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Evidence based recommendations on care for breast cancer survivors for general practitioners: a review of evidence based breast cancer guidelines

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Title page

Title: Evidence based recommendations on care for breast cancer survivors for general practitioners: a review of evidence based breast cancer guidelines

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ABSTRACT

Objective

To review what evidence based (EB) recommendations on survivorship care for GPs are available in EB breast cancer guidelines.

Design and setting

Guidelines were collected via experts and via literature database and internet searches.

Method

EB guidelines in any language published between 2012 and 2015 were collected. EB recommendations on survivorship care relevant for GPs were extracted and grouped into categories (recurrence detection, long-term effects and recurrence prevention). The content of the recommendations was analyzed and summarized in the number and type of clinical topics addressed.

Results

Five guidelines were included. One was specifically made for GPs. Fifteen clinical topics were identified. Guidelines differed in the clinical topics addressed and for some identical topics in the content of the recommendations. Many recommendations were based on low quality evidence. Recurrence detection perceived most attention, physical examination and mammography were often highlighted. The reporting of potential complications largely varied in number and type. Most were mentioned in one guideline. Vaginal dryness, fatigue, menopause symptoms and peripheral neuropathy were reported in two guidelines. Recurrence prevention was mentioned in four guidelines; all recommended physical activity.

Conclusion

There is a limited availability of EB recommendations. Moreover, recommendations differ between guidelines and most are based on low quality evidence. More high quality research is

needed to develop and adapt guidelines to support GPs in providing optimal breast cancer survivorship care.

Keywords

Breast neoplasms, aftercare, guideline, general practice

Strengths and limitations of this study

- This study is the first to evaluate what evidence based (EB) recommendations on care for breast cancer survivors relevant for general practitioners (GPs) are available in EB breast cancer guidelines.
- International input from 36 countries was received, hereby, we were able to create a fairly complete overview of EB recommendations on care for breast cancer survivors for GPs.
- The main limitation include the validation of translations by non-native speakers, hereby, details of recommendations may be misinterpreted.
- Other limitations are that we have not assessed GPs views on the guidelines and that we have not examined the use of the guidelines by GPs in practice.

INTRODUCTION

Due to the growth and ageing of the population, breast cancer prevalence rates are increasing.[1] Improvements in early detection and cancer treatment led to a growing number of women surviving breast cancer.[2]

After curative breast cancer treatment, patients usually receive follow-up care to detect cancer recurrence and to manage late and long-term consequences of treatment.[3] General practitioners (GPs) are increasingly involved in the follow-up care as a result of limited secondary care facilities, the growing number of breast cancer survivors and increasing costs.[4-6] Besides, a systematic review showed that there is evidence suggesting that follow-up for breast cancer survivors is effective in primary care.[7]

Another result of the rising number of survivors is the increasing demand of survivors for primary care.[8 9] Many breast cancer survivors face short and long-term health consequences from cancer and cancer treatment, including physical and psychological consequences such as depression, pain and fatigue[10 11] and have more contacts with their GP compared to control patients.[8 9]

Therefore, it is important that GPs are able to provide optimal care for cancer survivors and meet the needs of these patients. Studies examining GPs' views showed that GPs prefer more guidance regarding recurrence risk management and consequences of cancer treatment.[12 13] To investigate which evidence based (EB) recommendations on care for cancer survivors are currently available in clinical practice guidelines relevant to GPs, we assessed existing breast cancer guidelines and created an overview of EB recommendations on GPs' care for breast cancer survivors.

METHODS

Two strategies were used to collect guidelines. As part of the European Union Joint Action Cancer Control (CanCon; www.cancercontrol.eu), which aims to contribute to reducing the cancer burden in the European Union, an inventory of existing guidelines in European countries via national experts was undertaken. In addition, the scientific literature and the internet was searched to complete the inventory of guidelines.

European inventory of guidelines

In Autumn 2014, experts from all European Union Member States and four non-EU countries (Norway, Switzerland, Iceland and Turkey) were asked to collect existing guidelines in their own country. Experts included representatives from national primary care associations, nursing associations, universities with a medical department and CanCon associated partners. At least three experts per country were approached. In December 2014, also delegates were approached from the Cancer and Primary Care Research International Network (CA-PRI), the European Forum for Primary Care (EFPC), the European Society of General Practice/Family Medicine (WONCA Europe) and CanCon collaborating partners from non-responding countries. Inclusion criteria were that the guidelines needed to contain guidance on care for adult breast cancer survivors, subsequent to curative treatment, and that they were relevant to GPs. Both national and regional guidelines were eligible.

Internet and literature search

A bibliographical database search using the terms “guideline” and “breast cancer” was conducted in January 2015 to complete the inventory of guidelines. Databases included Embase and Medline. Also, the National Guideline Clearinghouse website in the United

States, the Guidelines International Network (G-I-N) website and national cancer agency websites were searched for relevant breast cancer guidelines (see Supplementary table 1 for all websites that were searched). Searches were conducted without any language restriction. The inclusion criteria were the same as for selection of the guidelines from the inventory. In January 2016, all searches were repeated to reveal updates from the guidelines.

Selection of guidelines

Guidelines obtained from literature and internet searches were selected on the basis of title. Screening of guidelines was done by one researcher (IS). Guidelines meeting the following criteria were considered: the guideline originated from Western countries (EU countries, Iceland, Norway, Switzerland, Turkey, USA, Canada, New Zealand and/or Australia) and focused on adult breast cancer patients. Inclusion criteria were a publication date from 2012 to 2015, as older guidelines may be outdated,[14] and meeting the definition of an EB guideline[15] including recommendations intended to optimize patient care that are informed by the best available literature. If more versions of a guideline existed, the most recent update of a guideline was used. Guidelines were excluded if oncologists were the only target audience, if they duplicated another guideline, if the guideline only focused on one phase in the care process such as early detection, screening, treatment or palliative care, on advanced cancer or metastasis, or on hereditary cancer survivors, and if guidelines did not link recommendations to graded evidence or to scientific citations.

Content analysis

Extraction of recommendations from guidelines not published in English or Dutch was based on translations validated by researchers from the NIVEL institute who are familiar with the language (German and Italian). Recommendations were categorized into ‘recurrence

detection', 'long-term effects' and 'recurrence prevention' by two researchers independently (IS and JK). Subsequently, a clinical topic list per category was composed. Recommendations were independently allocated to clinical topics by two researchers (IS and JK). Disagreements arising from decisions on either categorization or allocation into clinical topics were resolved by discussion with a third researcher (FS).

RESULTS

Guidelines

Response was received from 45 experts from 32 countries and 16 provided a current breast cancer guideline. The literature search yielded 365 results, the National Guideline Clearinghouse database 184 results and the G-I-N database 117. In total, 14 additional potentially relevant guidelines from the literature and internet search were considered (Figure 1). After removal of one duplicate and one guideline[16] of which recommendations on care for breast cancer survivors were included in another guideline that focused on breast cancer survivors[17] and elimination of guidelines based on other exclusion criteria, five guidelines were included (Table 1). These guidelines originated from Canada, Europe, Germany, Italy and the United States. Three guidelines were published in English;[17-19] one in German[20] and one in Italian.[21] One guideline was specifically made for GPs.[17]

Table 1. Included breast cancer guidelines

Country (ID code)	Year of publication	Title in English
Canada – Alberta (CA)	2015	Follow-up care for early-stage breast cancer[19]
Europe (EU)	2015	Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[18]
Germany (GE)	2012	Interdisciplinary S3 guideline for the diagnosis, treatment and aftercare of breast cancer[20]
Italy (IT)	2014	Breast cancer guideline[21]
United States (US)	2015	American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline[17]

Level of evidence

Guidelines used different systems to grade the evidence. To compare the level of evidence of selected recommendations, we created a uniform grading system of research studies: 1) Meta-analysis or systematic review, 2) RCT study, 3) non-RCT study. In supplementary table 2 the reclassification of gradations used in the guidelines is shown.

Clinical recommendations

Within the three categories (recurrence detection, long-term effects and recurrence prevention) 15 clinical topics were identified (Table 2). None of the guidelines contained recommendations on all topics. Most recommendations were available on **recurrence detection** and most of these concerned diagnostic testing. Mammography was recommended in the follow-up of breast cancer patients in four guidelines and physical examination in two. Other imaging or laboratory testing were not recommended in routine recurrence detection, except for ultrasound, which was recommended in one guideline in combination with mammography. Awareness was the only other topic on which more than one guideline provided recommendations. Two guidelines recommended genetic counselling for risk evaluation and one advised to educate patients about signs of recurrence.

Four guidelines contained recommendations on **long-term effects** of breast cancer. Potential complications of breast cancer and/or breast cancer treatment were reported. For some of these complications treatment options were given. Recommendations on psychological support were given in two guidelines; it was highlighted that psycho-oncological care is part of the overall concept of the care for breast cancer survivors and that psychosocial care should be offered if needed.

Table 2. Overview of clinical topics covered (Y) in included guidelines

	CA	EU	GE	IT	US
Recurrence detection					
Awareness	-	-	-	Y	Y
Self-examination	Y	-	-	-	-
Physical diagnostic tests	-	-	-	Y	Y
Laboratory diagnostic tests	-	Y	Y	Y	Y
Diagnostic imaging	-	Y	Y	Y	Y
Risk of recurrence	-	Y	-	-	-
Organization of care	-	-	-	-	Y
Long-term effects					
Potential complications	Y	Y	Y	-	Y
Treatment of complications	Y	-	Y	-	Y
Psychological support	-	-	Y	-	Y
Recurrence prevention					
Physical activity	Y	Y	Y	-	Y
Nutrition	-	-	-	-	Y
Weight management	Y	Y	-	-	Y
Alcohol consumption	Y	-	-	-	Y
Smoking cessation	-	-	-	-	Y

Note. CA = Canada-Alberta, EU = Europe, GE = Germany, IT = Italy, US = United States

Four guidelines included recommendations on **recurrence prevention** and all recommended an active lifestyle for breast cancer survivors. Counseling to achieve or maintain a healthy body weight was recommended in three guidelines. The other recommendations on recurrence prevention included a healthy diet, limited alcohol consumption and stop smoking.

Recommendations on frequency of diagnostic testing

Two guidelines provided recommendations on frequency of history taking and physical examination (Table 3). Both stated that history taking and physical examination are important to detect recurrence. The recommended frequency was the same in both guidelines despite that the level of evidence differed.

Three guidelines included recommendations on the frequency of mammography. All recommended annual mammography, but specific conditions differed (Table 3). One guideline recommended to perform mammography with ultrasound, two indicated at which side the mammography should take place, and one included a time frame after which the first mammography should take place.

Table 3. Evidence based recommendations on frequency of diagnostic tests after curative breast cancer treatment

Country of guideline	Recommendation	Level of evidence
History and physical examination		
IT	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	1
US	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	3
Mammography		
EU	Annually ipsilateral (after breast conserving therapy) and/or a contralateral with ultrasound	3
IT	One year after the diagnostic mammography or at least 6 months after the end of radiotherapy, then annually	3
US	Annually on the intact breast for women who have received a unilateral mastectomy and annually of both breasts for women with lumpectomies	3

Note. Level of evidence 1 = Meta-analysis or systematic review, level of evidence 3 = Non RCTstudy

Potential complications of breast cancer and breast cancer treatment

Four guidelines reported potential complications of breast cancer and breast cancer treatment but differed in the number and nature of these complications (Table 4). The EU guideline mentioned one potential complication, whereas the US guideline reported eight potential complications. The guidelines reported a total number of 17 potential complications, of which four (vaginal dryness, fatigue, menopause symptoms and peripheral neuropathy) were reported by two guidelines; thirteen unique complications were reported. Seven of these were

based on level 1 evidence, five on level 2 and five on level 3 evidence. All guidelines attributed (some of) the potential complications to associated treatment. Four potential complications were associated with hormone therapy, three were linked to chemotherapy and two to radiotherapy.

Table 4. Potential complications of breast cancer (treatment)

Potential complication	Associated treatment	Country of guideline	Level of evidence
Symptoms/complaints musculoskeletal system			
Osteoporosis	H	EU	1
Immobilized shoulder	NS	GE	1
Sexual problems			
Painful intercourse, loss of sensation, intimacy concerns, decreased libido	NS	CA	3
Vaginal dryness	H	CA	3
	H	US	2
Dyspareunia, other symptoms of vulvovaginal atrophy	H	CA	3
General/unspecified complaints			
Pain	G, H, R, S	US	1
Fatigue	NS	GE	1
	C, R	US	1
Shortness of breath	R	US	1
Menopausal problems			
(premature) symptoms of menopause	NS	CA	3
	NS	US	2
Neurological complaints			
Peripheral neuropathy	C	CA	3
	C, S	US	2
Psychological problems			
Cognitive impairment	C	US	2
Distress, depression and anxiety	G	US	1
Other problems			
Lymphedema	AL	GE	2

Note. H: Hormone therapy, NS: not specified, C: chemotherapy, R:Radiotherapy, S: Surgery, G:General, AL: axillary lymphadenectomy. Level of evidence 1 = Meta-analysis or systematic review, level of evidence 2 = At least one RCT study, level of evidence 3 = Non RCTstudy

DISCUSSION

Access to the best available evidence is a key ingredient for providing optimal care. EB clinical guidelines are an aggregation of the available evidence and contain scientifically valid recommendations in order to improve the quality of care. This guideline inventory study is the first to evaluate what EB recommendations on care for breast cancer survivors relevant for GPs are available in EB breast cancer guidelines, and it represents the current status of EB recommendations on care for breast cancer survivors. We identified only five EB guidelines, which included limited EB recommendations. Two guidelines were specific on care for breast cancer survivors and only one guideline was specifically made for GPs. Moreover, recommendations differed between guidelines and most were based on low quality evidence.

Strengths and limitations

A strength of the present inventory is the international input of 36 countries, including 32 European countries and Canada, USA, Australia and New Zealand. This enabled us to create a fairly complete overview of EB recommendations from EB guidelines for GPs on care for breast cancer survivors. A limitation of our study is the validation of translations by non-native speakers. Details may be misinterpreted, but we do not expect that the key recommendations of the guidelines differed. Another limitation is that we have not examined the views of GPs on the guidelines and their use of the guidelines in clinical practice. Finally, we did not investigate the views of breast cancer patients on the care of GPs.

Comparison with existing literature

Only one guideline was specifically made for GPs despite increasing demands for greater involvement of GPs in care for breast cancer survivors.[4-6] The fact that recommendations

are often not targeted for GPs, was also highlighted by a recent publication that stated that the role of the GP in care for cancer survivors is currently not well defined. However as soon as the role is clearly defined, GPs can have an important role in the care for cancer survivors as they know details of patient's history and social context, comorbidity, and are alert on considering individual views and preferences.[22]

The guidelines included recommendations on different categories and clinical topics. The categories identified were consistent with the domains described by the Institute of Medicine (IOM) report: 'From Cancer Patient to Cancer Survivor: Lost in Transition'.[3] In addition, we defined fifteen topics. None of the guidelines discussed all these topics. A possible explanation is lack of evidence on specific topics[23] or the focus on follow-up care and recurrence detection rather than on the whole care process for breast cancer survivors.

The content analyses on the available topics revealed consensus on seven topics, such as the frequency of tests to detect breast cancer recurrence. On four topics, recommendations differed between the guidelines. In particular, reported potential complications differed considerably. Univocal guidance would help GPs to raise awareness on the potential consequences of both cancer and its treatment.[24]

Guidelines were only included if published after 2011. This selection of publication dates was applied as it is has been demonstrated that guidelines may be outdated after a few years[14] and that the turnover rate of research evidence is high in the field of cancer.[22] Ten guidelines were excluded due to lack of transparency on the supporting evidence. A previous study[25] showed that the quality of oncology guidelines was higher than non-oncology guidelines. Our study revealed that there is still room for improvement concerning oncology guidelines.

Implications for practice and research

The only guideline[17] that was specifically made for GPs was specific on care for breast cancer survivors and yielded EB recommendations on most clinical topics (on 13 out of the 15 identified topics). Currently this guideline, entitled the 'American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline', is the guideline which seems to be the most useful guideline for GPs. However, these guideline does not include EB recommendations on all clinical topics and a lot of the recommendations are based on low quality evidence.

Thus, more high quality evidence is needed to develop and adapt breast cancer guidelines to support GPs in providing optimal breast cancer survivorship care. Besides, it is important to specifically mention GPs as target group of the EB guideline and to incorporate GPs in the development and adaptation of the EB guideline. In that way, EB guidelines can meet the requirements and needs of GPs in order to provide optimal breast cancer survivorship care. If GPs are supported with high quality EB guidelines, transfer of care for breast cancer survivors from secondary to primary care could be facilitated.

In addition to the availability of high quality EB guidelines, it is important to gain knowledge on the views of GPs on the guidelines and their use of the guidelines in clinical practice, as well as on the views of breast cancer patients on the care of GPs. Views of GPs and patients on the usefulness of guidelines and the preferred setting of care for breast cancer survivors is an area for future research.

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Contributors IS, JK, FS, TA, JB conceptualized the study and defined the content analysis strategy. IS collected and reviewed the guidelines and extracted the data. IS and JK categorized the recommendations and allocated recommendations into clinical topics. IS, JK, FS, JB provided preliminary interpretation of findings. IS, JK, FS, TA, JB contributed in drafting the manuscript, critically helped in the interpretation of the results and provided relevant intellectual input.

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Competing interests None declared

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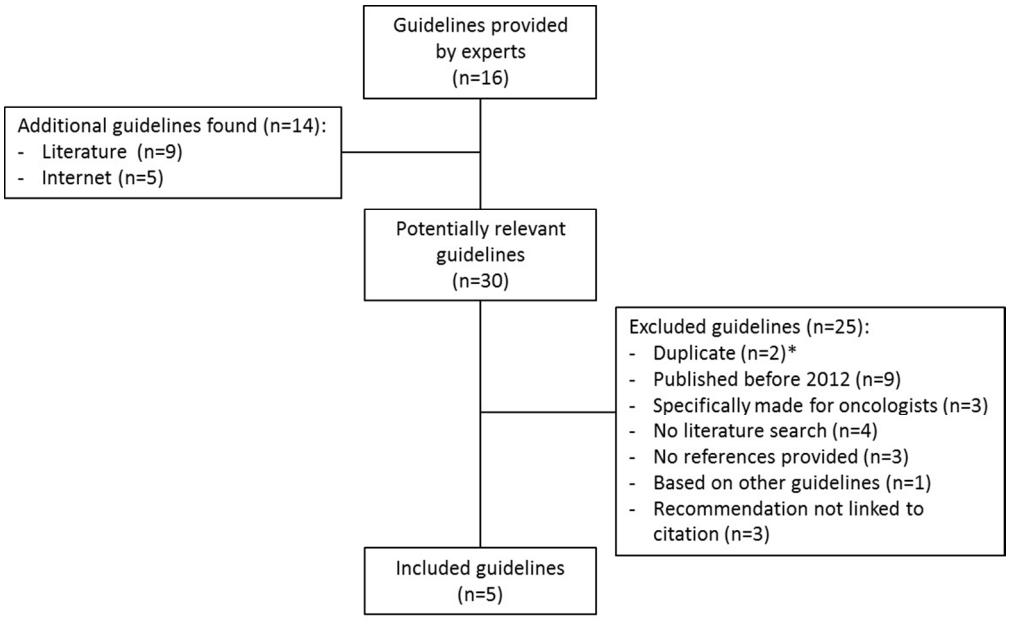

Figure 1. Selection of guidelines
*The ACS/ASCO guideline included recommendations from the NCCN guideline on care for cancer survivors.

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Supplementary table 1. Internet search

National guideline clearinghouse

http://www.guideline.gov/search/search.aspx?term=breast+cancer

Guidelines International Network (G-I-N)

http://www.g-i-n.net/library/international-guidelines-library/@@guideline_search_results?type=basic&basic-searchable-text=breast+cancer

Cancer agency websites

Alberta Health Services (http://www.albertahealthservices.ca/)

American Cancer Society (http://www.cancer.org/)

American Society for Clinical Oncology (ASCO) (http://www.asco.org/)

British Colombia Cancer Agency (BCCA) (http://www.bccancer.bc.ca/)

Cancer Care Ontario (https://www.cancercare.on.ca/)

Cancer Council Australia (http://www.cancer.org.au/health-professionals/clinical-guidelines/)

Comprehensive Cancer Centre the Netherlands (IKNL) (http://www.oncoline.nl/)

European Society for Medical Oncology (ESMO) (http://www.esmo.org/)

Haute Autorité de Santé (http://www.has-sante.fr)

National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/)

National Institute for Health and Clinical excellence (NICE) (https://www.nice.org.uk/)

New Zealand Guidelines Group (NZGG) (http://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group)

Saskatchewan Cancer Agency (http://www.saskcancer.ca/)

Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/)

Sociedad Espanola de Oncologia Medica (SEOM) (http://www.seom.org/)

Supplementary table 2. Reclassification of levels of evidence

Level of evidence*	EU	GE	IT	US
1 – Meta-analysis or systematic review	I	IA	1^{++} – 1^{+}	I
2 – At least one RCT study	II	IB	1^{-}	IA – IC
3 – Non RCTstudy	III and IV	IC – IV	2^{++} – 3	2A, IIA – III

*The CA guideline did not classify the evidence used.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (review)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 and 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and suppl. table 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6 and 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 and 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 and 7

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8 and 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10 and 11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

PRISMA 2009 Checklist

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Evidence based recommendations on care for breast cancer survivors for general practitioners: a review of evidence based breast cancer guidelines

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Title page

Title: Evidence based recommendations on care for breast cancer survivors for general practitioners: a review of evidence based breast cancer guidelines

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ABSTRACT

Objective

To review evidence based (EB) recommendations on survivorship care for GPs in EB breast cancer guidelines.

Design and setting

Guidelines were collected via experts and via literature database and internet searches.

Method

EB guidelines in any language published between 2012 and 2017 were collected. EB recommendations on survivorship care relevant for GPs were extracted and grouped into three categories (recurrence detection, long-term effects and recurrence prevention). The content of the recommendations was analyzed and summarized in the number and type of clinical topics addressed. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to evaluate the methodological quality of the guidelines.

Results

Six guidelines, of which two were of acceptable methodological quality, were included. One was specifically made for GPs. Fifteen clinical topics were identified. Guidelines differed in the clinical topics addressed and for some identical topics in the content of the recommendations. Many recommendations were based on low quality evidence. Recurrence detection received most attention, physical examination and mammography were often highlighted. Potential complications largely varied in number and type. Intimacy concerns, vaginal dryness, dyspareunia fatigue, menopause symptoms, peripheral neuropathy and lymphedema were reported in more than one guidelines. Recurrence prevention was mentioned in four guidelines; all recommended physical activity.

Conclusion

The number of EB recommendations in guidelines is limited. Moreover, recommendations differ between guidelines and most are based on low quality evidence. More high quality research is needed to develop and adapt guidelines to support GPs in providing optimal breast cancer survivorship care.

Keywords

Breast neoplasms, aftercare, guideline, general practice

Strengths and limitations of this study

- This study is the first to evaluate evidence based (EB) recommendations on care for breast cancer survivors relevant for general practitioners (GPs) in EB breast cancer guidelines.
- Input from 36 countries was received, hereby, we were able to create a fairly complete overview of EB recommendations on care for breast cancer survivors for GPs.
- The main limitation includes the validation of translations by non-native speakers, hereby, details of recommendations may be misinterpreted.
- Other limitations are that we have not assessed GPs' views on the guidelines and that we have not examined the use of the guidelines by GPs in practice.

INTRODUCTION

Due to the growth and ageing of the population, breast cancer prevalence rates are increasing.[1] Improvements in early detection and cancer treatment led to a growing number of women surviving breast cancer.[2]

After curative breast cancer treatment, patients usually receive follow-up care to detect cancer recurrence and to manage late and long-term consequences of treatment.[3] General practitioners (GPs) are increasingly involved in the follow-up care as a result of limited secondary care facilities, the growing number of breast cancer survivors and increasing costs.[4-6] Besides, a systematic review showed that there is evidence that follow-up for breast cancer survivors is effective in primary care.[7]

Another result of the rising number of survivors is that GPs are seeing an increased number of survivors.[8 9] Many breast cancer survivors face short and long-term health consequences from cancer and cancer treatment, including physical and psychological consequences such as depression, pain and fatigue[10 11] and have more contacts with their GP compared to control patients.[8 9]

Therefore, it is important that GPs are able to provide optimal care for cancer survivors and meet the needs of these patients. Studies examining GPs' views showed that GPs prefer more guidance regarding recurrence risk management and consequences of cancer treatment.[12 13] To investigate which evidence based (EB) recommendations on care for cancer survivors are currently available in clinical practice guidelines relevant to GPs, we assessed existing breast cancer guidelines and created an overview of EB recommendations on GP care for breast cancer survivors.

METHODS

Two strategies were used to collect guidelines. As part of the European Union Joint Action Cancer Control (CanCon; www.cancercontrol.eu), which aims to contribute to reducing the cancer burden in the European Union, an inventory of existing guidelines in European countries via national experts was undertaken. In addition, the scientific literature and the internet was searched to complete the inventory of guidelines.

European inventory of guidelines

In Autumn 2014, experts from all European Union Member States and four non-EU countries (Norway, Switzerland, Iceland and Turkey) were asked to collect existing guidelines in their own country. Experts included representatives from national primary care associations, nursing associations, universities with a medical department and CanCon associated partners. At least three experts per country were approached. In December 2014, delegates were approached from the Cancer and Primary Care Research International Network (CA-PRI), the European Forum for Primary Care (EFPC), the European Society of General Practice/Family Medicine (WONCA Europe) and CanCon collaborating partners from non-responding countries. Inclusion criteria were that the guidelines needed to contain guidance on care for adult breast cancer survivors, subsequent to curative treatment, and that they were relevant to GPs. Both national and regional guidelines were eligible.

Internet and literature search

A bibliographical database search using the terms “guideline” and “breast cancer” was conducted in January 2015 to complete the inventory of guidelines (see Supplement 1 for the search strategy). Databases included Embase and Medline. Also, the National Guideline Clearinghouse website in the United States, the Guidelines International Network (G-I-N)

website and national cancer agency websites were searched for relevant breast cancer guidelines (see Supplement 2 for all websites that were searched). Searches were conducted without any language restriction. The inclusion criteria were the same as for selection of the guidelines from the inventory. In June 2017, the literature and internet searches were repeated to reveal updates from the guidelines and guidelines published after January 2015.

Selection of guidelines

Guidelines obtained from the internet searches were selected on the basis of title. Records from the scientific literature search were screened on the basis of title and abstract/summary. Screening of guidelines was done by one researcher (IS). Records were considered if they included breast cancer guidelines. Guidelines meeting the following criteria were reviewed in full-text: the guideline originated from Western countries (EU countries, Iceland, Norway, Switzerland, Turkey, USA, Canada, New Zealand and/or Australia) and focused on adult breast cancer patients. Inclusion criteria were a publication date from 2012 to 2017, as older guidelines may be outdated[14], and meeting the definition of an EB guideline[15] including recommendations intended to optimize patient care that are informed by the best available knowledge. If more versions of a guideline existed, the most recent version of a guideline was used. Guidelines were excluded if oncologists were the only target audience, if they duplicated another guideline, if the guideline only focused on one phase in the care process such as early detection, screening, treatment or palliative care, on advanced cancer or metastasis, or on hereditary cancer survivors, and if guidelines did not link recommendations to graded evidence or to scientific citations. Information from guidelines in languages other than English or Dutch were translated. Data from the Croatian, Danish, Finnish, Norwegian and Polish guidelines were translated by the expert who provided the guidelines. Colleague researchers from the NIVEL institute who master the specific language translated the data from the French, German and Italian guidelines.

Quality assessment

The methodological quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[16] AGREE II is a validated 23-item instrument used to evaluate six domains: scope and purpose (3 items), stakeholder involvement (3 items), rigor of development (8 items), clarity of presentation (3 items), applicability (4 items) and editorial independence (2 items). These six domains are followed by two extra items ("Overall assessment"), which indicate the overall quality of the guideline and whether the reviewers recommend the guideline for use in practice. The English and Dutch guidelines were assessed by two researchers (IS, JK), the German and Italian guidelines were each reviewed by two colleagues with a high mastery of the specific language. All items were rated from 1 (strongly disagree) to 7 (strongly agree). Items for which scores differed more than one point were discussed by the reviewers. Rationales for scores were explained and scores were revised when this was considered necessary. Afterwards, a total score for each domain was calculated by summing up all item scores within a domain and by scaling the total score as a percentage of the maximum possible score of a domain.[17] Domain scores greater than 60% were considered acceptable.[18-21] Guidelines were recommended for use when three or more domains were acceptable targeted and when the rigor of development was of good quality.[18]

Content analysis

EB recommendations were categorized into 'recurrence detection', 'long-term effects' and 'recurrence prevention' by two researchers independently (IS and JK). Subsequently, a clinical topic list per category was composed. EB Recommendations were independently allocated to clinical topics by two researchers (IS and JK). Disagreements arising from decisions on either categorization or allocation into clinical topics were resolved by discussion with a third researcher (FS). The categorization and clinical topics were discussed and approved in a meeting of experts participating in work package 7 (community cancer

care) of the European Union Joint Action Cancer Control.[22 23] Experts from five European countries participated in this meeting.

RESULTS

Guidelines

Response was received from 45 experts from all 32 approached countries and 16 provided a current breast cancer guideline. The literature search yielded 419 results, the internet search in 279 results. In total, 16 additional potentially relevant guidelines from the literature and internet search were considered (Figure 1). After removal of one duplicate and one guideline[24] of which recommendations on care for breast cancer survivors were included in another guideline that focused on breast cancer survivors[25] and elimination of guidelines based on other exclusion criteria, six guidelines were included (Table 1). These guidelines originated from Canada, Germany, Italy, the Netherlands and the United States. And also the guideline from the European Society for Medical Oncology (ESMO) was included. This organization publishes guidelines that may be adopted by European countries. However, most European countries develop their own guideline. Three guidelines were published in English[25-27], one in Dutch[28], one in German[29] and one in Italian.[30] One guideline was specifically made for GPs.[28]

Table 1. Included breast cancer guidelines

Country (ID code)	Year of publication	Title in English
Canada – Alberta (CA)	2015	Follow-up care for early-stage breast cancer[27]
Europe (EU)	2015	Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[26]
Germany (GE)	2012	Interdisciplinary S3 guideline for the diagnosis, treatment and aftercare of breast cancer[29]
Italy (IT)	2016	Breast cancer guideline[30]
The Netherlands (NL)	2016	NHG Guideline Breast cancer[28]
United States (US)	2015	American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline[25]

Methodological quality

All guidelines were evaluated using the AGREE II instrument. Mean scaled domain percentages, mean overall appraisal scores and appraiser recommendations for the use of guidelines are shown in supplement 3. Two guidelines (NL and US) were recommended to use in clinical practice without modifications. Both of these guidelines scored acceptable on five out of the six domains, only the scores on the domain 'applicability' were moderate. For two other guidelines (CA and GE) modifications were advised before using these guidelines. These guidelines scored acceptable on two domains and moderate on the rigor of development domain. The last two guidelines (EU and IT) were not recommended for use due to the low methodological quality.

Mean overall scores ranged between 2.5 and 6, with the highest score for the US guideline. Domain scores varied per domain. The only domain on which all guidelines scored acceptable was the clarity of presentation domain (mean 71.3%, range: 63.9 – 80.6%). Four guidelines scored acceptable on the scope and purpose domain (mean 67.1%, range: 25.0 – 91.7%). More variable scores were seen on the domains 'rigor of development' (mean 51.9%, range: 35.4 – 66.7%), 'editorial independence' (mean 18.6%, range 12.5 – 70.8%), and 'stakeholder involvement' (mean 50.0%, range: 13.9 – 86.1%). The only domain that scored overall moderate was the applicability domain (mean 40.3%, range: 18.8 – 50.0%).

Level of evidence

Guidelines used different systems to grade the evidence. To compare the level of evidence of selected recommendations, we created a uniform grading system of research studies: 1) Meta-analysis or systematic review, 2) RCT study, 3) non-RCT study. Supplement 4 provides a table showing the reclassification of gradations used in the guidelines.

Clinical recommendations

Within the three categories (recurrence detection, long-term effects and recurrence prevention) 15 clinical topics were identified (Table 2). None of the guidelines contained recommendations on all topics. Most recommendations were available on **recurrence detection** and most of these concerned diagnostic testing. Mammography was recommended in the follow-up of breast cancer patients in five guidelines and physical examination in three. Other imaging or laboratory testing were not recommended in routine recurrence detection, except for ultrasound, which was recommended in one guideline in combination with mammography. Three guidelines recommended genetic counselling for risk evaluation and one advised to educate patients about signs of recurrence.

Five guidelines contained recommendations on **long-term effects** of breast cancer. Long-term effects are defined as "problems that are caused by breast cancer or the treatment of breast cancer that may continue for months or years".[31] Potential complications of breast cancer and/or breast cancer treatment were listed in the guidelines. For some of these complications treatment options were given. Recommendations on psychological support were given in two guidelines; it was highlighted that psycho-oncological care is part of the overall concept of the care for breast cancer survivors and that psychosocial care should be offered if needed.

Five guidelines included recommendations on **recurrence prevention** and all recommended an active lifestyle for breast cancer survivors. Counseling to achieve or maintain a healthy body weight was recommended in four guidelines. The other recommendations on recurrence prevention included a healthy diet, limited alcohol consumption and stop smoking.

Table 2. Overview of clinical topics covered (Y) in included guidelines

	CA	EU	GE	IT	NL	US
Recurrence detection						
Awareness	-	-	-	Y	-	Y
Self-examination	Y	-	-	-	Y	-
Physical diagnostic tests	-	-	-	Y	Y	Y
Laboratory diagnostic tests	-	Y	Y	Y	-	Y
Diagnostic imaging	-	Y	Y	Y	Y	Y
Risk of recurrence	-	Y	-	Y	-	-
Organization of care	-	-	-	-	-	Y
Long-term effects						
Potential complications	Y	Y	Y	Y	Y	Y
Treatment of complications	Y	-	Y	Y	Y	Y
Psychological support	-	-	Y	-	-	Y
Recurrence prevention						
Physical activity	Y	Y	Y	Y	-	Y
Nutrition	-	-	-	-	-	Y
Weight management	Y	Y	-	Y	-	Y
Alcohol consumption	Y	-	-	Y	-	Y
Smoking cessation	-	-	-	Y	-	Y

Note. CA = Canada-Alberta, EU = Europe, GE = Germany, IT = Italy, NL = The Netherlands, US = United States

Recommendations on frequency of diagnostic testing

Three guidelines provided recommendations on frequency of history taking and physical examination (Table 3). All stated that history taking and physical examination are important to detect recurrence. The recommended frequency was the same in two guidelines despite that the level of evidence differed. The third guideline, which was specific for GPs, included a recommendation for history taking and physical examination five years after primary treatment, as from that moment the GP is in charge of follow-up.

Four guidelines included recommendations on the frequency of mammography. Three recommended annual mammography and one recommended a mammogram every two years after five years. Specifications for mammography differed among the guidelines. One

guideline recommended to perform mammography with ultrasound, two indicated at which side the mammography should take place, and one included a time frame after which the first mammography after initial treatment should take place.

Table 3. Evidence based recommendations on frequency of diagnostic tests after curative breast cancer treatment

Country of guideline	Recommendation	Level of evidence
History and physical examination		
IT	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	1
NL	After five years[1]: annually	1
US	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	3
Mammography		
EU	Annually ipsilateral (after breast conserving therapy) and/or a contralateral with ultrasound	3
IT	One year after the diagnostic mammography or at least 6 months after the end of radiotherapy, then annually	3
NL	After five years[1]: every two years	1
US	Annually on the intact breast for women who have received a unilateral mastectomy and annually of both breasts for women with lumpectomies	3

Note. Level of evidence 1 = Meta-analysis or systematic review, level of evidence 3 = Non RCTstudy

[1]Five years after primairy treatment the GP is in charge of the care for cancer survivors

Potential complications of breast cancer and breast cancer treatment

All guidelines listed potential complications of breast cancer and breast cancer treatment but differed in the number and nature of these complications (Table 4). The EU guideline mentioned one potential complication, whereas the US guideline reported eight potential complications. The guidelines reported a total number of 14 different potential complications, of which seven (intimacy concerns, vaginal dryness, dyspareunia fatigue, menopause symptoms, peripheral neuropathy and lymphedema) were reported by two guidelines. All

guidelines attributed (some of) the potential complications to associated treatment. Five potential complications were associated with hormone therapy, four were linked to chemotherapy and three to radiotherapy.

Table 4. Potential complications of breast cancer (treatment)

Potential complication	Associated treatment	Country of guideline	Level of evidence
Symptoms/complaints musculoskeletal system			
Osteoporosis	H	EU	1
Immobilized shoulder	NS	GE	1
Sexual problems			
Painful intercourse, loss of sensation, intimacy concerns, decreased libido	NS	CA	3
	NS	NL	3
Vaginal dryness	H	CA	3
	H	US	2
Dyspareunia, other symptoms of vulvovaginal atrophy	H	CA	3
	NS	NL	3
General/unspecified complaints			
Pain	G, H, R, S	US	1
Fatigue	NS	GE	1
	C, G	NL	1
	C, R	US	1
Shortness of breath	R	US	1
Menopausal problems			
(premature) symptoms of menopause	NS	CA	3
	NS	US	2
Neurological complaints			
Peripheral neuropathy	C	CA	3
	C, S	US	2
Psychological problems			
Cognitive impairment	C	US	2
Distress, depression and anxiety	G	US	1
Other problems			
Lymphedema	AL	GE	2
	AL, R	NL	1
Cardiac problems	H	IT	2

Note. H: Hormone therapy, NS: not specified, C: chemotherapy, R:Radiotherapy, S: Surgery, G:General, AL: axillary lymphadenectomy. Level of evidence 1 = Meta-analysis or systematic review, level of evidence; 2 = At least one RCT study, level of evidence; 3 = Non RCT study

DISCUSSION

Access to the best available evidence is a key ingredient for providing optimal care. EB clinical guidelines are an aggregation of the available evidence and contain scientifically valid recommendations. This guideline inventory study is the first to evaluate what EB recommendations on care for breast cancer survivors relevant for GPs are available in EB breast cancer guidelines, and it represents the current status of EB recommendations on care for breast cancer survivors. We identified only six EB guidelines, of which only two were of acceptable methodological quality and which included a limited number of EB recommendations. Two guidelines were specific on care for breast cancer survivors and only one guideline targeted GPs specifically. Moreover, recommendations differed between guidelines and most were based on low quality evidence.

Strengths and limitations

A strength of the present inventory is the international input of 36 countries, including 32 European countries and Canada, USA, Australia and New Zealand. This enabled us to create a fairly complete overview of EB recommendations from EB guidelines for GPs on care for breast cancer survivors. A limitation of our study is the absence of validation of translations by non-native speakers. Details may be misinterpreted, but we do not expect that the key recommendations of the guidelines differed. Also, only one researcher screened the literature and internet to identify additional guidelines from the literature and internet. However, in case of any doubt, the inclusion was discussed with a second researcher. Another limitation is that we have not examined the views of GPs on the guidelines and their use of the guidelines in

clinical practice. Finally, we did not investigate the views of breast cancer patients on the care of GPs.

Comparison with existing literature

Only one guideline specifically mentioned GPs as target audience despite increasing demands for greater involvement of GPs in care for breast cancer survivors.[4-6] The fact that recommendations are often not targeted at GPs, was also highlighted by a recent publication that stated that the role of the GP in care for cancer survivors is currently not well defined. However, GPs can have an important role in the care for cancer survivors as they know details of patient's history and social context, comorbidity, and are alert on considering individual views and preferences.[32]

The guidelines included recommendations on different categories and clinical topics. The categories identified were consistent with the domains described by the Institute of Medicine (IOM) report: 'From Cancer Patient to Cancer Survivor: Lost in Transition'.[3] In addition, we defined fifteen topics. None of the guidelines discussed all these topics. A possible explanation for this is lack of evidence on specific topics[33] or the focus on follow-up care and recurrence detection rather than on the whole care process for breast cancer survivors.

The content analyses on the available topics revealed consensus on seven topics, such as the frequency of tests to detect breast cancer recurrence. On four topics, recommendations differed between the guidelines. In particular, listed potential complications differed considerably. Univocal guidance would help GPs to raise awareness on the potential consequences of both cancer and its treatment.[34]

Guidelines were only included if published after 2011. This selection criterion was applied as it is has been demonstrated that guidelines may be outdated after a few years[14] and that the turnover rate of research evidence is high in the field of cancer.[32] Ten guidelines were

excluded due to lack of transparency on the supporting evidence. A previous study[35] showed that the quality of oncology guidelines was higher than non-oncology guidelines. Our study revealed that there is still room for improvement concerning oncology guidelines.

Implications for practice and research

The 'American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline' yielded EB recommendations on most clinical topics (on 13 out of the 15 identified topics) and mentioned the GPs specifically as target group of the guideline. Furthermore, this guideline scored highest on the AGREE II evaluation and was recommended for use in clinical practice by both guideline appraisers. Currently this guideline seems to be the most useful guideline for GPs. However, this guideline does not include EB recommendations on all clinical topics and a lot of its recommendations are based on low quality evidence.

Therefore, more high quality evidence is needed to develop and adapt breast cancer guidelines to support GPs in providing optimal breast cancer survivorship care. Guidelines should not be solely designed for GPs as it is important to provide integrated care to breast cancer survivors. GPs are part of this integrated care and GPs indicated that they need more guidance in order to provide good quality care to cancer survivors. Therefore, it is important to incorporate GPs in the development and adaptation of the guidelines and to specifically mention GPs as target group of the guideline. In that way, guidelines can meet the requirements and needs of GPs in order to provide optimal breast cancer survivorship care. If GPs are supported with high quality EB guidelines, transfer of care for breast cancer survivors from secondary to primary care could be better facilitated.

In addition to the availability of high quality EB guidelines, it is important to gain knowledge on the views of GPs on the guidelines and their use of the guidelines in clinical practice, as

well as on the views of breast cancer patients on the care of GPs. Views of GPs and patients on the usefulness of guidelines and the preferred setting of care for breast cancer survivors is an area for future research.

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Contributors IS, JK, FS, TA, JB conceptualized the study and defined the content analysis strategy. IS collected and reviewed the guidelines and extracted the data. IS and JK categorized the recommendations and allocated recommendations into clinical topics. IS, JK, FS, JB provided preliminary interpretation of findings. IS, JK, FS, TA, JB contributed in drafting the manuscript, critically helped in the interpretation of the results and provided relevant intellectual input.

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Figure 1. Flowchart outlining guideline selection

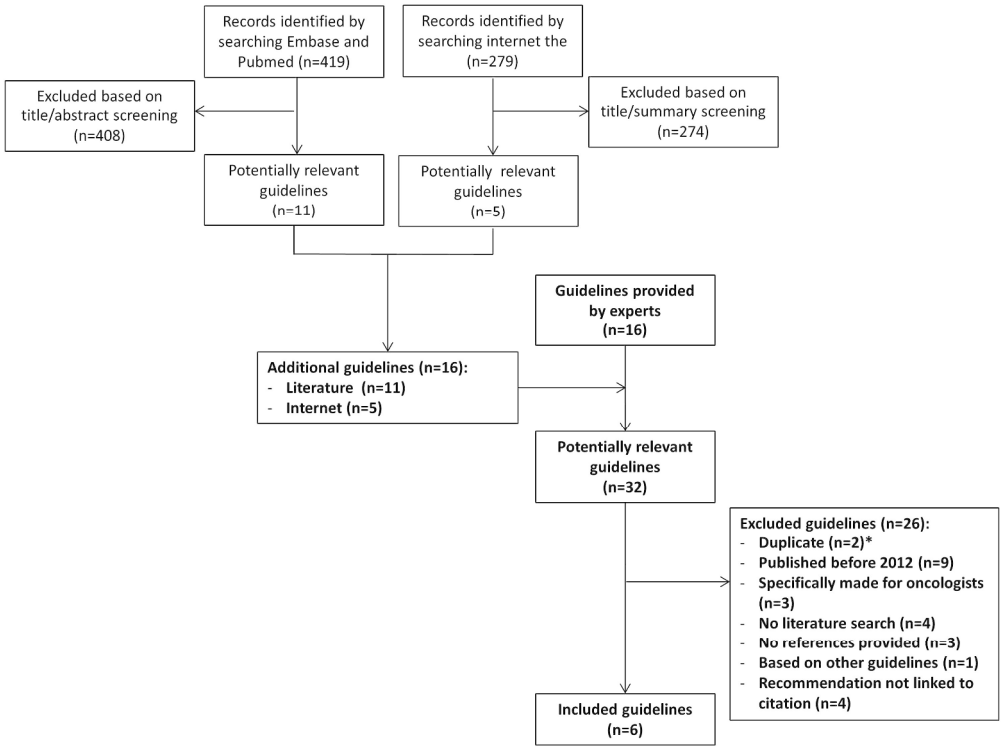

Figure 1. Flowchart outlining guideline selection

254x190mm (300 x 300 DPI)

Supplement 1. Search string Pubmed

(((((("breast cancer"[ti]) OR breast neoplasms[mesh]) OR "breast neoplasm*"[ti]) OR "breast carcinoma"[ti]) OR "breast tumor"[ti]) OR "breast tumour"[ti] Filters: Guideline; Publication date from 2012/01/01

Supplement 2. Internet search

National guideline clearinghouse

http://www.guideline.gov/search/search.aspx?term=breast+cancer

Guidelines International Network (G-I-N)

http://www.g-i-n.net/library/international-guidelines-library/@@guideline_search_results?type=basic&basic-searchable-text=breast+cancer

Cancer agency websites

Alberta Health Services (http://www.albertahealthservices.ca/)

American Cancer Society (http://www.cancer.org/)

American Society for Clinical Oncology (ASCO) (http://www.asco.org/)

British Colombia Cancer Agency (BCCA) (http://www.bccancer.bc.ca/)

Cancer Care Ontario (https://www.cancercare.on.ca/)

Cancer Council Australia (http://www.cancer.org.au/health-professionals/clinical-guidelines/)

Comprehensive Cancer Centre the Netherlands (IKNL) (http://www.oncoline.nl/)

European Society for Medical Oncology (ESMO) (http://www.esmo.org/)

Haute Autorité de Santé (http://www.has-sante.fr)

National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/)

National Institute for Health and Clinical excellence (NICE) (https://www.nice.org.uk/)

New Zealand Guidelines Group (NZGG) (http://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group)

Saskatchewan Cancer Agency (http://www.saskcancer.ca/)

Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/)

Sociedad Espanola de Oncologia Medica (SEOM) (http://www.seom.org/)

Supplement 3. Methodological assessment by AGREE II instrument

	CA	EU	GE	IT	NL	US
Domain 1. Scope and Purpose	69.4%	50.0%	80.6%	25.0%	91.7%	86.1%
Domain 2. Stakeholder Involvement	36.1%	13.9%	41.7%	38.9%	86.1%	83.3%
Domain 3. Rigour of Development	54.2%	35.4%	52.1%	41.7%	61.5%	66.7%
Domain 4. Clarity of Presentation	66.7%	69.4%	69.4%	63.9%	77.8%	80.6%
Domain 5. Applicability	45.8%	37.5%	41.7%	18.8%	50.0%	47.9%
Domain 6. Editorial Independence	33.3%	54.2%	54.2%	12.5%	66.7%	70.8%
Overall guideline assessment[1]	4.5	3	4	2.5	5.5	6
Recommended for use[2]	YM	YM	N	N	Y	Y

Note. Mean scaling domain percentages are presented. CA = Canada – Alberta, EU = Europe, GE = Germany, IT = Italy, NL = the Netherlands, US = United States

[1] Mean overall scores on a 1 (lowest possible quality) to 7(highest possible quality) scale.

[2] Y = Yes, YM = Yes with modifications, N = No

Supplement 4. Reclassification of levels of evidence

Level of evidence*	EU	GE	IT	US
1 – Meta-analysis or systematic review	I	IA	1^{++} – 1^{+}	I
2 – At least one RCT study	II	IB	1^{-}	IA – IC
3 – Non RCTstudy	III and IV	IC – IV	2^{++} – 3	2A, IIA – III

*The CA and NL guideline did not classify the evidence used.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (review)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 and 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and 6, and suppl. 1 and 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and suppl. 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7 and 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 - 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 (AGREE)

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 - 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 (AGREE), suppl. 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10 - 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10 - 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14 and 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Evidence based recommendations on care for breast cancer survivors for primary care providers: a review of evidence based breast cancer guidelines

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Breast tumours < ONCOLOGY, PRIMARY CARE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title page

Title: Evidence based recommendations on care for breast cancer survivors for primary care providers: a review of evidence based breast cancer guidelines

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ABSTRACT

Objective

To review evidence based (EB) recommendations on survivorship care for primary care providers (PCPs) in EB breast cancer guidelines.

Design and setting

Guidelines were collected via experts and via literature database, guideline database and cancer agency websites searches.

Method

EB guidelines in any language published between 2012 and 2017 were collected. EB recommendations on survivorship care relevant for PCPs were extracted and grouped into three categories (recurrence detection, long-term effects and recurrence prevention). The content of the recommendations was analyzed and summarized in the number and type of clinical topics addressed. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to evaluate the methodological quality of the guidelines.

Results

Six guidelines, of which two were of acceptable methodological quality, were included. One was specifically made for general practitioners. Fifteen clinical topics were identified. Guidelines differed in the clinical topics addressed and for some identical topics in the content of the recommendations. Many recommendations were based on low quality evidence. Recurrence detection received most attention, physical examination and mammography were often highlighted. Potential complications largely varied in number and type. Intimacy concerns, vaginal dryness, dyspareunia, fatigue, menopausal symptoms, peripheral neuropathy and lymphedema were reported in more than one guideline. Recurrence prevention was mentioned in four guidelines; all recommended physical activity.

Conclusion

The number of EB recommendations in guidelines is limited. Moreover, recommendations differ between guidelines and most are based on low quality evidence. More high quality research is needed to develop and adapt guidelines to support PCPs in providing optimal breast cancer survivorship care.

Keywords

Breast neoplasms, aftercare, guideline, primary care

Strengths and limitations of this study

- This study is the first to evaluate evidence based (EB) recommendations on care for breast cancer survivors relevant for primary care providers (PCPs) in EB breast cancer guidelines.
- Input from 36 countries was received, hereby, we were able to create a fairly complete overview of EB recommendations on care for breast cancer survivors for PCPs.
- The main limitation includes the validation of translations by non-native speakers, hereby, details of recommendations may be misinterpreted.
- Other limitations are that we have not assessed PCPs' views on the guidelines and that we have not examined the use of the guidelines by PCPs in practice.

INTRODUCTION

Due to the growth and ageing of the population, breast cancer prevalence rates are increasing.[1] Improvements in early detection and cancer treatment led to a growing number of women surviving breast cancer.[2]

After curative breast cancer treatment, patients usually receive follow-up care to detect cancer recurrence and to manage late and long-term consequences of treatment.[3] Primary care providers (PCPs) are increasingly involved in the follow-up care as a result of limited secondary care facilities, the growing number of breast cancer survivors and increasing costs.[4-6] Besides, a systematic review showed that there is evidence that follow-up for breast cancer survivors is effective in primary care.[7]

Another result of the rising number of survivors is that PCPs are seeing an increased number of survivors.[8 9] Many breast cancer survivors face short and long-term health consequences from cancer and cancer treatment, including physical and psychological consequences such as depression, pain and fatigue[10 11] and have more contacts with their PCP compared to control patients.[8 9]

Therefore, it is important that PCPs are able to provide optimal care for cancer survivors and meet the needs of these patients. Studies examining PCPs' views showed that PCPs prefer more guidance regarding recurrence risk management and consequences of cancer treatment.[12 13] To investigate which evidence based (EB) recommendations on care for cancer survivors are currently available in clinical practice guidelines relevant to PCPs, we assessed existing breast cancer guidelines and created an overview of EB recommendations on PCP care for breast cancer survivors.

METHODS

Two strategies were used to collect guidelines. As part of the European Union Joint Action Cancer Control (CanCon; www.cancercontrol.eu), which aims to contribute to reducing the cancer burden in the European Union, an inventory of existing guidelines in European countries via national experts was undertaken. In addition, the scientific literature, guideline databases and cancer agency websites were searched to complete the inventory of guidelines.

European inventory of guidelines

In Autumn 2014, experts from all European Union Member States and four non-EU countries (Norway, Switzerland, Iceland and Turkey) were asked to collect existing guidelines in their own country. Experts included representatives from national primary care associations, nursing associations, universities with a medical department and CanCon associated partners. At least three experts per country were approached. In December 2014, delegates were approached from the Cancer and Primary Care Research International Network (CA-PRI), the European Forum for Primary Care (EFPC), the European Society of General Practice/Family Medicine (WONCA Europe) and CanCon collaborating partners from non-responding countries. Inclusion criteria were that the guidelines needed to contain guidance on care for adult breast cancer survivors, subsequent to intentionally curative treatment, and that they were relevant to PCPs. Both national and regional guidelines were eligible.

Literature, guideline databases and cancer agency websites search

A bibliographical database search using the terms “guideline” and “breast cancer” was conducted in January 2015 to complete the inventory of guidelines (see Supplement 1 for the search strategy). Databases included Embase and Medline. Also, the National Guideline Clearinghouse website in the United States, the Guidelines International Network (G-I-N)

website and national cancer agency websites were searched for relevant breast cancer guidelines (see Supplement 2 for all cancer agency websites that were searched). Searches were conducted without any language restriction. The inclusion criteria were the same as for selection of the guidelines from the inventory. In June 2017, the literature, the guideline databases and cancer agency websites searches were repeated to reveal updates from the guidelines and guidelines published after January 2015.

Selection of guidelines

Guidelines obtained from the guideline databases and cancer agency websites searches were selected on the basis of title. Records from the scientific literature search were screened on the basis of title and abstract/summary. Screening of guidelines was performed by one researcher (IS). Records were considered if they included breast cancer guidelines. Guidelines meeting the following criteria were reviewed in full-text: the guideline originated from Western countries (EU countries, Iceland, Norway, Switzerland, Turkey, USA, Canada, New Zealand and/or Australia) and focused on adult breast cancer patients. Inclusion criteria were a publication date from 2012 to 2017, as older guidelines may be outdated[14], and meeting the definition of an EB guideline[15] including recommendations intended to optimize patient care that are informed by the best available knowledge. If more versions of a guideline existed, the most recent version of a guideline was used. Guidelines were excluded if oncologists were the only target audience, if they duplicated another guideline, if the guideline only focused on one phase in the care process such as early detection, screening, treatment or palliative care, on advanced cancer or metastasis, or on hereditary cancer survivors, and if guidelines did not link recommendations to graded evidence or to scientific citations. Information from guidelines in languages other than English or Dutch were translated. Data from the Croatian, Danish, Finnish, Norwegian and Polish guidelines were

translated by the expert who provided the guidelines. Colleague researchers from the NIVEL institute who master the specific language translated the data from the French, German and Italian guidelines.

Quality assessment

The methodological quality of the guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[16] AGREE II is a validated 23-item instrument used to evaluate six domains: scope and purpose (3 items), stakeholder involvement (3 items), rigor of development (8 items), clarity of presentation (3 items), applicability (4 items) and editorial independence (2 items). These six domains are followed by two extra items ("Overall assessment"), which indicate the overall quality of the guideline and whether the reviewers recommend the guideline for use in practice. The English and Dutch guidelines were assessed by two researchers (IS, JK), the German and Italian guidelines were each reviewed by two colleagues with a high mastery of the specific language. All items were rated from 1 (strongly disagree) to 7 (strongly agree). Items for which scores differed more than one point were discussed by the reviewers. Rationales for scores were explained and scores were revised when this was considered necessary. Afterwards, a total score for each domain was calculated by summing up all item scores within a domain and by scaling the total score as a percentage of the maximum possible score of a domain.[17] Domain scores greater than 60% were considered acceptable.[18-21] The researchers recommended to use guidelines when three or more domains were scored as acceptable and the rigor of development was of good quality.[18] In addition, the researchers recommended modifications before using the guideline when at least two domains were considered acceptable and when the rigor of development was of moderate quality. Lower scores resulted in the recommendation to not using the guideline.

Content analysis

EB recommendations were categorized into 'recurrence detection', 'long-term effects' and 'recurrence prevention' by two researchers independently (IS and JK). Subsequently, a clinical topic list per category was composed. EB Recommendations were independently allocated to clinical topics by two researchers (IS and JK). Disagreements arising from decisions on either categorization or allocation into clinical topics were resolved by discussion with a third researcher (FS). The categorization and clinical topics were discussed and approved in a meeting of experts participating in work package 7 (community cancer care) of the European Union Joint Action Cancer Control.[22 23] Experts from five European countries participated in this meeting.

RESULTS

Guidelines

Response was received from 45 experts from all 32 approached countries and 16 provided a current breast cancer guideline. The literature search yielded 419 results, the guideline databases and cancer agency websites searches in 279 results. In total, 16 additional potentially relevant guidelines were considered (Figure 1). After removal of one duplicate and one guideline[24] of which recommendations on care for breast cancer survivors were included in another guideline that focused on breast cancer survivors[25] and elimination of guidelines based on other exclusion criteria (Figure 1), six guidelines were included (Table 1). These guidelines originated from Canada, Germany, Italy, the Netherlands and the United States. And also the guideline from the European Society for Medical Oncology (ESMO) was included. This organization publishes guidelines that may be adopted by European countries. However, most European countries develop their own guideline. Three guidelines were

published in English[25-27], one in Dutch[28], one in German[29] and one in Italian.[30] One guideline was specifically made for general practitioners.[28]

Table 1. Included breast cancer guidelines

Country (ID code)	Year of publication	Title in English
Canada – Alberta (CA)	2015	Follow-up care for early-stage breast cancer[27]
Europe (EU)	2015	Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[26]
Germany (GE)	2012	Interdisciplinary S3 guideline for the diagnosis, treatment and aftercare of breast cancer[29]
Italy (IT)	2016	Breast cancer guideline[30]
The Netherlands (NL)	2016	NHG Guideline Breast cancer[28]
United States (US)	2015	American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline[25]

Methodological quality

The guidelines were evaluated by the researchers using the AGREE II instrument. Mean scaled domain percentages, mean overall appraisal scores and appraiser recommendations for the use of guidelines are shown in supplement 3. Two guidelines (NL and US) were recommended by the reviewers for use in clinical practice without modifications. Both of these guidelines scored "acceptable" on five out of the six domains, only the scores on the domain 'applicability' were moderate. For two other guidelines (CA and GE) modifications were recommended by the reviewers before using these guidelines in practice. These guidelines scored "acceptable" on two domains and moderate on the rigor of development domain. In particular, the quality of the rigor of development of these guidelines needed improvement. Two guidelines (EU and IT) were not recommended for use due to the low methodological quality.

Mean overall scores ranged between 2.5 and 6, with the highest score for the US guideline. Domain scores varied per domain. The only domain on which all guidelines scored "acceptable" was the clarity of presentation domain (mean 71.3%, range: 63.9 – 80.6%). Four

guidelines scored "acceptable" on the scope and purpose domain (mean 67.1%, range: 25.0 – 91.7%). More variable scores were seen on the domains 'rigor of development' (mean 51.9%, range: 35.4 – 66.7%), 'editorial independence' (mean 18.6%, range 12.5 – 70.8%), and 'stakeholder involvement' (mean 50.0%, range: 13.9 – 86.1%). The only domain that scored overall "moderate" was the applicability domain (mean 40.3%, range: 18.8 – 50.0%).

Level of evidence

Guidelines used different systems to grade the evidence. To enable comparisons of the level of evidence of selected recommendations, we created a uniform grading system of research studies: 1) Meta-analysis or systematic review, 2) RCT study, 3) non-RCT study. Supplement 4 provides a table showing the reclassification of gradations used in the guidelines.

Clinical recommendations

Within the three categories (recurrence detection, long-term effects and recurrence prevention) 15 clinical topics were identified (Table 2). None of the guidelines contained recommendations on all topics. Most recommendations were available on **recurrence detection** and most of these concerned diagnostic testing. Mammography was recommended in the follow-up of breast cancer patients in five guidelines and physical examination in three. Other imaging or laboratory testing was not recommended in routine recurrence detection, except for ultrasound, which was recommended in one guideline in combination with mammography. Three guidelines recommended genetic counselling for risk evaluation and one advised to educate patients about signs of recurrence.

Five guidelines contained recommendations on **long-term effects** of breast cancer. Long-term effects are defined as "problems that are caused by breast cancer or the treatment of breast cancer that may continue for months or years".[31] Potential complications of breast cancer

and/or breast cancer treatment were listed in the guidelines. For some of these complications treatment options were given. Recommendations on psychological support were given in two guidelines; it was highlighted that psycho-oncological care is part of the overall concept of the care for breast cancer survivors and that psychosocial care should be offered if needed.

Five guidelines included recommendations on **recurrence prevention** and all recommended an active lifestyle for breast cancer survivors. Counseling to achieve or maintain a healthy body weight was recommended in four guidelines. The other recommendations on recurrence prevention included a healthy diet, limited alcohol consumption and stop smoking.

Table 2. Overview of clinical topics covered (Y) in included guidelines

	CA	EU	GE	IT	NL	US
Recurrence detection						
Awareness	-	-	-	Y	-	Y
Self-examination	Y	-	-	-	Y	-
Physical diagnostic tests	-	-	-	Y	Y	Y
Laboratory diagnostic tests	-	Y	Y	Y	-	Y
Diagnostic imaging	-	Y	Y	Y	Y	Y
Risk of recurrence	-	Y	-	Y	-	-
Organization of care	-	-	-	-	-	Y
Long-term effects						
Potential complications	Y	Y	Y	Y	Y	Y
Treatment of complications	Y	-	Y	Y	Y	Y
Psychological support	-	-	Y	-	-	Y
Recurrence prevention						
Physical activity	Y	Y	Y	Y	-	Y
Nutrition	-	-	-	-	-	Y
Weight management	Y	Y	-	Y	-	Y
Alcohol consumption	Y	-	-	Y	-	Y
Smoking cessation	-	-	-	Y	-	Y

Note. CA = Canada-Alberta, EU = Europe, GE = Germany, IT = Italy, NL = The Netherlands, US = United States

Recommendations on frequency of diagnostic testing

Three guidelines provided recommendations on frequency of history taking and physical examination (Table 3). All stated that history taking and physical examination are important to detect recurrence. The recommended frequency was the same in two guidelines despite that the level of evidence differed. The third guideline, specifically targeting general practitioners, included recommendations on history taking and physical examination five years after primary treatment, when the PCP is in charge of follow-up.

Four guidelines included recommendations on the frequency of mammography. Three recommended annual mammography and one recommended a mammogram every two years after five years. Specifications for mammography differed among the guidelines. One guideline recommended to perform mammography with ultrasound, two indicated at which side the mammography should take place, and one included a time frame after which the first mammography after initial treatment should take place.

Table 3. Evidence based recommendations on frequency of diagnostic tests after curative breast cancer treatment

Country of guideline	Recommendation	Level of evidence
History and physical examination		
IT	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	1
NL	After five years[1]: annually	1
US	Every 3 to 6 months in the first three years after primary treatment, then every 6 to 12 months for the next two years, then annually	3
Mammography		
EU	Annually ipsilateral (after breast conserving therapy) and/or a contralateral with ultrasound	3
IT	One year after the diagnostic mammography or at least 6 months after the end of radiotherapy, then annually	3
NL	After five years[1]: every two years	1
US	Annually on the intact breast for women who have received a unilateral mastectomy and annually of both breasts for women with lumpectomies	3

Note. Level of evidence 1 = Meta-analysis or systematic review, level of evidence 3 = Non RCTstudy

[1]Five years after primairy treatment the PCP is in charge of the care for cancer survivors

Potential complications of breast cancer and breast cancer treatment

All guidelines listed potential complications of breast cancer and breast cancer treatment but differed in the number and nature of these complications (Table 4). The EU guideline mentioned one potential complication, whereas the US guideline reported eight potential complications. The guidelines reported a total number of 14 different potential complications, of which seven (intimacy concerns, vaginal dryness, dyspareunia fatigue, menopausal symptoms, peripheral neuropathy and lymphedema) were reported by two guidelines. All guidelines attributed (some of) the potential complications to cancer treatment. Five potential complications were associated with hormone therapy, four were linked to chemotherapy and three to radiotherapy.

Table 4. Potential complications of breast cancer (treatment)

Potential complication	Associated treatment	Country of guideline	Level of evidence
Symptoms/complaints musculoskeletal system			
Osteoporosis	H	EU	1
Immobilized shoulder	NS	GE	1
Sexual problems			
Painful intercourse, loss of sensation, intimacy concerns, decreased libido	NS	CA	3
	NS	NL	3
Vaginal dryness	H	CA	3
	H	US	2
Dyspareunia, other symptoms of vulvovaginal atrophy	H	CA	3
	NS	NL	3
General/unspecified complaints			
Pain	G, H, R, S	US	1
Fatigue	NS	GE	1
	C, G	NL	1
	C, R	US	1

Shortness of breath	R	US	1
Menopausal problems			
(premature) symptoms of menopause	NS	CA	3
	NS	US	2
Neurological complaints			
Peripheral neuropathy	C	CA	3
	C, S	US	2
Psychological problems			
Cognitive impairment	C	US	2
Distress, depression and anxiety	G	US	1
Other problems			
Lymphedema	AL	GE	2
	AL, R	NL	1
Cardiac problems	H	IT	2

Note. H: Hormone therapy, NS: not specified, C: chemotherapy, R:Radiotherapy, S: Surgery, G:General, AL: axillary lymphadenectomy. Level of evidence 1 = Meta-analysis or systematic review, level of evidence; 2 = At least one RCT study, level of evidence; 3 = Non RCT study

DISCUSSION

Access to the best available evidence is crucial for providing optimal patient care. EB clinical guidelines summarize the available evidence and contain scientifically valid recommendations. This guideline inventory study is the first to evaluate whether recommendations on care for breast cancer survivors relevant for PCPs are available in EB breast cancer guidelines, representing the current status of EB recommendations on care for breast cancer survivors. We identified six EB guidelines, of which only two had acceptable methodological quality, including a limited number of EB recommendations. Two guidelines were specific on care for breast cancer survivors and only one guideline specifically targeted PCPs. Moreover, recommendations differed between guidelines and most were based on low quality evidence.

Strengths and limitations

A strength of this study is the international input of 36 countries, including 32 European countries and Canada, USA, Australia and New Zealand. This enabled us to create a fairly complete overview of EB recommendations from EB guidelines for PCPs on care for breast cancer survivors. A limitation of our study is the absence of validation of translations by non-native speakers. Details may be misinterpreted, but we do not expect that the key recommendations of the guidelines differed. Another limitation is that only one researcher screened the literature, the guideline databases and cancer agency websites to identify additional guidelines. However, in case of any doubt, the inclusion was discussed with a second researcher. Finally, we have not examined the views of PCPs on the guidelines and their use of the guidelines in clinical practice nor the views of breast cancer patients on the care of PCPs.

Comparison with existing literature

Only one guideline specifically mentioned PCPs as target audience despite increasing demands for greater involvement of PCPs in care for breast cancer survivors.[4-6] The fact that recommendations are often not targeted at PCPs, was also highlighted in a recent publication that stated that the role of the PCP in care for cancer survivors is currently not well defined. However, PCPs can have an important role in the care for cancer survivors as they know details of patient's history and social context, comorbidity, and are alert on considering individual views and preferences.[32]

The guidelines included recommendations on different categories and clinical topics. The categories identified were consistent with the domains described by the Institute of Medicine (IOM) report: 'From Cancer Patient to Cancer Survivor: Lost in Transition'.[3] In addition, we defined fifteen topics. None of the guidelines discussed all these topics. A possible

explanation for this is lack of evidence on specific topics[33] or the focus on follow-up care and recurrence detection rather than on the whole care process for breast cancer survivors.

The content analyses on the available topics revealed consensus on seven topics, such as the frequency of tests to detect breast cancer recurrence. On four topics, recommendations differed between the guidelines. In particular, listed potential complications differed considerably. Univocal guidance would help PCPs to raise awareness on the potential consequences of both cancer and its treatment.[34]

Guidelines were only included if they were published after 2011. This selection criterion was applied as it is has been demonstrated that guidelines may be outdated after a few years[14] and that the turnover rate of research evidence is high in the field of cancer.[32] Ten guidelines were excluded due to lack of transparency on the supporting evidence. A previous study[35] showed that the quality of oncology guidelines was higher than non-oncology guidelines. Our study revealed that there is still room for improvement concerning oncology guidelines.

Implications for practice and research

The 'American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline' yielded EB recommendations on most clinical topics (on 13 out of the 15 identified topics) and mentioned the PCPs specifically as target group of the guideline. Furthermore, this guideline scored highest on the AGREE II evaluation and was recommended for use in clinical practice by both researchers that appraised the guidelines. Currently this guideline seems to be the most useful guideline for PCPs. However, this guideline does not include EB recommendations on all clinical topics and many recommendations are based on low quality evidence.

Therefore, more high quality evidence is needed to develop and adapt breast cancer guidelines to support PCPs in providing optimal breast cancer survivorship care. Guidelines should not be solely designed for PCPs as it is important to provide integrated care to breast cancer survivors. PCPs being part of integrated care indicated that they need more guidance in order to provide good quality care to cancer survivors. Therefore, it is important to involve PCPs in the development and adaptation of the guidelines and to specifically consider PCPs as target group of the guideline in order to provide optimal breast cancer survivorship care. If PCPs are supported by high quality EB guidelines, transfer of care for breast cancer survivors from secondary to primary care could be better facilitated.

In addition to the availability of high quality EB guidelines, it is important to consider the views of PCPs and breast cancer patients on optimal care in developing guidelines. Exploring views of PCPs and patients on the usefulness of guidelines and the preferred setting of care for breast cancer survivors is an area for future research.

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Contributors IS, JK, FS, TA, JB conceptualized the study and defined the content analysis strategy. IS collected and reviewed the guidelines and extracted the data. IS and JK categorized the recommendations and allocated recommendations into clinical topics. IS, JK, FS, JB provided preliminary interpretation of findings. IS, JK, FS, TA, JB contributed in drafting the manuscript, critically helped in the interpretation of the results and provided relevant intellectual input.

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Competing interests None declared

Availability of data: The guidelines, translations and categorization system used during the current study are available from the corresponding author on reasonable request.

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Figure 1. Flowchart outlining guideline selection

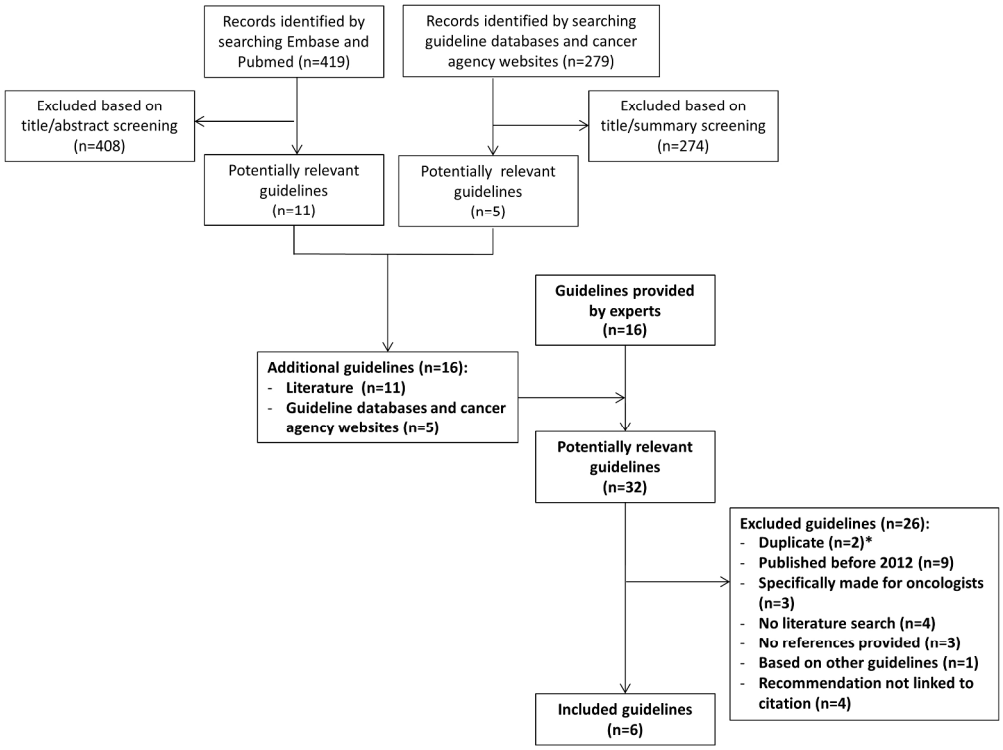

Figure 1. Flowchart outlining guideline selection

254x190mm (300 x 300 DPI)

Supplement 1. Search string Pubmed

(((((("breast cancer"[ti]) OR breast neoplasms[mesh]) OR "breast neoplasm*"[ti]) OR "breast carcinoma"[ti]) OR "breast tumor"[ti]) OR "breast tumour"[ti] Filters: Guideline; Publication date from 2012/01/01

Supplement 2. Cancer agency websites searched

Cancer agency websites
Alberta Health Services (http://www.albertahealthservices.ca/)
American Cancer Society (http://www.cancer.org/)
American Society for Clinical Oncology (ASCO) (http://www.asco.org/)
British Colombia Cancer Agency (BCCA) (http://www.bccancer.bc.ca/)
Cancer Care Ontario (https://www.cancercare.on.ca/)
Cancer Council Australia (http://www.cancer.org.au/health-professionals/clinical-guidelines/)
Comprehensive Cancer Centre the Netherlands (IKNL) (http://www.oncoline.nl/)
European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
Haute Autorité de Santé (http://www.has-sante.fr)
National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/)
National Institute for Health and Clinical excellence (NICE) (https://www.nice.org.uk/)
New Zealand Guidelines Group (NZGG) (http://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group)
Saskatchewan Cancer Agency (http://www.saskcancer.ca/)
Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/)
Sociedad Espanola de Oncologia Medica (SEOM) (http://www.seom.org/)

Supplement 3. Methodological assessment by AGREE II instrument

	CA	EU	GE	IT	NL	US
Domain 1. Scope and Purpose	69.4%	50.0%	80.6%	25.0%	91.7%	86.1%
Domain 2. Stakeholder Involvement	36.1%	13.9%	41.7%	38.9%	86.1%	83.3%
Domain 3. Rigour of Development	54.2%	35.4%	52.1%	41.7%	61.5%	66.7%
Domain 4. Clarity of Presentation	66.7%	69.4%	69.4%	63.9%	77.8%	80.6%
Domain 5. Applicability	45.8%	37.5%	41.7%	18.8%	50.0%	47.9%
Domain 6. Editorial Independence	33.3%	54.2%	54.2%	12.5%	66.7%	70.8%
Overall guideline assessment[1]	4.5	3	4	2.5	5.5	6
Recommended for use[2]	YM	N	YM	N	Y	Y

Note. Mean scaling domain percentages are presented. CA = Canada – Alberta, EU = Europe, GE = Germany, IT = Italy, NL = the Netherlands, US = United States

[1] Mean overall scores on a 1 (lowest possible quality) to 7(highest possible quality) scale.

[2] Y = Yes, YM = Yes with modifications, N = No

Supplement 4. Reclassification of levels of evidence[1]

Level of evidence[2]	EU	GE	IT	US
1 – Meta-analysis or systematic review	I	IA	1^{++} – 1^{+}	I
2 – At least one RCT study	II	IB	1^{-}	IA – IC
3 – Non RCTstudy	III and IV	IC – IV	2^{++} – 3	2A, IIA – III

[1]Guidelines used different systems to grade the evidence. To compare the level of evidence of selected recommendations, the authors created a uniform grading system of research studies.

[2]The CA and NL guideline did not classify the evidence used.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 (review)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 and 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and 6, and suppl. 1 and 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 and suppl. 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7 and 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 - 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 (AGREE)

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 - 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9 (AGREE), suppl. 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10 - 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10 - 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16 and 17
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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