Mapping Systematic Reviews of Breast Cancer Survivorship Interventions: A Network Analysis

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abstract

PURPOSE Despite a large volume of research, breast cancer survivors continue to experience high levels of unmet need. To better understand the breadth of evidence, we mapped systematic review-level evidence across cancer survivorship domains and outcomes and conducted network analyses of breast cancer survivorship care interventions.

METHODS Umbrella review methodology was used to identify published systematic reviews reporting on survivorship care interventions for breast cancer survivors. Included reviews were mapped against domains and health care outcomes as specified by the Cancer Survivorship Quality Framework, and network analyses were conducted to determine the extent of clustering of reviews, and connectivity across domains and outcomes.

RESULTS Of 323 included reviews, most focused on management of physical (71.5%) or psychologic (65.3%) effects, health-related quality of life (55.1%), and physical activity (45.2%). Few focused on financial/employment effects, chronic conditions, health care delivery domains, or health service use or cost outcomes. Network analysis indicated 38.6% of reviews were connected to a single domain, 35.0% to two domains, and 16.5% to three domains, indicating a relatively siloed nature of research, with greater community clustering between health care delivery domains but limited connection between these and the other domains. Reviews published between 2011 and 2021 were more likely to examine financial toxicity and chronic conditions, but these domains remained under-represented compared with physical and psychologic effects.

CONCLUSION Despite vast volume of breast cancer survivorship intervention research, systematic review-level research is unevenly distributed, siloed, and with significant gaps in key domains and outcomes. Assessment of evidence gaps in primary research and strategic planning of future research, in consultation with survivors, is needed.

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INTRODUCTION Breast cancer is the most common type of cancer globally,1 and one most frequently researched.2 However, despite the large volume of evidence, breast cancer survivors continue to experience high levels of unmet needs,3-5 highlighting a gap between research and improvement of outcomes, either because of interventions not addressing relevant needs or not being translated into practice.6 Survivorship interventions in prostate and colorectal cancers have been systematically reviewed against survivorship care guidelines, and have identified gaps and priorities for future research.7,8 No such review has been conducted for breast cancer.

The large volume of research in breast cancer survivorship poses a challenge to data synthesis. The analysis needs to capture both the breadth and diversity of evidence across different interventions and outcomes, and to provide insights regarding connections between them and any gaps that may explain the evidence-translation gap. This study combined two approaches: mapping the existing systematic review-level evidence against the Quality of Cancer Survivorship Care Framework9 and network analysis.10 In combining these two approaches, the study aimed to (1) examine the evidence in a systematic way that aligns with best practice survivorship care, (2) assess distribution of and gaps in evidence, and (3) examine connections/overlap between domains and between outcomes.

METHODS We undertook a systematic search of MEDLINE, Embase, CINAHL, PsycInfo, Scopus, and Cochrane Database of Systematic Reviews, from database inception to April 2021, using text words and subject
CONTEXT

Key Objective
As cancer survivorship research grows, it is important to understand where evidence exists and gaps remain. This study mapped 323 systematic reviews of breast cancer survivorship interventions across domains and outcomes as specified by the Quality of Cancer Survivorship Care Framework. We also conducted a network analysis analyzing distribution and connectivity between domains.

Knowledge Generated
The distribution of domains and outcomes was uneven with the majority of reviews focusing on management of physical and/or psychologic effects and quality-of-life outcomes. Fewer addressed management of financial/employment effects and chronic conditions, or cost and health service outcomes. We observed a modest level of connectivity across domains and outcomes.

Relevance
This mapping and network analysis of a large volume of evidence allowed identification of areas that are well represented to inform translation into clinical practice. Moreover, it informs future research planning in areas that are under-represented or siloed.

Network Analysis
Network analysis allows for the quantification of the strength of connection between domains and outcomes, thus providing insights into the relationships between evidence.10 We created two bipartite networks with network nodes represented by the domains and papers (network 1) and outcomes and papers (network 2), as mapped against the framework. For each network, we generated a network graph representing the nodes and the papers attributed to each node. We assessed network connectivity by calculating the degree distribution of each node (ie, number of other nodes that each node connected to). We also determined the number of communities (subset of nodes within the graph such that connections between the nodes in each community are denser than connections with the rest of the network) in each network and the resulting modularity of the network (extent to which the network is

framework includes five domains of cancer survivorship care, four contextual domains, and specifies four health care outcomes. The framework components are derived on the basis of principles of survivorship care dating back to the Institute of Medicine report in 2005,13 making it a relevant tool for systematic mapping of survivorship evidence. Reviews of interventions mapped within the surveillance and management of psychosocial effects domain of survivorship care were classified as addressing the psychologic, employment/financial, and/or interpersonal subdomains of psychosocial survivorship care. Where reviews examined outcomes pertaining to more than one domain of survivorship care, the review paper was categorized under all relevant domains and outcomes. Categories of interventions included physical activity; pharmacologic, complementary, and alternative medicine, psychotherapeutic or counseling; and telehealth/digital health interventions. Data synthesis specified the number of systematic reviews/meta-analyses examining identified intervention types within each and across all domain(s), and the number of reviews/meta-analyses examining each outcome within each and across all domain(s). We also extracted the number of studies in each review, number of breast cancer survivors (if specified), year of publication, and country of origin. Degree of overlap between primary studies was not assessed.

Network Analysis
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TABLE 1. The Quality of Cancer Survivorship Care Framework

| Domains of cancer survivorship care pertaining to cancer and its treatment |
| Prevention and surveillance for recurrence and new cancers |
| Surveillance and management of physical effects |
| Surveillance and management of psychosocial effects |
| Psychologic |
| Interpersonal |
| Financial/employment |

| Domains of cancer survivorship care pertaining to general health care |
| Surveillance and management of chronic medical conditions |
| Health promotion and disease prevention |

| Contextual domains of health care delivery |
| Clinical structure |
| Communication/decision making |
| Care coordination |
| Patient/caregiver experience |

Health care outcomes |
| Health-related quality of life/function |
| Health care utilization (emergency services and hospitalisations/critical care) |
| Costs of care (to survivor and health care system) |
| Mortality (all-cause and cancer-specific) |

Divided into different communities. To assess changes in the focus and volume of survivorship research over time, we undertook additional network analyses across two separate time periods: 1997-2010 and 2011-2021.

All network analyses were performed using Python (version 3.8.8). The network graphs were generated using the NetworkX library (version 2.5). We used Clauset-Newman-Moore greedy modularity maximization from within the network.algorithms.community API library in Python to determine the network communities. The information on the modularity and degree of the nodes were also extracted from the NetworkX objects.

RESULTS

After removal of duplicates, 7,282 individual records were screened, which resulted in 323 included systematic reviews, 176 (54.5%) of which reported meta-analyses (Fig 1 and Data Supplement). The reviews were published from 1997 to 2021: one (0.3%) before 2000, 29 (9.0%) from 2000 to 2009, 226 (70.0%) from 2010 to 2019, and 67 (20.7%) from 2020 onward. The reviews reported on data ranging from two to 610 primary studies (median 13), with 51 reviews reporting on mixed populations with breast cancer survivor data analyzed and presented separately and included between 56 and 16,002 breast cancer survivors as participants (median, 1,067). The majority of reviews originated from China and the United States (n = 58; 18.0% and n = 56, 17.3%, respectively), as well as the United Kingdom (n = 27; 8.4%); 229 (70.9%) originated from countries with high-income economies.14

Framework Mapping

The results of mapping of evidence against the domains and outcomes of the framework and intervention types are summarized in Table 2 and the Data Supplement. The most represented domains included surveillance and management of physical effects (n = 231; 71.5%) and surveillance and management of psychosocial effects (n = 212; 65.6%), particularly psychologic (n = 211; 65.3%). The most common intervention type was physical activity (n = 146; 45.2%) followed by psychologic/psychosocial interventions (n = 67; 20.7%). A total of 200 reviews (61.9%) examined at least one health care outcome, predominantly health-related quality of life/function (n = 178; 55.1%). Few reviews mapped against surveillance and management of chronic health care conditions (n = 7; 2.1%) and surveillance and management of financial/employment effects domains (n = 6; 1.9%), or cost of care (n = 8; 2.5%) and hospitalization/use of emergency services outcomes (n = 5; 1.5%).

Network Analysis

Figure 2 shows the bipartite network graph for the 11 domains and 323 reviews. The degree of the nodes, which shows the connectedness of the domains and reviews, ranged from 1 to 231; surveillance and management of physical effects was the largest hub, with connections to 231 reviews. The highest number of connections between domains (ie, the number of reviews connecting to both domains) was observed between surveillance and management of physical effects, and surveillance and management of psychologic effects (151 connecting reviews). Of the 323 reviews, 129 (39.9%) had degree 1, indicating connection to one domain, 117 (36.2%) had degree 2, indicating connection to two domains, and 55 (17.0%) had degree 3, indicating connection to three domains; thus, 93.1% of the reviews were connected to one to three domains (for details regarding node degree and degree distribution of each reported network, see the Data Supplement.)

The community cluster algorithm identified five separate communities, with a modularity of 0.341 demonstrating a considerable level of clustering. We found larger communities composed of (1) the physical effects domain alone (n = 111 reviews), (2) the psychologic and interpersonal effects domains (n = 96 reviews), and (3) health promotion and chronic conditions domains (n = 77 reviews). The smaller domains (prevention and surveillance of recurrence and new cancers, communication and decision making, clinical structure, patient/caregiver experience, and care coordination) clustered together as a single community (n = 34 reviews), and many of the papers within this community were connected to more than one of the other domains within this community (Data Supplement). The financial/employment effects domain formed a community consisting of five reviews, all of which were connected to at least one other domain.

Figure 3 shows the bipartite network graph for the four health care outcomes across the 200 reviews examining these outcomes. The degree of nodes ranged from 1 to
178; health-related quality of life/function was the largest hub, with connections to 178 papers. Of the 200 reviews, 174 (87.0%) had degree 1, 22 (11.0%) had degree 2, and 3 (1.5%) had degree 3, thus, 99.5% of the reviews examining these outcomes were connected to one to three outcomes.

The community cluster algorithm identified three separate communities: (1) health-related quality of life/function (n = 153 reviews), (2) mortality (n = 35 reviews), and (3) emergency services/hospitalizations/cost (n = 12 reviews), with a modularity of 0.311 demonstrating a considerable level of clustering. The emergency services/hospitalizations/cost community consisted of the two least represented outcomes, and reviews in this community showed a high degree of connection with outcomes in other communities.

Figures 4A and 4B depict the bipartite network graphs for domains across the two time periods: 1997-2010 and 2011-2021, respectively, with 38 (12%) reviews in the earlier and 285 (88%) in the later period. For both periods, largest hubs were surveillance and management of physical effects (n = 27 reviews; n = 204 reviews, respectively) and surveillance and management of psychologic effects (n = 27 reviews; n = 184 reviews, respectively), with the highest number of connections observed between these two domains.

For both periods, the community cluster algorithm identified five separate communities, with modularity of 0.351 and 0.340, respectively, indicating a considerable level of clustering. For both periods, the larger communities were composed of (1) the physical effects (n = 13 and n = 99 reviews) and (2) the psychologic and interpersonal effects (n = 11 and n = 86 reviews) domains. For 1997-2010, the third largest community consisted of the health promotion domain (n = 9 reviews), whereas for 2011-2021, this community consisted of health promotion and chronic conditions domains (n = 68 reviews).

Figures 4C and 4D show the bipartite network graph for health care outcomes across the two time periods. For 1997-2010, two outcomes were represented across 27 (71.1%) reviews, whereas for 2011-2021, four outcomes were represented across 173 (60.7%) reviews. For both time periods, health-related quality of life/function was the dominant outcome (n = 19 and 159 reviews, respectively),
| Individual level | Domain/Subdomain | Physical effects | Psychosocial effects | Psychosocial effects: psychologic | Psychosocial effects: interpersonal | Psychosocial effects: financial/employment | Health promotion | Recurrence and new cancers | Chronic conditions | Context level | Total |
|------------------|------------------|------------------|---------------------|-------------------------------|-----------------------------------|-----------------------------------|-----------------|--------------------------|----------------|-------------|-------|
| Domain/Subdomain | Representation, No. of Reviews (%) | PA | Psychosocial | CAMs | Pharmacologic | Physiotherapy | Digital/ Telehealth | Other* | HRQoL | Mortality | Hospitalizations | Cost |
| Physical effects | 231 (71.5) | 105 (32.5) | 34 (10.5) | 53 (16.4) | 33 (10.2) | 26 (8.0) | 11 (3.4) | 25 (7.7) | 145 (44.9) | 24 (7.4) | 5 (1.5) | 7 (2.2) |
| Psychosocial effects | 212 (65.6) | 101 (31.3) | 64 (19.8) | 36 (11.1) | 12 (3.7) | 4 (1.2) | 13 (4.0) | 27 (8.4) | 152 (47.1) | 18 (5.6) | 4 (1.2) | 6 (1.9) |
| Psychosocial effects: psychologic | 211 (65.3) | 101 (31.3) | 64 (19.8) | 35 (10.8) | 12 (3.7) | 4 (1.2) | 13 (4.0) | 27 (8.4) | 151 (46.7) | 18 (5.6) | 4 (1.2) | 6 (1.9) |
| Psychosocial effects: interpersonal | 17 (5.3) | 5 (1.5) | 7 (2.2) | 1 (0.3) | 3 (0.9) | 1 (0.3) | 3 (0.9) | 4 (1.2) | 11 (3.4) | 1 (0.3) | 0 (0) | 1 (0.3) |
| Psychosocial effects: financial/employment | 6 (1.9) | 4 (1.2) | 3 (0.9) | 1 (0.3) | 0 (0) | 0 (0) | 1 (0.3) | 1 (0.3) | 5 (1.5) | 0 (0) | 0 (0) | 0 (0) |
| Health promotion | 87 (26.9) | 72 (22.3) | 6 (1.9) | 3 (0.9) | 1 (0.3) | 0 (0) | 8 (2.5) | 10 (3.1) | 51 (15.8) | 10 (3.1) | 3 (0.9) | 4 (1.2) |
| Recurrence and new cancers | 18 (5.6) | 1 (0.3) | 0 (0) | 1 (0.3) | 2 (0.6) | 0 (0) | 2 (0.6) | 12 (3.7) | 9 (2.8) | 10 (3.1) | 2 (0.6) | 2 (0.6) |
| Chronic conditions | 7 (2.2) | 5 (1.5) | 5 (1.5) | 0 (0) | 0 (0) | 1 (0.3) | 0 (0) | 1 (0.3) | 3 (0.9) | 1 (0.3) | 1 (0.3) | 0 (0) |
| Context level | | | | | | | | | | | | | |
| Patient/caregiver experience | 16 (5.0) | 3 (0.9) | 2 (0.6) | 0 (0) | 0 (0) | 0 (0) | 1 (0.3) | 4 (1.2) | 11 (3.4) | 11 (3.4) | 5 (1.5) | 4 (1.2) |
| Clinical structure | 14 (4.3) | 0 (0) | 2 (0.6) | 0 (0) | 0 (0) | 0 (0) | 1 (0.3) | 14 (4.3) | 9 (2.8) | 7 (2.2) | 3 (0.9) | 3 (0.9) |
| Communication/ decision making | 14 (4.3) | 2 (0.6) | 4 (1.2) | 0 (0) | 0 (0) | 0 (0) | 2 (0.6) | 13 (4.0) | 11 (3.4) | 2 (0.6) | 2 (0.6) | 3 (0.9) |
| Care coordination | 14 (4.3) | 1 (0.3) | 3 (0.9) | 0 (0) | 0 (0) | 0 (0) | 2 (0.6) | 12 (3.7) | 11 (3.4) | 7 (2.2) | 3 (0.9) | 4 (1.2) |
| Total | 323 (100.0) | 146 (45.2) | 67 (20.7) | 56 (17.3) | 35 (10.8) | 26 (8.0) | 15 (4.6) | 47 (14.6) | 178 (55.1) | 40 (12.4) | 8 (2.5) | 5 (1.5) |

Abbreviations: CAMs, complementary and alternative medicines; HRQoL, health-related quality of life; PA, physical activity.

*aIncludes adherence, dietary, multidisciplinary/multidimensional rehabilitation, patient navigation, peer support, return to work/employment information/education, screening/follow-up, self-management support, specialist nurse, and survivorship care plan interventions, and reviews not specifying intervention types (eg, review of coping and review of supportive care).
and mortality the second most represented (n = 13 and 27 reviews, respectively). For 1997-2010, 22 (81.5%) reviews had degree 1 (connection to a single outcome) and five (18.5%) reviews had degree 2 (connection to both outcomes). The community cluster algorithm identified the two outcomes as two separate communities with a modularity of 0.343 (moderate level of clustering). For 2011-2021, the highest number of connections between outcomes was observed between health-related quality of life/function and mortality (115 reviews). Of the 173 reviews in the network, 152 (87.9%) had degree 1 and 17 (9.8%) had degree 2. The community cluster algorithm identified three separate communities, with a modularity of 0.282 demonstrating reasonable clustering. The largest community was health-related quality of life/function alone (n = 159 reviews) and the second largest contained the emergency services use/hospitalizations and mortality health care outcomes (n = 29 reviews). Cost formed a separate community (n = 8 reviews).

**DISCUSSION**

This network analysis of interventions for survivors of breast cancer demonstrates growth and high volume of review-level evidence. However, despite the vast volume of
research, the breadth of review-level evidence is unevenly distributed, siloed, and displays gaps in clinically important domains and outcomes. The 323 systematic reviews focused on physical (71.5%) or psychologic (65.6%) effects and health-related quality of life (55.1%). Fewer reviews addressed prevention and surveillance of recurrence and new cancers (5.6%), interpersonal effects (5.3%), management of chronic medical conditions (2.1%), or financial/employment issues (1.9%). Likewise, few reviews examined contextual domains pertaining to health care delivery, such as patient-caregiver experience (5.0%), clinical structure, care coordination, and communication or decision making (all 4.3%). Analysis of reviews before 2011 and from 2011 onward demonstrated better representation of smaller domains in the latter years, possibly reflecting growing recognition of their importance in cancer survivorship research. For example, the growing focus on financial toxicity coincides with the 2013 Institute of Medicine report, which highlighted cost as a concern for survivors.15 However, we found that relative distribution and connectivity of domains and outcomes remained similar across the two time periods, with greater focus on physical and psychologic effects, likely reflecting priorities of cancer survivors and researchers.16,17

Our results share similarities with reviews of colorectal and prostate cancer, which have shown gaps related to cancer/recurrence surveillance and care coordination, and identified minimal evidence relating to management of chronic conditions.7,8 Our study identified specific gaps in management of chronic conditions and additional gaps in management of financial/employment issues for breast cancer survivors. These findings may reflect our mapping against the Quality of Cancer Survivorship Care Framework, which places more emphasis on these concerns than the survivorship guidelines that other reviews used as a comparator. It is also likely that current systematic review-level evidence lags behind in reflecting emergent issues for

FIG 3. A bipartite outcome/reviews network graph showing the three communities across the four health care outcomes and 323 review papers. COST, cost of care; ESHP, emergency services use/hospitalizations; HRQOL, health-related quality of life/function; MORT, mortality.
Breast cancer survivors experience high levels of comorbidity and financial toxicity, both of which result in inferior outcomes including mortality. Management of chronic/comorbid conditions and financial/employment effects are also increasingly recognized as research priorities of cancer survivors, underscoring the importance of these relatively under-represented areas. Also evident from our review and less apparent in the colorectal and prostate reviews were gaps in...
research examining cost and health service use, both of which are explicitly identified in the framework and likely to influence the uptake of these interventions into clinical practice.

Our research shows that systematic reviews focusing on the most represented domains were frequently siloed in addressing a single domain, with more connections observed between the less represented domains. Specifically, health care delivery domains clustered in one community with the domain of prevention and surveillance for recurrence and new cancers. By contrast, interventions in other domains did not focus as much on the contextual (health system) domains, which may contribute to their limited translation into current clinical practice. Greater connection between the prevention and surveillance for recurrence and new cancers domain and domains relating to contextual health care delivery may also reflect that surveillance and follow-up tends to be part of core oncology services, whereas other aspects of survivorship care such as management of psychologic effects, health promotion, and care for comorbid conditions tend not to be as integrated into oncology services, with survivorship care historically commencing after acute treatment is completed.

The limited connectivity of the domains and outcomes may also reflect a focus on a single disease or problem/symptom as is commonly adopted in health care interventions. However, evidence increasingly demonstrates that cancer survivors frequently experience multiple concerns spanning various dimensions of health that need addressing. Patients with cancer report to experience an average of 11 concurrent symptoms, leading to growing interest in the symptom complexes or clusters. With more than 300 reviews on survivorship interventions, there is no shortage of high-level evidence to improve outcomes for survivors of breast cancer but the continuing unmet needs of breast cancer survivors suggest a translation gap between published evidence and clinical practice.

Our research provides several insights into potential contributors to the evidence-implementation gap, including (1) lack of evidence for some domains, and (2) lack of focus on outcomes critical to implementation (ie, health care utilization and costs). Future research on interventions for breast cancer survivors should aim to fill identified gaps, be informed by survivor needs/priorities, and integrate implementation science methodology into the research design.

Our study presents a novel methodology that enables a detailed analysis of complex data set that could be applied in other areas of health care delivery. We were able to capture both the breadth and diversity of evidence across different types of interventions and outcomes and provide insights into connections and gaps between them. However, our findings need to be interpreted in light of the study limitations. The framework against which we mapped the evidence was recently developed and may not adequately reflect the earlier priorities of survivorship care, although

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**FIG 5.** Degree and relative inclusion of domains and outcomes by calendar period. “Relative inclusion: domain/outcome degree as a percent of all reviews published in each period. The size of each circle indicates the absolute degree of each domain/outcome. CCOO, care coordination; CHRC, surveillance and management of chronic conditions; CLIN, clinical structure; COMM, communication and decision making; COST, cost of care; EMPL, surveillance and management of financial/employment effects; ESHP, emergency services use/hospitalizations; HPRM, health promotion and disease prevention; HRQoL, health-related quality of life; INTP, surveillance and management of interpersonal effects; MORT, mortality; PEXP, patient/caregiver experience; PHYS, surveillance and management of physical effects; PREV, prevention and surveillance of recurrence and new cancers; PSYC, surveillance and management of psychologic effects.
the included domains are based on principles of survivorship care dating back to the seminal 2005 Institute of Medicine report. We examined interventions at the systematic reviews/meta-analyses level and did not examine categorization of domains and outcomes in the primary papers. We may also be missing more recently published interventions that may have not yet been included in systematic reviews. Because of the large number of reviews, with a median of 13 interventions (range, 2-610 interventions), we were not able to assess for potential overlap of primary papers. Although such overlap is possible, we do not believe that it alters the current findings and implications.

In conclusion, despite the vast volume of breast cancer survivorship intervention research, systematic review-level research is unevenly distributed, siloed, and with significant gaps in clinically important domains and outcomes. Assessment of evidence gaps in primary research and strategic planning of future research, in consultation with cancer survivors, is needed.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Mapping Systematic Reviews of Breast Cancer Survivorship Interventions: A Network Analysis

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