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REVIEW

Direct and Indirect Costs of Breast Cancer and Associated Implications: A Systematic Review

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ABSTRACT

Introduction: Breast cancer is currently the leading cause of global cancer incidence. Breast cancer has negative consequences for society and economies internationally due to the high burden of disease which includes adverse epidemiological and economic implications. Our aim is to systematically review the estimated economic burden of breast cancer in the United States (US), Canada, Australia, and Western Europe (United Kingdom, France, Germany, Spain, Italy, Norway, Sweden, Denmark, Netherlands, and Switzerland), with an objective of discussing the policy and practice implications of our results.

Methods: We included English-language published studies with cost as a focal point using a primary data source to inform resource usage of women with breast cancer. We focussed on studies published since 2017, but with reported costs since 2012. A systematic search conducted on 25 January 2023 identified studies relating to the economic burden of breast cancer in the countries of interest. MEDLINE, Embase, and EconLit databases were searched via Ovid. Study quality was assessed based on three aspects: (1) validity of cost findings; (2) completeness of direct cost findings; and (3) completeness of indirect cost findings. We grouped costs based on country, cancer stage (early compared to metastatic), and four resource categories: healthcare/medical, pharmaceutical drugs, diagnosis, and indirect costs. Costs were standardized to the year 2022 in US (US$2022) and International (Int$2022) dollars.

Results: Fifty-three studies were included. Studies in the US (n = 19) and Canada (n = 9) were the majority (53%), followed by Western European countries (42%). Healthcare/medical costs were the focus for the majority (89%), followed by pharmaceutical drugs (25%), then diagnosis (17%) and indirect (17%) costs. Thirty-six (68%) included early-stage cancer costs, 17 (32%) included metastatic cancer costs, with 23% reporting costs across these cancer stages. No identified study explicitly compared costs across countries. Across cost categories, cost ranges tended to be higher in the US than any other country. Metastatic breast cancer was associated

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with higher costs than earlier-stage cancer. When indirect costs were accounted for, particularly in terms of productivity loss, they tended to be higher than any other estimated direct cost (e.g., diagnosis, drug, and other medical costs).
Conclusion: There was substantial heterogeneity both within and across countries for the identified studies' designs and estimated costs. Despite this, current empirical literature suggests that costs associated with early initiation of treatment could be offset against potentially avoiding or reducing the overall economic burden of later-stage and more severe breast cancer. Larger scale, national, economic burden studies are needed to be updated regularly to ensure there is an ongoing and evolving perspective of the economic burden of conditions such as breast cancer to inform policy and practice.

Keywords: Breast cancer; Cost; Direct cost; Indirect cost; Women; Economic burden; Oncology; International

Key Summary Points

The direct and indirect costs of breast cancer present a significant burden on patients, caregivers, and society. However, indirect costs such as costs associated with productivity loss and informal caring are often underrepresented in the literature, which restricts our ability to contextualise such costs alongside, or against, direct costs associated with healthcare.

There was substantial heterogeneity in how studies were conducted and associated cost estimates within countries, types of breast cancer (e.g., hormone receptor-positive, triple-negative breast cancer), as well as categories of cost (e.g., diagnosis, drug, and indirect cost).

A variety of costing studies exist internationally; however, most cost-related studies are limited to setting-specific direct costs associated with breast cancer, rather than more national (and international) holistic costing studies covering both direct and indirect costs. This suggests a potentially limited scope is informing policy and practice, which could have far-reaching implications for patients, families, healthcare systems, and the broader economy.

INTRODUCTION

Cancers are a major contributor to the global burden of disease, both in terms of epidemiological (e.g., mortality and disability-adjusted life-years lost) and economic (e.g., medical and societal cost) considerations [1, 2]. Despite advances in medical interventions, the morbidity and mortality associated with breast cancer remains high [1, 3–5]. Breast cancer contributes more than 25% of new female cancer cases globally, making it the most common cancer among women [6]. Global cancer statistics in 2020 showed that breast cancer surpassed lung cancer as the leading cause of global cancer incidence, with breast cancer representing 11.7% of all new cancer cases [5]. The estimated global economic cost of 29 cancers from 2020 forecast up to 2050 has been estimated as $25.2 trillion in international dollars (Int$2017), with 7.7% of this cost being attributed to breast cancer as the third highest contributor at $1964 billion [95% uncertainty intervals (95% UI): $1402b–$2759b] [1].

Decision-analytic models like that by Chen et al. [1] provide powerful statistics as to the economic burden of cancer (including breast cancer) now and forecast into the future to facilitate global debate as to prioritisation and resource-allocation for addressing cancer concerns. This includes informing public (e.g., governmental) and private (e.g., pharmaceutical) investment into cancer priorities, such as developing prevention and screening policies and strategies, research and development into new diagnostics

and treatments, and supportive care from the point of cancer diagnosis onwards (e.g., supporting employment). However, decision-analytic models are dependent on the country-specific input estimates used and then associated assumptions to facilitate the analyses. To fully assess the economic burden of breast cancer, a further review of evidence from different healthcare systems is needed to estimate the economic burden of breast cancer within countries and by other relevant factors (e.g., breast cancer stage) to inform within- and across-country policies and research agendas [7]. Country-specific and breast cancer stage factors that will have implications for the amount and type of resources consumed include the established healthcare systems, health technology assessment (HTA) and price reimbursement/negotiation processes, alongside cultural, political, policy, and sociodemographic factors. All the aforementioned (and more) will affect both direct medical (e.g., diagnostics, treatments, drugs) and indirect resource use and costs (e.g., productivity/employment) associated with the overall economic burden of breast cancer [8, 9]. These costs contribute to the significant burden that breast cancer has on patients, caregivers, and society, which includes contributing to emotional distress and financial toxicity. The indirect costs associated with the loss of productivity, absenteeism, disability, and informal caring are often under-represented when quantifying the economic burden associated with breast cancer. Overall, the costs of breast cancer have far reaching implications for patients, carers, families, health systems, and the economy internationally; as such, it is important that these costs are recorded well and transparently, then reported appropriately to inform policy and practice when prioritising the allocation of finite resources.

Our aim is to systematically review the estimated economic burden of breast cancer by stage, i.e., early (Stage I–III) compared to metastatic (Stage IV), in the US, Canada, Australia, and Western Europe (UK, France, Germany, Spain, Italy, Norway, Sweden, Denmark, Netherlands and Switzerland). We hypothesise that the economic burden of breast cancer should be well studied and documented (i.e., in published journal articles) in these countries, for reasons such as: electronic health or welfare records; national payment systems and/or reference costs; investment in large national and local real-world databases; established HTA processes and agencies; and the track record of publicly and privately funded research studies. Although countries outside our remit also have these aspects, it was necessary to refine our focus to make the review manageable. We focus on studies published since 2017, but with reported resource-use/costs since 2012, to try and capture the most relevant resource use and cost patterns over the last decade given the ever changing epidemiological and economic landscape associated with breast cancer. Subsequently, our objectives are to highlight key cost drivers for consideration, discuss the policy and practice implications of our results, alongside strengths and limitations of our identified studies and review, to subsequently suggest future areas of research priority to tackle the far-reaching impacts associated with the economic burden of breast cancer.

METHODS

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The PRISMA checklist is presented in Appendix S1. Our systematic review protocol was submitted and published within PROSPERO prior to starting data extraction (Record ID: CRD42023440537) [11]. Full protocol details are documented within PROSPERO, as well as this manuscript and associated supplementary material. No changes have been made to the final conducted study compared to what was documented within the registered protocol.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

We included published economic studies, written in the English language, that have cost as a focal point using a primary data source to inform resource usage of women with breast cancer. The primary data sources can include trials, cohort studies, registries, electronic health records, and surveys; expert opinion (either elicited or not) was not considered a valid primary data source for this review. The eligibility criteria were based on the PICO (Population, Intervention, Comparator, Outcomes) framework; although, all interventions were eligible and specifying a comparator was not applicable.

Population included studies of women of all ages with any diagnosis of breast cancer (e.g., ICD-10 C50), regardless of subtype or stage of breast cancer. We restricted eligibility to studies conducted within the following countries: US, Canada, Australia, and Western Europe (UK, France, Germany, Spain, Italy, Norway, Sweden, Denmark, Netherlands and Switzerland). We excluded studies looking at the costs of managing secondary conditions (e.g., atrial fibrillation) alone in a breast cancer population, breast cancer in men only, where men make up a non-trivial proportion of the population (> 5% men), and studies in the general population (e.g., screening studies). Outcomes included costs (and resource use where applicable) related to direct healthcare and medical care costs, which we separate out into diagnosis, drugs, and (other) healthcare and medical costs, alongside indirect costs (e.g., work productivity, both time missed from work and reduced productivity at work, and informal carer burden).

Search Strategy

A systematic search was conducted on 25 January 2023 to identify studies relating to the economic burden of breast cancer in the countries of interest. The databases MEDLINE, Embase, and EconLit were searched, all via Ovid. For MEDLINE and Embase, terms for breast cancer (free-text and subject headings where available) were combined with an economic search filter, which was adapted by removing the terms relating to economic models and integrating additional terms from a burden of illness filter [12]. Geographic search filters were applied where available [13]. For countries where a geographic search filter did not exist, subject heading terms for the countries were used (where available) along with free-text terms relating to the country. Multiple fields were searched for the country terms, including country of publication, and institution [14]. For EconLit, a simplified, broader search version was conducted due to the specific focus of the database and associated limited amount of literature indexed. All searches were limited to studies published within the last five years (i.e., 2017 to 25 January 2023). Search results were imported in the EndNote reference management software, and duplicates were removed. Appendix S2 details the search strategy for each database consulted, including search strings.

Quality Assessment

There is currently no consensus on assessing the methodological quality of studies reporting on costs. As such, we followed a quality assessment proposed by Escalante et al. [15]. In essence, the quality assessment has three-levels ('high', 'unclear', 'low') within three categories: (1) validity of cost findings; (2) completeness of direct cost findings; and (3) completeness of indirect costs findings. For (1), 'high' focussed on a comparison of relevant costs in women with breast cancer compared to women without, 'unclear' included bottom-up costs based on acceptable costing methodology, whereas 'low' included neither of the aforementioned. For (2) and (3), the levels were based on the set of cost items reported: 'high', comprehensive list; 'unclear', limited list; 'low', one item. Full details of the quality assessment can be found in Appendix S3.

Selection of Studies and Data Extraction

Records from our literature searches were exported into the EndNote reference manager

database and de-duplicated. With reference to our pre-specified eligibility criteria, a two-staged selection of studies process was conducted by two reviewers (AR, YS) then checked by two other reviewers (DP, MF) using a cross-over approach, e.g., DP checked an equal proportion of the studies selected/extracted by AR and YS, as did MF but not the same studies as checked by DP. Appendix S4 provides further details of the study screening, selection, and data extraction process.

Cost Standardisation and Enabling Comparability

All costs are standardised to the year 2022 in both US Dollars (US$2022) and International Dollars (Int$2022) using the US healthcare inflation indices, and Organisation for Economic Co-operation and Development exchange rates and purchasing power parity estimates [16–18]. The costs presented in this article focus on US$2022 and we focus particularly on mean costs to generate ranges in mean estimates, as the best guess of the average costs within and across countries and categories. In comparison, Supplementary Excel Sheet 1 presents a range of results for the costs as extracted from the identified articles (e.g., means, medians, inter-quartile ranges, standard deviations) alongside cost comparisons in US$2022 and Int$2022.

As costing studies tend to be heterogenous, we grouped and discuss patient-level (not cohort) costs on the following basis to enable and improve comparability and interpretation of magnitude: (1) procedure costs; (2) costs over 1 year. Other costs outside these grouping are provided in Supplementary Excel Sheet 1. We did not attempt to convert costs over a shorter/longer period to patient-level costs over 1 year, due to issues with sunk/upfront costs leading to over/underestimation when standardising costs to a common time frame.

RESULTS

As a result of searching the target databases, 9175 relevant items were retrieved using the search queries, with 2010 duplicate items being discarded. Of the remaining 7165 items, 6643 were excluded at the title or abstract screening phase, which included conference abstracts. Subsequently, 491 items were then sought for retrieval from which 451 were retrieved, with 40 items not retrieved due to journal inaccessibility issues. Of these 451 items, the full texts were screened for eligibility, from which 53 articles were included. Our study selection process is shown in Fig. 1.

Quality Assessment

The quality of all 53 studies was evaluated. The validity of all 53 included studies were classed as 'unclear'. For completeness of direct costs, there were 24 classed as 'high', 25 'unclear', and 4 as 'low'. For completeness of indirect costs, there were 0 classed as 'high', '8' unclear, and '45' as low. Most (i.e., 49) included studies focussed on direct costs with some also including indirect costs, albeit no study covered a comprehensive range of indirect costs. Additional quality assessment details are provided in Appendix S3.

Study Characteristics and Cross-Country Comparability

A summary of study characteristics for our 53 included articles are shown in Tables 1 and 2, with additional detail in Supplementary Excel Sheet 1. Included articles were published between 2017 and 2023, with data collection spanning 2012–2020. Studies in the US (n = 19; 36%) [19–37] and Canada (n = 9; 17%) [38–46] made up the majority of our identified studies (n = 28; 53%), followed collectively by the Western European countries (n = 22; 42%). In Western Europe, most studies were in Italy (n = 5; 9%) [47–51], then Spain (n = 4; 8%) [52–55], France (n = 4; 8%) [56–59], Netherlands (n = 3; 6%) [60–62], UK (n = 3; 6%) [63–65], Sweden (n = 2; 4%) [66, 67], and Germany (n = 1; 2%) [68]. Three (6%) studies were in Australia [69–71].

Of our 53 included studies, 15 (28%) reported person-level procedure costs [20, 27, 28, 32, 34, 35, 46, 47, 49, 51, 60, 63, 64, 69, 71]; 19 (36%) reported person-level costs over a 1-year time

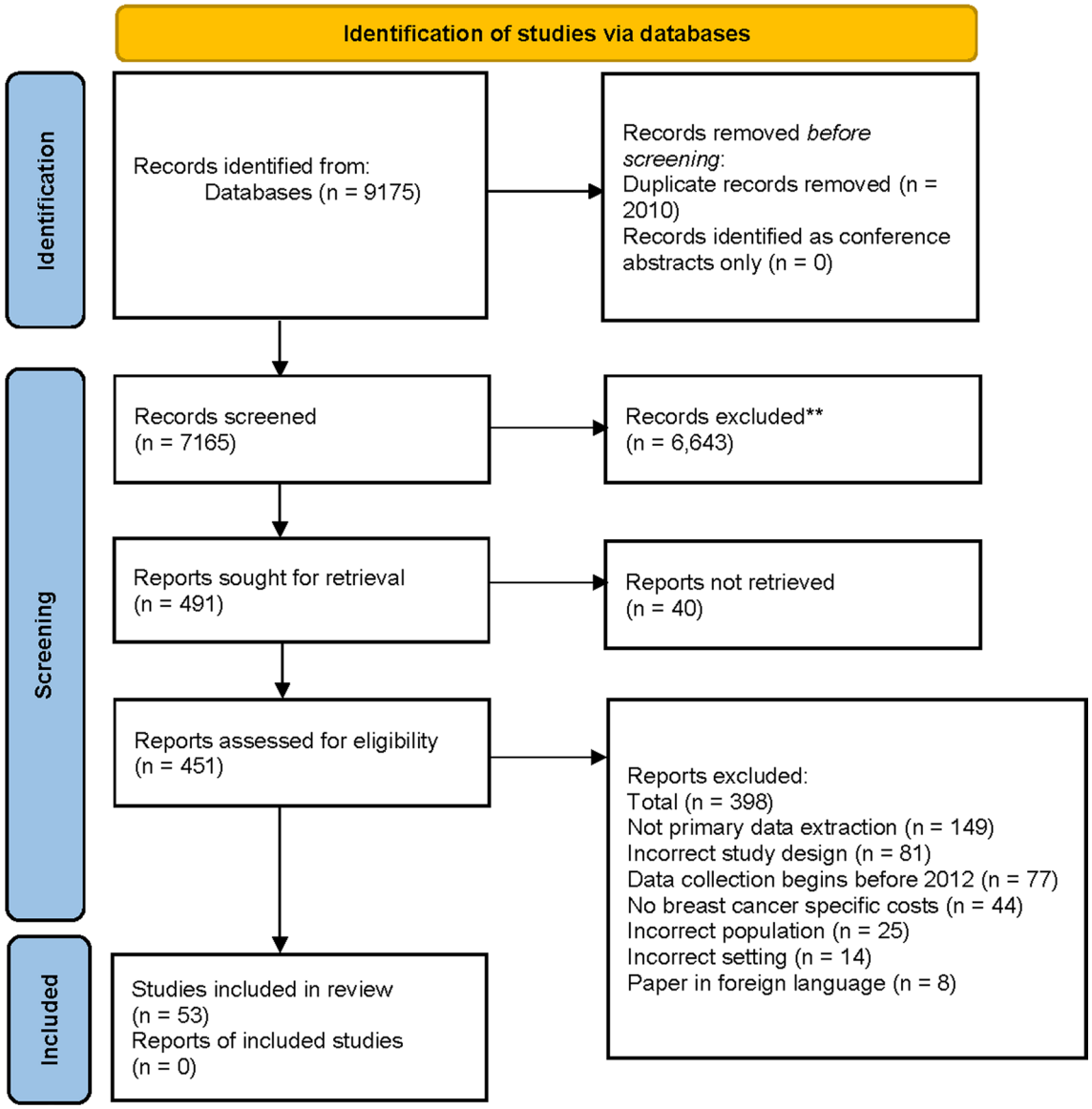

Fig. 1 PRISMA 2020 flow diagram

horizon [19, 23, 25, 26, 29, 33, 38–40, 43, 45, 48, 50, 52, 56–59, 65]. As such, the costs from 34 (64%) studies per person for procedures and then over a 1-year time frame are presented in Table 3 and 4, respectively, with the other included studies' costs presented in Supplementary Excel Sheet 1.

Direct Healthcare and Medical Costs

Of the 47 (89%) studies which reported direct medical care costs (exclusive of drug and diagnosis costs) [20–33, 35–55, 58–60, 62–68, 70, 71], our included studies focussed on specific types of surgery (e.g., lumpectomy, re-excision, mastectomy), non-surgical treatments (e.g., chemotherapy, radiation oncology), and supportive

Table 1 Study characteristics of included articles

Lead author's last name	Publication year	Country	Sample size	Cancer stage	Time horizon	Data collection years (and month when available)
Alia Ramos	2019	Spain	840	Not reported	Annual cost	January 2014–April 2014
Allen	2017	US	128	Early	1 year follow-up	January 2014–January 2016
Arfi	2018	France	297	Early	Annual cost	December 2014–March 2016
Brezden-Masley	2020	Canada	3271	Both	Annual cost	2012–2017
Brezden-Masley	2021	Canada	4889	Both	Annual cost	2012–2017
Brezden-Masley	2021	Canada	21,360	Both	Annual cost	2012–2017
Chakedis	2022	US	8804	Both	Cost of procedure	2016–2020
Corsi	2017	Italy	976	Early	Cost of procedure	January 2013–April 2016
Crouch	2019	US	1470	Metastatic	6 months follow-up	2013
De la Flor	2022	Spain	204	Both	Cost of procedure	2018–2019
Farolfi	2017	Italy	114	Early	Annual cost	January 2014–December 2014
Ferrier	2021	France	168	Early	1 year follow-up	2014–2016
Franken	2020	Netherlands	68	Both	Cost of procedure	March 2017–July 2018
Gautam	2018	US	1918	Both	6 months follow-up	January 2015–October 2016
Gordon	2020	Australia	192	Not reported	Cost of procedure	2017–2018
Grant	2019	UK	212	Not reported	Cost of procedure	April 2015–March 2016
Grant	2022	UK	232	Not reported	Cost of procedure	2014–2020
Hedayati	2019	Sweden	178	Early	Cost of procedure	2015
Hequet	2019	France	604	Early	1 year follow-up	2014–2016
Houts	2019	US	114	Metastatic	1 year follow-up	2013–2015
Kleijburg	2022	Netherlands	145	Early	3-month cost	January 2018 and June 2019
Konen	2020	US	490	Early	Cost of procedure	January 2014–December 2016

Table 1 continued

Lead author's last name	Publication year	Country	Sample size	Cancer stage	Time horizon	Data collection years (and month when available)
Law	2021	Canada	435	Not reported	Annual cost	January 2014–December 2016
Lopez-Vivanco	2017	Spain	307	Early	Cost of procedure	January–July 2012
Mahtani	2022	US	423	Both	Cumulative annual cost	2015–2018
Mariotto	2019	US	164,092	Early	1 year follow-up	2010–2015 and 2018
Martinez Del Prado	2018	Spain	401	Early	Unclear	2012–2015
Mattar	2021	Italy	3912	Not reported	Cost of procedure	2013–2018
Mittmann	2018	Canada	998	Not reported	20 months follow-up	2012–2013
Nabelsi	2019	Canada	268	Not reported	Annual cost	2015–2016
Nagra	2022	US	2264	Both	Cost of procedure	2019–2020
Park	2021	US	120	Not reported	Cost of procedure	2015–2018
Piccinni	2019	Italy	355	Metastatic	1st or 2nd year follow-up	2013–2015
Politi	2021	US	395	Early	1 year follow-up	September 2017–May 2019
Rocque	2018	US	1522	Both	Quarterly cost	2012–2015
Saulsberry	2021	US	75,197	Early	120 days follow-up	2008–2017
Schwartz	2021	US	449	Not reported	Cost of procedure	2018–2019
Schwartz	2021	US	1506	Metastatic	1 year follow-up	January 2012–September 2018
Schwarz	2022	Germany	431	Metastatic	Monthly cost	2019–2020
Sittenfeld	2021	US	718	Early	Cost of procedure	2015 and 2018
Skarping	2022	Sweden	1405	Early	Unclear	2020
Specchia	2023	Italy	338	Not reported	Cost of procedure	January 2019–March 2021
Squeo	2022	US	Unclear	Early	Cost of procedure	2020
Sun	2020	UK	55,662	Early	1 year follow-up	2014–2016
Tesch	2022	Canada	2066	Early	Cost of procedure	January 2013–June 2019
Thomas	2021	US	539	Both	6 months follow-up	July 2016–July 2018

Table 1 continued

Lead author's last name	Publication year	Country	Sample size	Cancer stage	Time horizon	Data collection years (and month when available)
Tilleul	2017	France	375	Not reported	Annual cost	2013–2014
Watzek	2022	Australia	60	Both	12 weeks follow-up	2016–2017
Williams	2019	US	1177	Early	Monthly cost	2012–2015
Witmer	2022	Netherlands	220	Early	18 months follow-up	2014–2016
Wright	2021	Australia	659	Early	Cost of procedure	September 2013–March 2019
Yaremko	2021	Canada	Unclear	Early	Annual cost	2020
Zhang	2017	Canada	347	Early	Cost of procedure	April 2014–March 2016

care (e.g., end of life care). Medical costs were often focussed on the cost of specific procedures which were compared and contrasted, such as the material cost for intravenous (IV) administration ($23,930) compared to subcutaneous (SC) administration ($2,462) [66], or the cost of having Stage III triple negative breast cancer with reconstruction ($30,730) compared to without reconstruction surgery ($20,660) [27]. In our identified studies, it was almost as common for a study to focus on a specific procedure cost compared to patient-level (or cohort-level) overall care costs over a specified time horizon. For example, Hequet et al. [58] reported the 1-year follow-up cost for three groups of categorised patients at the patient-level: (1) conservative breast surgery without axillary dissection or chemotherapy ($13,921); (2) conservative breast surgery with axillary dissection or chemotherapy ($18,565); and (3) all patients treated by radical breast surgery ($19,253).

Pharmaceutical Drugs Costs

Of the 13 (25%) studies that reported pharmaceutical drug costs [23, 25, 38–40, 42, 48, 50, 54, 55, 59, 60, 68], these studies focussed on overall drug use by breast cancer stage (see Sect. "Early (stages I-III) compared to metastatic (stage IV)"), mode of administration (e.g., home vs. hospital, IV vs. SC), and specific drug/therapy comparisons (e.g., neoadjuvant vs. adjuvant chemotherapy) [38]. For example, Houts et al. [23] reported the overall per person cost of systemic anti-cancer therapy drugs for triple-negative and hormone receptor-positive (HR +) breast cancer over 1 year as $12,722. There were estimated cost differences in drug costs across subtypes of breast cancer, as described in Sect. "Early (stages I-III) compared to metastatic (stage IV)" [38–40]. Costs for other treatments like endocrine therapy were not well captured in our included studies.

Diagnosis Costs

Of the 9 (17%) studies that reported diagnosis costs [19, 33, 38–40, 58, 59, 67, 69], these studies focussed on aspects such as radiology (e.g., mammography), biopsy, laboratory tests, and genomic sequencing. Specific diagnostic procedure costs were not always reported, although Gordon et al. [69] estimated the cost of genomic sequencing per procedure/person: $320. Alternatively, studies identified the costs of diagnostics dependent on cancer stage or for specific groups of patients with cancer on a per-patient level over 1 year, e.g., three studies by Brezden-Masley et al. [38–40] (see Sect. "Early (stages I-III) compared to metastatic (stage IV)").

Table 2 Number of identified articles by country, by specific resource or economic categories, or by breast cancer stage

Country	Articles, *n*	Proportion, %	Categories of costs, *n* (%*N*)				Breast cancer stage, *n* (%*N*))			
			Diagnosis	Medical	Drugs	Indirect	Early (stage I–III)	Metastatic (stage IV)	Both (early and metastatic)	Not reported
Canada	9	16.98	3 (33.3)	9 (100.0)	4 (44.4)	1 (11.1)	6 (66.7)	3 (33.3)	3 (33.3)	3 (33.3)
US	19	35.85	2 (10.5)	17 (89.5)	2 (10.5)	1 (5.3)	14 (73.7)	9 (47.4)	6 (31.6)	2 (10.5)
Italy	5	9.43	0 (0.0)	5 (100.0)	2 (40.0)	0 (0.0)	2 (40.0)	1 (20.0)	0 (0.0)	2 (40.0)
Spain	4	7.55	0 (0.0)	4 (100.0)	2 (50.0)	2 (50.0)	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)
France	4	7.55	2 (50.0)	2 (50.0)	1 (25.0)	3 (75.0)	3 (75.0)	0 (0.0)	0 (0.0)	1 (25.0)
Netherlands	3	5.66	0 (0.0)	2 (66.7)	1 (33.3)	2 (66.7)	3 (100.0)	1 (33.3)	1 (33.3)	0 (0.0)
Australia	3	5.66	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)
UK	3	5.66	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (66.7)
Sweden	2	3.77	1 (50.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Germany	1	1.89	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Europe total	22	41.51	3 (13.6)	19 (86.4)	7 (31.8)	7 (31.8)	14 (63.6)	4 (18.2)	2 (9.1)	6 (27.3)
Total	53	100.00	9 (17.0)	47 (88.7)	13 (24.5)	9 (17.0)	36 (67.9)	17 (32.1)	12 (22.6)	12 (22.6)

Table 3 Cost per person per procedure by specific resource or economic categories, by country or by breast cancer stage

By country or stage	Diagnosis costs			Drug costs			Other medical costs			Indirect costs			Across all categories		
	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range
US	–	–	–	–	–	–	10/5	$7,096	(707, 30,730)	2/1	$278	(276, 280)	12/6	$3,809	(276, 30,730)
Canada	–	–	–	–	–	–	2/1	$616	(224, 1009)	–	–	–	2/1	$616	(224, 1009)
Australia	1/1	$320	(320, 320)	–	–	–	1/1	$258	(258, 258)	–	–	–	2/2	$289	(258, 320)
UK	–	–	–	–	–	–	6/2	$3,187	(1347, 8916)	–	–	–	6/2	$3,187	(1347, 8916)
Italy	–	–	–	–	–	–	8/3	$3,607	(1989, 4500)	–	–	–	8/3	$3,607	(1989, 4500)
Netherlands	–	–	–	2/1	$2,149	(2149, 2149)	2/1	$2,466	(2400, 2533)	2/1	$24	(13, 34)	6/1	$2,149	(13, 2533)
Europe total	–	–	–	2/1	$2,149	(2149, 2149)	16/6	$3,592	(1347, 8916)	2/1	$24	(13, 34)	20/6	$2,619	(13, 8916)
Early only	–	–	–	–	–	–	12/5	$3,607	(224, 30,730)	2/1	$278	(276, 280)	14/6	$3,592	(224, 30,730)
Metastatic only	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Both	–	–	–	2/1	$2,149	(2149, 2149)	3/2	$2,400	(1322, 2533)	2/1	$24	(13, 34)	7/2	$2,149	(13, 2533)
Not reported	1/1	$320	(320, 320)	–	–	–	14/6	$3,187	(707, 20,772)	–	–	–	15/7	$2,704	(320, 20,772)
Total	1/1	$320	(320, 320)	2/1	$2,149	(2149, 2149)	29/13	$3,586	(224, 30,730)	4/2	$155	(13, 280)	36/15	$2,466	(13, 30,730)

The country inclusion criteria were the US, Canada, Australia and Western Europe (UK, France, Germany, Spain, Italy, Norway, Sweden, Denmark, Netherlands and Switzerland). If a country does not appear in the table, it is because a relevant article and/or cost for this table was not identified. All costs are standardised to US$2022

[a]*C/S* costs/studies: the median and range is constructed across a range of individual procedure cost estimates both within and across studies which were not combined. As such, the C/S statistic suggests how many costs and studies the median and range was constructed from. For example, 1/1 means one cost from one study was included (in these cases, the range is the same as the median). Alternatively, 16/6 means 16 cost estimates are accounted across 6 studies, with the median being from the 16 cost estimates, and the range indicating the lower and highest cost estimates

Table 4 Cost per person over 1 year by specific resource or economic categories, by country or by breast cancer stage

By country	Diagnosis costs			Drug costs			Other medical costs			Indirect costs			Across all categories		
or stage	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range	C/S[a]	Median	Range
US	3/2	$1,342	(506, 16,987)	4/2	$132,293[c]	(12,722, 196,226)	10/5	$7,802	(1133, 65,144)	–	–	–	17/6	$12,722	(505, 196,226)
Canada	6/3	$155	(129, 267)	6/3	$3,654	(1634, 45,889)	12/5	$11,235	(667, 176,947)	1/1	$1,031	(1031, 1031)	25/5	$1,096	(128, 176,946)
UK	–	–	–	–	–	–	3/1	$12,160	(8253, 21,291)	–	–	–	3/1	$12,160	(8252, 21,291)
France	7/2	$454	(152, 8345)	4/1	$5,712	(4082, 8345)	7/2	$19,253	(13921, 26,009)	7/3	$2,663	(1617, 29,753[d])	25/4	$4,415	(151, 29,753)
Italy	–	–	–	5/2	$22,787	(1158, 23,619)	5/2	$1,115	(199, 9089)	–	–	–	10/2	$3,286	(1157, 9089)
Spain	–	–	–	–	–	–	1/1	$8,007	(8007, 8007)	–	–	–	1/1	$8,007	(8006, 8006)
Europe Total	7/2	$454	(152, 1355)	9/3	$7,009	(1158, 23,619)	16/6	$13,040	(199, 26,009)	7/3	$2,663	(1617, 29,753[d])	39/8	$7,009	(151, 29,753)
Early Only	7/5	$506	(128, 1355)	6/4	$20,027	(1634, 23,619)	21/9	$2,794	(199, 46,045)	3/2	$11,577[d]	(10,114, 29,753)	37/12	$2,592	(129, 46,045)
Metastatic Only	5/4	$267	(159, 16,986)	6/5	$3,654	(1158, 45,889)	8/6	$8,519	(4227, 176,947)	–	–	–	19/6	$5,411	(160, 176,947)
Both	–	–	–	3/1	$137,875[c]	(126,712, 196,226)	3/1	$52,551[c]	(52017, 65,144)	–	–	–	6/1	$95,928[c]	(52017, 196,226)
Not Reported	4/1	$331	(151, 453)	4/1	$5,712	(4082, 8345)	6/3	$19,296	(1096, 26,009)	5/2	$2,071	(1031, 2663)	19/3	$2,663	(152, 26,009)
Total	6/7[b]	$331	(129, 16,987)	19/8[b]	$8,345	(1158, 196,226)	38/16[b]	$10,625	(199,176947)	8/4	$2,443	(1031, 29,753)	81/19[b]	$4,415	(128, 196,226)

The country inclusion criteria were the US, Canada, Australia and Western Europe (UK, France, Germany, Spain, Italy, Norway, Sweden, Denmark, Netherlands and Switzerland). If a country does not appear in the table, it is because a relevant article and/or cost for this table was not identified. All costs are standardised to US$2022

[a]*C/S* costs/studies: the median and range is constructed across a range of per person/year cost estimates both within and across studies which were not combined due to concerns with double counting and/or comparability. As such, the 'C/S' statistic suggests how many costs and studies the median and range was constructed from. For example, 1/1 means one cost estimate from one study was included (in these cases, the range is the same as the median). Alternatively, 16/6 means 16 cost estimates are accounted across 6 studies, with the median being from the 16 cost estimates, and the range indicating the lower and highest cost estimates

[b]The three included articles by Bresden-Masley et al. each report metastatic and early breast cancer costs separately within the same paper; thus, the total is does not reflect the "by stage" sum of studies (i.e. for 'metastatic only' or 'early only')

[c]The article by Mahtani et al. examined the costs associated with patients treated with human epidermal growth factor receptor 2 (HER2)-targeted agents. This study estimated much higher drugs costs than any other included study, which was attributed specifically to the HER2-Targeted Agents costs within their study; thus, this cost is relevant for inclusion, but does represent a specifically high cost which contributes to a higher median and range where this cost is included in the calculation, e.g., including across countries, breast cancer stages, and cost categories

[d]The article by Ferrier et al. used the human capital and friction cost approach to estimate productivity loss, which was the only article included this table which used that method. The estimated productivity loss using this approach tends to be quite high, with the human capital approach tending to produce a higher cost than the friction cost approach. It is this approach to estimating productivity loss as an indirect cost which is associated with this particularly high indirect cost estimate within this table

Indirect Costs

Nine (17%) studies reported indirect costs [34, 43, 54–57, 59–61]. Productivity loss is a key indirect cost for consideration, often estimated via the human capital approach, i.e., take the patient's perspective and count any hour not worked as an hour lost, or the friction cost approach, i.e., take the employer's perspective and only count lost hours not worked until another employee takes over the patient's work [72]. However, only one of our included studies, Ferrier et al. [57], estimated the productivity loss per person during the year following diagnosis of operable breast cancer (US$2022): human capital, $29,753, and friction, $10,114. Another study by Arfi et al. [56] estimated the cost of sick leave of patients with breast cancer to the French National Health Insurance (US$2022): $11,577; this is akin to the human capital approach, but from the health insurance perspective.

Early (Stages I-III) Compared to Metastatic (Stage IV)

Thirty-six (68%) of our included studies reported costs for early-stage cancer [19, 20, 22, 24–27, 29–31, 34–40, 44–48, 53–58, 60–62, 65–67, 70, 71]; 17 (32%) included metastatic cancer [20–23, 25, 27, 30, 33, 36, 38–40, 50, 53, 60, 68, 70]; 12 (23%) included both early and metastatic cancer [20, 22, 25, 27, 30, 36, 38–40, 53, 60, 70]; for 12 (23%), the cancer stage was not reported [28, 32, 41–43, 49, 51, 52, 59, 63, 64, 69]. Generally, across our included studies, metastatic breast cancer was associated with higher costs than earlier stage cancer (see Figs. 2 and 3); however, this was particularly noticeable in the range of costs (i.e., metastatic cancer had a much higher maximum value reported) than the median, due to the nature of what costs were included in our identified studies.

Three studies by Brezden-Masley et al. [38–40] across three breast cancer types (triple-negative, HER2-positive, HER2-negative) reported that costs across all cost categories were higher in Stage IV than in Stage I–III cancer populations; additionally, they reported that healthcare medical costs were higher than drug costs followed by diagnostic costs. Diagnostic costs (Stage I–III vs. Stage IV) [38–40]: triple-negative, $151 vs. $267; HER2-positive, $129 vs. $160; HER2-negative, $143 vs. $167. Drug costs (Stage I–III vs. Stage IV) [38–40]: triple-negative, $2,592 vs. $3,650; HER2-positive, $17,267 vs. $45,889; HER2 negative, $1634 vs. $3659. Healthcare costs (Stage I–III vs. Stage IV) [38–40]: triple-negative, $34,691 vs. $176,947; HER2-positive, $34,790 vs. $134,840; HER2 negative, $21,374 vs. $90,789. Unfortunately, the studies by Brezden-Masley et al. [38–40] did not capture indirect costs to provide a direct comparison of direct to indirect

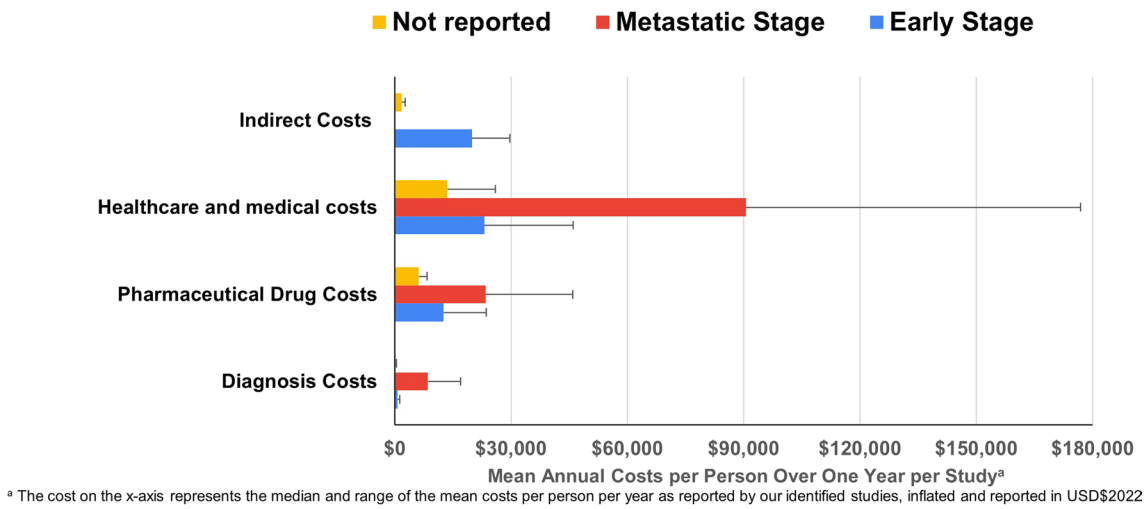

Fig. 2 The median and range of reported mean per person annual costs by cancer stage and healthcare care resource category

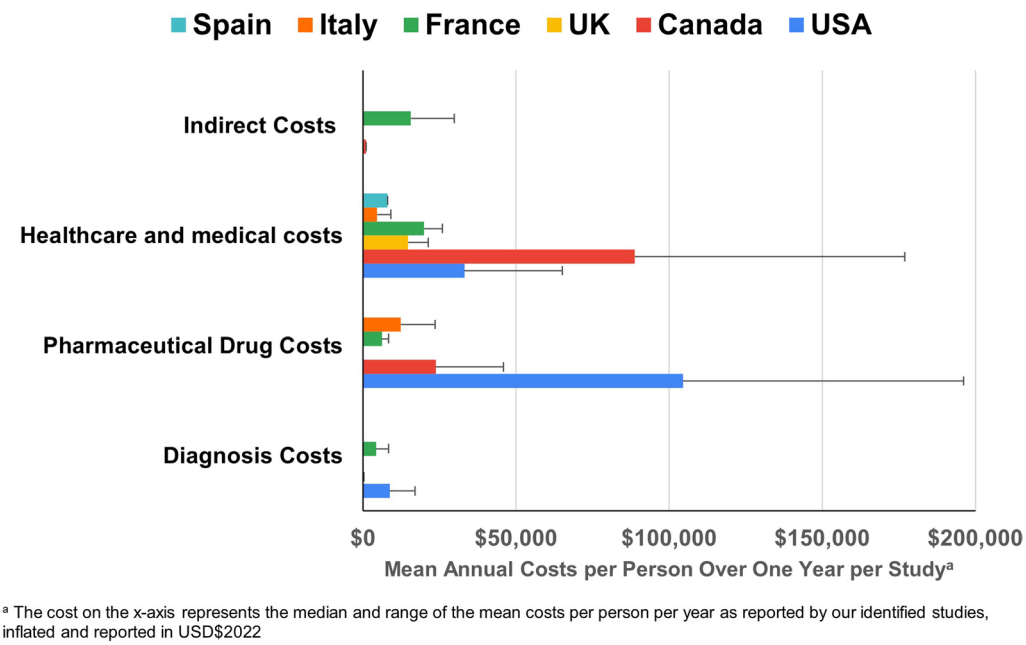

Fig. 3 The median and range of reported mean per person annual costs by country and healthcare care resource category

costs across cancer stages, despite other studies suggesting that indirect costs could potentially dwarf these direct costs across all cancer stages [1, 34, 43, 54–57, 59–61, 73].

US Compared to Other Countries

No identified study explicitly compared costs across countries, also noting that the heterogenous nature of the costing studies between (and within) countries greatly restricted comparability. However, the cost range tended to be higher in the US both for procedure and yearly-per-patient costs than any other country (see Fig. 3). For other medical costs, though, the yearly-per-patient cost range was similarly high for Canada as for the US. Although the median cost identified was sometimes higher across Europe (e.g., yearly-per-patient for other medical costs), the upper limit of the range tended to be smaller than in the US.

DISCUSSION

The current study systematically reviewed the estimated economic burden of breast cancer in the US, Canada, Australia, and across Western Europe. Generally, there was substantial heterogeneity both within and across countries of the identified studies in terms of resource/cost perspective, sample size, methodology, and time horizon, among other characteristics which influenced the associated cost estimates. This is not a specific criticism of any given study, as each costing study had their own focus which stemmed from very specific micro-costs to more aggregated national costs. However, from the perspective of wanting to understand the overall economic burden of breast cancer, we were not able to combine/synthesise (e.g., using meta-analyses) estimates across studies due to heterogeneity and concerns around double counting, nor were there sufficient studies capturing important costs (e.g., indirect costs) at person or national levels within all the countries we focussed on. As such, there seems to be a scarcity of appropriate, well-conducted, large-scale national or cross-country studies that have estimated the broader economic burden of breast cancer, at least over the 5-year publication time horizon our review focussed on. Although older studies may be/are available, understanding the economic burden of breast cancer should be an ongoing and iterative

processes, given the ever-changing epidemiological and economic landscape.

What Do We Know About the Economic Burden of Breast Cancer?

Given the heterogeneity of the identified and included studies, a pertinent question is: what do we know about the economic burden of breast cancer? To answer this question, we focussed on our identified studies alongside systematic reviews and specific studies from the broader literature that focussed particularly on the national and (where possible) international scope of the economic burden, while contrasting this with the more micro-costing studies from our identified literature.

Direct Costs

Within our identified studies over three healthcare categories (diagnosis, drugs, and medical care), diagnosis was the smallest proportion of the costs, then drugs, with medical care being the largest contributor. Naturally, medical care is a broader categorisation of costs than drugs or diagnosis, so it likely to be a higher cost in part due to the amount of resource accounted for in this categorisation. Also, despite drug costs generally being lower than medical care costs, this was not true in all circumstances. For example, Mahtani et al. [25] estimated that the cost of HER2-targeted therapy is very high, which influenced our median and range of costs in Table 4.

Except for the study by Mahtani et al. [25], our other generalised results and categorisations align with the broader empirical literature. For example, Dieleman et al.'s [74] US study provides a clearer picture of healthcare spending, suggesting that the majority of breast cancer costs are associated with inpatient (48.9%) and then ambulatory care (31.0%), with only 2.8% and 2.1% of costs associated with prescribed pharmaceuticals and emergency department visits, respectively.

Indirect Costs

External to our identified studies, Chen et al. [1] estimated indirect costs (i.e., productivity loss based on the human capital approach due to mortality, morbidity, and informal care) as being a much larger contributor to overall economic burden than treatment costs. For example, in high-income countries, productivity (human capital) loss and treatment costs accounted for approximately 77% and 24% of total cancer economic burden, respectively; for low-income to upper-middle income countries, productivity loss contributed approximately 90–95%. Similarly, Mohammadpour et al.'s [73] systematic review focussed specifically on breast cancer indirect costs: across 33 studies (2000–2020), indirect costs ranged from $22,386 to $308bn, depending on the study approach (i.e., human capital or friction cost), and if focussing on premature death or informal caregivers.

Our identified studies revealed three key things: (1) when indirect costs are accounted for in terms of productivity loss, premature death or informal care, they can be potentially higher than any other direct cost (e.g. diagnosis, drug, and other medical costs); (2) there is a lack of studies estimating indirect costs related to breast cancer published since 2017 that have used data post-2012 in our eligible countries; and (3) studies do not often capture spill-over effects such as the impact on informal caregivers (e.g., physical/mental health and well-being burdens) alongside additional indirect out-of-pocket payments (e.g., childcare expenses), which are potentially substantial [75]. Given the potential magnitude of indirect costs, larger scale, up-to-date studies are required. There is a particular gap in studies that capture indirect costs associated with premature death and informal caring, with these costs then also compared to direct costs.

Economic Burden by Breast Cancer Stage

Breast cancer stage is an important predictor of costs: previous studies have shown the amount and intensity of treatment tends to be higher at more advanced than earlier stages [8, 9]. Our identified studies generally suggested that metastatic (Stage IV) cancer was more costly than early (Stage I–III) cancer [20, 22, 25, 27, 30, 36, 38–40, 53, 60, 70]. However, it is important to recognise the heterogeneous nature of these

costing studies and that our suggestion comes particularly from the range of costs rather than the median across cost estimates and studies; although the three identified studies by Brezden-Masley et al. [38–40] greatly aided with direct comparisons of costs by breast cancer stage across three cancer types (triple-negative, HER2-positive, HER2-negative). Generally though, our suggestion that metastatic cancer is more costly than earlier stage cancer concurs with other reviews [8, 9]. Sun et al. [9] included 22 studies, with 11 using the FIGO staging system: mean treatment costs of breast cancer at Stages II, III and IV were 32%, 95%, and 109%, respectively, higher than Stage I; other staging systems also generally suggested late/more severe cancers were more expensive than earlier/less severe stages. Given late-stage breast cancer is more costly than early-stage, there is rational to suggest upfront costs for early initiation could be offset by avoiding the economic burden associated with later stage/more severe breast cancer.

Overall Economic Burden on a Global Scale

Based on our identified studies, breast cancer procedure costs ranged from $13 to $30,730 (Table 3), with the cost per person over a year ranging from $128 to $196,226 (Table 4). To put these numbers in context, the World Health Organisation (WHO) stated that, in 2020, 2.3 million women were diagnosed with breast cancer globally and that 7.8 million were alive who were diagnosed with breast cancer in the past 5 years [76]. Assuming the cost of breast cancer over any given year was our upper identified amount of $196,226, for the 2.3 million new cases, this would equate to $451 billion and, for the 7.8 million existing cases, this would be $1531 billion. Although this is extrapolating essentially a single upper mean cost estimate to a population of newly diagnosed or existing breast cancer cases, at the upper range of our mean per person yearly costs for the 7.3 million women, this amount of $1531 billion is certainly tending toward Chen et al.'s [1] estimate of $1964 billion (95% UI: $1402 bn–$2759 bn) [1]. Based on our systematic review, it is not wholly possible to suggest to what extent Chen et al.'s [1] modelling estimate could be true or not; however, it seems certainly with the realm of possibility. There is no primary study (that we identified) that has brought together this range of information for any single country, never mind on a global scale. This represents a gap of evidence to consistently estimate the economic burden of breast cancer globally.

What Does This Mean for Society and Policymakers?

Policymakers have a crucial role in shaping and influencing the future of cancer care, which includes prioritising the allocation of finite resources; understanding the economic burden of breast cancer, such as for what and for whom this economic burden is associated, can aid inform such resource allocation decision-making.

As an example, our review identified that the economic burden of late-stage breast cancer costs is generally estimated to be higher than early-stage breast cancer costs [20, 22, 25, 27, 30, 36, 38–40, 53, 60, 70]. Although these costs differed by country, this overall result generally remained consistent across countries. It therefore seems logical to suggest that investing in early breast cancer detection and treatment could be a cost-saving strategy over the longer term, given that the initial cost of early intervention could be offset by avoiding the longer-term economic burden of late-stage breast cancer. Our suggestion is based on a hypothesis derived from the costs estimated within those studies identified by our review; however, this suggestion is echoed in other research and strategic articles focused on more preventive measures, such as earlier cancer detection and treatment. For example, recent modelling-based analyses focussed on the UK suggests that, in terms of preventative strategies, higher levels of screening, more cancer nurse specialists, and better help for people returning to work could be the highest impact interventions [77]. Part of the economic case evidenced by this modelling analysis is due to trading off the financial investment in early intervention against avoiding the economic burden (direct and indirect costs) of more severe cancer in the future [77]. At an international

level, this suggestion is further echoed by the WHO's Global Breast Cancer Initiative Implementation framework, which includes three pillars for change and associated key performance indicators (KPIs): Pillar 1, health promotion for early detection (KPI: > 60% of invasive cancer are Stage 1 or II at diagnosis); Pillar 2, timely breast diagnostics (KPI: diagnostic evaluation, imaging, and tissue sampling and pathology within 60 days); Pillar 3, comprehensive breast cancer management (KPI: > 80% undergo multimorbidity treatment without abandonment) [78]. The WHO suggests the implementation of their framework could save 2.5 million lives by 2040, which is focussed particularly on the patient health-related benefit side of the considerations, rather than the financial side which is the purview of our review. However, based on the cost evidence identified by our review and reflecting on related modelling-based economic studies [1, 20, 22, 25, 27, 30, 36, 38–40, 53, 60, 70, 77], it could be that this type of early intervention initiative could also potentially be cost saving over the longer term alongside these patient-focussed life-saving benefits, the exact financial impact of which should be a focus for future research [78].

Our review also shows that drugs represent a relatively small portion of the overall economic burden of breast cancer. In comparison, indirect costs such as loss of productivity, and the financial impact associated with informal caregiving, have been shown to be relatively bigger cost drivers, when indirect costs were estimated [34, 43, 54–57, 59–61]. The lack of studies estimating the indirect costs of breast cancer is concerning, given that these indirect costs can land both on the broader economy (e.g., productivity loss) but also on the person with breast cancer and their families; such aspects are an area of growing concern and consideration for policy makers. Given that breast cancer predominantly affects women, such indirect costs can also lead to financial toxicity for women which represents an inequality in society, but this financial burden can also extend to entire families and communities. As such, as our review indicates the high potential indirect costs associated with breast cancer, we can infer that this could lead to sex inequalities that are important considerations for policy makers. Also, our review suggests indirect costs are not currently a key focus for research projects and costing studies, perhaps because indirect costs are more difficult to quantify than direct costs; however, estimating the indirect cost burden of breast cancer is an important evidence gap identified by our review, which should be filled given the broad impact indirect costs can have on patients with breast cancer, survivors, their families, health and welfare systems, and the broader economy [1, 34, 43, 54–57, 59–61, 77].

As such, it is our suggestion that understanding the economic burden associated with preventing and treating breast cancer, both related to direct and indirect costs, has important and far-reaching policy implications, particularly when considered and put in the context of other relevant empirical evidence. As breast cancer is an ongoing epidemic that needs resource allocation, it is imperative for physicians, payers, and policymakers to determine pathways to detect and treat breast cancer early, the cost of those pathways, if short-term costs can be traded-off against avoiding longer-term costs, and how these costs are potentially exacerbating inequalities, particularly due to indirect costs that are currently understudied based on the studies identified by our review.

Strengths, Limitations, and Future Implications

Studies such as Dieleman et al. [74] in the US are a clear indication of how important good quality, national, and linked data are to aid our understanding of healthcare spending (and even the broader economic burden) of conditions within a country. The estimates provided by Dieleman et al. [74] were because of the data available to inform that study: government budgets, insurance claims, facility records, household surveys, and official US records. The US has useful standalone and linkable data to facilitate such analyses, which other countries have also developed but perhaps not to the same extent, particularly in relation to linked data at the same scale. The evaluation of real-world data such as electronic health records should be seen as a means of facilitating direct care, but also secondary research for public benefit [79, 80]. Although some of our identified

studies did make use of such routine data, we did not identify any high-quality, national studies like Dieleman et al. [74]. Also, of the studies we did identify, they were so heterogenous that comparisons between studies were difficult or not possible; as such, we focussed particularly on 34 (64%) of our 53 identified studies for which costs were considered potentially comparable. Although not all costing studies have to be the same, costing studies should seek to produce results at common levels such as per procedure or per-patient over a common timeframe (e.g., 1 year, to also account for seasonal differences). Additionally, the costs of newer pharmaceutical interventions including CDK4/6 inhibitors were not well documented in the literature due to the time period of the studies that were included. It is difficult to impossible to accurately standardise shorter/longer time frames to 1 year due to issues with sunk/upfront costs, which means that costs in the shorter term tend to be higher than longer-term costs post-treatment/diagnosis, e.g., see Mahtani et al. [25]. Difficulties with comparability were a key limitation of using a systematic review approach to understand the economic burden of breast cancer, although no one identified study sufficiently captured the whole economic burden of breast cancer. It should also be noted that, due to issues with identifying appropriate inflation indices (e.g., healthcare inflation indices) for all the relevant countries included within our review, we used just the US healthcare inflation indices across all countries; this approach improves comparability for how we updated the relevant cost information across countries, but may not best represent inflation within any specific country other than the US. Finally, although this article focuses on quantitative evidence, qualitative evidence from the patient perspective is just as important for policy shaping and can provide further contextual information to quantitative evidence, which is not provided as part of our review as another limitation.

CONCLUSION

Current empirical literature suggests that it could be cost saving to invest in shorter-term earlier detection and treatment of breast cancer, if this shorter-term investment is considered a trade-off for avoiding higher costs in the future due to avoiding or reducing later stage and more severe breast cancer. Compared to direct healthcare and medical costs, indirect costs such as associated with lost productivity and informal caring are understudied and this limits policy makers' ability to consider the broader economic burden of conditions like breast cancer when prioritizing the allocation of finite resources for prevention and treatment. Although large national costing studies do exist based on routinely collected data, such as in the US, we did not identify any within our countries of interest over the time frame of our review. However, providing such national (and international) costs estimates is important to inform policy makers and so should be considered a research and policy important agenda item to be updated regularly (e.g., every 2–5 years) to ensure that there is an ongoing and evolving perspective of the economic burden of conditions such as breast cancer. All public and private sectors internationally are constrained by finite resources and therefore quantifying the direct and indirect costs of conditions should be seen as a key objective if healthcare systems are to be sustainable given current breast cancer incidence rates alongside other health conditions and a growing population. Overall, our review suggests that, although there are a range of costing studies that exist internationally, we still only know aspects of the economic burden of breast cancer, meaning that a limited scope is potentially informing policy and practice which could have far-reaching implications for patients, families, healthcare systems, and the broader economy.

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Data Availability. The extracted information from the identified studies are provided within the supplementary material.

Declarations

Conflict of Interest. Janvi Sah, France Dube, Lei Qin are employees of AstraZeneca and hold shares at AstraZeneca. The authors have no other conflicts of interest to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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