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A Review of the Research Landscape for Treatment of Early Breast Cancer

Implications for future research, policy and practice

Ioana Ghiga, Camilla D'Angelo, Sarah King, Josephine Exley, Amelia Harshfield, Daniela Rodriguez-Rincon, Brandi Leach, Catriona Manville and Sonja Marjanovic

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Published by the RAND Corporation, Santa Monica, Calif., and Cambridge, UK

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This research programme was sponsored by F. Hoffman-La Roche Ltd

Preface

This document presents the findings from one element of a body of work sponsored by F. Hoffmann-La Roche on the topic of early breast cancer. This report presents the findings of a mapping review on the published literature on the impact of treatment of early breast cancer. It highlights the available evidence and state of research on treatment of early breast cancer and identifies areas where more research could prove beneficial.

This document is complemented by a full systematic review exploring the non-clinical impacts of recurrence of early breast cancer following treatment on individuals, their support network and wider society (Elmore et al. 2019), and a qualitative study using key informant interviews and desk research to assess the drivers and enablers to accessing treatment for early breast cancer in a selection of five countries (Brazil, Canada, Italy, Spain, the UK), as well as a pan-European overview (Rodriguez-Rincon et al. 2019).

This report is of interest to researchers, policy makers, healthcare professionals, patient advocates and others within the healthcare system. It aims to look at not only the current policy and evidence but also opportunities for the future.

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For more information about this report or RAND Europe please contact:

Dr Catriona Manville

RAND Europe

Westbrook Centre

Milton Road

Cambridge CB4 1YG

UK

manville@rand.org

Executive summary

Breast cancer is the most frequent cancer in women. Early diagnosis of breast cancer results in earlier treatment of breast cancer, which has been associated with better survival prospects and improved quality of life. However, the risk of disease progression after treatment of early breast cancer is still relatively high and some treatment challenges exist. There is still a need for innovation in treatment for early breast cancer, and to make the case for this investment, more comprehensive evidence is required on the range of impacts of early breast cancer treatment.

This study was divided into three interconnected phases, which together aim to enrich the evidence base on the broader health, societal and economic impacts of treatment of early breast cancer, using a mixed methods approach. It highlights the available evidence and state of research on early breast cancer and considers the impact and 'cost' of disease progression for patients and their carers, as well as wider society.

The first phase consisted of a mapping review on the published literature on the impacts of treatment of early breast cancer. The key findings of this mapping phase are summarised below; there are more detailed analyses in the core report:

- **Study designs**: Most primary research that considers the impacts from treating early breast cancer report on either observational studies (48.0%) or randomised controlled trials (RCTs) (41.1%). There is comparatively much less evidence being drawn from economic analyses (5.3%) and qualitative studies (2.9%). Just 1.1% of the included papers adopted other designs (e.g. pre-post-test or pooled analyses).
- **Outcomes considered in the literature**: The most frequently reported outcomes across the pool of analysed primary papers are survival (55.0%) and recurrence (53.7%). Substantially less attention is paid to psychosocial outcomes (21.4%), patient pathway outcomes (1.5%), economic outcomes (7.4%), and disease progression (4.5%). The types of economic outcomes reported are predominantly cost-effectiveness or cost-benefit of treatments (70.7%) or all studies focusing on economic outcomes). A minority of studies consider economic outcomes for patients (e.g. out-of-pocket expenses) and for the wider health system or wider society (e.g. direct costs of treatments or indirect costs associated with resource use, staff time or hospital stays).
- **Types of treatment**: Chemotherapy, surgery and radiotherapy are the most common therapies (38.3%, 36.2% and 29.2% of all primary research studies respectively), followed by hormonal therapy (22.3%) and biological therapy (12.8%).
- **Study setting**: only 15.6% of all primary papers in the sample analysed for the mapping review mentioned the country of focus for the studies they report on in the title and abstract, covering

33 countries, across diverse regions globally. Canada, Denmark, Germany, Italy, Japan, Sweden, the UK and the US were each the focus of at least ten studies.

The mapping review revealed existing gaps in the evidence on the non-clinical impacts of treatment of early breast cancer to patients, carers or wider society. Studies of treatment effectiveness clearly dominate the literature and there is much less evidence on other types of outcomes extending beyond traditional treatment effectiveness evaluations. Yet understanding the wider impacts of cancer survivorship is important to better understand the impacts beyond treatment of breast cancer, and there is a need for more detailed analyses of these to inform better-informed decision making.

One of the key aims of the mapping review phase was to help identify and target the focus of a full systematic review on a specific outcome type where the current evidence gaps are high and to refine associated inclusion and exclusion criteria used. Based on the findings of this mapping review we subsequently undertook a systematic review on non-clinical burden-of-illness types of evidence using both quantitative data (e.g. observational studies) and qualitative data (e.g. surveys) (Elmore et al. 2019).

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Abbreviations

NHS	National Health System
NICE	National Institute for Health and Care Excellence
QALYs	Quality adjusted life years
RCT	Randomised controlled trial
TNM	Tumour, lymph node and metastasis
UK	United Kingdom
US	United States

Acknowledgements

RAND Europe researchers would like to thank Dr Simon Sutcliffe and Professor Shirley Hodgson for their advice in helping us to understand classifications of early breast cancer. We would also like to thank Jody Larkin from RAND US for assisting with the literature searches for the mapping review and Dr Susan Guthrie and Dr Sarah Ball from RAND Europe for their quality assurance roles.

1. Introduction

1.1. Background and context: the need for better evidence on the impacts of treating early stage breast cancer

1.1.1. Breast cancer continues to exert a high toll on society.

Breast cancer is the most common form of cancer, accounting for 25% of all cancer diagnosis worldwide; it is the leading cause of cancer-related mortality in women (Ferlay et al. 2015; World Health Organization 2018). The majority of women with breast cancer are diagnosed with early stage breast cancer rather than regionally advanced or metastatic cancer, when disease is confined to the breast with or without regional lymph node involvement (Union for International Cancer Control 2014).

Treatment of breast cancer when it is diagnosed at an early stage is associated with reduced risks of progression, reduced rate of recurrence and better survival prospects (McPhail et al. 2015; NHS 2015; Walters et al. 2013). Early stage breast cancer is potentially curable with local and systemic therapy (Anampa et al. 2015), whereas survival rates for metastatic disease remain poor (García Rodríguez et al. 2010; Union for International Cancer Control 2014). Approximately 5 to 10% of breast cancers are metastatic at diagnosis; of women with metastatic breast cancer, approximately only one-fifth survive five years[1] (Cardoso et al. 2012). Therefore, continued efforts in earlier diagnosis are needed.

There are substantial differences in survival rates among early stage breast cancer patients, both between European countries and worldwide (Walters et al. 2013). This variation is explained by several factors, including accuracy of staging assessments, as well as access to or the effectiveness of stage-specific treatment (Walters et al. 2013). Treatment challenges may also stem from a poor understanding of cancer subtypes likely to benefit from specific treatment (Di Leo et al. 2015). Therefore, improved treatment options, as well as a better understanding of their impacts, could help to improve survival outcomes for early stage breast cancer patients.

1.1.2. Managing cancer survivorship is important for patients, their families and society more widely.

Being diagnosed with early stage breast cancer can exert a significant impact on the individuals affected, their families and wider society. Breast cancer can affect the emotional, physical, psychological and social

[1] Further insights on comparative survival rates for those with non-metastatic cancers would help with comparative assessments of survival.

well-being of the patient and their families and long-term quality of life (Glück et al. 2010). It can result in substantial lifestyle changes during treatment and can reduce household income (e.g. because of the personal costs of receiving treatment and ability to work). Breast cancer impacts directly on society through health systems costs (e.g. expenses associated with treatment) and indirectly (e.g. through loss of labour productivity). A recent report calculated that in a given year cancer deaths result in a loss of £585 million to the UK economy (Creighton et al. 2015). In 2010 it was estimated that the overall cost of breast cancer care to the UK health system was £542 million due to hospital care, with metastatic breast cancer associated with markedly higher costs than early stage disease (Laudicella et al. 2016).

Several studies have investigated the effect of treatment of early stage breast cancer on outcomes such as recurrence and progression, and found that various treatment combinations reduce recurrence and distant metastasis (Early Breast Cancer Trialists' Collaborative Group 2011, 2015a, 2015b; McGale et al. 2014). However, the impacts of treatment of early stage breast cancer on the economy are currently not well understood (e.g. labour productivity and retention, health system costs) and society more widely (e.g. on carers, families); this is an area where better evidence has the potential to influence policy and practice. There is also a lack of systematic mapping evidence that could shed light on where the focus of research effort has been and provide more insight on the comparative attention paid to different types of outcomes.

1.1.3. What is early breast cancer?

Defining early breast cancer is a challenge for both researchers and practitioners, and there is no universally accepted definition. In order to define the term 'early breast cancer' for this study, the project team conducted desk research and sought expert advice from several key opinion leaders in the field as well as the F. Hoffmann-La Roche commissioning team. Considering the literature and expert opinion,[2] the study team determined that for the purposes of this study, early breast cancer refers to both non-invasive (pre-cancerous state, found only in the milk lobes or ducts) and invasive cancer that is confined to the breast, with or without regional lymph node involvement, and that has not metastasised. This includes breast cancer manifesting as locally advanced tumours, as these are potentially operable and do not necessarily show metastatic dissemination. Another way of categorising breast cancer involves the primary tumour, lymph node and metastasis (TNM) classification system (Gospodarowicz, Brierley, and Wittekind 2017). Therefore the study's definition of early breast cancer also included these stages.

It is recognised that biological markers, such as oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2, are relevant in identifying tumours with different molecular characteristics and their presence or absence can be predictive of disease prognosis, selection of therapy and response to therapy (Di Leo et al. 2015; Gospodarowicz, Brierley, and Wittekind et al. 2017). However, incorporating biological markers into the classification system for this study was not possible nor advised as it is not possible to relate them accurately to the definition of 'early'. The molecular profile of a tumour could dictate the pace of progression from early to late, but *per se* does not indicate the stage.

[2] We consulted an academic, a healthcare professional and a representative from the F. Hoffmann-La Roche oncology team.

1.2. Aims and objectives of the study

This study was conducted between September 2017 and May 2018 and aimed to answer the following question: What is published in the literature on the impact of treatment of early breast cancer?

Particularly, we sought to assess the different types of research being conducted, the different outcomes and impacts considered in the literature, and the main countries of focus for these studies.

The mapping review summarised the evidence base on the full range of outcomes considered in the literature on treating early breast cancer and in doing so sought to provide a more nuanced understanding of the weight of evidence that exists (and is by extension likely to influence policy and practice).

We set out to consider a broad range of outcomes, including survival, recurrence, progression, patient well-being and quality of life; economic impacts on individuals, the health system and wider society (e.g. the cost-effectiveness or cost-benefit of treatments, out-of-pocket expenses for patients and carers, days lost from work, labour productivity effects on society); and other societal or potential impacts on patients and carers (e.g. psychological impacts such as depression or anxiety). We did not seek to examine what the literature says about the nature of these outcomes within the scope of this work (the mapping review focused on the weight of evidence and the diversity considered in the literature; a systematic review will follow for a selected type of outcome and examine the nature of outcomes discussed in more depth).

2. Methodology

The mapping review was guided by a systematic approach and conducted following key guidance published by the Centre for Reviews and Dissemination 2009 and the Cochrane Handbook (Deeks et al. 2011). The review was based on the information presented in the title and abstract of identified studies only. We followed the five steps below:

- Step 1: develop search terms
- Step 2: determine the eligibility criteria
- Step 3: identify relevant literature
- Step 4: select studies and extract data based on information presented in the title and abstract
- Step 5: map the outcomes reported in the identified literature and their categorisation.

More specifically, the aim in Step 1 was to define 'early breast cancer' in a way that would allow us to robustly identify relevant literature within the scope of the mapping phase, and to develop search terms and a search strategy from that definition.

During Step 2 we determined the eligibility inclusion and exclusion criteria for studies to include in the mapping review, looking at population, interventions, outcomes and study designs. The eligibility criteria used for the screening of titles and abstracts was women who had received any of the following treatment options: surgery, radiotherapy, systemic therapy, targeted therapy, or a combination of therapies. No restrictions were applied to study methodology or the outcomes of the treatment, with the exception of solely reporting on adverse events or toxicity. For a full breakdown of the eligibility criteria used, please see Annex A.

In Step 3, an information specialist from the RAND Knowledge Services performed a database search using search sequences to identify the relevant literature (see Annex B for full search sequences). The focus of the mapping review was on academic publications. Searches were conducted on 8 December 2017 and performed in three databases: PubMed, Cochrane and Web of Science. The search was limited to the preceding 10 years (2007–2017) and restricted to the English language. The search yielded 13,714 hits.

In Step 4, five researchers independently screened titles and abstracts of studies identified against the eligibility criteria.[3] The screening and data extraction process ran concurrently with researchers extracting the information available from the study's abstract.[4]

[3] Five researchers performed the screening and extraction: CdA, CC, IG, JE and SK. Differences in views on relevance or nature of outcomes were resolved by discussion or, if necessary, by a sixth reviewer: SM.

Step 5 consisted of the mapping exercise, calculating the frequency of occurrence of treatments, study designs and outcomes reported to present an overview of the evidence landscape on the treatment of early stage breast cancer and the range of outcomes being assessed.

2.1. Caveats and limitations

There are some caveats to bear in mind in regard to the mapping review: by pre-specifying the broad categories of outcome types of relevance in our search (in order to ensure a manageable number and sufficient focus for the scope of the mapping review), it is possible that we may not have captured all possible outcomes. However, we were reassured by the diversity of outcomes captured within the broad overarching categories. We also only considered studies that explicitly stated the breast cancer stage within the title and abstract; a full text review may have revealed some additional information or additional studies but is out of the scope of a mapping review design.

[4] Data extraction consisted of populating an Excel template, which identified the study design, country where the study population was located, type of intervention (e.g. surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy, combination therapy or 'other') and type of outcome reported (categorised into the following overarching categories: survival, recurrence, progression, quality of life, depression, economic outcomes and 'other').

Members of the study team piloted the data extraction approach to ensure the coding categories were appropriate for the literature contents. Owing to the high volume of relevant articles identified, double screening and extraction were not possible at this phase, but the team consulted each other on all inconclusive cases. Other team members, the project manager or project leaders carried out spot checks of each individual researcher's screenings and data extraction. On completion of data extraction IG checked for omissions such as blank fields in the main sections and SK performed additional quality checks on approximately a quarter of the sample of included studies to ensure consistent practice. Throughout the screening and data extraction process the project leader and researchers had several conversations to ensure consistency of approach and to discuss challenges or areas of uncertainty that arose, and find ways to address them. This helped ensure accuracy of the final coding.

3. Results

In total, from the screening of 13,714 hits, 1,101 primary articles were included as relevant in the mapping review, following title and abstract review by the research team. The excluded articles did not meet the inclusion criteria, described in detail in Annex A.

In addition to the included primary papers, the mapping exercise also captured 68 papers presenting systematic reviews and meta-analyses. These were not included in the overall descriptive analysis for the primary papers in order to avoid double counting of studies that might have been included in the systematic review and meta-analysis but also might have been captured individually.

When analysing the findings, please note that the total number of treatments or outcomes identified does not necessarily equal the total number of studies reviewed. This is because a single study can report on more than one type of treatment or outcome.

In the sections below, we present the distribution of studies by:

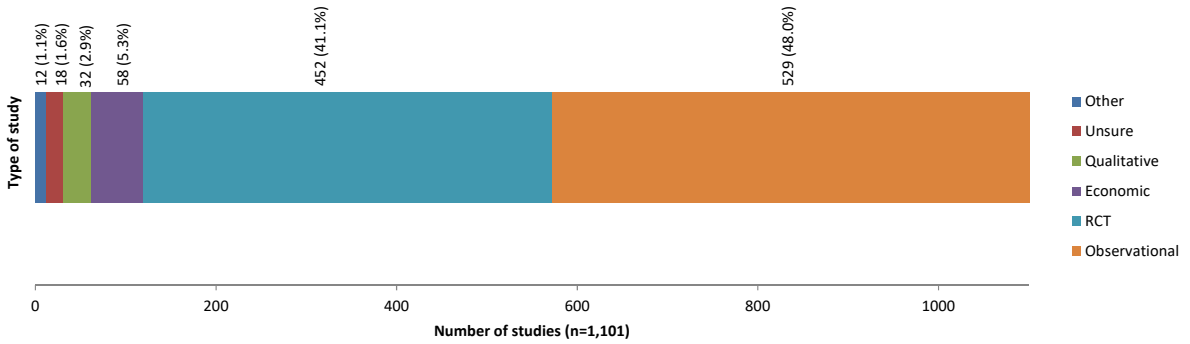
- Type of impacts of treating early breast cancer, by study design
- Type of treatment
- Outcomes considered
- Country of study population.

3.1. Distribution of studies considering the impacts of treating early breast cancer, by study design

3.1.1. Most studies on the impact of treatment of early breast cancer were observational studies or RCTs

Out of the total of 1,101 primary papers, the majority were either observational studies – cohort or case-control studies, case reports, or series and cross-sectional studies (529 studies or 48.0%) or RCTs (452 studies or 41.1%) (Figure 3.1). The rest presented economic analyses (58 studies or 5.3%) or qualitative studies (32 studies or 2.9%). The titles and abstracts for the remainder of the papers (30 studies or 2.7%) either did not present sufficient information to classify studies by study design, were classified 'unsure' or were classified as 'other' (e.g. pre-post-test or pooled analysis).

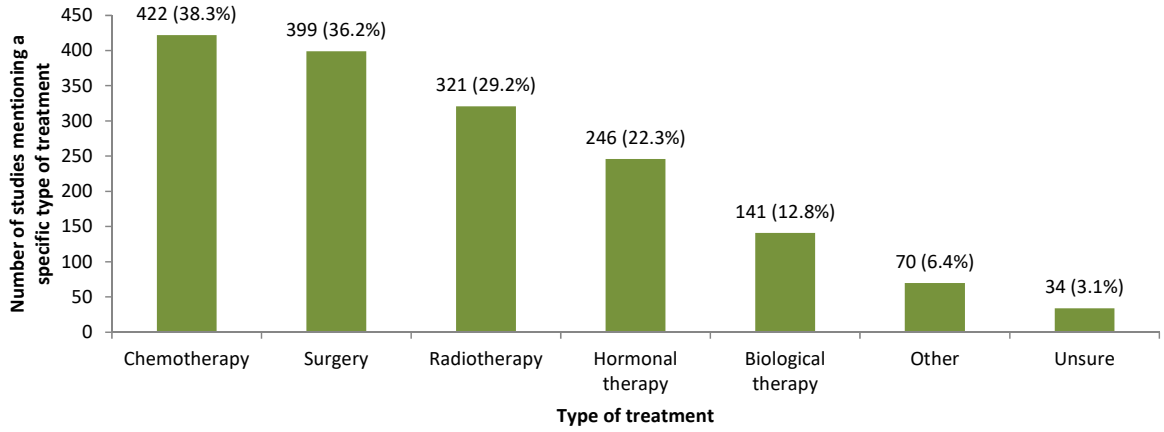
Figure 3.1 Distribution of studies by type of study design



3.2. Distribution of overall studies by type of treatment

Overall, the mapping exercise revealed chemotherapy, surgery and radiotherapy as the main types of treatments[5] studied in the screened primary literature with 29–38% of studies mentioning these three types (Figure 3.2). It is important to note that one study may have reported on more than one type of treatment, therefore the number of studies mentioning a specific outcome are not mutually exclusive.

Figure 3.2 Distribution of studies by type of treatment[6]



3.2.1. Traditional therapies for breast cancer are the most documented types of treatment found in the literature for early breast cancer

Traditional therapies for early breast cancer include chemotherapy, surgery and radiotherapy. Chemotherapy was the most common type of treatment reported for early breast cancer found in the

[5] For all the distributions by treatment please note that often one study involved multiple treatments.

[6] Calculation of percentages is based on the number of primary studies included in this review (n=1,101). However, one study may mention more than one type of treatment and therefore the number of studies does not add up to 1,101 and the percentages do not add up to 100.

literature considered in this mapping review. Chemotherapy is one of the main treatments for early breast cancer and consists of cytotoxic drugs that are given systemically (the treatment affects cells throughout the body) (National Institutes of Health n.d.-a). Major classes of chemotherapy agents include alkylating agents, antimetabolites, plant alkaloids and antibiotic-derived agents (National Institutes of Health n.d.-a). Chemotherapy was reported in 422 (38.3%) of included studies, which typically investigated outcomes such as survival, recurrence, side-effects and quality of life following treatment with different chemotherapy regimens (e.g. 'TAC regimen'[7] versus 'AC+P regimen'[8]), chemotherapy alone or in combination with other treatments (typically targeted biological therapies) and neoadjuvant versus adjuvant treatment. Studies also looked at the prognostic importance of the timing and sequence in which a particular chemotherapy regimen is administered (e.g. administered sequentially or concurrently) relative to other chemotherapy regimens or other treatments (e.g. radiotherapy or hormone therapy).

Surgery was the second most common type of treatment for early breast cancer found in the literature considered in this review and usually the first treatment option (National Institute for Health and Care n.d.). Surgery was reported in 399 (36.2%) of studies included in this review. The types of surgery reported in the literature included mastectomy, breast-conserving surgery or axillary lymph node surgery. The majority of studies focusing on surgery typically investigated outcomes such as survival, recurrence or quality of life following different types of breast surgery (e.g. breast-conserving surgery and mastectomy) or compared different types of surgical treatments (e.g. oncoplastic versus conventional breast-conserving surgery). Some studies compared axillary lymph node dissection versus alternative approaches (e.g. no dissection), and others investigated the impact of the size of the surgical margin on recurrence.

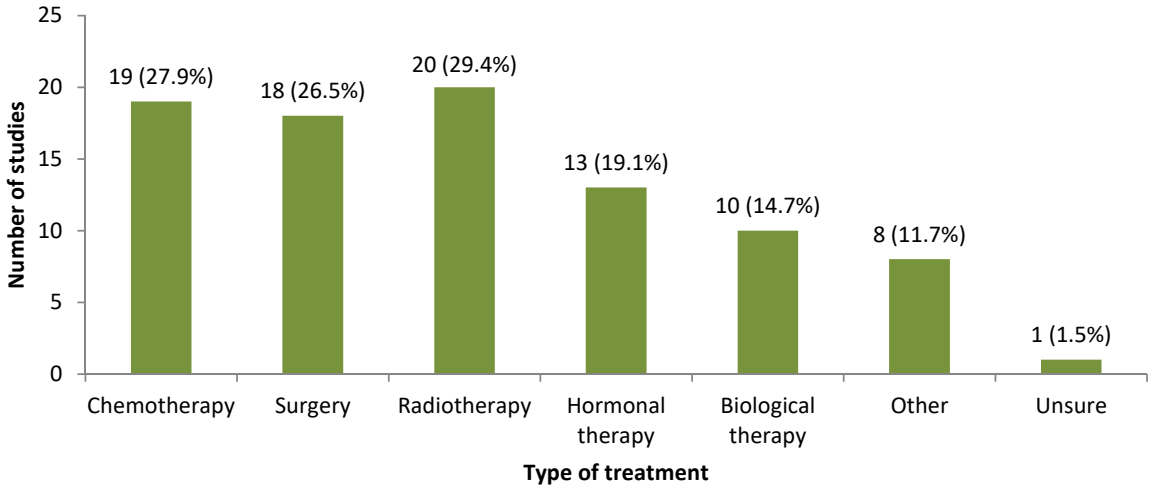
The third most reported type of treatment for early breast cancer in the literature was radiotherapy (321 studies or 29.2%). Radiotherapy uses x-rays, gamma rays and other sources of radiation to kill cancer cells (National Institutes of Health n.d.-b). Studies typically included comparisons of different types of radiotherapy (e.g. intraoperative radiation therapy or whole breast irradiation) or comparisons of different radiotherapy regimens within a given radiotherapy category (e.g. different doses). Studies also focused on comparisons of outcomes (e.g. survival or recurrence) following treatment with a radiotherapy regimen alone or in combination with another treatment (e.g. chemotherapy, hormone therapy), as well as the impact of different radiotherapy regimens on different outcomes.

As mentioned above there were 68 additional papers categorised as systematic reviews or meta-analyses. The distribution of these was similar to the overall distribution of all the studies, with chemotherapy, surgery and radiotherapy being the most reported types of treatment (Figure 3.3). Radiotherapy was the most reported type of treatment (20 studies or 29.4% of included studies), followed by chemotherapy (19 studies or 27.9%) and surgery (18 studies or 26.5%). This is expected as the systematic reviews should be informed by the individual studies.

[7] Docetaxel, doxorubicine, cyclophosphamide.

[8] Doxorubicin, cyclophosphamide, paclitaxel.

Figure 3.3 Distribution of studies by type of treatment in systematic reviews and meta-analyses[9]



3.2.2. Less than a quarter of studies reported on hormonal and biological therapies

Hormonal therapy and biological therapy were also reported in the literature as treatment types for early breast cancer, although in less than a quarter of studies. Hormonal therapy consists of drugs that inhibit the actions of the hormones oestrogen and progesterone on tumours (Cancer Research UK, n.d.-a). It is used to treat hormone receptor-positive breast cancer. Examples of hormone therapy include tamoxifen, aromatase inhibitors, luteinising hormone inhibitors and ovarian suppression or ablation. Hormone therapy was reported in 246 studies (22% of included primary studies). Studies on the use of hormone therapy typically investigated the impact of different hormonal therapies (tamoxifen, aromatase inhibitors or goserelin) on outcomes such as survival, recurrence and quality of life, and compared the effect of different hormonal treatments (e.g. aromatase inhibitors versus tamoxifen) on survival, recurrence or cognitive function. Studies also assessed the prognostic importance of the timing and sequence in which a particular hormone therapy regimen is administered (whether sequentially or concurrently) relative to other hormonal regimens or other treatment types (e.g. surgery, chemotherapy and radiotherapy). Several studies investigated the cost-effectiveness of different hormonal treatments.

Biological therapy involves the use of living organisms, substances derived from living organisms or laboratory-produced versions of such substances to treat disease (National Cancer Institute 2018). Biological therapies for cancer comprise treatments that stimulate the body's immune system to act against cancer cell (immunotherapy) or therapies, such as antibodies, that target molecules responsible for tumour cell growth (Masoud & Pagès 2017; National Cancer Institute 2018). The most common category of biological therapy used in early breast cancer includes monoclonal antibodies, but other categories being investigated in clinical trials include cancer growth blockers (e.g. tyrosine kinase inhibitors, mTOR inhibitors) and angiogenesis inhibitors (e.g. vascular endothelial growth factor inhibitors) (Cancer Research UK, n.d.-b; National Institutes of Health 2018). Biological therapy was

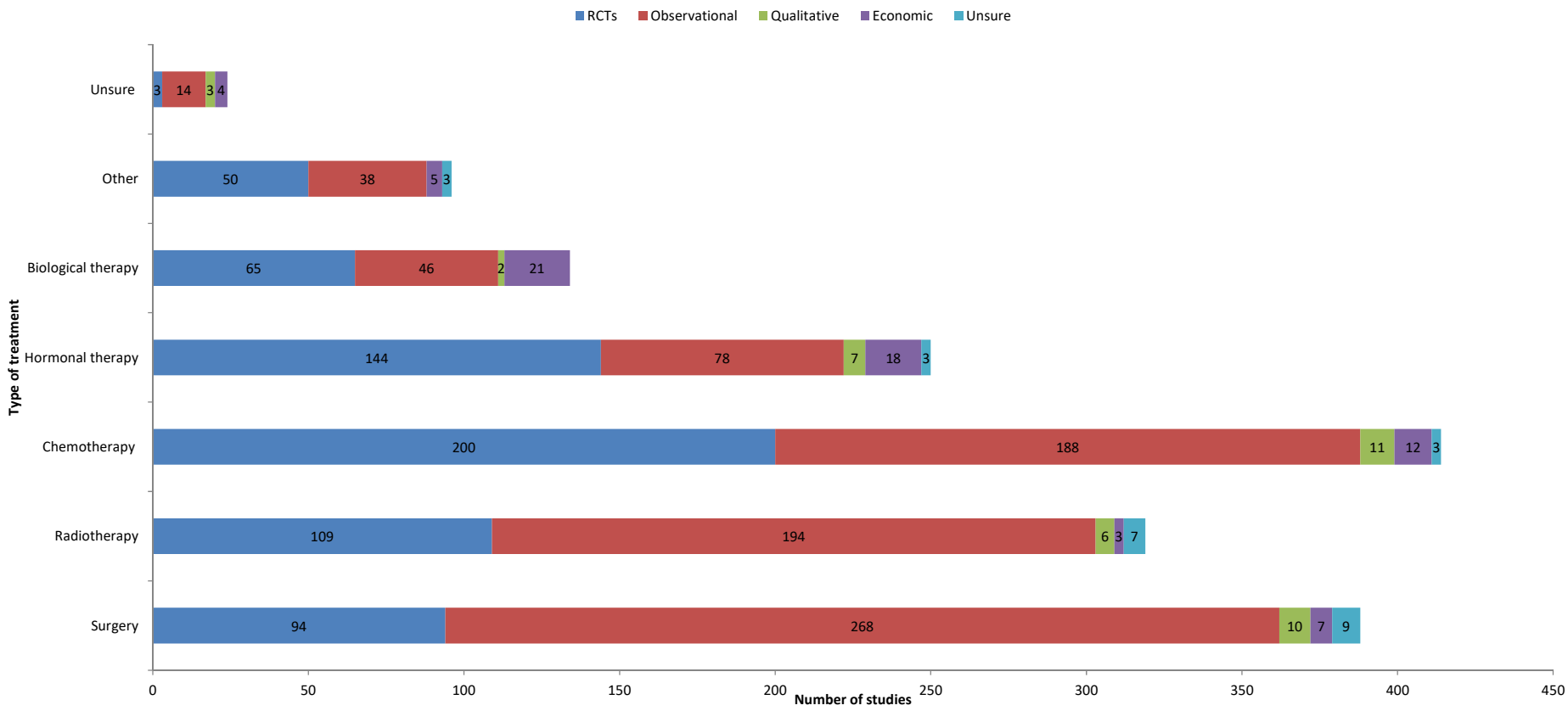
[9] Calculation of percentages is calculated based on the number of systematic reviews and meta-analyses included in this review (n=68). However, one study may mention more than one type of treatment and therefore the number of studies does not add up to 68 and the percentages do not add up to 100.

reported in 141 studies (12.8%% of included primary studies). Most studies looking at biological therapies investigated outcomes such as survival and quality of life following treatment with trastuzumab for HER2-positive breast cancer. Some studies also investigated the cost-effectiveness of trastuzumab treatment.

Fewer studies focused on immunotherapies for the treatment of early breast cancer (4 studies). Immunotherapy refers to a range of agents that stimulate the immune system to kill cancer cells (National Institutes of Health 2015). Therapies reported included cancer vaccines (e.g. that stimulated HER2 intracellular-domain-specific T cell and antibody responses and dendritic cell vaccines), interleukin 2 alone or combined with cyclosporine A and interferon gamma, and natural-killer cell-based autologous immune enhancement therapy.

Whereas chemotherapy, surgery and radiotherapy were the most reported types of treatment in RCTs, observational and qualitative studies, biological therapy was the most commonly reported type of treatment in economic studies (Figure 3.4). Out of 58 economic studies, 21 studies (36%) were on biological therapy. This was followed by 18 studies (31% of economic studies) looking at hormonal therapy. Biological therapy was the most commonly reported treatment type in economic studies, followed by hormonal therapy). The high number of cost-effectiveness studies on targeted biological therapies is consistent with these being relatively newer therapies.

Figure 3.4 Distribution of studies by type of treatment reported in the different study designs[10]



[10] This figure does not contain percentage points as the denominator would be different for the different segments within a bar. One study may mention more than one type of treatment and therefore the number of studies does not add up to 1,101.

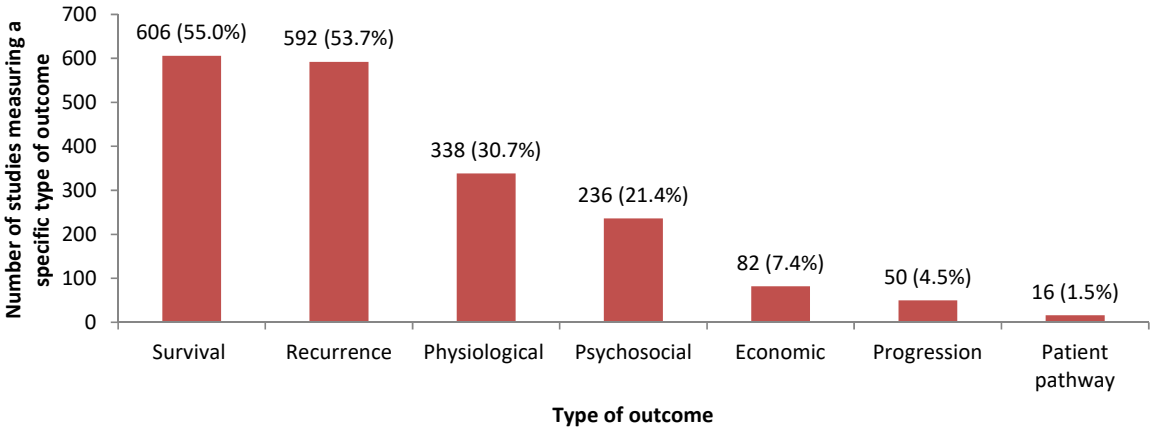
3.2.3. Other types of treatment reported in the literature

Of the primary studies included in this review, 70 (6.4%) focused on other types of treatment for early breast cancer and 34 did not specify the type of treatment (and were classified as 'unsure'). Other treatment types included studies investigating a range of treatments given in combination with standard forms of treatment (e.g. surgery, chemotherapy, radiotherapy, hormone therapy). Of the studies classified as 'other', 32 investigated outcomes such as survival and recurrence following treatment with bisphosphonates, in particular zoledronic acid but also clodronate, pamidronate and ibandronate, typically in combination with hormone therapy or chemotherapy. Other types of treatment covered in the literature were statins, non-steroidal anti-inflammatory drugs, beta-blockers, metformin and Jin Long Capsule.

3.3. Distribution of studies by outcomes

A variety of outcomes for treatment of early breast cancer was reported in the literature (Figure 3.5). We have grouped them into seven categories: survival, recurrence, physiological, psychosocial, economic, disease progression and patient pathway.

Figure 3.5 Distribution of studies by outcomes



3.3.1. Survival and recurrence are the most frequently reported outcomes

The most frequently reported outcomes across the pool of primary research papers we analysed were survival and recurrence. There were 606 studies (55% of primary studies) that assessed survival. Studies assessing survival outcomes typically assessed overall mortality at five or 10 years after beginning treatment, breast cancer-specific mortality or disease-free survival, among other definitions of survival. Survival outcomes were reported in a wide variety of studies including those comparing multiple treatment options, the impact of patient compliance with treatment regimens, and clinical trials on individual treatments.

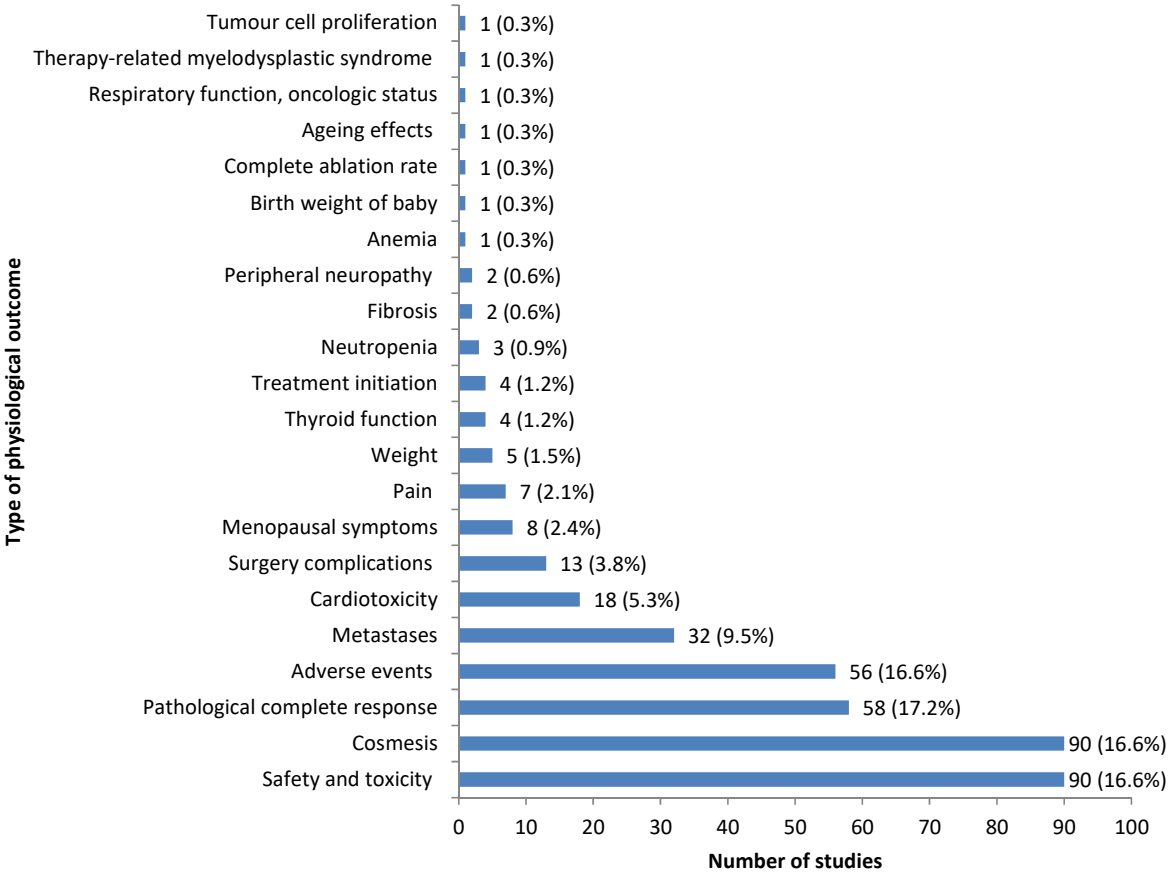
The second most common type of outcome reported in the literature was recurrence (592 studies or 53.7%). Recurrence was variably defined as local, regional or distant recurrence, with local recurrence

being breast cancer that reoccurs in the same place as the original cancer, regional recurrence as cancer that reoccurs in the nearby lymph nodes (e.g. ipsilateral axillary, internal mammary, supraclavicular or infraclavicular), and distant recurrence being cancer that has spread to another area of the body (Botteri et al. 2010). There was substantial overlap between those studies that report on recurrence and those reporting on survival; 160 studies reported on both survival and recurrence.

A large proportion of results, diverse in nature, were also reported under physiological outcomes (338 studies) and psychosocial outcomes (236 studies). Physiological outcomes are those associated with physiological or bodily factors; they include examples such as safety and toxicity, adverse events, pathological complete responses and cosmesis (Figure 3.6). Safety and toxicity, and cosmesis were the most frequent physiological outcomes reported in the literature.[11] They included studies such as those looking at the effect of radiation therapy on skin toxicity, and the toxicity of chemotherapy. In the studies we reviewed, cosmesis referred to the preservation or restoration of the appearance of the breast. It was commonly reported as an outcome in studies of the effects of radiation, but also arose in studies on other topics such as those considering breast reconstruction techniques.

[11] Please note that studies which reported only on safety, toxicity or adherence in isolation were excluded from this mapping exercise. However, where these outcomes were reported in conjunction with one or more outcome(s) of interest, these were recorded as well.

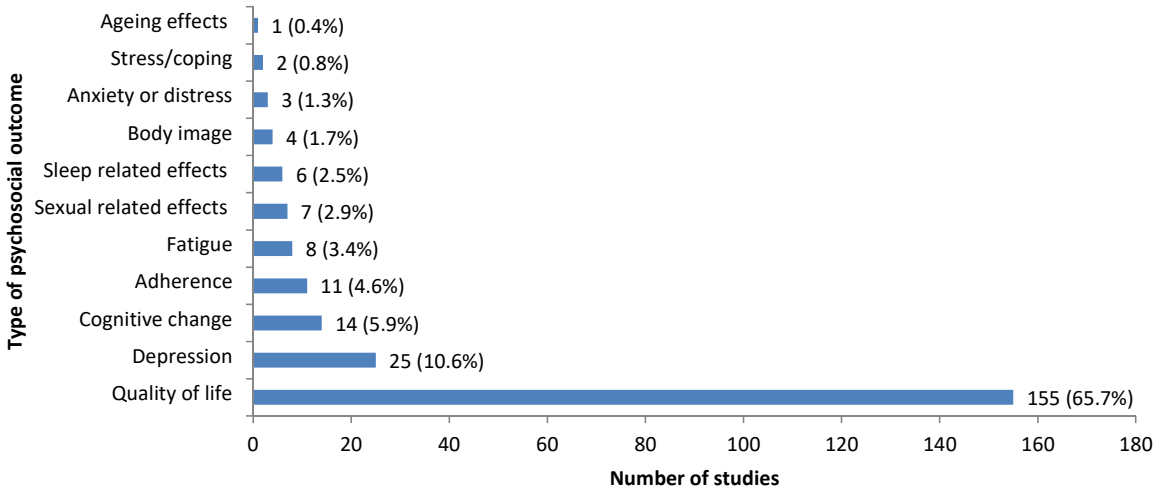
Figure 3.6 Number of studies by type of physiological outcome[12]



Many studies reported on psychosocial outcomes. This category included factors that capture the interrelation of social and psychological factors such as depression, anxiety, body image issues, stress and coping, and non-physiological sexual-related effects of breast cancer. Figure 3.7 presents a comprehensive breakdown of the types of psychosocial outcome covered in the studies.

[12] Calculation of percentages is based on the number of primary studies reporting on physiological outcomes in this review (n=338). However, one study may mention more than one type of outcome and therefore the number of studies does not add up to 338 and the percentages do not add up to 100.

Figure 3.7 Number of studies by type of psychosocial outcome[13]

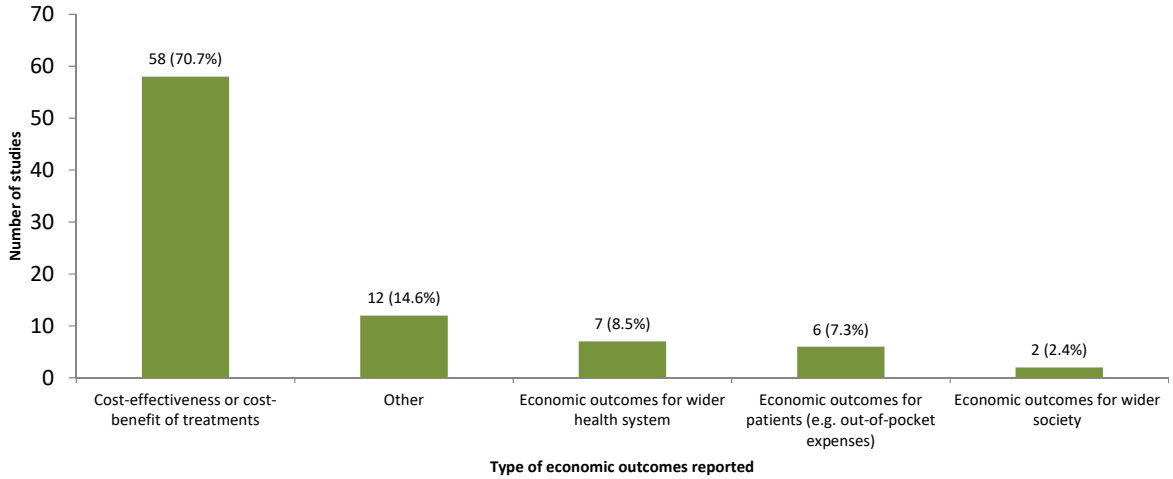


A smaller proportion of studies focused on economic outcomes (82 studies or 7.4% of primary studies), disease progression (50 studies or 4.5% of primary studies), or outcomes associated with the care pathway or care process such as patients' experience and satisfaction, time patients spend in infusion chairs, adherence to treatment protocols, and emergency room visits and hospitalisations (16 studies or 1.5% of primary studies).

Most of the 82 studies that reported economic outcomes, the majority focused on cost-effectiveness of treatment (58 studies or 70.7% of studies focusing on economic outcomes) (Figure 3.8). However, studies assessing economic outcomes looked at other outcomes as well, including those for the wider health system (7 studies or 8.5%), for patients (e.g. out-of-pocket expenses) (6 studies or 7.3%) and for wider society (2 studies or 2.4%). Beyond this categorisation, studies in the 'other' category (12 studies or 14.6%) looked at a variety of outcomes, such as facilitating discharges, cost per patient per disease stage, cost of treatment, costs from both a payer and hospital perspective, global cost of sentinel lymph node detection, time-saving costs, direct and indirect costs of treating female outpatients (at a Mexican public hospital), associations between nationwide pay-for-performance scheme enrolment and quality of care, cost of patient, and other costs not clearly categorised.

[13] Calculation of percentages is based on the number of primary studies reporting on physiological outcomes in this review (n=236). However, one study may mention more than one type of outcome and therefore the number of studies does not add up to 236 and the percentages do not add up to 100.

Figure 3.8 Number of studies by economic outcome[14]



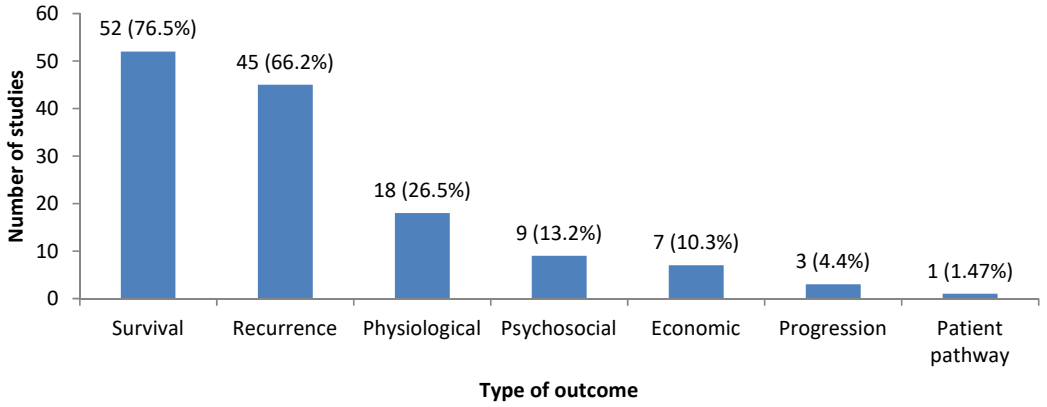
Cost-effectiveness studies looked at a range of treatments and country contexts. The main outcome measure of interest was quality adjusted life years (QALYs); other frequent measures included life years and healthcare costs from a health system perspective. The countries explored in the studies include high income countries such as Australia, Belgium, Canada, Finland, Germany, Italy, Japan, Korea, the Netherlands, Norway, Sweden, Switzerland, Taiwan, the UK and the US; middle income countries including China; and low income countries including Brazil, Columbia and Iran. The majority of studies examined trastuzumab (18) followed by hormone therapy (16), chemotherapy (9), radiotherapy (2), recombinant granulocyte colony-stimulating factors (1), and finally pre-operative sentinel lymph node mapping (1).

Cost analysis studies also explored a range of treatments and country contexts. High income countries included Canada, France, Germany, Spain and the US; low income countries included Mexico, Morocco and Vietnam. Most studies considered surgical treatment (7) followed by chemotherapy (3) and trastuzumab (2). Some studies (4) considered the costs of a variety of treatment types together. Most considered the direct (drug) costs and indirect costs of treatment on health systems (measuring length of hospital stay and staff time). A few considered direct and indirect costs for patients (e.g. out-of-pocket costs and time spent getting treatment).

In addition, the distribution of outcomes was similar in the 68 additional papers categorised as systematic reviews or meta-analyses, with survival and recurrence being the main outcomes (Figure 3.9). As with the type of treatment, this is expected as systematic reviews should be informed by individual studies. There were 52 studies (76.5%) classified as systematic reviews or meta-analyses that focused on survival, and 45 (66.2%) that focused on recurrence. There was less focus on psychosocial (9 studies or 13.2%), economic (7 studies or 10.3%), disease progression (3 studies or 4.4%) and patient pathway (1 study or 1.47%) outcomes in the studies classified as systematic reviews or meta-analyses.

[14] Calculation of percentages is based on the number of primary studies reporting on physiological outcomes in this review (n=82). However, one study may mention more than one type of outcome and therefore the number of studies does not add up to 82 and the percentages do not add up to 100.

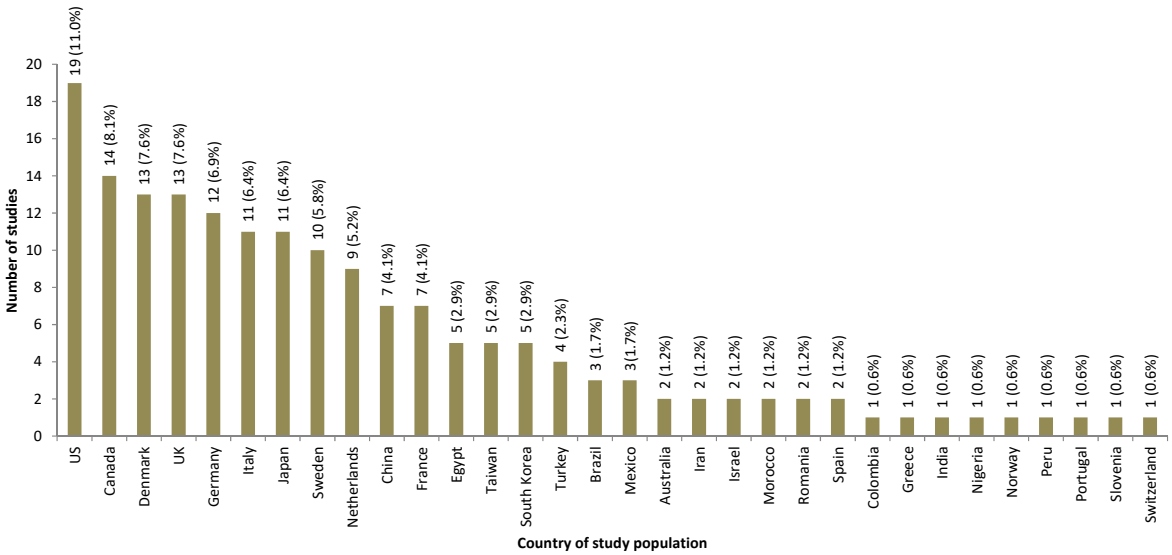
Figure 3.9 Distribution of studies by type of outcome in systematic reviews and meta-analyses[15]



3.4. Distribution of studies by study population country

Just 172 of the 1,101 articles named the study population country in their title or abstract (15.6%). Figure 3.10 presents the distribution of studies by country of study population, and shows that 32 countries had at least one article on the topic.

Figure 3.10 Geographical distribution of primary studies that named the study population country in the title or abstract[16]



[15] Calculation of percentages is based on the number of systematic reviews and meta-analyses included in this review (n=68). However, one study may mention more than one type of outcome and therefore the number of studies does not add up to 68 and the percentages do not add up to 100.

[16] The percentages are calculated based on the number of studies that reported a study population country included in this review (n=172). However, one study may mention more than one population country and therefore the number of studies does not add up to 172 and the percentages do not add up to 100.

Figure 3.11 presents the distribution of outcomes reported in studies from countries with 10 or more papers on the topic of interest. Most attention across countries is on survival and recurrence outcomes (57 studies or 33.1% and 48 studies or 27.9% respectively of studies provided a country for the study population). Within publications on a population from the US, 12 studies reported on survival outcomes, six of which focused on adjuvant or neoadjuvant chemotherapy. There were also seven studies reporting on recurrence outcomes, including after lymph node biopsy, breast conservation therapy, and adjuvant and neoadjuvant chemotherapy. Within publications on a population from Canada, seven studies reported on survival and five reported on recurrence. These studies covered a range of topics including outcomes after treatment with letrozole, radiotherapy, and survival differences by socioeconomic status and cancer type within a universal healthcare system.

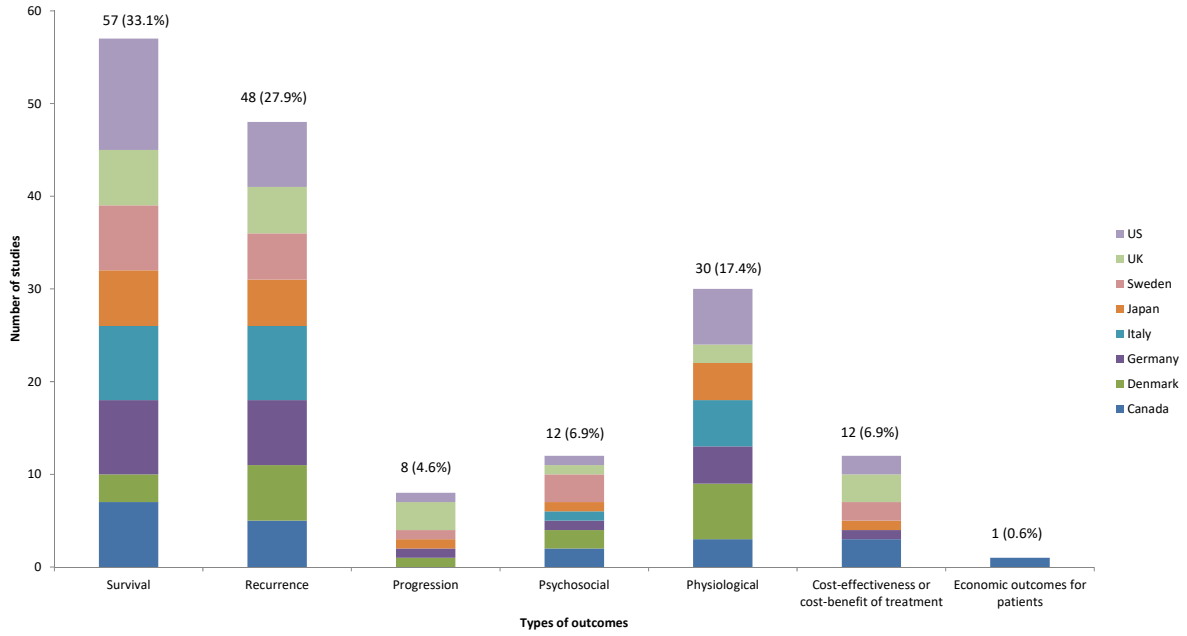
Authors of publications looking at population in European countries also predominantly focused on survival and recurrence. As previously, there was substantial overlap between the categories, with many studies reporting on survival and recurrence. Common topics were European populations reporting on survival and recurrence, endocrine therapy, breast conservation surgeries, and treatments with docetaxel, a chemotherapy drug.

The third most commonly reported outcome in papers specifying study population was physiological effects (32 studies or 18.6% of those that provided a country for the study population). Of these 32 studies, six covering three countries (Canada, Germany and the US) reported on toxicity. Three papers focused on adverse events of treatment on a population in Japan. Additionally, three studies in two countries (Japan and UK) assessed the pathological response of treatment. Other physiological outcomes reported were prophylactic surgery and contralateral breast cancer. Sweden was the only country not reporting on physiological outcomes from the countries on whose populations more than 10 studies were based.

The main psychosocial outcome reported in the literature for studies specifying country population was quality of life. Two looking at a population in Denmark focused on cognitive function and quality of life after breast cancer treatment, and two reported on quality of life outcomes after treatment in a population in Sweden and in Canada. A single study from the US reported on quality of life outcomes, though its main focus was on the cost-effectiveness of chemotherapy. One paper focused on a UK population examined anxiety and depression in women with early breast cancer.

We found very little focus on economic outcomes, though 14 studies investigated cost-benefit and cost-effectiveness in seven countries (Canada, Germany, Japan, the Netherlands, Sweden, the UK and the US). Out of these papers, the most common treatment considered was hormonal therapy, followed by chemotherapy and targeted biological therapy.

Figure 3.11 Distribution of outcomes for countries with ten or more studies[17]



[17] The percentages are calculated based on the number of primary studies reporting a country for the study population in the title of abstract of the publication (n=172). However, one study may mention more than one country and therefore the number of studies does not add up to 172 and the percentages do not add up to 100.

4. Discussion

This mapping review provides a detailed characterisation of the published literature examining the impacts and outcomes from the treatment of early breast cancer. In particular, the study identifies the range of outcomes considered, the types of study design used, and the location in which research is occurring.

We identified 1,101 primary studies on the impact of treatment of early breast cancer. The vast majority of them were either observational studies or RCTs.

Studies on treatment effectiveness, measured as survival and recurrence, dominate this space. The dominance of measures of clinical effectiveness is potentially unsurprising given the research funding landscape. For example, in the UK in 2016/17 the National Cancer Research Institute estimates that 35% of research funding was spent on treatment[18] compared with 6% spent on cancer control, survivorship and outcomes research (National Cancer Research Institute 2018).[19]

There is a comparatively smaller but important body of literature that focuses on other types of outcomes extending beyond traditional treatment effectiveness evaluations, such as literature focusing on women who have survived early breast cancer treatment and studies that evaluate outcomes such as patient psychosocial well-being, patient out-of-pocket costs or loss of employment.

The most commonly reported treatments were chemotherapy, surgery and radiotherapy. This is not surprising as chemotherapy has long been the cornerstone of treatment in cancer, together with surgery and radiotherapy. Biological therapy is a more recent line of therapy, which explains why the volume of reported research on it in the literature is smaller than that on other forms of medication.

The recentness of biological therapies may explain why there are fewer studies in our sample focusing on them than on traditional therapies. The comparatively greater focus of economic analyses on biological therapies is perhaps unsurprising, given the higher costs that may be associated with recent innovation. Information on cost-effectiveness is likely to be particularly important for allowing decision makers to determine approaches to introduction and reimbursement of new treatments.

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[18] This includes identifying and testing treatments administered locally (such as radiotherapy and surgery) and systemically (treatments like chemotherapy which are administered throughout the body) as well as non-traditional treatments (such as supplements, herbs), and research into the prevention of recurrence and treatment of metastases.

[19] Includes a broad range of areas: patient care and pain management; tracking cancer cases in the population; beliefs and attitudes that affect behaviour regarding cancer control; ethics; education and communication approaches for patients, family/caregivers, and health care professionals; supportive and end-of-life care; and health care delivery in terms of quality and cost effectiveness.

Where studies looked at populations within countries, most analysed populations in high income countries (Canada, Denmark, Germany, Italy, Japan, Sweden, the UK and the US). This finding is not unusual, as research is generally more prolific in high income countries. Additionally this could be partially because novel and more costly treatments for early breast cancer may be available in these countries and not necessarily in lower income countries.

In addition to profiling the literature, one of the key aims of this mapping review was to help inform the direction of a subsequent stage of this research – to help identify and target the focus of a full systematic review on a specific outcome type where the current evidence gaps are large. Nearly all of the 68 systematic reviews identified focused on survival or recurrence from a clinical perspective. We did not identify systematic reviews that explicitly aimed to investigate impacts on the wider health system or wider society, although there is some literature which could help inform learning by systematically reviewing this space. We believe that a systematic review of the long term effects among survivors who were treated for breast cancer at an early stage of the disease would therefore make an important contribution to the field.

5. References

Anampa, J., D. Makower, and J. A. Sparano. 2015. "Progress in Adjuvant Chemotherapy for Breast Cancer: An Overview." *Bmc Medicine* 13 (August): 13. https://doi.org/10.1186/s12916-015-0439-8.

Botteri, E., V. Bagnardi, N. Rotmensz, O. Gentilini, D. Disalvatore, B. Bazolli, A. Luini, and U. Veronesi. 2010. "Analysis of Local and Regional Recurrences in Breast Cancer after Conservative Surgery." *Annals of Oncology* 21 (4): 723–28. https://doi.org/10.1093/annonc/mdp386.

Cancer Research UK. n.d.-a "About Hormone Therapy for Breast Cancer." Accessed February 7, 2019a. https://www.cancerresearchuk.org/about-cancer/breast-cancer/treatment/hormone-therapy/about.

———. n.d.-b "Breast Cancer Targeted Cancer Drugs." Accessed February 7, 2019b. https://www.cancerresearchuk.org/about-cancer/breast-cancer/treatment/breast-targeted-cancer-drugs.

Cardoso, F., N. Harbeck, L. Fallowfield, S. Kyriakides, E. Senkus, and ESMO Guidelines Working Group. 2012. "Locally Recurrent or Metastatic Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up." *Annals of Oncology* 23 (suppl_7): vii11–19.

Centre for Reviews and Dissemination. 2009. *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. University of York, Centre for Reviews & Dissemination.

Creighton, Helen, Brian Beach, and Sally-Marie Bamford. 2015. "Rethinking Cancer. The Big 'C': Quantifying the Social and Economic Impact."

Deeks, J. J., J. P. T. Higgins, D. G. Altman, and S. Green. 2011. "Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 (Updated March 2011)." *The Cochrane Collaboration*.

Di Leo, Angelo, Giuseppe Curigliano, Véronique Diéras, Luca Malorni, Christos Sotiriou, Charles Swanton, Alastair Thompson, Andrew Tutt, and Martine Piccart. 2015. "New Approaches for Improving Outcomes in Breast Cancer in Europe." *The Breast* 24 (4): 321–30.

Early Breast Cancer Trialists' Collaborative Group. 2011. "Effect of Radiotherapy after Breast-Conserving Surgery on 10-Year Recurrence and 15-Year Breast Cancer Death: Meta-Analysis of Individual Patient Data for 10 801 Women in 17 Randomised Trials." *The Lancet* 378 (9804): 1707–16.

———. 2015a. "Adjuvant Bisphosphonate Treatment in Early Breast Cancer: Meta-Analyses of Individual Patient Data from Randomised Trials." *The Lancet* 386 (10001): 1353–61.

———. 2015b. "Aromatase Inhibitors versus Tamoxifen in Early Breast Cancer: Patient-Level Meta-Analysis of the Randomised Trials." *The Lancet* 386 (10001): 1341–52.

Elmore, Natasha, Sarah King, Josephine Exley, Daniela Rodriguez-Rincon, Jody Larkin, Molly Morgan Jones, and Catriona Manville. 2019. "Findings from a Systematic Review to Explore the Patient and Societal Impacts of Disease Progression in Women Who Were Treated for Early Breast Cancer." Santa Monica, CA: RAND Corporation.

Ferlay, Jacques, Isabelle Soerjomataram, Rajesh Dikshit, Sultan Eser, Colin Mathers, Marise Rebelo, Donald Maxwell Parkin, David Forman, and Freddie Bray. 2015. "Cancer Incidence and

Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012." *International Journal of Cancer* 136 (5).

García Rodríguez, José, Carmen García Colmenero, Ramón Clèries Soler, and Isabel Oleaga Sánchez. 2010. "Five Years Survival of Women Diagnosed with Breast Cancer during the Period 1997-1999 in Toledo-Centro and Mancha Area, Spain." *Revista Espanola de Salud Publica* 84 (6): 843–50.

Glück, Stefan, Terry Mamounas, and Jennifer Klem. 2010. "Improving Outcomes in Early-Stage Breast Cancer." *Oncology; San Francisco* 24 (4).

Gospodarowicz, Mary K., James D. Brierley, and Christian Wittekind. 2017. *TNM Classification of Malignant Tumours*. John Wiley & Sons.

Laudicella, Mauro, Brendan Walsh, Elaine Burns, and Peter C. Smith. 2016. "Cost of Care for Cancer Patients in England: Evidence from Population-Based Patient-Level Data." *British Journal of Cancer* 114 (11): 1286.

Masoud, Viviana, and Gilles Pagès. 2017. "Targeted Therapies in Breast Cancer: New Challenges to Fight against Resistance." *World Journal of Clinical Oncology* 8 (2): 120–34. https://doi.org/10.5306/wjco.v8.i2.120.

McGale, P., C. Taylor, C. Correa, D. Cutter, F. Duane, Marianne Ewertz, R. Gray, G. Mannu, R. Peto, and T. Whelan. 2014. "Effect of Radiotherapy after Mastectomy and Axillary Surgery on 10-Year Recurrence and 20-Year Breast Cancer Mortality: Meta-Analysis of Individual Patient Data for 8135 Women in 22 Randomised Trials." Elsevier.

McPhail, Sean, Sam Johnson, David Greenberg, Mick Peake, and Brian Rous. 2015. "Stage at Diagnosis and Early Mortality from Cancer in England." *British Journal of Cancer* 112 (s1): S108.

National Cancer Institute. n.d. "NCI Dictionary of Cancer Terms."

———. 2018. "Biological Therapies for Cancer." CgvFactSheet. National Cancer Institute. May 21, 2018. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet.

National Cancer Research Institute. 2018. "Spend by Research Category and Disease Site." 2018.

National Institute for Health and Care Excellence. 2018a. "Glossary." 2018.

———. 2018b. "Methods for the Development of NICE Public Health Guidance (Third Edition), Appendix E." 2018.

———. n.d. "BNF: British National Formulary - NICE." Accessed February 7, 2019. https://bnf.nice.org.uk/treatment-summary/breast-cancer.html.

National Institutes of Health. 2015. "Immunotherapy." National Cancer Institute. April 29, 2015. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy.

———. 2018. "Targeted Cancer Therapies." National Cancer Institute. May 14, 2018. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.

———. n.d.-a "Introduction to Chemotherapy | SEER Training." Accessed February 7, 2019a. https://training.seer.cancer.gov/treatment/chemotherapy/.

———. n.d.-b "Introduction to Radiation Therapy | SEER Training." Accessed February 7, 2019b. https://training.seer.cancer.gov/treatment/radiation/.

NHS. 2015. "Achieving World-Class Cancer Outcomes: A Strategy for England 2015-2020 One Year on 2015-16."

Rodriguez-Rincon, Daniela, Brandi Leach, Camilla D'Angelo, Amelia Harshfield, and Catriona Manville. 2019. "Factors Affecting Access to Treatment of Early Breast Cancer: Case Studies from Brazil, Canada, Italy, Spain and UK." Santa Monica, CA: RAND Corporation.

Union for International Cancer Control. 2014. "2014 Review of Cancer Medicines on the WHO List of Essential Medicines."

Walters, S., C. Maringe, J. Butler, B. Rachet, P. Barrett-Lee, J. Bergh, J. Boyages, et al. 2013. "Breast Cancer Survival and Stage at Diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: A Population-Based Study." *British Journal of Cancer* 108 (5): 1195–1208. https://doi.org/10.1038/bjc.2013.6.

World Health Organization. 2018. "Breast Cancer." http://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/.

Annex A. Eligibility criteria and developing search terms

In line with the study's objectives we initially defined a broad set of eligibility criteria covering population, interventions and study designs, which are described below. We then performed a scoping search to determine the number of studies yielded. We pilot tested search terms based on population, intervention and study design criteria and obtained 27,808 hits. To ensure a manageable number of hits within the scope and purpose of this work it was necessary to specify exclusion criteria for outcomes, as described in Section A.3.

A.1. Populations

Our target population is women and men[20] who have been diagnosed with early breast cancer and have received some medical form of treatment for it.[21] The literature, in line with prevalence, is dominated by cases considering women but we did not want to exclude studies based on gender.

A.2. Interventions

We included studies that explicitly aimed to evaluate medical treatments for early breast cancer. These treatments included *surgery* (e.g. mastectomy, lumpectomy or lymph node removal – sentinel lymph node biopsy or axillary lymph node dissection), *radiotherapy*, *systemic therapy* (chemotherapy and hormonal therapy such as tamoxifen or aromatase inhibitors) and *targeted therapy* (e.g. biological therapy such as trastuzumab and pertuzumab). Medical therapy can also be given in combination. The mapping review separately categorised studies that looked at the impact of two or more combinations of therapies.

An important caveat to bear in mind is that we only considered combination therapy studies that were explicitly based on title and abstract (a full text review may have revealed additional information about whether a particular paper considered combination therapies, but this may not always be apparent in a mapping review of titles and abstracts). Studies that evaluated the impact of early diagnosis, biomarkers, predictors of disease outcomes, physical exercise and yoga, or other physiological interventions such as cognitive behavioural therapy, were not eligible for inclusion. These studies would give an indication of the effectiveness of these interventions (e.g. of yoga, exercise or cognitive behavioural therapy) rather than medical interventions and therefore would not be in line with the focus of our research question and scope of this work.

[20] This was deemed appropriate as the research aimed to capture society-wide impact therefore both women and men were relevant as study population.

[21] Our definition of early breast cancer included the following stages: ductal carcinoma in situ (stage 0) and stages I-IIIA (or stage III breast cancers if the stage breakdown was not clear from the abstract), (National Cancer Institute n.d.). Stages IIIB and greater reflect tumours that are not operable and were not included.

A.3. Outcomes

Studies were eligible for inclusion if they reported one or more of the outcomes listed in Box A.1 as a primary outcome of interest. For studies that reported multiple outcomes, we extracted information on all outcomes reported, including those that fall outside our inclusion criteria.

Please note that we decided not to include studies that reported solely on adverse events and toxicity in the mapping review, though we recorded studies that simultaneously reported other outcomes and also considered toxicity of adverse events. Researchers discussed whether studies that reported cosmetic results should be included, deciding to include them for this stage as cosmesis may have implications for quality of life – however this is just an assumption and not necessarily something that is explicit in the quality of life literature. Therefore while we include them at this stage we do not consider them to be of key relevance for the overall research question.

Box A.1 Outcomes considered in the mapping review

Health-related outcomes
Survival
Recurrence
Progression
Patient well-being and quality of life
Psychological (e.g. depression, anxiety)
Impacts on carers and families
Economic outcomes
Cost-effectiveness or cost-benefit of treatments
For patients (e.g. out-of-pocket expenses)
For carers (e.g. out-of-pocket expenses)
For the wider health system (e.g. direct and indirect costs)
For wider society (e.g. days lost from work and labour productivity)
On carers and families

A.4. Study designs

The following study designs were eligible for inclusion: systematic reviews, experimental studies[22] (e.g. RCTs), quasi-experimental studies[23] (e.g. non-RCTs), observational studies (National Institute for Health

[22]A study in which participants are randomly assigned to intervention or control groups into two or more groups. At least one will be a control group.

[23] A study in which comparisons are drawn between two or more groups in which participants are not randomly assigned to receive the intervention.

and Care Excellence 2018a, 2018b)[24] (e.g. cohort studies and case-control studies), qualitative studies and economic evaluations. Studies published as abstracts or conference presentations were included if enough data were presented for a decision about relevance to be made. Letters, editorials and commentaries were not eligible for inclusion.

[24] A retrospective or prospective study in which the investigator observes the natural course of events with or without control groups.

Annex B. Final search sequence for the mapping review

Table A.1 provides information on the different databases used for the literature search, the search sequence and the number of results yielding from each search.

Table A.1 Final search sequence

Database searched	Search sequence	Yield
PubMed Filters: English language; 2007–2017; no comment or editorial	((early breast cancer*[tiab] OR (early[tiab] AND breast tumour* [tiab]) OR (early[tiab] AND breast tumor*[tiab]) OR early breast carcinoma*[tiab] OR 'early breast neoplasia'[tiab] OR (early[tiab] AND breast neoplasm*[tiab]) OR ('early detection of cancer' [Mesh] AND 'Breast Neoplasms'[Mesh])) OR ('early invasive breast cancer'[tiab] OR ('early invasive'[tiab] AND breast tumour*[tiab]) OR ('early invasive'[tiab] AND breast tumor*[tiab]) OR 'early invasive breast carcinoma' OR ('early invasive'[tiab] AND 'breast neoplasia'[tiab]) OR ('early invasive'[tiab] AND breast neoplasm*[tiab])) OR (primary breast cancer*[tiab] OR primary breast tumour*[tiab] OR primary breast tumor*[tiab] OR primary breast carcinoma* OR (primary[tiab] AND 'breast neoplasia'[tiab]) OR primary breast neoplasm*) OR ('non metastatic breast cancer'[tiab] OR 'non-metastatic breast cancer'[tiab] OR ('non metastatic'[tiab] AND breast tumour*[tiab]) OR ('non-metastatic'[tiab] AND breast tumour*[tiab]) OR 'non metastatic breast carcinoma'[tiab] OR 'non-metastatic breast carcinoma'[tiab] OR ('non metastatic'[tiab] AND 'breast neoplasia'[tiab]) OR ('non-metastatic'[tiab] AND 'breast neoplasia'[tiab]) OR ('non metastatic'[tiab] 'breast neoplasm'[tiab]) OR ('non-metastatic'[tiab] AND breast neoplasm*[tiab])) OR (('stage 0'[tiab] OR 'stage 1'[tiab] OR 'stage I'[tiab] OR 'Stage 1A'[tiab] OR 'stage IA'[tiab] OR 'stage 1B'[tiab] OR 'stage IB'[tiab] OR 'stage 2'[tiab] OR 'stage II'[tiab] OR 'Stage 2A'[tiab] OR 'stage IIA'[tiab] OR 'stage 2B'[tiab] OR 'stage IIB'[tiab] OR 'stage 3A'[tiab] OR 'stage IIIA'[tiab]) AND (breast cancer*[tiab] OR breast tumour*[tiab] OR	**Results: 8,100**

	breast tumor*[tiab] OR breast carcinoma*[tiab] OR 'breast neoplasia'[tiab] OR breast neoplasm*[tiab] OR 'Breast Neoplasms'[Mesh])) OR ((early[tiab] OR primary[tiab] OR 'non metastatic'[tiab] OR 'non-metastatic'[tiab] OR 'stage 0'[tiab] OR 'stage 1'[tiab] OR 'stage I'[tiab] OR 'Stage 1A'[tiab] OR 'stage IA'[tiab] OR 'stage 1B'[tiab] OR 'stage IB'[tiab] OR 'stage 2'[tiab] OR 'stage II'[tiab] OR 'Stage 2A'[tiab] OR 'stage IIA'[tiab] OR 'stage 2B'[tiab] OR 'stage IIB'[tiab] OR 'stage 3A'[tiab] OR 'stage IIIA'[tiab]) AND ('ductal carcinoma in situ'[tiab] OR DCIS[tiab] OR 'intra-ductal carcinoma'[tiab] OR 'lobular carcinoma in situ'[tiab] OR LCIS[tiab] OR 'lobular in situ neoplasia'[tiab] OR 'atypical lobular hyperplasia'[tiab] OR ALH[tiab])) OR (('early detection of cancer' [Mesh] AND 'Carcinoma, Intraductal, Noninfiltrating'[Mesh]))) AND (Health[tiab] OR survival[tiab] OR recurrence[tiab] OR progression[tiab] OR 'quality of life'[tiab] OR 'quality of life'[mesh] OR 'well being'[tiab] OR 'well-being'[tiab] OR depression[tiab] OR 'depression'[Mesh] OR 'depressive disorder'[Mesh] OR 'cost-effectiveness'[tiab] OR 'cost-benefit'[tiab] OR 'cost-efficiency'[tiab] OR 'cost-utility'[tiab] OR cost[tiab] OR 'economic evaluation' OR societal[tiab]) OR ((effect[tiab] OR impact[tiab] OR burden[tiab]) AND (carer[tiab] OR Carers[tiab] OR caretaker*[tiab] OR caregiver*[tiab] OR family[tiab]))	
Cochrane Filters:2007–2017	'early breast cancer*' OR 'early breast tumour*' OR 'early breast tumor*' OR 'early breast carcinoma*' OR 'early breast neoplasia*' OR 'early breast neoplasm*' OR 'early invasive breast cancer' OR 'early invasive breast tumour*' OR 'early invasive breast tumor*' OR 'early invasive carcinoma' OR 'early invasive breast neoplasia' OR 'early invasive breast neoplasm*' OR 'primary breast cancer*' OR 'primary breast tumour*' OR 'primary breast tumor*' OR 'primary breast carcinoma*' OR 'primary breast neoplasia*' OR 'primary breast neoplasm*' OR 'non metastatic breast cancer' OR 'non-metastatic breast cancer' OR 'non metastatic breast	**Results: total: 1,843 − duplicates = 1,016*** **Reviews: 30 − duplicates = 26** **Cochrane Controlled**

	tumour*' OR 'non-metastatic breast tumor*' OR 'non metastatic breast carcinoma' OR 'non-metastatic breast carcinoma' OR 'non metastatic breast neoplasia' OR 'non-metastatic breast neoplasia' OR 'non metastatic breast neoplasm*' OR 'non-metastatic and breast neoplasm*' OR (('stage 0' OR 'stage 1' OR 'stage I' OR 'Stage 1A' OR 'stage IA' OR 'stage 1B' OR 'stage IB' OR 'stage 2' OR 'stage II' OR 'Stage 2A' OR 'stage IIA' OR 'stage 2B' OR 'stage IIB' OR 'stage 3A' OR 'stage IIIA') AND ('breast cancer*' OR 'breast tumour*' OR 'breast tumor*' OR 'breast carcinoma*' OR 'breast neoplasia' OR 'breast neoplasm*')) OR ((early OR primary OR 'non metastatic' OR 'non-metastatic' OR 'stage 0' OR 'stage 1' OR 'stage I' OR 'Stage 1A' OR 'stage IA' OR 'stage 1B' OR 'stage IB' OR 'stage 2' OR 'stage II' OR 'Stage 2A' OR 'stage IIA' OR 'stage 2B' OR 'stage IIB' OR 'stage 3A' OR 'stage IIIA') AND ('ductal carcinoma in situ' OR DCIS OR 'intra-ductal carcinoma' OR 'lobular carcinoma in situ' OR LCIS OR 'lobular in situ neoplasia' OR 'atypical lobular hyperplasia' OR ALH)) AND (Health OR survival OR recurrence OR progression OR 'quality of life' OR 'well-being' OR 'well-being' OR depression OR depressive OR 'cost-effectiveness' OR 'cost-benefit' OR 'cost-efficiency' OR 'cost-utility' OR cost OR 'economic evaluation' OR societal) OR ((effect OR impact OR burden) AND (carer OR Carers OR caretaker* OR caregiver* OR family))	**Register of Trails (CENTRAL): 1,724 – duplicates = 938** **Database of abstracts of Reviews of effects (DARE) (through 2015): 30 – duplicates = 24** **Health Technology Assessment (HTA): 28 – duplicates = 22** **NHS Economic Evaluation Database (NHSEED) (through 2015) 32 – duplicates = 6**
Web of Science 2007–2017; indexes = SCI-EXPANDED; article or review; English	TOPIC: ('early breast cancer*' OR 'early breast tumour*' OR 'early breast tumor*' OR 'early breast carcinoma*' OR 'early breast neoplasia*' OR 'early breast neoplasm*' OR 'early invasive breast cancer' OR 'early invasive breast tumour*' OR 'early invasive breast tumor*' OR 'early invasive carcinoma' OR 'early invasive breast neoplasia' OR 'early invasive breast neoplasm*' OR 'primary breast cancer*' OR 'primary breast tumour*' OR 'primary breast tumor*' OR 'primary breast carcinoma*' OR 'primary breast	**Results: 8,481 – duplicates = 4,599**

	neoplasia*' OR 'primary breast neoplasm*' OR 'non metastatic breast cancer' OR 'non-metastatic breast cancer' OR 'non metastatic breast tumour*' OR 'non-metastatic breast tumor*' OR 'non metastatic breast carcinoma' OR 'non-metastatic breast carcinoma' OR 'non metastatic breast neoplasia' OR 'non-metastatic breast neoplasia' OR 'non metastatic breast neoplasm*' OR 'non-metastatic and breast neoplasm*') OR TOPIC: ((('stage 0' OR 'stage 1' OR 'stage I' OR 'Stage 1A' OR 'stage IA' OR 'stage 1B' OR 'stage IB' OR 'stage 2' OR 'stage II' OR 'Stage 2A' OR 'stage IIA' OR 'stage 2B' OR 'stage IIB' OR 'stage 3A' OR 'stage IIIA') AND ('breast cancer*' OR 'breast tumour*' OR 'breast tumor*' OR 'breast carcinoma*' OR 'breast neoplasia' OR 'breast neoplasm*'))) OR TOPIC: (((early OR primary OR 'non metastatic' OR 'non-metastatic' OR 'stage 0' OR 'stage 1' OR 'stage I' OR 'Stage 1A' OR 'stage IA' OR 'stage 1B' OR 'stage IB' OR 'stage 2' OR 'stage II' OR 'Stage 2A' OR 'stage IIA' OR 'stage 2B' OR 'stage IIB' OR 'stage 3A' OR 'stage IIIA') AND ('ductal carcinoma in situ' OR DCIS OR 'intra-ductal carcinoma' OR 'lobular carcinoma in situ' OR LCIS OR 'lobular in situ neoplasia' OR 'atypical lobular hyperplasia' OR ALH))) AND TOPIC: ((Health OR survival OR recurrence OR progression OR 'quality of life' OR 'well-being' OR 'well-being' OR depression OR depressive OR 'cost-effectiveness' OR 'cost-benefit' OR 'cost-efficiency' OR 'cost-utility' OR cost OR 'economic evaluation' OR societal) OR ((effect OR impact OR burden) AND (carer OR Carers OR caretaker* OR caregiver* OR family)))	
Total	**13,714**	