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REVIEW

A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer

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Abstract Breast cancer is a global health concern. In fact, breast cancer is the primary cause of death among women worldwide and constitutes the most expensive malignancy to treat. As health care resources are finite, decisions regarding the adoption and coverage of breast cancer treatments are increasingly being based on "value for money," i.e., cost-effectiveness. As the evidence about the cost-effectiveness of breast cancer treatments is abundant, therefore difficult to navigate, systematic reviews of published systematic reviews offer the advantage of bringing together the results of separate systematic reviews in a single report. As a consequence, this paper presents an overview of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer to inform policy and reimbursement decision-making. A systematic review was conducted of published systematic reviews documenting cost-effectiveness analyses of breast cancer treatments from 2000 to 2014. Systematic reviews identified through a literature search of health and economic databases were independently assessed against inclusion and exclusion criteria. Systematic reviews of original evaluations were included only if they targeted breast cancer patients and specific breast cancer treatments (hormone therapy, chemotherapy, and targeted therapy only), documented incremental cost-effectiveness ratios, and were reported in the English language. The search strategy used a combination of these key words: "breast cancer," "systematic review/meta-analysis," and "cost-effectiveness/economics." Data were extracted using predefined extraction forms and qualitatively appraised using the assessment of multiple systematic reviews (AMSTAR) tool. The literature search resulted in 511 bibliographic records, of which ten met our inclusion criteria. Five reviews were conducted in the early-stage breast cancer setting and five reviews in the metastatic setting. In early-stage breast cancer, evidence about trastuzumab value differed by age. Trastuzumab was cost-effective only in women with HER2-positive breast cancer younger than 65 years and over a life-time horizon. The cost-effectiveness of trastuzumab in HER2-positive metastatic breast cancer yielded conflicting results. The same conclusions were reached in comparisons between vinorelbine and taxanes. In both early stage and advanced/metastatic breast cancer, newer aromatase inhibitors (AIs) have proved cost-effective compared to older treatments. This overview of systematic reviews shows that there is heterogeneity in the evidence concerning the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. The cost-effectiveness of these treatments depends

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not only on the comparators but the context, i.e., adjuvant or metastatic setting, subtype of patient population, and perspective adopted. Decisions involving the cost-effectiveness of breast cancer treatments could be made easier and more transparent by better harmonizing the reporting of economic evaluations assessing the value of these treatments.

Keywords Breast cancer · Hormone therapy · Chemotherapy · Targeted therapy · Economic evaluation · Cost-effectiveness · Systematic review

Background

Breast cancer, a type of cancer that develops from breast tissue, [1] is a global health concern. In fact, breast cancer is the primary cause of death among women worldwide [2] and constitutes one of the most expensive malignancies to treat. [3] As such, breast cancer puts a heavy burden on patients and their families, as well as healthcare systems across the world. [4].

Strategies to combat the breast cancer pandemic are geared toward prevention, early detection, and treatment. [5] Over the past decades, medical breakthroughs have shown that breast cancer is a multifaceted disease with different subtypes and stages. This medical progress has shaped the development of strategies to treat breast cancer more efficiently.

Since health care systems worldwide have finite resources, the adoption (clinical decision) and coverage of new breast cancer treatments are increasingly being made based on the concept of "value for money" (cost-effectiveness), which takes into consideration the costs associated with the selection of a particular treatment over its comparators. [6–8].

There is a plethora of published studies (individual studies and systematic reviews) of the cost-effectiveness of breast cancer treatments that decision-makers can access. However, for most decision-makers, it is difficult to navigate through and utilize this large body of evidence when making decisions routinely. Systematic reviews of published systematic reviews are designed to help solve this issue by bringing together the results of separate systematic reviews in a single report. Systematic reviews themselves vary in terms of quality and scope and may duplicate studies. [9, 10] Using evidence from reviews of systematic reviews allows quick and easy comparison of existing findings of a large volume of studies, and identification of the direction (unidirectional or conflicting evidence) and magnitude of the evidence.

The objective of this study was to systematically identify and review published systematic reviews on the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer, building on the methods proposed by Smith et al. [10] Based on the findings of the review, the authors make recommendations for future research aimed at documenting the cost-effectiveness of breast cancer treatments in order to enlighten policy and reimbursement decision-making.

Methods

Sources and search strategy

A systematic review was conducted of published systematic reviews documenting the cost-effectiveness of breast cancer treatments. As such, the unit of analysis in the current study is a systematic review of studies of the topic under evaluation, unlike traditional systematic reviews. The systematic reviews were identified through a literature search of the following databases for the period January 1, 2000–December 31, 2014: Ovid Medline and Embase, the US National Library of Medicine's PubMed, and ISI's Web of Knowledge, Cochrane Database of Systematic Reviews, Center for Reviews and Dissemination (CRD) database (including the National Health Service Economic Evaluation Database, the Database of Abstracts of Reviews of Effects, and Health Technology Assessments), and Econlit. Keywords used to develop the search strategy comprised "breast cancer" terms coupled with "systematic review/meta-analysis" and "cost-effectiveness/economics" terms using Boolean operators as well as truncation and wildcard operators (see Appendix). In addition, a manual search of the reference lists of previously captured articles was carried out to increase the likelihood of locating relevant systematic reviews. The grey literature was also searched using "Grey Matters," [11] a tool developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) to help find evidence that is not commercially published. Finally, one expert AJM in the field of breast cancer provided the authors with feedback on potential sources of evidence on the topic.

Review selection process

The records obtained from the literature search, containing titles and abstracts of the reviews, were exported into Refworks. Figure 1 depicts the selection process of articles included in our systematic review. First, duplicates were identified and removed from the pool of bibliographic records. Then, three independent reviewers (VD, RT, and VS) screened the abstracts of the unique records, and those considered out of scope [no systematic review conducted, review targeting interventions other than treatments and a

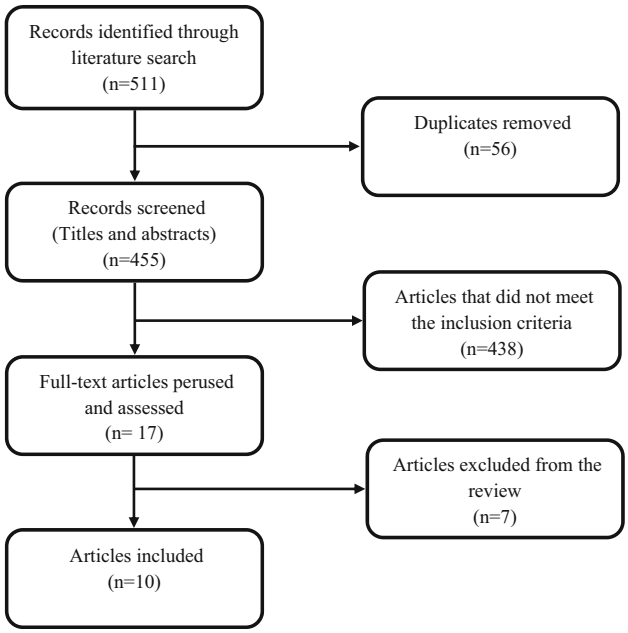

Fig. 1 Flow diagram depicting the articles selection process

different disease than breast cancer] were discarded. Afterward, available full-text copies of the remaining papers were retrieved, perused, and assessed against the inclusion and exclusion criteria by VD, RT, and VS. Disagreements were resolved by consulting with two additional reviewers (HX and AJM). Systematic reviews were included only if they targeted breast cancer patients, specific breast cancer treatments (hormone therapy, chemotherapy, and targeted therapy), documented incremental cost-effectiveness ratios and were reported in English language. The review was not restricted to a specific subtype or stage of breast cancer. However, articles were excluded if they presented costs or benefits information only, described a methodological approach only, or were non-journal papers except reports.

Study characteristics, findings, and quality assessment of reviews

Data from the included papers were extracted and synthesized (numerically) using predefined extraction forms documenting the characteristics of the systematic reviews (Tables 1, 2). The characteristics of the studies included in the assessed systematic reviews (Tables 3, 4, 5) were interventions, objectives, main conclusions, (Table 6) and the quality assessment of systematic reviews (Table 7). As suggested by Smith et al. [10] the quality and strength of evidence of each systematic review were assessed against a validated tool named assessment of multiple systematic reviews (AMSTAR). [12] The tool covers 11 domains from the establishment of the research question to the assessment of publication bias. AMSTAR is purported to be an enhanced and refined version of previous tools. [12] Since the tool does not allow for quantifying the performance of the systematic reviews against its domain, we developed a scoring scale matching the fourth-point response choices of the AMSTAR, based on previously published approaches. [5, 13] The four-point response choices, *Yes*, *No*, *Can't answer*, assign the scores 1, 0, 0. For dimensions that were not applicable, the maximum score was reduced by 1 for comparability purposes across studies. The new scoring scale was used to adapt the existing AMSTAR tool to fit our needs (Table 1). The scores were expressed in percentages to facilitate the comparison of the performances of the systematic review with regard to quality.

Results

Literature search

The literature search yielded 511 bibliographic records (including records obtained from manual and grey literature searches) (Fig. 1). From this initial pool of records, 56 duplicates were identified and excluded. Following the titles and abstracts review, 455 (including one reference retrieved by hand search) studies were rejected for being out of scope. Of the remaining records subject to the full-text review, seven were removed using the exclusion criteria. The final set of bibliographic records reviewed was composed of ten systematic reviews.

Characteristics of the reviews and their included studies

Ten systematic reviews that both assessed studies on the cost-effectiveness of breast cancer treatment strategies and met our inclusion criteria were published between 2001 and 2014. The reviews were similar in regard to their purpose, but different in the stated objectives and interventions compared. Table 2 highlights the main characteristics of each systematic review. Regarding the time horizon covered for review searches, only one study was from inception of the database to 2011. [14] For the remainder, three review searches covered 15 years of publications, [15–17] two review searches were conducted over a 10-year period, [18, 19] two review studies had a time horizon of 6 years, [20, 21] and the last two review searches covered, respectively, 9 [22] and 3 years. [23] The sample sizes of the systematic reviews ranged between four [16, 23] and 23. [20] Tables 3, 4, 5 highlight the main characteristics of studies that were included in each of the systematic reviews. All of the reviews covered a wide

Table 1 Modified AMSTAR tool

Domains	Response choice	Scoring scale
1. Was an ''a priori'' design provided?	Yes	1
The research question and inclusion criteria should be established before the conduct of the review	No	0
	Can't answer	0
	Not applicable	−1*
2. Was there duplicate study selection and data extraction?	Yes	1
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place	No	0
	Can't answer	0
	Not applicable	−1*
3. Was a comprehensive literature search performed?	Yes	1
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found	No	0
	Can't answer	0
	Not applicable	−1*
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes	1
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc	No	0
	Can't answer	0
	Not applicable	−1*
5. Was a list of studies (included and excluded) provided?	Yes	1
A list of included and excluded studies should be provided	No	0
	Can't answer	0
	Not applicable	−1*
6. Were the characteristics of the included studies provided?	Yes	1
In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported	No	0
	Can't answer	0
	Not applicable	−1*
7. Was the scientific quality of the included studies assessed and documented?	Yes	1
"A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant	No	0
	Can't answer	0
	Not applicable	−1*
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	1
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations	No	0
	Can't answer	0
	Not applicable	−1*
9. Were the methods used to combine the findings of studies appropriate?	Yes	1
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?)	No	0
	Can't answer	0
	Not applicable	−1*
10. Was the likelihood of publication bias assessed?	Yes	1
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test)	No	0
	Can't answer	0
	Not applicable	−1*
11. Was the conflict of interest included?	Yes	1
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies	No	0
	Can't answer	0
	Not applicable	−1*

spectrum of geographical areas [Euro zone; North America; Asia Latin America; and Australasian eco zone (Table 3)] in which the individual economic evaluations were conducted. In terms of breast cancer stage, 54 % of economic evaluations assessed treatment strategies for advanced stage cancer, while 45 % of them evaluated treatment options for early stage. 59 % of these economic evaluations were cost-effectiveness analyses, while 41 % were cost-utility analyses. The majority (76 %) of these evaluations were model-based and the remaining evaluations were trial-based. With regard to the temporal framework of the economic evaluations included in the reviews, 18 and 82 % of these studies were conducted over a short-term (between 0 and 5 years) and long-term (beyond 5 years) periods, respectively. The most commonly adopted perspective in reviewed economic evaluations was the payer perspective (71 %). The societal perspective was adopted in 10 % of the cases, while other perspectives (different than payer or societal—e.g., US hospital) represented 19 % of the cases. Data sources were relatively well-documented in the majority of individual studies. These studies generally applied discounting, conducted sensitivity analyses, and presented incremental analyses.

Study findings and quality assessment of the reviews

The study findings can be categorized into two groups, results for early breast cancer and advanced/metastatic breast cancer. These results are summarized in Table 6.

Early breast cancer

Five reviews examined the cost-effectiveness of treatments for early breast cancer.

John-Baptiste et al. [17] reviewed economic evaluations that compared AIs (anastrozole and letrozole) versus tamoxifen. Studies included in this review suggest that choosing AIs for first-line therapy for early breast cancer represents good value for money compared to tamoxifen. However, John-Baptiste et al. [17] recommended that caution be used when drawing conclusions about the value of AIs versus tamoxifen, as these studies tend to overestimate the cost-effectiveness of AIs. Their results may, therefore, be suboptimal to inform policy decisions. This review was of relative good scientific quality (score = 70 %) as per the standards of the modified AMSTAR tool.

In the same vein, Frederix et al. [19] appraised economic evaluations comparing AIs (anastrozole, letrozole, exemestane, combinations) versus tamoxifen. Unfortunately, the included studies did not come to a consensus as to whether AIs represent better value for money compared to tamoxifen. In fact, some economic evaluations presented a very low incremental cost-effectiveness ratio (ICER) while others presented very high ICER, although they used very similar data sources. The review by Frederix et al. was judged of relatively good scientific quality (score = 70 %), according to the modified AMSTAR tool standards.

Ferrusi et al. [14] reviewed economic evaluations of adjuvant trastuzumab targeted therapy to assess the extent to which decision support recommendations were adopted by economic evaluations producers. The adjuvant use of trastuzumab was the base-case scenario in these economic evaluations, while the long-term use of trastuzumab in MBC was considered in sensitivity analyses. Trastuzumab appeared to be generally cost-effective when its use was limited to a year. The short-term use (base-case scenario) of trastuzumab was more cost-effective than longer term use (sensitivity analysis) from a health economic point of view. The cost-effectiveness of trastuzumab was heavily influenced by the choice of testing strategy (details not reported). The scientific quality of this review was judged fair (score = 60 %), according to the modified AMSTAR standards.

Chan et al. [18] assessed economic evaluations comparing trastuzumab versus standard treatment/chemotherapy without trastuzumab. The authors stated that the ICERs reported in their systematic review supported the conclusion that trastuzumab was cost-effective as adjuvant therapy in women with HER2-positive breast cancer younger than 65 years, over a life-time horizon. However, adjuvant trastuzumab was not found to be cost-effective when used in HER2-positive breast cancer patients older than 75 years, or with a time horizon of less than 10 years. Using the modified AMSTAR tool, this review was judged fair (score = 60 %) in terms of its scientific quality.

Norum 2006 [23] assessed the cost-effectiveness of adjuvant trastuzumab in early breast cancer and made recommendations for future economic evaluations. Even though the number of individual studies (4) included in the review was limited, the adjuvant trastuzumab in early breast cancer was found cost-effective, except for subgroups of stage III breast cancer and seniors (65 years and beyond). The scientific quality of this review was deemed relatively good (score = 70 %), based on the modified AMSTAR tool.

Advanced/metastatic breast cancer

In the metastatic setting, five reviews examined the cost-effectiveness of treatments for breast cancer.

Benedict et al. [21] evaluated the cost-effectiveness of aromatase inhibitors (AIs)—letrozole, exemestane, anastrozole, and fulvestrant in metastatic hormone receptor-positive breast cancer relative to either tamoxifen or megestrol as first- and second-line therapy, respectively.

Table 2 Characteristics of the systematic reviews

Authors, year	Study objectives	Interventions compared	Time Horizon covered	Sample size
Benedict and Brown [21]	To review the cost-effectiveness of hormonal treatment options for advanced breast cancer	Aromatase inhibitors versus Tamoxifen for first-line therapy. Newer aromatase inhibitors (letrozole, anastrozole, exemestane, fluvestrant) versus older treatments (megestrol, tamoxifen) for second-line therapy for advanced breast cancer	1998–2004	17
John-Baptiste et al. [17]	To evaluate published cost-effectiveness analyses of aromatase inhibitors and tamoxifen in early-stage breast cancer	Aromatase inhibitors (anastrazole and letrozole) versus tamoxifen	1996–2011	18
Frederix et al. [19]	To primarily identify published cost-effectiveness analyses and cost-utility analyses of endocrine therapies for the treatment of early breast cancer. Secondly, to identify whether differences in seven modeling characteristics are related to differences in outcome of these cost-effectiveness and cost-utility analyses	Aromatase inhibitors compared to tamoxifen	2000–2010	20
Chan et al. [18]	To identify published, original, cost-effectiveness analyses presenting cost/quality-adjusted life year (QALY) ratios for trastuzumab used as an adjuvant treatment for HER2 + early breast cancer and to evaluate the quality of reporting the favorable cost-effectiveness ratios	Standard treatment/chemotherapy without trastuzumab.	1998–2008	13
Blank et al. [22]	To review the evidence on the cost effectiveness of conventional chemotherapy and targeted therapy for metastatic breast cancer	Conventional cytotoxic chemotherapy versus targeted therapy (trastuzumab).	2000–2009	13
Lewis et al. [16]	To evaluate the clinical effectiveness and cost-effectiveness of vinorelbine in the management of breast cancer	Vinorelbine, docetaxel, paclitaxel, 5-fluorouracil, and gemcitabine	1986–2001	14
Foster et al. [20]	To understand the economic impact of metastatic breast cancer (MBC) and its treatment, and to evaluate the designs of these studies	Treatments for metastatic breast cancer including trastuzumab, capecitabine, and nab-paclitaxel	2004–2010	23
Ferrusi et al. [14]	To facilitate the decision-making process of economic evaluations based on recommendations	Trastuzumab targeted therapy and other treatment modalities	Inception-2011	15
Parkinson et al. [15]	To assess the quality of economic evaluations of trastuzumab, and identify potential drivers of conflicting conclusions	trastuzumab versus any comparator	1996–2011	12
Norum J. [23]	To assess the cost-effectiveness of adjuvant of trastuzumab in early breast cancer and make recommendations for future economic evaluations	Adjuvant trastuzumab versus any comparator	2003–2006	4

These analyses suggested, that AIs were highly cost-effective in the metastatic setting irrespective of country and the line of therapy. This review was judged of relative good scientific quality as suggested by the score (70 %) obtained using the modified AMSTAR tool.

Foster et al. [20] assessed the economic impact of various metastatic breast cancer (MBC) treatments including hormonal and targeted therapies. The results of the economic evaluations included in the review suggest that endocrine therapies were very cost-effective. Specifically, newer AIs (anastrozole and letrozole) were found to be cost-effective in the first-line therapy when compared to tamoxifen, in patients with hormone receptor-positive breast cancer. In addition, various studies included in the systematic review by Foster al. [20] looked at the cost-effectiveness of fulvestrant (second or third line option) in hormone receptor-positive postmenopausal women with MBC. The cost-effectiveness of adding fulvestrant to existing treatment sequences, including adding fulvestrant to a chemotherapy sequence, was either cost-saving or highly cost-effective compared to a non-fulvestrant sequence. In regard to the cost-effectiveness of targeted therapies, the

Table 3 Characteristics of the studies included in the assessed systematic reviews

Authors, year	Country/region	Target population	Breast cancer stage				Type of economic evaluation				Study design		
			I	II	III	IV	CMA	CEA	CUA	CBA	Trial-based	Model-based	Unknown/Other
Benedict and Brown [21]	Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK, US	Women with advanced breast cancer	0	0	0	17	0	11	6	0	0	17	0
John-Baptiste et al. [17]	Euro zone, US, UK, Canada, Brazil, Colombia, Korea	Postmenopausal women with early-stage breast cancer	18	0	0	0	0	18	16	0	0	18	0
Frederix et al. [19]	US, UK, Canada, Brazil, Belgium, Germany, Sweden and Spain	All patients recommended for the adjuvant treatment of breast cancer	20	0	0	0	NS	14	19	NS	20	0	0
Chan et al. [18]	US, Canada, Brazil, Italy, Belgium, Sweden, Norway, Poland, Switzerland, Australia, Taiwan	Women with HER2 + early-stage breast cancer	13	0	0	0	0	13	0	0	0	13	0
Blank et al. [22]	UK, Greece, France, Norway, Switzerland, US, Canada	Women with metastatic breast cancer	0	0	0	13	0	13	0	0	6	4	(3 Other)
Lewis et al. [16]	US, Canada, UK, France	Women with metastatic breast cancer	0	0	0	4	0	1	4	0	0	4	0
Foster et al. [20]	Australia, Canada, France, Germany, Italy, Spain, Sweden, Switzerland, UK, US.	Women with metastatic breast cancer	0	0	0	35	0	7	14	0	NS	13	9
Ferrusi et al. [14]	US, UK, Canada	Women with early-stage breast cancer	15	0	0	0	NS	NS	NS	NS	NS	12	2
Parkinson et al. [15]	US, Australia, Sweden, UK, Italy Norway, France, Switzerland, Belgium	Women with HER2 + metastatic breast cancer	0	0	0	12	0	9	6	0	3	8	4
Norum J. [23]	Belgium, US, Canada, Denmark	Women eligible for adjuvant treatment of HER2 + breast cancer.	3	0	1	0	0	4	0	0	0	4	0

NS not specified clearly, *CMA* cost minimization analysis, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *CBA* cost-benefit analysis
HER2+: Human epidermal growth factor receptor 2 positive

ICERs were influenced by the chemotherapy that these targeted therapies were paired with. Trastuzumab was found cost-effective when administered alone as first-line therapy in HER2-positive breast cancer patients compared to standard chemotherapy. The same conclusion was reached when trastuzumab was combined with paclitaxel compared with chemotherapy alone or when trastuzumab was compared to Vinorelbine. However, the combination of trastuzumab plus capecitabine versus capecitabine alone was not found cost-effective. Other targeted therapies were also assessed as part of the systematic review by Foster et al. [20]. The combination of lapatinib and capecitabine, for the treatment of HER2-positive advanced and MBC patients (not naïve to trastuzumab), was cost-saving compared with trastuzumab-containing regimens. The combination was not cost-effective compared to capecitabine alone or vinorelbine alone. The same conclusion was reached when bevacizumab was combined with

Table 4 Characteristics of the studies included in the assessed systematic reviews

Authors, year	Time frame		Perspective			Measure of effectiveness	Data sources clearly documented	
	0–5 years	6 years and +	Payer	Societal	Other/NS		Yes	No
Benedict and Brown [21]	8	9	16	0	US hospital (1)	Life years gained (17) and both Life years and QALYs (6)	17	0
John-Baptiste et al. [17]	0	18	16	1	Multiple perspective (1)	QALYs and Life years (10); QALYs only (6) and Life years only (2)	18	0
Frederix et al. 2012 [19]	0	20	20	0	0	Life years (14); QALYs (19)	16	4
Chan et al. [18]	0	11	5	4	4	Life years (5) QALYs (11)	13	0
Blank et al. [22]	2	11	5	2	7	Progression-free (1); Life years (6); QALYs (7)	13	0
Lewis et al. [16]	4	0	0	1	3	QALYs; HRQoL; QALMs; QAPFS	4	0
Foster et al. [20]	Not clearly specified. Few studies had life-time and 10-year time horizon		The majority of studies used third-party payer perspective. No further information provided			QALYs (16); PFLYs (4); Life years gained (3)	23	0
Ferrusi et al. [14]	1	14	12	2	2	QALYs; Life years gained	15	0
Parkinson et al. [15]	6	8	9	2	4	Life years (12); QALYs (9); PFLYs (1)	Reported for the majority of studies.	
Norum J. [23]	0	4	3	0	1	Life years (3)	2	2

NS not specified clearly, *N/A* not applicable, *QALYs* quality-adjusted life years, *HRQoL,* health-related quality of life, *QALMs* quality-adjusted life months, *QAPFS* quality-adjusted progression-free survival, *PFLYs* progression-free life years

chemotherapy regimens in the treatment of HER2-positive MBC patients. Using the modified AMSTAR tool, this review was judged fair (score = 60 %) in terms of its scientific quality.

Blank et al. [22] reviewed the data on the cost-effectiveness of cytotoxic chemotherapy and targeted therapy (trastuzumab and bevacizumab) for MBC. The pharmacoeconomic studies included in this review yielded varying conclusions. Evaluations on cytotoxic agents showed mainly favorable ICERs, while those on targeted therapies indicated both favorable and non-favorable ratios. Indeed, Bevacizumab used in combination with paclitaxel as first-line option was not cost-effective compared with paclitaxel alone. As for trastuzumab, its cost-effectiveness differed according to the perspective of the studies (payer, hospital, societal) and the regimen it was part of. The scientific quality of this review was considered relatively good (modified AMSTAR score = 70 %).

Parkinson et al. [15] appraised the quality of economic evaluations of trastuzumab in the metastatic setting, and identified potential determinants of conflicting results. Trastuzumab was paired with a taxane (docetaxel or paclitaxel), an AI (anastrozole), or a cytotoxic agent (capecitabine). The assessed economic evaluations were not in agreement regarding the cost-effectiveness of trastuzumab in the treatment of HER2-positive MBC. The authors suggested potential explanations for these results. The differences may be attributed to the judgments made by the authors selecting the comparators, extrapolating randomized controlled trial data, and making assumptions in modeling costs and outcomes. In terms of scientific quality, the review was judged fair with a modified AMSTAR score of 60 %.

Lewis et al. [16] aimed at evaluating the clinical effectiveness and cost-effectiveness of vinorelbine compared to taxane therapy (docetaxel or paclitaxel, both administered every 3 weeks) in the metastatic setting. The review yielded conflicting results. In fact, one economic evaluation reported that vinorelbine was a preferred strategy over taxane therapy, while another concluded that vinorelbine was less effective and less expensive than taxane therapy, and a third evaluation found vinorelbine to be inferior to taxanes. The authors concluded that additional studies were needed to shed light on the true cost-

Table 5 Characteristics of the studies included in the assessed systematic reviews

Authors, year	Discounting			Sensitivity analysis		Incremental analysis	
	Yes	No	N/A	Deterministic	Probabilistic	Yes	No
Benedict and Brown 2005 [21]	17	0	0	Often used (no quantification)	2	15	2
John-Baptiste et al. [17]	17	1	0	12	11	18	0
Frederix et al. [19]	20	0	0	19	13	20	0
Chan et al. [18]	13	0	0	Sensitivity analysis conducted for 11 out of the 13, but type not specified		13	0
Blank et al. [22]	5	The remained studies did not state discount rates.		6	5	13	0
Lewis et al. [16]	3	1	0	Sensitivity analysis conducted for 3 out of the 4, but type not specified		3	1
Foster et al. [20]	NS	NS	NS	NS	NS	22	NR
Ferrusi et al. [14]	NS	NS	NS	12	10	Yes	NS
Parkinson et al.[15]	10	5	0	Sensitivity analysis was conducted in all evaluations. Deterministic in most studies and few probabilistic.		12	0
Norum J. [23]	3	1	0	Sensitivity analysis was done for 1 study, but type not specified.		3	1

NS not specified clearly, *NR* not reported

effectiveness of vinorelbine in treating metastatic breast cancer. This review had the highest score in terms of scientific quality (modified AMSTAR score = 100 %) among the systematic reviews.

Discussion

This review has focused on published systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer, conducted from 2000 to 2014. A total of 511 bibliographic records were found, with 10 included and fully reviewed. The time horizon for literature review searches ranged from three [23] to 15 years [15–17]. In addition, the sample size of the systematic reviews varied between four [16, 23] and 23 studies [20]. Most economic evaluations covered a long-term temporal framework while adopting a model-based cost-effectiveness analysis (CEA) design, and a payer perspective. The studies included in the review included patients from most of the world except for Africa. The study findings can be summarized as follows. First, in early stage postmenopausal hormone receptor-positive breast cancer, there was heterogeneity in the evidence regarding the cost-effectiveness of AIs versus tamoxifen, i.e., studies investigating these treatments both low and high ICERs. As such, additional studies are needed to shed light on the cost-effectiveness of AIs versus tamoxifen at this stage. [17, 19] That being said, we can reasonably anticipate that future economic studies will likely find AIs highly cost-effective compared to tamoxifen because of longer follow-up in adjuvant AI studies and lower cost of AIs since they have become all generic. In the advanced/metastatic breast cancer setting, newer AIs have proved cost-effective compared to older treatments. [20, 21] Second, the cost-effectiveness of trastuzumab was influenced by age and time horizon. Trastuzumab was cost-effective as adjuvant therapy in women with HER2 + breast cancer younger than 65 years and over a life-time horizon. However, trastuzumab was not found to be cost-effective as adjuvant therapy in HER2 + breast cancer patients older than 75 years or with a time horizon of less than 10 years. [18] The cost-effectiveness of trastuzumab was also evaluated in the metastatic setting. The systematic reviews appraising the cost-effectiveness of trastuzumab for metastatic breast cancer were inconclusive, meaning that individual evaluations yielded conflicting results. [15, 20] Similarly, Lewis et al. [16] assessed the clinical effectiveness and cost-effectiveness of vinorelbine compared to taxane therapy in the management of MBC. The review also yielded conflicting results. We did not find a connection between the discrepancies in cost-effectiveness results of studies and their geographical area of origin, although most studies were carried out in middle- to high-income countries. All the reviews were assessed for scientific quality against the modified AMSTAR tool. Their quality ranged from fair [14, 15, 18, 20] to excellent [16].

Like all systematic reviews, ours is prone to a number of limitations. In fact, our searches were limited to English articles and restricted to a time frame between 2000 and 2014. The review focused on specific

Table 6 Interventions, objectives, and main conclusions of systematic reviews

Authors, year	Interventions compared	Study objectives	Main conclusions
Benedict and Brown [21]	Aromatase inhibitors versus tamoxifen for first-line therapy. Newer aromatase inhibitors (letrozole, anastrozole, exemestane, fluvestrant) versus older treatments (megestrol, amoxifen) for second-line therapy for advanced breast cancer	To review the cost-effectiveness of hormonal treatment options for advanced breast cancer	These analyses suggest, that new AIs are good value for money compared with older treatments (megestrol, tamoxifen) irrespective of country and the line of therapy
John-Baptiste et al. [17]	Aromatase inhibitors (anastrazole and letrozole) versus tamoxifen	To evaluate published cost-effectiveness analyses of aromatase inhibitors and tamoxifen in early-stage breast cancer	Studies that compared aromatase inhibitors versus tamoxifen tend to overestimate the cost-effectiveness of AIs, making the results suboptimal to inform policy
Frederix et al. [19]	Aromatase inhibitors compared to tamoxifen	To primarily identify published cost-effectiveness analyses and cost-utility analyses of endocrine therapies for the treatment of early breast cancer. Secondly, to identify whether differences in seven modeling characteristics are related to differences in outcome of these cost-effectiveness and cost-utility analyses	Harmonization of modeling techniques for different therapeutic groups/diseases and transparent modeling practices need to be adhered to in order to increase comparability across pharmacoeconomic evaluations
Chan et al. [18]	Standard treatment/chemotherapy without trastuzumab.	To identify published, original, cost-effectiveness analyses presenting cost/quality-adjusted life year (QALY) ratios for trastuzumab used as an adjuvant treatment for HER2 + early breast cancer and to evaluate the quality of reporting the favorable cost-effectiveness ratios	Most studies suggest that trastuzumab may be cost-effective for treatment of early breast cancer in a 1-year treatment regimen
Blank et al. [22]	Conventional cytotoxic chemotherapy versus targeted therapy (trastuzumab).	To review the evidence on the cost-effectiveness of conventional chemotherapy and targeted therapy for metastatic breast cancer	The pharmacoeconomic studies yielded varying conclusions. Studies on cytotoxic agents showed mainly attractive cost-effectiveness ratios while targeted therapies presented both attractive and less attractive ratios
Lewis et al. [16]	Vinorelbine, docetaxel, paclitaxel, 5-fluorouracil, and gemcitabine	To evaluate the clinical effectiveness and cost-effectiveness of vinorelbine in the management of breast cancer	One economic evaluation reported that vinorelbine was more effective and less costly than taxane therapy, one found vinorelbine to be less effective and less expensive than either of the taxanes and a third evaluation found vinorelbine to be less effective and more expensive than taxane therapy. Conflicting results
Foster et al. [20]	Treatments for metastatic breast cancer including trastuzumab, capecitabine, and nab-paclitaxel	To understand the economic impact of metastatic breast cancer (MBC) and its treatment, and to evaluate the designs of these studies	Hormonal therapies seem to be very cost-effective. Specifically, newer aromatase inhibitors (anastrozole and letrozole) have shown to be cost-effective in the first-line therapy when compared to tamoxifen in estrogen-receptor-positive patients. trastuzumab is generally cost-effective. Other targeted therapies (HER2 receptor) have not been considered cost-effective
Ferrusi et al. [14]	Trastuzumab targeted therapy and other treatment modalities	To facilitate the decision-making process of economic evaluations based on recommendations	Trastuzumab appeared to be generally cost-effective when its use was limited to a year. The short-term use of trastuzumab was more attractive than its longer term use, from a health economic point of view

Table 6 continued

Authors, year	Interventions compared	Study objectives	Main conclusions
Parkinson et al. [15]	Trastuzumab versus any comparator	To assess the quality of economic evaluations of trastuzumab, and identify potential drivers of conflicting conclusions	The economic evaluations did not arrive at a consensus regarding the cost-effectiveness of trastuzumab for metastatic breast cancer
Norum J. [23]	Adjuvant trastuzumab versus any comparator	To assess the cost-effectiveness of adjuvant of trastuzumab in early breast cancer and make recommendations for future economic evaluations	The adjuvant trastuzumab in early breast cancer is cost-effective, except for subgroups of stage III breast cancer and seniors

Table 7 Quality assessment of systematic reviews

Authors, year	Domains of the modified AMSTAR tool											Final scores (%)
	1	2	3	4	5	6	7	8	9	10	11	
Benedict and Brown [21]	1	1	1	0	0	1	1	1	−1*	0	1	7 (70)
John-Baptiste et al. [17]	1	1	1	1	0	0	1	1	−1*	0	1	7 (70)
Frederix et al. [19]	1	0	1	0	0	1	1	1	−1*	0	1	7 (70)
Chan et al. [18]	1	1	1	0	0	1	1	1	−1*	0	0	6 (60)
Blank et al. [22]	1	0	1	0	1	1	1	1	−1*	1	1	7 (70)
Lewis et al. [16]	1	1	1	1	1	1	1	1	−1*	−1*	1	9 (100)
Foster et al. 2011 [20]	1	1	0	1	0	1	1	1	−1*	0	0	6 (60)
Ferrusi et al. [14]	1	1	1	0	0	1	1	1	−1*	0	0	6 (60)
Parkinson et al. [15]	1	0	1	1	0	1	1	1	−1*	0	0	6 (60)
Norum J. 2006 [23]	1	0	1	1	0	1	1	1	−1*	0	1	7 (70)

% percentage

treatments only, although breast control treatment strategies have a broader scope, including additionally early detection and diagnosis. The limitations inherent in this review may have resulted in some studies being missed in the literature searches. We also acknowledge the possibility that errors may have been made in the interpretation of the results of the systematic reviews that were reviewed. That being said, it is the authors' understanding that the guidelines for overview of systematic reviews were adhered to [10].

Concluding remarks

Evidence produced by economic evaluations in general, and in the breast cancer field in particular, have the potential of informing clinical and reimbursement decision-making. The literature contains a plethora of economic evaluations dealing with different aspects of breast cancer treatments. It is therefore, important to ensure that all relevant economic evidence is appropriately synthesized to enable and facilitate reimbursement of potentially valuable treatments by decision-makers. Based on the review of the studies included in the current paper, some recommendations previously published by many authors apply and are recapped here.

The ability for decision-makers to arrive at an appropriate conclusion about the cost-effectiveness of breast cancer treatment strategies could be made easier and more transparent by better harmonizing the reporting of economic evaluations assessing the value of these treatment strategies. Even though some efforts have been made to tackle this issue (e.g., task forces on best practices in reporting the results of economic evaluations from different professional societies, such as the International Society for Pharmacoeconomics and Outcomes Research), room still exists to improve and strengthen recommendations for standardization in modeling

treatment strategies in breast cancer. Doing so will facilitate comparability and consistency of economic evaluations of breast cancer treatments across healthcare jurisdictions worldwide. The stakes are high since providing coverage for a treatment that, in reality, is not cost-effective will result in huge opportunity costs and prevent other patients from accessing alternatives that are potentially valuable. In turn, a policy decision that denies coverage of a treatment that, in reality, is cost-effective will certainly prevent patients from getting access to effective treatments, which itself may result in productivity losses. Future research investigating ways to improve and ensure adherence to guidelines for the reporting of economic evaluations is therefore warranted.

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Conflict of interest The authors have no conflicts of interest to declare.

Appendix

Search strategies for databases included in the review

See Tables 8, 9, 10, 11, 12, 13, 14.

Table 8 Search in Ovid Medline (Searched on January 17th, 2015)

	Search query	Records
1	Exp breast neoplasms/	220,788
2	Breast$ adj3 neoplasm$.tw.	1359
3	((Breast$ adj3 cancer$) OR (breast$ adj3 carcino$)).tw.	195,725
4	OR/1–3	257,657
5	Cost:.mp.	415,611
6	Cost-benefit analys:.mp.	61,927
7	Health care costs.mp.	33,335
8	OR/5–7	415,620
9	(Systematic$adj2 review$).mp.	0
10	(Systematic$adj2 overview$).mp.	0
11	(Meta analy* OR metaanaly*).ti,ab,pt.	74,616
12	Review.pt.	1,904,235
13	Search:.tw.	223,617
14	OR/9–13	2,069,965
15	4 AND 8 AND 14	1343
16	Limit 15 to (English and year = "2000–2014″)	37

Table 9 Search in OVID Embase

	Search query	Records
1	Breast tumor.mp. or (breast and cancer).ti,ab.	94,033
2	(Cost or costs).tw.	107,6024
3	(Research synthesi OR pooled OR systematic review.de OR meta-analysis.de OR (evidence base OR evidence based OR methodol* OR systematic OR quantitative* OR studies OR search* AND (review.de OR review.it)))	243,398
4	1 AND 2 AND 3	725
5	Limit 4 to english	725
6	Limit 5 to year = "2014"	55
7	Limit 6 to humans	55

Table 10 Search in Pubmed (Searched on January 17th, 2015)

	Search query	Records
1	"Breast Neoplasms"[mesh:exp]	220,426
2	"Carcinoma, Ductal, Breast"[mesh:exp]	12,090
3	"Inflammatory Breast Neoplasms"[mesh:exp]	205
4	"Triple Negative Breast Neoplasms"[mesh:exp]	484
5	(("breast"[mesh] OR "breast diseases"[mesh:exp]) AND ("Neoplasms"[mesh:exp] OR "Adenocarcinoma"[mesh:exp] OR "Carcinoma"[mesh:exp]))	224,201
6	Brca[tiab]	2403
7	(Breast[tiab] AND (adenocarcinoma*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR metasta*[tiab] OR neoplasm*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab]))	244,490
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	296,390
9	(Meta-Analysis[ptyp] OR systematic[sb])	233,666
10	Cost*[tiab]	384,322
11	"Costs and cost analysis"[mesh:noexp]	41,888
12	Cost-benefit analys*[tiab]	3261
13	Cost-benefit analysis[mesh]	60,696
14	Health care costs[mesh:noexp]	27,761
15	#10 OR #11 OR #12 OR #13 OR #14	431,794
16	#8 AND #9 AND #15	378
17	#16 AND ("2000/01/01"[PDAT]: "2014/12/31"[PDAT]) AND English[Language] AND "humans"[MeSH Terms]	268

Table 11 Search in ISI's Web of Knowledge

	Search query	Records
1	TS = (Systematic review* or Meta-analysis*)	123,684
2	TS = Economics*	62,123
3	TS = (Breast cancer* or Breast Neoplasm*)	284,995
5	#1 AND #2 AND #3	18

Limiters – English language and Publication year (2000–2014); Limiters apply to all searches

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED

Table 12 Search in Cochrane Database of Systematic Reviews (Searched on January 17th, 2015)

	Search query	Records
1	((Breast$ or mammary) adj3 (neoplas$ or tumor$ or cancer$ or carcinom$)).mp.	108
2	((Beast$ or mammary) adj3 (neoplas$ or tumor$ or cancer$ or carcinom$)).kw.	34
3	OR/1-2	119
4	(Econom* or cost* or pric* or pharmacoecon* or cost NEXT (effectiveness or utili* or benefit or minimi*) or (expenditure) or (value NEAR/2 money) or budget* or preference or qaly or (quality NEXT adjusted) or utility or utilities or financ* NEXT (management or support or organized))	83,659
5	AND/3–4	108
6	#5 and Publication year from 2000 to 2014	33

Table 13 Search in Center for Reviews and Dissemination (CRD) database (Searched on January 19th, 2015)

	Search query	Records
1	((Systematic* adj review*) OR (Meta-analysis*)) IN DARE, NHSEED, HTA	48,534
2	(Economics*) OR (Cost*) OR (Costs*) IN DARE, NHSEED, HTA	23,784
3	(Drug*$therapy*) OR (Chemotherapy*) OR (Adjuvant*) IN DARE, NHSEED, HTA	3689
4	(Breast cancer:ti) IN DARE, NHSEED, HTA	1322
5	(English:lp) IN DARE, NHSEED, HTA from 2000 to 2014	27,686
6	#1 AND #2 AND #3 AND #4 AND #5	94

Table 14 Search in EconLit—(Searched on January 19th, 2015)

	Search query	Records
1	Systematic review* or meta-analysis*	1091
2	Economics*	565,958
3	Breast cancer* or breast neoplasm*	245
4	LA english	1,299,261
5	S1 AND S2 AND S3 AND S4	3

Limiters—published date: 20000101-20141231; limiters apply to all searches

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