 and 5 days following treatment) [8]. It is the side effect most feared by patients, decreasing their overall quality of life [9-12], and may lead to metabolic complications [13]. In addition, CINV can lead to dose reduction, postponement of treatment, and even discontinuation [14], which can decrease the effectiveness of treatment [15]. To prevent and control both acute and delayed CINV, antiemetic drugs are prescribed; the main ones used are 5-hydroxytrytamine 3 receptor antagonists, dexamethasone, and neurokinin-1 receptor antagonists [8,13]. While vomiting is well controlled, nausea remains a significant problem in practice [16]. In addition to the emetogenicity of the chemotherapy, various parameters may also lead to CINV, including risk factors (ie, age, sex, alcohol use, history of motion sickness, and history of pregnancy-related vomiting) [10], antiemetic treatment adherence [17], and the gap in perception of CINV between health professionals and patients [18,19].

To treat their cancer and the side effects of treatment, as well as to improve quality of life, patients with cancer are increasingly using complementary and alternative medicines (CAMs) [20,21]. According to a European survey reported by Molassiotis et al, 35.9% of patients with cancer use CAMs [21]. For various reasons, some patients do not inform the caregivers that they use CAMs [22,23]; however, certain CAMs may potentially interact with conventional cancer treatments [24,25]. According to the citizen science study reported by Tran et al, in France, patients with chronic disease, including cancer, have clearly expressed a desire for nonpharmacological treatments and CAMs to be used in hospitals to improve their care [26]. In parallel, oncologists lack information about the safety and efficacy of CAMs to inform their patients [27-29] and they request more rigorous evaluation [28,29]. Among the most frequently provided CAMs in private and public oncology centers in European countries [30], foot reflexology seems very interesting. Foot reflexology involves applying pressure to specific areas of the feet, which helps the body restore homeostasis. The premise is that reflex zones in the feet correspond to organs, glands, and systems of the body [31]. Foot reflexology used concomitantly with conventional treatment seems to decrease some side effects induced by chemotherapy; more specifically, this combination improves quality of life [32,33], significantly decreases pain intensity and anxiety in patients with metastatic cancer [34], and significantly improves the perceived pain and anxiety in postoperative patients with gastric cancer and hepatocellular cancer [35]. Moreover, a significant decrease in CINV has been observed in patients with breast cancer receiving chemotherapy and foot reflexology [36,37]. But these studies were conducted among women only, whereas female sex is a risk factor for CINV [38,39]. In addition, the design of these studies did not provide a high level of evidence, a point underlined by systematic reviews that conclude that there is a necessity to confirm these results by randomized controlled trials (RCTs) [40,41].

Our primary hypothesis is that foot reflexology performed in association with conventional care will improve the management of acute nausea. Thus, the aim of this RCT is to determine whether foot reflexology provides better control of CINV in patients with lung or digestive cancer who are receiving platinum-based chemotherapy.

Methods

Trial Design

The REFYO-R (Reflexology/Yoga–Reflexology trial) study is an open-label RCT, the protocol of which has been published elsewhere [42]. Briefly, the patients were randomized to either conventional care with foot reflexology or conventional care without foot reflexology at a ratio of 1:1. This report followed the CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments [43]. This study was approved by the regional ethics committee (Comité de Protection des Personnes Île de France X) on April 3, 2018 (ID No. RCB 2018-A00571-54). Regarding clinical research supported by the Hospices Civils de Lyon, processing of personal data complied with the methodological recommendations of the

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MR001 reference established by the French Data Protection Authority, Commission Nationale de l'Informatique et des Libertés (No. 18-071). Enrollment started in June 2018. This study was registered with ClinicalTrials.gov (NCT03508180) on June 28, 2018.

Participants

Participants were selected according to the following criteria:

1. Aged ≥18 years.
2. Had lung cancer (ie, non–small cell lung carcinomas, small cell lung cancer, squamous cell carcinoma, or mesothelioma lung cancer) or digestive cancer (ie, colorectal cancer, pancreatic cancer, or liver cancer) at stages IV, IIIB, IIIA, or II.
3. Patients on platinum-based chemotherapy with or without concomitant radiation therapy.
4. Had World Health Organization performance status of ≤2.
5. Patients affiliated with the national social security system or equivalent.
6. Patients able to complete the questionnaires (ie, comprehension of oral and written French language).
7. Gave written informed consent.

The exclusion criteria were (1) phlebitis, (2) vena cava syndrome, (2) weight loss of >5% in the 3 months before the inclusion date, (3) uncontrolled pain, (4) patients receiving morphine or morphine derivatives, (5) brain metastases, (6) patients receiving foot reflexology outside the study, and (7) patients under guardianship or curatorship, or having been deprived of his or her rights. Patients gave written informed consent before inclusion and randomization. Patients in the control group received two sessions of foot reflexology after completion of the study.

Settings

The study was conducted between April 25, 2018, and April 8, 2020, at the university hospitals of Lyon (Hospices Civils de Lyon, France).

Intervention

The patients randomized to the intervention group (n=40) received four sessions of foot reflexology (30 minutes each) during chemotherapy infusion every 2 or 3 weeks, according to the chemotherapy protocol. Three qualified reflexologists administered the sessions. The three reflexologists had same skills training approved by the French Federation of Reflexologists. The reflexology chart used in this clinical study is based on the one proposed by Eunice Ingham [31]. The intervention was standardized (Figure 1): to calm nausea and vomiting, the upper and lower digestive reflex points, as well as the metabolism of the smooth muscle reflex points (ie, lymphatic system, kidneys and bladder, lungs, thyroid, and parathyroid), were stimulated. To provide deep relaxation to target anxiety, the diencephalon reflex points, scapular belt reflex points, reflex points of the diaphragm, and reflex points of the spine were stimulated. After each stimulation of the reflex points, relaxation movements were performed [31].

During the first reflexology session, the reflexologist trained the patients in the foot reflexology group regarding the appropriate zones on the hands to relieve nausea. The reflexologist delivered to the patient a figure illustrating the palmar massage points (Figure 2).

All patients received standard antiemetic drugs (eg, 5-hydroxytryptamine 3 receptor antagonists, dexamethasone, and/or neurokinin-1 receptor antagonists) in accordance with guidelines [8,13].

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Figure 1. Reflex zones stimulated. L: left; R: right. (developed by C Rentler).

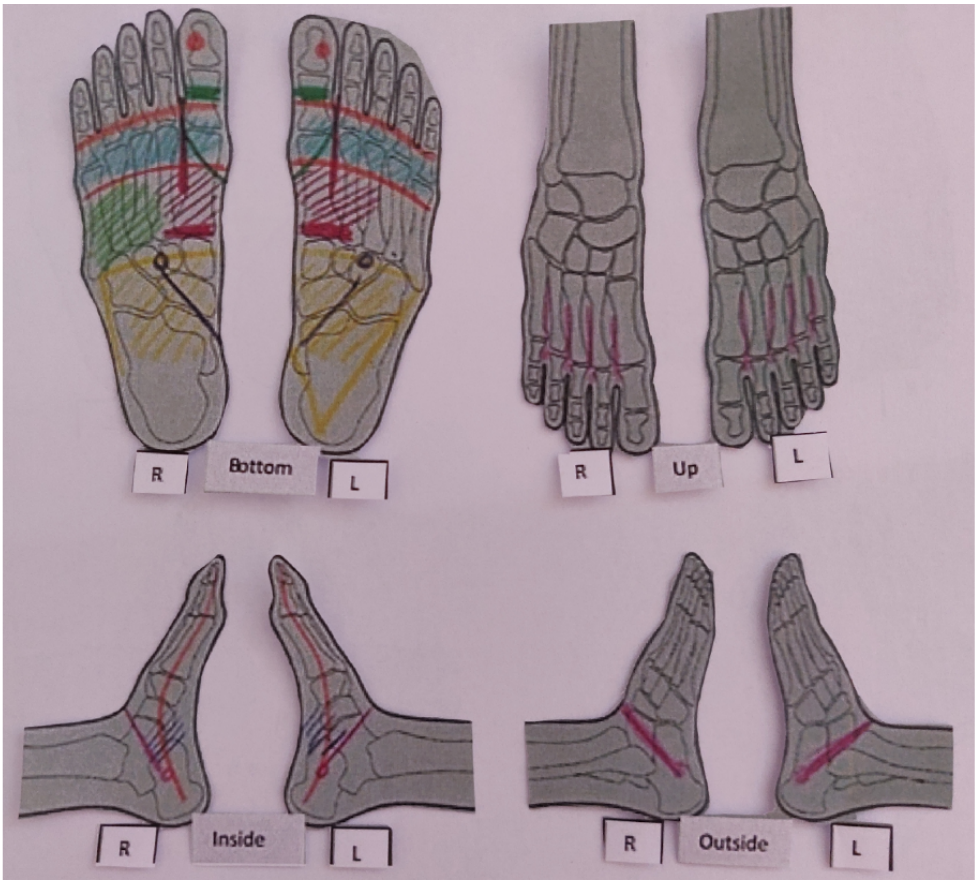
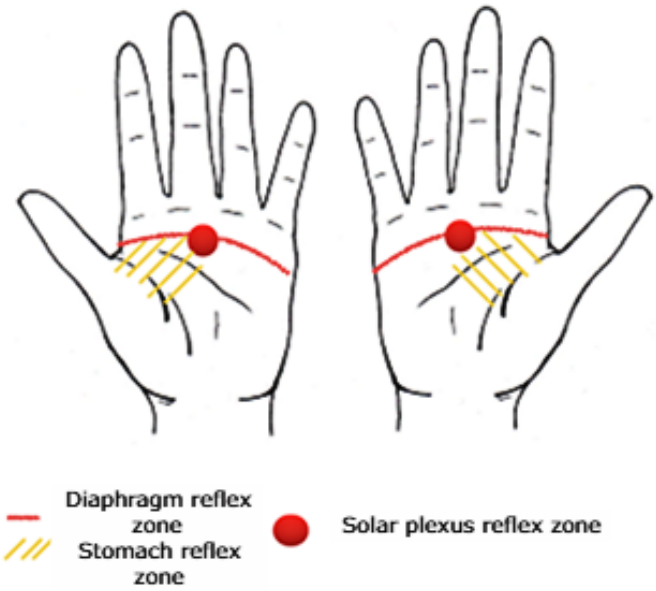


Figure 2. Self-massage diagram (developed by C Rentler).



Adverse Events

All adverse events were collected during this study and the causality with foot reflexology was assessed by the oncologist.

Outcome Measures

Primary Outcome

The primary outcome was the relative change in the severity of acute CINV, as assessed by a visual analog scale (VAS) during the second cycle of chemotherapy. The patient was asked to mark their current nausea level on the horizontal line, ranging from a happy face (minimum: no nausea = 0 mm) on the left to a very sick green face (maximum: paroxysm of nausea or vomiting = 100 mm) on the right. Unlike vomiting, which is measurable by the number of episodes per day, nausea is a subjective experience, the severity of which can be assessed using a VAS [44]. For those in the intervention group, this was measured before and after the foot reflexology session; for those

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in the control group, this was measured when the patient arrived at the outpatient or inpatient appointment and before leaving hospital.

Secondary Outcomes

The benefits of foot reflexology on delayed CINV were assessed using a diary completed every day by patients between the first and fourth cycle of chemotherapy. Every day, the patient assessed the frequency of nausea and vomiting, recording each emetic and nausea episode, and assessed the intensity of the worst nausea and vomiting episodes using a 6-point Likert scale with the following possible responses: 1 (“very low”), 2 (“low”), 3 (“moderate”), 4 (“severe”), 5 (“very severe”), and 6 (“unbearable”). Patients also recorded all rescue antiemetic medications, which were taken in addition to what was prescribed at baseline to prevent nausea and vomiting.

At baseline and at the end of the study period, the quality of life, anxiety, and self-esteem of participants were assessed. The score from the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30) [45] was used to assess health-related quality of life. This questionnaire includes five functional scales (ie, physical, daily activity, emotional, cognitive, and social), three symptomatic scales (ie, fatigue, nausea and vomiting, and pain), six unique items relating to certain symptoms or problems (ie, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), and two global scales of health status and quality of life.

The Hospital Anxiety and Depression Scale (HADS) score [46] was used to assess anxiety; this scale has been validated in French [47,48] and consists of 14 items, including seven items each for the anxiety subscale (HADS-A) and the depression subscale (HADS-D). As a self-rating scale, its scoring system ranged from the absence of symptoms (score of 0) to the maximal presentation of symptoms (score of 3).

To assess self-esteem, the Body Image Questionnaire (BIQ) [49-51] was used at the end of the study and was compared to the level of self-esteem assessed with the Rosenberg Self-Esteem Scale (RSES) administered at baseline [52]. The BIQ consists of 19 items on 5-point bipolar scales, which display antithetical terms. The RSES consists of 10 statements assessing a set of feelings about self-esteem and self-acceptance; each statement is rated on a 4-point Likert scale ranging from 1 (“totally disagree”) to 4 (“totally agree”).

Sample Size

In the study reported by Billhult et al [53], the mean relative improvement in CINV, as measured using a VAS, was 49.5% (SD 32.3%) in the placebo group and 73.5% (SD 32.2%) in the massage group. Assuming the same hypotheses, for a two-sided α risk of 5%, it was necessary to include 40 patients into each group to demonstrate a statistically significant difference between the two groups with a power of 90%.

Randomization

Randomization was stratified by the type of cancer (ie, digestive or lung) and the presence or absence of metastases, with permuted blocks and random block sizes. It was performed by the Interactive Web Response System (version 7.5.720.1; Ennov Inc). Participants were enrolled by physicians at the Lyon Sud Hospital Centre thoracic and hepato-gastroenterology departments. Participants were allocated to the intervention group (ie, with foot reflexology) or to the control group (ie, without foot reflexology) before starting their treatment. Clinical research assistants generated the random allocation sequence and assigned participants to the intervention.

Statistical Analysis

A detailed statistical analysis plan was written and validated before the data were unblinded. Initially, a linear model was considered to compare the variation in VAS points relative to acute nausea during the second cycle of chemotherapy between the two arms, adjusted by the type of cancer and by the presence or absence of metastases. Because of the low number of patients with nausea, we had to reconsider the statistical methods that were initially planned in the protocol to analyze the primary outcome. Instead of modeling the primary outcome, we compared the proportion of patients with an increase in VAS points of at least 2 between the two groups using the Fisher exact test. Statistical analyses of treatment effects were performed in the intention-to-treat (ITT) population for the primary endpoint, which included all randomized patients. Patients with missing acute nausea assessment during the second cycle of chemotherapy were considered as failure (VAS increase ≥2) in both treatment groups. Sensitivity analyses were performed by excluding patients without VAS assessments during the second cycle of chemotherapy (ie, per-protocol analysis). Other endpoints were analyzed on available data, without imputation of missing data (ie, patients lost to follow-up and questionnaires not completed or returned). Baseline clinical parameters were described using mean and SD or median and IQR for normally and nonnormally distributed continuous variables, respectively, and using frequency and percentage for categorical variables. Unless otherwise specified, categorical variables were compared between treatment groups using the Fisher exact test, and continuous variables were compared using the nonparametric Wilcoxon rank-sum test, with a two-sided *P* value of less than .05 being considered as statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc) in a Windows environment.

Results

A total of 80 patients were included and analyzed: 40 in the intervention group and 40 in the control group (Figure 3).

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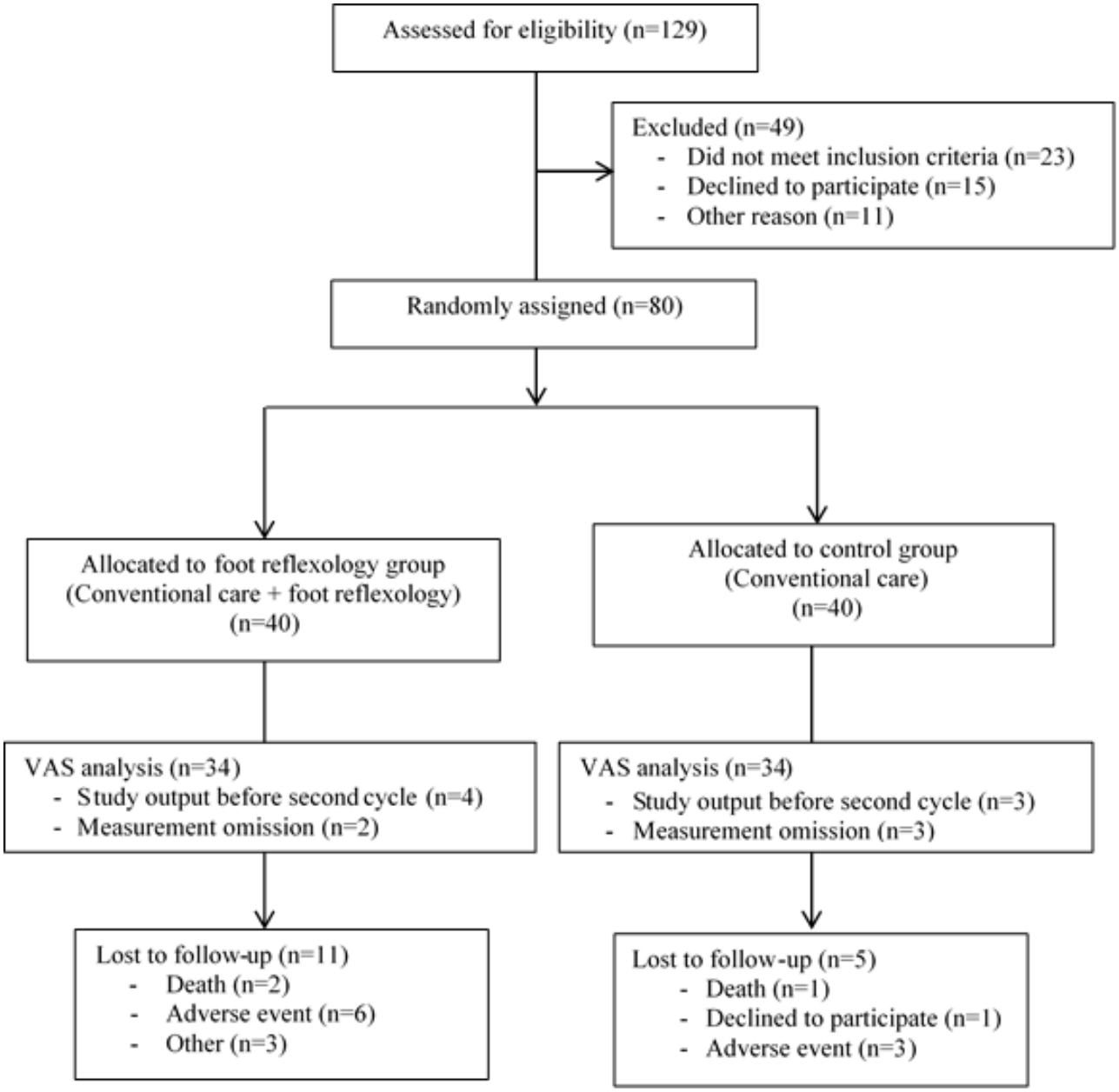
Figure 3. Modified CONSORT flow diagram for the individual randomized controlled trial REFYO-R of nonpharmacological treatment. REFYO-R: Reflexology/Yoga–Reflexology trial; VAS: visual analog scale.



Demographic and Clinical Characteristics

The majority of the participants in the foot reflexology and control groups were male. The mean age of the participants in the foot reflexology group was 63.4 (SD 11.5) years, and the mean age in the control group was 62.9 (SD 12.4) years. Most participants were diagnosed with lung cancer with metastasis and received moderately emetogenic chemotherapy (Table 1).

A total of 29 out of 40 (73%) participants in the foot reflexology group and 35 out of 40 (88%) participants in the control group received four cycles of chemotherapy (Table 2); 29 out of 40 (73%) patients in the foot reflexology group had their foot reflexology sessions at each cycle. The reasons for not performing the foot reflexology sessions were death, adverse events, and cancelled sessions owing to the COVID-19 pandemic.

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Table 1. Characteristics of the study population (N=80).

Characteristic	Foot reflexology group (n=40)	Control group (n=40)
Sex (female), n (%)	13 (33)	17 (42)
Age in years, mean (SD)	63.4 (11.5)	62.9 (12.4)
Smoking, n (%)	14 (35)	6 (15)
Diagnosis, n (%)		
Digestive cancer	16 (40)	17 (42)
Lung cancer	24 (60)	23 (57)
Metastasis, n (%)	24 (60)	23 (57)
Type of chemotherapy (emetogenic level), n (%)		
Carboplatin (MEC[a])	15 (37)	15 (37)
Oxaliplatin (MEC)	13 (32)	14 (35)
Cisplatin (HEC[b])	12 (30)	11 (27)

[a]MEC: moderately emetogenic chemotherapy.

[b]HEC: highly emetogenic chemotherapy.

Table 2. Chemotherapy cycles received by participants (N=80).

Number of cycles	Foot reflexology group (n=40), n (%)	Control group (n=40), n (%)	*P* value
1	3 (8)	3 (8)	.21
2	4 (10)	0 (0)	—[a]
3	4 (10)	2 (5)	—
4	29 (73)	35 (88)	—

[a]The *P* value for the entire group comparison is reported only in the top row.

Efficacy Regarding CINV

Most participants in the foot reflexology (28/34, 82%) and control (32/34, 94%) groups had no nausea at the start of the second chemotherapy cycle. In the ITT analysis, where we considered all patients with missing assessments as having an increase of at least 2 VAS points, 6 out of 40 (15%) patients had an increase of at least 2 VAS points in the foot reflexology group compared with 13 out of 40 (33%) in the control group (*P*=.20). In the per-protocol analysis, there were significantly more patients with an increase of at least 2 VAS points among the control group (7/34, 21%; *P*=.001; Table 3).

A total of 22 out of 40 (55%) participants in the foot reflexology group and 29 out of 40 (73%) participants in the control group completed their daily diaries after at least one cycle. Regardless of the group, we observed that the incidence of delayed nausea was lower than delayed vomiting (Table 4). Across all cycles, there was a trend toward less frequent delayed nausea in the foot reflexology group (*P*=.28), a significantly less frequent consumption of antiemetic drugs (*P*=.04), and no significant difference in vomiting (*P*=.99; Table 4). There was a trend toward a perception of stronger severity for delayed nausea in the control group (*P*=.39; Table 5). Among 21 patients in the foot reflexology group who completed daily diaries and who answered the question (ie, “If you practiced self-massage, was it effective?”), 6 (29%) practiced self-massage and all considered it to be effective to decrease delayed nausea.

Table 3. Acute nausea during the second cycle of chemotherapy, as measured by the visual analog scale (VAS).

Measure	Foot reflexology group (n=34), n (%)	Control group (n=34), n (%)	*P* value
VAS1[a] score >0	6 (18)	2 (6)	—[b]
VAS2[c] score >0	4 (12)	8 (24)	—
VAS score increase ≥2	0 (0)	7 (21)	.001

[a]VAS1 is the VAS administered before the foot reflexology session for the intervention group and when the patient arrived at the outpatient or inpatient appointment for the control group.

[b]The *P* value concerns only the variation of the VAS score between VAS1 and VAS2 if ≥2.

[c]VAS2 is the VAS administered after the foot reflexology session for the intervention group and before leaving the hospital for the control group.

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Table 4. Delayed nausea, delayed vomiting, and antiemetic drug use.

Outcome	Cycle 2, n (%)		Cycle 3, n (%)		Cycle 4, n (%)		End of study, n (%)		*P* value
	FR[a] group (n=22)	Control group (n=29)	FR group (n=21)	Control group (n=28)	FR group (n=20)	Control group (n=26)	FR group (n=20)	Control group (n=25)	
Delayed nausea	11 (50)	18 (62)	9 (43)	17 (61)	7 (35)	15 (58)	7 (35)	12 (48)	.28
Delayed vomiting	5 (23)	5 (17)	3 (14)	5 (18)	4 (20)	4 (15)	4 (20)	4 (16)	.99
Antiemetic drug use	5 (23)	12 (41)	2 (10)	11 (39)	3 (15)	10 (38)	2 (10)	7 (28)	.04

[a]FR: foot reflexology.

Table 5. Severity of delayed nausea between cycles of chemotherapy.

Severity	Cycle 2, n (%)		Cycle 3, n (%)		Cycle 4, n (%)		End of study, n (%)		*P* value
	FR[a] group (n=9)	Control group (n=16)	FR group (n=9)	Control group (n=17)	FR group (n=7)	Control group (n=14)	FR group (n=7)	Control group (n=12)	
Very low to moderate	7 (78)	11 (69)	8 (89)	12 (71)	6 (86)	11 (79)	6 (86)	8 (67)	.39
Severe to unbearable	2 (22)	5 (31)	1 (11)	5 (29)	1 (14)	3 (21)	1 (14)	4 (33)	—[b]

[a]FR: foot reflexology.

[b]The *P* value for the entire group comparison is reported only in the top row.

Efficacy Regarding Quality of Life and Anxiety

There was no significant difference in terms of quality of life (*P*=.32) or anxiety (*P*=.53) between the intervention and the control groups (Table 6).

Table 6. Quality of life (EORTC QLQ-C30) and anxiety (HADS) of the participants.

Measure	Baseline		End of study		*P* value
	Foot reflexology group (n=40)	Control group (n=40)	Foot reflexology group (n=40)	Control group (n=40)	
EORTC-QLQ-C30[a]					
Participants, n (%)	36 (90)	36 (90)	27 (68)	33 (83)	—[b]
Score, mean (SD)	63.3 (14.6)	55.9 (11.4)	61.7 (15.4)	58.2 (12.4)	.32
HADS[c]					
Participants, n (%)	36 (90)	35 (88)	26 (65)	34 (85)	—
Score, mean (SD)	8.1 (3.4)	6.6 (3.5)	6.2 (2.5)	5.6 (3.85)	.53

[a]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30.

[b]*P* values were only calculated for score comparisons.

[c]HADS: Hospital Anxiety and Depression Scale.

Efficacy Regarding Self-esteem

At baseline, all patients reported having good self-esteem (RSES score >31); the median RSES score was 35 (IQR 32-38) for the control group among the 35 patients with assessment, and 33 (IQR 30-36.5) for the foot reflexology group among the 35 patients with assessment. At the end of the study, the average of BIQ score was 67.12 (SD 11.10) for the control group (25/40, 63%) and 59.76 (SD 10.15) for the foot reflexology group (17/40, 43%). After adjustment based on the initial RSES score and with a comparable RSES score, the average BIQ score decreased by 6.1 (95% CI –13.4 to –1.2) for the foot reflexology group compared to the control group (*P*=.10).

Adverse Events

Adverse events were experienced by 12 participants: 7 (58%) participants in the foot reflexology group and 5 (42%) participants in the control group. Dyspnea, tinnitus, and leg-vein thrombosis were experienced by participants in the foot reflexology group only. Sepsis, neutropenia, and pulmonary embolism were experienced by participants in the control group only. Renal failure and radiation esophagitis were experienced by participants in both groups. None of the adverse events were attributed to foot reflexology, according to the physicians.

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Discussion

Principal Findings

The main objective of this study was to assess the benefits of foot reflexology in acute CINV. More than half of the participants were men with metastatic lung cancer, with an average age of 63 years, who received moderately emetogenic chemotherapy. These results, which included both male and female patients, showed that foot reflexology significantly decreased acute nausea in patients with lung or digestive cancer who were receiving chemotherapy. These results confirm those of previous studies that included only female patients and that provided only a low level of evidence [36,37].

Among the secondary objectives, we assessed the benefits of foot reflexology in terms of the frequency of delayed CINV, because no study published to date has assessed this outcome. Regarding the frequency of delayed vomiting, foot reflexology did not show any benefit. Regarding the frequency of delayed nausea, we observed that patients in the foot reflexology group tended to have less delayed nausea. We can assume that the benefits of foot reflexology observed in acute nausea contributed to better control of delayed nausea, resulting in a decrease in its severity; in fact, Schnell [54] has shown that effective prevention and control of acute CINV significantly reduced the risk of delayed symptoms in the same cycle. We also assessed the perception of the severity of delayed CINV, because taking into account the subjective points of view of patients contributes to the improvement of the management of treatment toxicities [55]. Regarding the perception of the severity of delayed CINV, patients in the control and foot reflexology groups reported it as more severe than in Morin et al's survey [19]. One of the objectives of this survey was to assess the differences in perception of the incidence and impact of CINV and radiotherapy-induced vomiting between health care professionals and patients. In that study [19], 12% of the patients reported that their delayed CINV was severe. The difference with the results in this study may be explained by the fact that Morin et al's survey included patients with cancer who had chemotherapy in the last 24 months, which may have led to memory bias; furthermore, that survey did not indicate the type of chemotherapy patients received. Regarding the perception of the severity of delayed nausea in this study in particular, patients in the foot reflexology group expressed lower severity with a decreasing trend between the first and fourth chemotherapy treatment. Lastly, although vomiting is better controlled, delayed nausea remains a significant problem in practice [16]. Several factors contribute to the suboptimal management of delayed nausea, such as health care professionals' underestimation of their severity and nonadherence to antiemetic regimens [16]; patients reported nonadherence, particularly because they were already taking several pills, and they reported that CINV was accepted as an inevitable side effect of treatment [19]. However, nausea has a negative impact on patients' quality of life [12]. This is why the foot reflexology group was taught self-massage to relieve their CINV in a nonmedicinal way, if they desired. The 29% of patients who practiced self-massage all reported that it was effective. Moreover, we observed in the foot reflexology group that the consumption of antiemetic drugs between each cycle was significantly lower. In consideration of these results, we can suggest that self-massage seems to be a promising complementary care treatment to standard antiemetic treatment to improve the management of delayed nausea. We could also consider involving family caregivers. In fact, Stephenson et al [34] have shown that foot reflexology practiced by family caregivers significantly reduced pain and anxiety in patients with metastases, while promoting social connections.

Overall, irrespective of the group, we observed that the occurrence of acute and delayed nausea was more frequent than vomiting, as has also been reported in previous studies [9,10,18,19,56,57]. Nevertheless, the results of this study demonstrated that acute nausea was lower than in those studies. Among risk factors, sex of participants is a predictive value in the development of CINV [10], and we observed a high representation of males in our study. On another note, since previous studies were conducted before 2016, we can assume that new antiemetic drugs, specifically the fixed-combination drug netupitant/palonosetron (NEPA) and rolapitant, which were marketed after 2017, are more effective for acute nausea [8,13].

In France, an update of the AFSOS (Association Francophone des Soins Oncologiques de Support) standard for nausea and vomiting induced by cancer treatments was also made in 2018 [13]. According to these guidelines, acupuncture and the treatment of anxiety with psychotropic drugs in association with, or alternatively to, nondrug practices (meditation, relaxation, hypnosis, etc) and cannabinoids, in addition to conventional antiemetic drug prophylaxis, may also prove effective but are in need of further investigation [8,13]. The results of this study may suggest that foot reflexology could be added to these guidelines in the future.

In contrast, foot reflexology did not have a significant effect on quality of life and anxiety, unlike findings reported in previous studies [32-35]. However, three of those previous studies [32,34,35] were conducted using pre- and postinterventions and suggested that the efficacy of foot reflexology had short-term effects. Furthermore, the Sharp et al study [33] demonstrated a significant effect on quality of life in patients with breast cancer. Patients received a single 1-hour session weekly for 8 weeks. We can, thus, suggest that the number of sessions was insufficient to demonstrate a benefit in terms of quality of life in this study. Even if no significant effect on anxiety was found, we observed a decrease in the anxiety score in both groups between baseline and the end of the study. This may be due to the effectiveness of the psychological support that was offered to all patients, as the Sharp et al study highlighted [33]. Finally, we can also question whether the HADS was the most appropriate scale to use. In fact, a recent study has underlined that the HADS is quicker in terms of administration and scoring when using in oncology settings than the two gold-standard tools (ie, the STAI-S [State-Trait Anxiety Inventory–State] and the CES-D [Center for Epidemiological Studies–Depression]) that were employed but presents more false positives [58].

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Limitations

This study had some limitations. First, patient recruitment was only done at one cancer center, so the results are not representative of the general population; a larger study would ensure that the results are generalizable. Second, the number of subjects necessary to assess the primary endpoint was not reached because few patients had acute nausea at cycle 2; however, the benefits of reflexology were demonstrated, as the results were significant. Moreover, few patients completed the BIQ, questions of which were not cancer specific and may not have been adapted to patients with cancer; semistructured interviews seem more appropriate to assess these outcomes. Lastly, some patients did not complete their daily diary. To best assess delayed nausea, we should consider calling the patient within 5 days of hospital discharge after each cycle.

Conclusions

In conclusion, according to the results of this study, foot reflexology significantly decreased acute nausea with significantly less consumption of antiemetic drugs between each cycle among patients with lung or digestive cancer. We also observed a lower occurrence of delayed nausea in the reflexology group. Therefore, foot reflexology seems to be a promising and innovative complementary treatment to conventional antiemetic drugs. To assess the performance of this intervention in routine practice, a larger study with several health care centers would be relevant with a cluster RCT. We also plan to investigate the relationship between nausea and vomiting and foot reflexology at the cerebral level using functional magnetic resonance imaging.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
2017 CONSORT checklist of information to include when reporting a randomized trial assessing nonpharmacologic treatments (NPTs) - REFYO-R.
[PDF File (Adobe PDF File), 730 KB - cancer_v7i4e25648_app1.pdf]

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Abbreviations

AFSOS: Association Francophone des Soins Oncologiques de Support
APICIL: Association de Prévoyance Interprofessionnelle des Cadres et Ingénieurs de la région Lyonnaise
BIQ: Body Image Questionnaire
CAM: complementary and alternative medicine
CES-D: Center for Epidemiological Studies–Depression
CINV: chemotherapy-induced nausea and vomiting
DRCI: Direction de la Recherche Clinique et de l'Innovation
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30
HADS: Hospital Anxiety and Depression Scale
HADS-A: Hospital Anxiety and Depression Scale–Anxiety
HADS-D: Hospital Anxiety and Depression Scale–Depression
ITT: intention-to-treat
NEPA: netupitant/palonosetron
RCT: randomized controlled trial
REFYO-R: Reflexology/Yoga–Reflexology trial
RSES: Rosenberg Self-Esteem Scale
STAI-S: State-Trait Anxiety Inventory–State
VAS: visual analog scale

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Corrigenda and Addenda

Correction: Examining the Interaction Between Medical Information Seeking Online and Understanding: Exploratory Study

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Related Article:

Correction of: https://cancer.jmir.org/2019/2/e13240/

(JMIR Cancer 2021;7(4):e35222) doi:10.2196/35222

In "Examining the Interaction Between Medical Information Seeking Online and Understanding: Exploratory Study" (JMIR Cancer 2019;5(2):e13240) the authors noted one error.

In the originally published manuscript, the following sentence appeared under the "Understanding Relevant Medical Information" and "Ratings of the Explanations by Medical Professionals" section:

> *To assess the reliability of the rating, the inter-rater reliability, Cronbach alpha, which is frequently utilized in computing internal consistency [29], was calculated.*

This sentence has been corrected to:

> *To assess the reliability of the rating, the inter-rater reliability, ICC(3,k), which is frequently utilized in computing internal consistency [29], was calculated.*

The correction will appear in the online version of the paper on the JMIR Publications website on December 2, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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