



EUROPE



# Understanding the societal impact of treatment of early breast cancer

What are the non-clinical outcomes associated with disease progression?

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RAND Europe has conducted a programme of research into the societal impact of treatment of early breast cancer. Breast cancer is the most frequently occurring cancer in women, accounting for 25 per cent of all cancer diagnoses (Ferlay et al. 2015; World Health Organization 2018). Diagnosis and treatment of breast cancer at an early stage is associated with decreased risk of disease progression, better survival prospects and improved quality of life. However, the risk of disease progression after treatment of early breast cancer is still relatively high – up to one in four women with HER2-positive early breast cancer

will experience disease progression despite current advances in treatment (Jackisch 2015). Therefore, there remains a need for innovation in treatment for early breast cancer and for comprehensive evidence on the impacts of early breast cancer and disease progression on society in order to support innovation.

Our research focused on mapping the research landscape of treatment for early breast cancer, assessing the impact of recurrence on patients, their carers and wider society, and identifying the opportunities and barriers to accessing diagnosis and treatment in a selection of



**Early breast cancer:** Non-invasive and invasive cancer that is confined to the breast, with or without regional lymph node involvement, and has not metastasised (Union for International Cancer Control 2014).

countries (Brazil, Canada, Italy, Spain and the UK). The methods used for this research were: a mapping review, a systematic review and a qualitative study using desk research and stakeholder interviews guided by a PESTLE framework. In analysing and synthesising this work we have brought together the findings from each phase of the study under some common themes presented below.

### **Existing effective treatment for early breast cancer may lead policymakers and payers to underestimate the need for investment in further improvements and innovation in treatment and delivery of care in early breast cancer.**

Early breast cancer is generally perceived to be a disease with existing effective treatment options. As evidenced by our mapping review, most research published on treatment for early breast cancer is focused on longstanding existing treatment options, mainly chemotherapy, surgery and radiotherapy (Ghiga et al. 2019). This point was repeated

in our interviews with stakeholders, where interviewees suggested that policymakers and payers may underestimate the need for investment in new drugs in the belief that there are existing effective treatment options for early breast cancer. They further commented that policymakers and payers may over-emphasise the direct costs of treatment (e.g. the cost of a drug or therapy) when making decisions around access to new therapies (Rodriguez-Rincon et al. 2019). However, the indirect costs to society of early breast cancer are substantial, with one study from Sweden estimating the indirect costs of breast cancer to comprise more than 50 per cent of the total costs of patients (Lidgren, Wilking and Jönsson 2007). Lidgren et al. identified sick leave, early retirement, mortality and loss of quality-adjusted life years as the indirect costs to society of breast cancer (Lidgren, Wilking and Jönsson 2007). Therefore, there is a need to consider a wide range of factors when assessing the value of therapy, for example factors such as patient satisfaction from new therapies, the broader benefits and potential cost saving from early treatment (e.g. avoiding loss of productivity and return to work), and prevention of disease progression to metastatic disease (Rodriguez-Rincon et al. 2019).



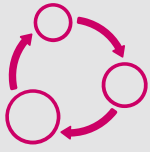
**Disease progression:** In cancer, at least 20 per cent growth in the size of the tumour or spread of the tumour following treatment (Eldridge and Paul 2018).



**Mapping review:** Literature review that seeks to identify linkages between the literature rather than results, focusing on aspects of the literature such as topics being covered, location of studies and funding sources (Cooper 2016)

### **The cost of treating metastatic disease and breast cancer recurrence is greater than the cost of treating early breast cancer.**

When considering the economic costs of treating breast cancer, there is ample evidence



**Recurrence:** Breast cancer that reappears after completion of initial treatment; it may occur months or years after treatment, may reappear in the same location as the original cancer (local recurrence) or may have spread to other locations in the body (distant or metastatic recurrence) (Mayo Clinic 2018).

that it costs less to treat people with early stage breast cancer than with metastatic disease. This is true for each of the five case study examples within our qualitative study (Brazil, Canada, Italy, Spain and the UK) (Figure 1) (Rodriguez-Rincon et al. 2019). In general, the costs of treatment rise progressively along with the stage of the disease (Capri and Russo 2017; Justo et al. 2013). Key drivers of the difference in costs are the number and type of cancer clinic visits (including the number of treatment cycles required), physician billings and hospitalisations (Albanell et al. 2016; Mittmann et al. 2014). Furthermore, the costs of treating both early breast cancer and metastatic disease are typically borne by public health systems as they cover the majority of the direct costs of cancer care (Rodriguez-Rincon et al. 2019).

An additional driver of the cost of treatment is recurrence. Our systematic review found that healthcare costs were significantly higher for patients who experienced recurrent breast cancer than for those who did not (Elmore et al. 2019). For example, one study found that compared with patients who did not recur, patients who had local and distant recurrences had increased mean total care charges of \$66,927 and \$102,504, respectively (Lamerato et al. 2006).

**Figure 1 The cost of treating early breast cancer compared with the cost of treating metastatic disease in the five countries of focus of the study**

**Differences between the costs of treatment for early breast cancer as compared to metastatic disease can be quite substantial**



#### **BRAZIL**

Average per patient direct costs (private system) (Justo et al. 2013):

- Stage I breast cancer: \$21,659
- Stage IV breast cancer: \$63,697



#### **CANADA**

Overall mean cost (Mittman et al. 2014):

- First 2 years of diagnosis: \$41,686
- Stage I breast cancer: \$29,938
- Stage IV breast cancer: \$66,627
- Drivers: cancer clinic visits, physician billings, and hospitalisations



#### **ITALY**

Average cost of treatment (Capri and Russo 2017):

- Non-metastatic breast cancer: €10,315.23
- Metastatic breast cancer: €12,825.90



#### **SPAIN**

Chemotherapy (Paladio Duran 2008):

- Estimated €428.5 per patient per cycle
- Increased in metastatic breast cancer to €640.4 per cycle

Hospital admission (Pockett et al. 2010):

- Average cost early breast cancer: €2,374
- Average cost metastatic breast cancer: €3,515



#### **UNITED KINGDOM**

Cost of treating breast cancer (Woltensholme et al. 1998):

- Stage I breast cancer: £8,638
- Stage IV breast cancer: £15,918



**Metastatic breast cancer:** Occurs when cancer cells spread to parts of the body away from the original tumour site; these new cell clusters, called metastases, can be local (right next to the original tumour), regional (in the lymph nodes near the original tumour) or distant (further away) (Metastatic Breast Cancer: Overview 2016).

### Early breast cancer has impacts beyond clinical outcomes. In particular there are a range of non-clinical outcomes associated with treatment and disease progression.

As evidenced by our mapping review, most research focusing on the impact of treatment of early breast cancer examines clinical effectiveness measured as survival, recurrence and physiological impacts (Ghiga et al. 2019). However, there are also important non-clinical outcomes to consider, such as psychosocial effects, as illustrated in Figure 2. The types of economic outcomes reported were predominantly cost-effectiveness or cost-benefit of treatments (around 70 per cent of all studies focusing on economic outcomes). A minority of studies considered economic outcomes for patients (e.g. out-of-pocket expenses) and economic outcomes for the wider health system or wider society (e.g. indirect costs associated with resource use, staff time or hospital stays).

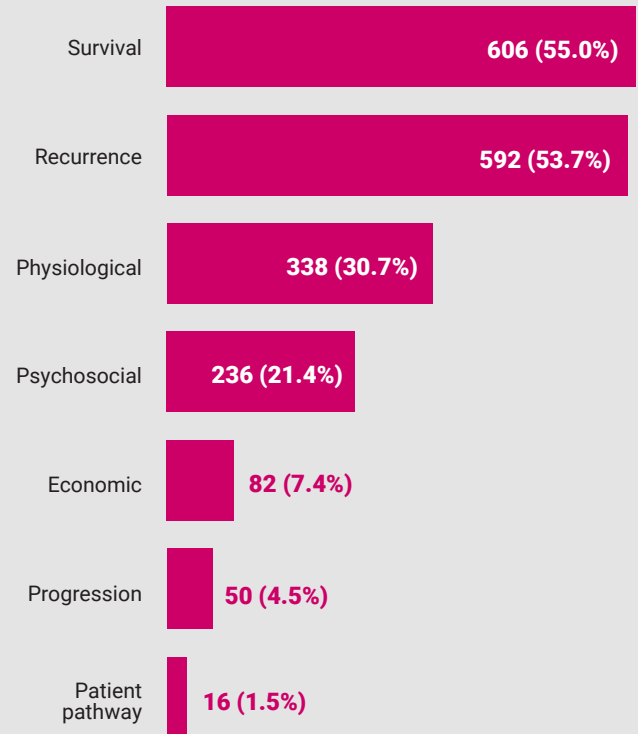


**Lumpectomy or breast conserving surgery:** Surgery to remove an area of cancer from the breast and some of the surrounding breast tissue (Cancer Research UK 2017).

**Figure 2 Outcomes explored in the literature on treatment of early breast cancer**

**Most research focusing on the impact of treatment of early breast cancer examines clinical effectiveness**

**Number of studies measuring a specific type of outcome:**



When studies did examine non-clinical impacts of treatment they often found that quality of life, emotional and psychological well-being, and workforce participation were affected by breast cancer treatment (Ghiga et al. 2019). For example, three studies found that women who underwent mastectomies were more at risk of reduced or lost wages in comparison with those who underwent breast conserving lumpectomies (Gorisek, Krajnc and Krajnc 2009; Hauglann et al. 2012; Mujahid et al. 2010). Furthermore, mastectomies were also associated with lowered social status due to increased financial difficulties and more physical symptoms than lumpectomies, with patients who underwent lumpectomy

being more satisfied with their body image and sexual life (Gorisek, Krajnc and Krajnc 2009). These findings were confirmed by our systematic review, which found that when comparing treatment types, body image, sexual and social functioning were all lower in women who underwent a mastectomy than in those who received breast conserving treatment (Elmore et al. 2019).



**Mastectomy:** Surgery to remove the whole breast (Breastcancer.org 2018).

Additional psychosocial impacts of early breast cancer treatment identified by research include emotional well-being, fatigue and depression, and lower quality of life and sexual enjoyment. For example, a considerable number of breast cancer patients report that emotional well-being post-treatment declines over time, in part due to insufficient information about risk of recurrence early in the period of survivorship (Janz et al. 2014). Evidence from our systematic review suggests that when undergoing treatment women experienced greater fatigue and depression, and lower quality of life and sexual enjoyment, than those who had finished treatment. It is important to note that fatigue was also greater in women who did not receive treatment for recurrence than in those that had finished treatment. This is likely to be because fatigue is a common symptom of breast cancer and breast cancer treatment (Curt et al. 2000; Lawrence et al. 2004). These findings suggest that innovations to treatment regimens and improvements to the duration of treatment or the severity of its side-effects could improve the psychosocial well-being of women who experience breast cancer recurrence.

Early breast cancer also impacts on workforce participation. For example, a cohort study of breast cancer patients looking at permanently reduced work ability found that compared with cancer-free controls, breast cancer patients were significantly more likely to receive a disability pension after adjustment for unmatched socio-demographic variables (Hauglann et al. 2012). Research from Sweden found that women with a breast cancer diagnosis, at any cancer stage, were more likely to require at least part-time sickness or disability benefits at three and five years post-treatment, suggesting that early breast cancer presents barriers to returning to work (Eaker et al. 2011). There is evidence that women who have been diagnosed with breast cancer place a high value on returning to work, in part because it can bring psychological benefits and signal a return to normality, yet factors such as treatment side-effects, longer-term pain resulting from surgery and non-medical barriers such as the lack of employer support can impede women's efforts to reintegrate into the workforce (The Economist Intelligence Unit 2017).



**Human epithelial growth factor receptor 2 (HER2):** Gene product that if overexpressed in the cell is associated with cancer (Gutierrez and Schiff 2011).

**Taking non-clinical outcomes into account, the cost of early breast cancer extends beyond the direct cost of care. It includes costs associated with quality of life, out-of-pocket expenses and costs as a result of loss of productivity.**

The indirect costs of early breast cancer are generally not covered by healthcare systems, yet they are numerous (Rodriguez-Rincon et





**PESTLE analysis:** Framework tool used to assess the influence of the political, economic, social, technological, legal and environmental landscape on a particular issue.

al. 2019). These costs include unemployment or lost income and out-of-pocket expenses for patients and carers, such as travel expenses and uncovered treatments. Out-of-pocket costs vary by context and socio-demographic factors. For example, one study assessing out-of-pocket costs in the year after diagnosis of early breast cancer among Canadian women and their spouses found that median net out-of-pocket costs were Can \$1,002 with 74.4 per cent of these costs being attributable to expenses related to treatments and follow-up (Lauzier et al. 2013). This same study found that spouses' median out-of-pocket costs were Can \$111, and that higher costs for women were associated with higher education, working at the time of diagnosis, living more than 50 km from the hospital where surgery was performed, and having two and three different types of adjuvant treatment. Additional support costs are not generally covered by public health systems but are rather borne by patients. However, interviewees from countries in our qualitative analysis reported that in limited examples breast cancer charities and not-for-profit organisations would sometimes offer additional forms of support (Rodriguez-Rincon et al. 2019).

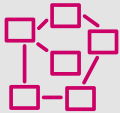
Costs associated with loss of productivity, including income losses for individuals and pension or disability payments, are one of the largest indirect economic costs to society of early breast cancer. For example, one study found that on average women lost 27 per cent of their projected usual annual salary after a breast cancer diagnosis, and that those with lower levels of education, lower social support, shorter tenure in their job, or who were

self-employed or had worked part-time had higher proportional income losses (Lauzier et al. 2008). A second study by the same authors suggests that income losses explain most of the decline in families' financial situation post-diagnosis (Lauzier et al. 2013).

Studying a sample of Irish breast cancer survivors in 2008, Hanly et al. (2012) estimated the overall productivity costs of breast cancer to be €193,425. This included €108,939 associated with disability costs (e.g. temporary disability, workforce departure and reduced hours after returning to work) and €84,486 costs associated with premature mortality. Within their sample of respondents, the average amount of time taken off work for breast cancer patients was 44.9 weeks. Additionally, 12.9 per cent of the sample indicated they had permanently departed from the workforce after their diagnosis of breast cancer (Hanly et al. 2012). When considered along with the previously cited evidence that women with a breast cancer diagnosis, at any cancer stage, were more likely to require at least part-time sickness or disability benefits at three and five years post-treatment (Eaker et al. 2011), the costs associated with productivity losses and societal support through sickness, unemployment and disability benefits for women diagnosed with breast cancer are substantial. Cancer survivors can be supported in their return to work and in improving their quality of life (National Cancer Survivorship Initiative 2013). Clinicians, employers and the government can all play a role in helping women re-enter the workforce after treatment for breast cancer. For example, research on employers suggests that most want to support employees' return to work for moral and ethical reasons, and that their failure to do so successfully is often more about a lack of knowledge around the issue and/or failing to have appropriate policies in place to support cancer survivors (The Economist Intelligence Unit 2017).

## The indirect impacts of early breast cancer treatment are not fully understood.

Studies suggest that women who undergo treatment for early breast cancer experience a range of psychosocial outcomes including effects of ageing, and effects associated with stress and coping, anxiety or distress, body image, sleep, sexuality, fatigue, adherence, cognitive change, depression and quality of life. However, our mapping review highlighted that these issues, which are central to managing cancer survivorship, are underexplored in the literature on early breast cancer (Ghiga et al. 2019).



**Systematic review:** Literature review that summarises the results of carefully designed healthcare studies (controlled trials) to provide evidence on a given intervention (Cochrane Consumer Network n.d.).

Moreover, our systematic and mapping reviews found that the few studies which examined non-clinical impacts of early breast cancer used a range of definitions and a variety of tools to measure outcomes, complicating synthesis efforts. The 17 studies in our systematic review identified 22 outcomes, but used different tools to measure them (Elmore et al. 2019). For example, 15 tools were used across 10 studies to measure the psychosocial well-being of the patient – and most studies lacked a clear definition of the outcomes measured. These variations make it difficult to provide generalised conclusions from the findings of the systematic review, as well as limit attempts in different countries to include psychosocial outcomes into the assessment

for reimbursement in the Health Technology Assessment process.

## Some data are available to show a significant difference in quality of life (often a reduction) between those in whom the disease has progressed and a control population.

Our systematic review found evidence to suggest that women who experience recurrence of breast cancer have significantly greater cancer-specific stress, greater use of antidepressants and lower frequency of sexual intercourse than women who remain disease-free (Figure 3). However, our review also found recurrence to be associated with higher levels of self-esteem, and no evidence for a significant difference in mood, body image, social distress, social support, emotional functioning, mental health, fatigue, sexual satisfaction,<sup>1</sup> insomnia or quality of life between women with breast cancer recurrence and women who remained disease-free (Figure 4). The review found conflicting evidence regarding the outcomes of depression and

**Figure 3 Outcomes found in the systematic review to be significantly different between patients who experienced a recurrence of breast cancer and patients who remained disease-free**



Greater cancer-specific stress



Greater use of antidepressants



Higher levels of self-esteem



Lower frequency of sexual intercourse

1

Sexual satisfaction includes scores for kissing frequency, sexual and relationship satisfaction

**Figure 4 Outcomes for which the systematic review found no evidence of being significantly different between patients who experienced a recurrence of breast cancer and patients who remained disease-free**



anxiety, relationship satisfaction and financial difficulties experienced by women who had a breast cancer recurrence compared with those who remained disease-free. Interestingly, although there was no difference in levels of insomnia between women with breast cancer recurrence and women who remained disease-free, levels of insomnia was found to be higher in women with recurrence than in healthy women, which may suggest that the presence of cancer is associated with insomnia, rather than the specific stage of the disease (Elmore et al. 2019).

Furthermore, evidence from our systematic review suggests that women who undergo more invasive treatments, such as mastectomies, have lower quality of life. Body image, breast sexual functioning and social functioning were all found to be poorer in women who underwent a mastectomy than in those who had breast conserving treatment

(Elmore et al. 2019). Finally, fatigue and depression were greater, and quality of life and sexual enjoyment lower, for women undergoing treatment than for those who did not undertake or had finished treatment.

**The economic impact of early breast cancer is not being linked to investing in treatment for early breast cancer. Therefore there is a need to communicate the importance and highlight the benefits of new treatment options for early breast cancer.**

Our research found that few studies considered economic impacts of early breast cancer, yet there is clear evidence of this economic impact, which shows costs rising progressively with the stage of cancer (Capri and Russo 2017; Justo et al. 2013). Economic impact includes not only the direct costs of treatment but also the indirect costs, such as reduced quality-adjusted life years and loss of productivity. To reduce the economic impact to society of breast cancer, it could prove beneficial for health systems to consider and potentially cover the additional costs associated with early breast cancer, such as those related to support services, which may result in productivity gains for the workforce due to reduced absence from work and greater productivity when at work. Additionally, increased investment into research and approval of new treatments that reduce the side-effects associated with cancer treatment, treatments that can be administered at home, or treatment that require fewer sessions, could also reduce the indirect costs of early breast cancer.

There is therefore a need to communicate to policymakers the link between evidence on the cost of disease progression and the potential benefits of investment in treatments for early breast cancer. Although this study focused on



early breast cancer, it is likely that the findings related to the cost of social outcomes being under evaluated could be applied to a variety of health conditions. Our research found that patient advocacy groups are effective at raising awareness of breast cancer among patients, the public and policymakers (Rodriguez-Rincon et al. 2019). Within our qualitative analysis, interviewees perceived patient advocacy groups as one effective channel for providing education on and raising awareness of breast cancer among patients, the public and policymakers. Public and policymaker awareness can highlight the need for investment in innovation and improvements to current treatment and systems going forwards.

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