Prevention and the economic burden of breast cancer

A report commissioned by GE Healthcare, authored by Bengt Jönsson and Nils Wilking
About the authors

Professor Bengt Jönsson

Bengt Jönsson is Professor Emeritus (Health Economics), department of economics, Stockholm School of Economics, and Director of the Center for Health Economics. He is currently member of the European Academy of Cancer Sciences, and of the EU Expert Panel on effective ways of investing in health.

He has been a member of the Karolinska University Hospital Board, and the Scientific Advisory Board, National Board of Health and Welfare, Sweden. He was also Chair of the Expert Group to the Committee on Funding and Organization of Health Services and Medical Care in Sweden (HSU 2000), and a member of the National Social Insurance Board from 1992 to 1994, and of SBU (The Swedish Council on Technology Assessment in Health Care), Scientific Advisory Board 1988-2004.

Professor Jönsson is a member of the editorial boards of several journals, including the Journal of Cancer Policy, European Journal of Health Economics, and International Journal of Technology Assessment in Health Care. He has also been a temporary adviser to the WHO and a consultant to OECD and UNIDO. Professor Jönsson’s extensive publications in the field of health economics include over 200 papers, reports, and book chapters. Presently he is past president and member of the board of the SHEA, the Swedish Health Economics Association and past president of iHEA, the international Health Economists Association.

Nils Wilking MD PhD

Associate Professor Nils Wilking MD PhD has worked in clinical oncology for 30 years after graduating from the Karolinska Institute in Stockholm, Sweden. He has worked for many years in the field of surgical oncology, but has since the late 1980s mainly worked within medical oncology with a focus on breast and GI cancer.

He headed the Breast and GI Cancer Unit at the Karolinska Hospital during 1992-1998. During this period, he also set up and headed the clinical trial unit at the Department of Oncology.

In 1998, he joined Eli Lilly as a senior research physician. In 2001, he moved to BMS where he held a European position in their oncology team. Since 2003, he has worked in a research context linked to the Karolinska Institute. Since 2010, he also serves as Senior Strategic Advisor for the Southern Health Care Region in Sweden.

His main focus has been on research in relation to health service delivery. This work, in collaboration with Professor Bengt Jönsson at the Stockholm School of Economics, has resulted in a number of reports with a focus on patient’s access to cancer therapy. These reports include information on more than 55 countries.

As of 2013 Nils Wilking is the head of the department of oncology at Skånes University Hospital, Lund/ Malmö Sweden.
CONTENTS

Executive Summary 3
Introduction 3
Epidemiology 4
Disease Adjusted Life Years (DALYs) 7
Economic burden 8
Outcome in breast cancer 10
Prevention in high risk groups 12
Secondary prevention, early diagnosis 13
Mammography screening programs 14
Current controversy about screening 15
Breast MRI and other emerging technologies 17
Cost effectiveness of breast cancer screening 17
Conclusions and policy implications 18
References 20
Executive summary

- The disease burden of breast cancer is high; every year over 1.4 million women worldwide get breast cancer, and approximately 459,000 women die of the disease. Breast cancer is the second most common cancer form overall and the most common cancer for women, constituting 25% of all female cancer.

- Accurate data on breast cancer incidence at a national level is lacking in several countries due to limited cancer registration. Available data show that breast cancer incidence rates have steadily increased in developed countries over the last 50 years. In the last decades increased incidence rates are also being seen in many developing countries, in particular in parts of Asia. The increased incidence of breast cancer is mainly due to increased life expectancy but also relates to lifestyle changes, such as women having fewer children as well as hormonal interventions like post-menopausal hormonal therapy.

- The mortality trends are diverging, with declining mortality in many developed countries, while mortality is increasing in developing and newly industrialized countries. Survival rates are also lower in these countries mainly due to the late stage of the disease when diagnosed, but also due to limitations in access to proper diagnostics and treatment of both early and advanced breast cancer.

- The economic burden of breast cancer is considerable in terms of both direct and indirect costs. The direct health care costs attributable to breast cancer vary greatly between countries, reflecting differences in total health care spending. Hospitalizations dominate the direct costs, but costs of pharmaceuticals are also high and increasing. The indirect costs of breast cancer are larger than the direct treatment costs since many breast cancer cases occur in women below 65 years.

- While progress in treatment has contributed to improvements in survival, the cost of treatment, particularly for advanced breast cancer, has also increased significantly. The potential benefit of primary and secondary prevention thus remains high, both in health and economic terms, and this applies to both developed and developing countries.

- New evidence on chemoprevention to reduce breast cancer risk has resulted in revised guidelines, recommending this preventive option for women at high risk.

- While screening has contributed to improvements in survival, there is a debate about benefits, harms and cost-effectiveness of alternative approaches to screening. While decreasing incidence in some populations and improved outcome of treatment may have reduced the benefits of screening, this is not evidence for dismissing this option for prevention. In populations with increasing incidence and high mortality/incidence rate, the potential benefits of early detection are increasing. There is still a need and opportunities for appropriately designed screening programs, and for new options for early detection. Targeting specific risk groups and improving the internal efficiency of the diagnostic process can improve cost-effectiveness. The present focus in health care systems on comparative effectiveness makes it mandatory for new effective methods to provide data for assessment of their value in relation to established alternatives.

Introduction

The sustainability of health care systems, and the need to make priorities for investments in improved health are at the top of the health policy agenda [1]. Breast cancer is an important and interesting example of the issues involved. The disease is well defined, and over the last four decades a number of new technologies for prevention, early detection and treatment have been introduced, that have significantly improved the outcome. But the implementation varies between health care systems, and the search for evidence on best practices is still far from completed. The epidemiology of the disease is also changing, and the most important change is the growing incidence of breast cancer in developing countries. It is also in the developing countries that we see the shortest survival due to late diagnosis of the disease. There are also variations in survival within developed countries related to socioeconomic status. In the US, despite improvements in survival across poverty levels for all known stages of disease, relative survival remains lower among women residing in poor areas compared with affluent areas. This poor outcome probably relates to a more advanced stage of disease at diagnosis. In 2008, 51.4% of poor women had undergone a screening mammogram in the past 2 years compared with 72.8% of more affluent women [2].
Investing in health is not only about sustainability of the health care systems, equity in health and access to health care. Breast cancer is an example where investments in health create benefits outside the health care system as breast cancer affects many women of working age. The opportunities to reduce the number of working days lost are an important additional benefit from investment in improving outcomes in breast cancer.

This paper reviews the economic burden of breast cancer, with particular focus on opportunities to reduce the burden through prevention and early detection. The focus on prevention and early detection is important for several reasons. During the last decade focus has been on the costs and survival benefits from the introduction of new drugs for treatment of breast cancer, and to some extent on the refinement of breast surgery, aimed at improving quality of life. During the same period we have seen a growing controversy about the benefits and harms of mammography for early detection in developed countries with decreasing incidence of breast cancer. But at the same time we see increasing incidence in developing and newly industrialized countries, where cases are detected at a late stage. There is thus the need to review the case for development of cost-effective methods for prevention and early detection of breast cancer.

**Epidemiology**

Epidemiological data is the basis for determining the burden of a disease.

Breast cancer is the most common cancer form in women; with an estimated 1.4 million new cases worldwide each year, breast cancer constitutes about 25% of all cancer cases in women and is the second most common cancer form overall [3]. Breast cancer can also occur in men, but this is very uncommon. Incidence rates of breast cancer are significantly higher in developed countries than in developing countries (72 and 29 per 100,000 respectively, see table 1); the difference in incidence rates between developed and developing countries is probably due to a combination of demographic, hereditary, environmental and lifestyle risk factors. Incidence rates are rapidly increasing in many newly industrialized countries due to changing lifestyles reflecting those patterns in developed countries where we already see high incidence rates. Risk factors that may contribute to breast cancer incidence include: low parity, late first pregnancy, early start of menstruation as well as exposure to hormonal treatment, oral contraception, obesity and alcohol consumption. As explained below, the ageing of populations is a major factor behind the increasing incidence.

Table 1 shows the incidence and mortality for breast cancer in different regions of the world in 2008. The total number of cases, or crude incidence, and mortality, are the best measures for assessing the actual health and economic burden of breast cancer in a country or region. The age-adjusted incidence and mortality is of interest as it shows the influence of risk factors other than age in the development of breast cancer. The age span of women affected by breast cancer is broad. Although uncommon, breast cancer may affect women already in their 20s and 30s, but close to 90% of all cases are diagnosed from the age of 40 and onwards. Countries with younger populations have lower crude than age-adjusted incidence rates.

The ratio of mortality divided by incidence is an indicator of how successful a country is in early detection and treatment of breast cancer; the lower the ratio in Table 1 the better. If all cases were cured,
i.e. women diagnosed with breast cancer would die from something else, the ratio should be zero, and if all die from breast cancer, the ratio is 1.0. The ratio of mortality to incidence is 0.24 in more developed regions, and 0.40 in less developed regions. The differences are large with a ratio of 0.20 in countries such as Sweden for example, and a ratio of 0.60 in parts of Africa and Melanesia. This difference is mainly explained by differences in the stage of the tumour at diagnosis, which reflects the presence of screening programs as well as education and public awareness. Well organized breast cancer care is also a key factor (4).

North America has an age adjusted incidence and mortality of 83.5 and 16.7 respectively which gives a mortality incidence ratio of 0.20, similar to the countries in Western Europe. A closer look at statistics from the US, reveals large differences between segments of the population. There are ethnic differences with a higher rate of breast cancer and an inferior outcome in African American women compared to white. On the other hand the incidence in Asian American women and in Hispanic/Latina women is lower than that among white and African American women (2).

Figures 1a and 1b show incidence and mortality, both crude and age-adjusted, for a selection of countries. As can be seen when comparing figures, in Mexico, Brazil, and Turkey, the crude incidence is lower than the age-adjusted incidence since these countries have relatively young populations. In these countries the burden of breast cancer is expected to increase rapidly with increasing life expectancy and life style changes. For example, the total number of reported cases in Mexico in 1999 was 10,000 compared to 7,000 in Sweden in 2007, although Mexico has a population 10 times as large as the Swedish population.

Figure 2 (below), illustrates the age distribution across the total number of breast cancer cases in Mexico and Sweden respectively. In Mexico, the average age at diagnosis of breast cancer is approximately 50 years while the average age at diagnosis in Sweden is 60 years due to the younger population on average in Mexico compared to Sweden [5, 6]. In both countries, the majority of women are under 65 years when they are first affected by breast cancer, which contributes to the large health and economic burden of the disease.
A barrier to the estimation of global breast cancer incidence is the limited data availability in many countries. Incidence figures in many countries are based on data from small geographic areas that are pooled and extrapolated to represent national data. This is not only the case in most developing countries; the majority of the European countries do not have a 100% national coverage of cancer registration. The Nordic countries are exceptions and Denmark was the first of the countries to establish a national cancer registry in 1942, and other Nordic countries followed with registration on a national level in the 1950s. (10, 11).

Figure 3 presents the breast cancer incidence and mortality trends over the last 60 years from the Nordic registries (12).

A review of breast cancer incidence and mortality in 9 countries in the Middle East (8) showed that incidence rates are comparatively low, with Lebanon as an exception, which partly can be explained by underreporting. Incidence rates are increasing, and rates also vary within countries between different parts of the population. While progress is made in terms of early detection, many cancers are diagnosed at a late stage.

The incidence of breast cancer is low in India, but rising. Due to low awareness of the disease, and absence of screening programs, the majority of breast cancers are diagnosed in a rather late stage (9).

China currently has the lowest age-adjusted incidence of the study countries, but one may expect that the fundamental changes in reproductive patterns in China brought about by the implementation in the 1970s of the one-child policy, as well as current lifestyle changes in China caused by rapid economic growth, will potentially lead to dramatically increased rates of breast cancer in Chinese women. Such trends can already be seen in the middle-aged population in urban areas of China, where a 20–30% increase in breast cancer incidence has been documented over the past decade, although part of the increase may also be due to earlier diagnosis and better diagnostic methods, such as the introduction of mammography (7).

The main picture is one of increasing incidence, and since mid 1990s a declining mortality. Incidence rates seem to have been stable or fallen slightly during the last part of the period. Still, in countries like Sweden there has been an increased incidence over the last 5 years (see figure 4) (overleaf). This increase is at present difficult to explain, especially since the use of post-menopausal hormone therapy has declined significantly over the last decade.

Figure 2b shows the huge difference in the incidence of breast cancer at different ages in Sweden and Mexico. Source (4).

Figure 3 Breast cancer incidence and mortality rates in the Nordic countries since the 1950s. Source (4).
US and Canada show a similar pattern to the Nordic countries, with reduced incidence and mortality since the early 2000s. For Asian countries, including Japan, incidence is increasing rapidly. (76).

**Disability- adjusted life years (DALYs)**

Disability-adjusted life years (DALYs) is a measurement for the overall burden of disease that combines years of potential life lost due to premature mortality and years of productive life lost due to disability, with the intention to quantify the gap between current health status and an ideal health situation (13).

Figure 5 (below), shows the estimated disease burden of breast cancer in DALYs per 100,000 women, separated into years of life lost and years lost due to disability, in the relevant WHO MDG (Millennium Development Goals) Regions.

The first conclusion is that mortality is the main contributor to the burden of breast cancer measured by DALY. But when more cases are detected, and survival increases, the impact of quality of life during and after treatment is of increasing importance.

Although the burden per 100,000 women is highest in developed countries, where incidence rates are high, it is important to recognize that the disease burden per breast cancer case is higher in developing countries due to higher mortality rates in breast cancer and the younger age of women at diagnosis.
DALYs estimates must be interpreted with some caution. The incidence and mortality data that serve as input to the DALYs estimates are for some countries based on estimates and extrapolation and the calculation method in itself is based on a range of assumptions in order to make this kind of assessment possible. However, the DALY estimates are important both for comparisons between diseases, countries and over time. Table 2 shows an update from 2008 of DALYs lost distributed on more or less developed regions. About two thirds of DALYs lost occur in developing countries, mainly due to reduced survival.

Table 2 Breast cancer (2008) Estimated disability-adjusted life years (DALYs), years of life lost (YLLs) and years lived with disability (YLDs).
Source: http://globocan.iarc.fr

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>DALYs</th>
<th>YLLs</th>
<th>YLDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>15127050</td>
<td>422</td>
<td>11569990</td>
</tr>
<tr>
<td>More developed</td>
<td>5533146</td>
<td>514</td>
<td>3733196</td>
</tr>
<tr>
<td>More developed</td>
<td>9593905</td>
<td>387</td>
<td>7830794</td>
</tr>
</tbody>
</table>

Economic burden

Breast cancer is not only a large health burden but also a significant economic burden to society. The economic burden of breast cancer is not well documented and comprehensive estimations of the cost of breast cancer are limited. A Swedish cost-of-illness study estimated that while the direct costs (the costs directly linked to treatment, detection, prevention, or care), of breast cancer are significant, the indirect costs of the disease (the cost of lost productivity due to the patients’ disability and illness and premature mortality), are more than twice as large as the direct costs (14). This Swedish study also estimated a monetary value of intangible costs due to loss of quality of life and reduced survival, thus providing a link to the measure of health burden as DALY lost. A comparison of the size of the different cost components is shown in table 3 below.

Table 3 Cost of breast cancer distributed by the different cost items.
Source (14). 1 SEK=0.15 USD=0.11 Euro.

This Swedish study estimated that direct health care costs account for less than 10 per cent of the total social costs. Indirect costs for loss of production are twice the direct costs. Screening accounts for about two percent of the total social costs and drugs only about one percent. However, since 2002 the costs for drugs have increased, and in 2011 expenditures on trastuzumab (Herceptin) (for the treatment of HER2 positive breast cancer; approximately 20% of the total breast cancer population) alone was 326 million Swedish Krona (SEK); four times higher than the total cost of drugs in 2002 (83 million SEK).

Intangible costs are valued at 600,000 SEK per Quality Adjusted Life Years (QALY) lost, which is less than what is accepted for cancer drugs in Sweden (1 million SEK) (77), but a figure representing a more relevant value for intra-marginal changes. It is slightly higher than what has been accepted in National Institute for Clinical Excellence (NICE) decisions about recommending cancer drugs for the NHS in England.

The estimates above represent the cost of breast cancer from a social perspective. It is common that estimates of the costs of breast cancer only take into account part of the social costs. In a study of the cost of breast cancer in the Nordic countries, direct treatment costs were estimated at 538 million Euro or just over 20 million Euro per million population, and the public expenditures for sickness and early retirement payments at 216 million Euro (Denmark excluded due to lack of data) (15). The direct cost estimates also excluded part of the costs for ambulatory care, and public expenditures for sickness and
early retirement account for only about one third of the social costs due to lost productivity. Indirect costs due to premature mortality were ignored as well.

Variability in the methodology used and costs included in different studies should be kept in mind when assessing estimates from different countries of the total cost of breast cancer. In France, the total healthcare cost for breast cancer was calculated to be €1,456 million in 2004, of which 55% was for hospital care and 45% was for primary care. Surgery represented approximately 34% of the total hospital care, drug administration and drugs 37%, and radiotherapy 13%. Total indirect costs in France due to potential lost production capacity were estimated to be €1,652 million (16). In Germany the total direct cost of female breast cancer in 2008 was estimated to be €1,956 million. In addition, there is 59,000 years of lost production annually, 17,000 due to disability, 19,000 due to invalidity and 23,000 due to premature mortality (17). In Finland, the cost of breast cancer including direct costs and transfer payments, i.e. healthcare costs, sick day payments and invalidity pension, were estimated to be €65 million in 2004 (16). Figure 6 gives an overview of the cost estimated from a identified sample of studies.

Data was recalculated to the average cost per new breast cancer case to make it possible to relate data from different countries; however explicit comparisons between countries must be done with caution since the studies have used different methods. The indirect cost per breast cancer case in Germany presented in the figure was calculated by multiplying the years of lost productivity due to breast cancer in Germany with the average gross salary in Germany.

Most of these cost analyses were based on cost data that are now 5-7 years old. Since then, some relevant changes have taken place in the treatment of breast cancer, specifically when it comes to the range of drugs available to patients. Drugs were estimated to constitute approximately 10% of direct healthcare costs in breast cancer care in the Swedish study based on data from 2002 (14). The drug share of the total cost of care in cancer has increased in recent years with the introduction of new, targeted biological therapies for the treatment of breast cancer (15). In metastatic breast cancer, according to available data, drug costs constitute a significantly larger share of total healthcare costs in Sweden. They represent 35-40% of total costs (20, 21) and 25% of total costs in the UK (22). The treatment of advanced

Figure 6a Average direct costs per breast cancer case (16-19).

Figure 6b Average indirect costs per breast cancer case (16-19).
stages of breast cancer is generally more expensive than treatment in earlier stages (19-23).

Studies of the cost of breast cancer from an incidence perspective generally only include estimates of the direct health care expenditures. A review of studies of the cost of treating breast cancer in the US, reveal that the costs are high during the first year after diagnosis and in the last phases of the disease (24). Estimates of lifetime per-patient costs of breast cancer ranged from $US20,000 to $US100,000. Estimates of life time costs are important as a source of data for modeling the cost-effectiveness of different interventions, from screening and initial treatment to strategies for management of late stages of the disease. It is thus not surprising that cost estimates vary, but a consistent result is that treatment costs for later stages (stage III and IV) are higher than for treatment of breast cancer in stage I and II.

Economic evaluations of trastuzumab (Herceptin®) in Sweden, indicate typical life time costs for both adjuvant treatment and treatment of recurrent disease are, 50-60,000 Euros, over an estimated survival time of 12 versus 2 years respectively. Cost for adjuvant treatment is reduced due to lower costs from fewer recurrences (25-26).

Even though data on the economic burden of breast cancer is only available from a selection of countries, the available cost analysis presented above illustrates how the cost per patient differs significantly between countries. This is, to a large extent, a consequence of the total healthcare resources available in a country, and difference in the care provided (e.g. access to high cost cancer drugs).

There is no direct link between per capita expenditures in healthcare (see figure 7 above) and the resources or health care services available to the individual patient. Therefore, one must also take into account how efficiently available resources are utilized in the healthcare system and the different relative costs of, for example, healthcare personnel in different countries. For countries with low health care spending in an international context, it is important to make a distinction between resources that are available locally at relatively low costs, and those that need to be imported at international prices.

Some of the therapies used in the treatment of breast cancer, such as radiation and diagnostic equipment, require sophisticated technology for which the cost of establishing and maintaining these medical facilities is high. The WHO recommends that in limited-resource countries, medical facilities should initially be concentrated in relatively few places to optimize the use of resources. On the other hand, in countries with social and economic inequalities, high-tech medical facilities may often be based in areas of the country where wealth is concentrated, resulting in a sharp contrast in access to treatments that the wealthier and poorer populations can achieve, which can be further compounded by the remoteness of the more often poorer rural regions (28).

Access to innovative medicines may also be a problem in countries with low income and health care expenditures, since prices are determined by ability to pay in high income countries with well established health insurance systems. Patients may thus have to wait for access to these medicines until the patent has expired and low price generics become available. However, it should be recognized that there is also a challenge to make optimal use of old medicines, since resources are needed for diagnosis and follow-up to make the treatments effective in clinical practice.

Outcome in breast cancer

The long-term prognosis for breast cancer patients has improved significantly; 10-year survival rates are now 80% in those countries with the best outcomes compared to just over fifty per cent 50 years ago. But we can observe very large differences in survival rates between countries. Such comparisons must be interpreted with caution, since studies often refer to different time periods and patient populations. Table 4 below shows latest data from GLOBOCAN 2008(3).
Survival rates are higher for developed than developing countries and regions. This is mainly due to the observed differences in survival linked to different stages of the disease at diagnosis. Much of the variation in breast cancer survival between countries is thus likely to be caused by disparities in early detection programs and access to appropriate diagnostics and treatment services. Figure 8 below illustrates the continuous improvement in 5 year survival over time, but also the persistent great difference in long term survival for breast cancer detected at different stages.

The 5-year observed survival rate refers to the percentage of patients who live at least 5 years after being diagnosed with cancer (Figure 8). Many of these patients live much longer than 5 years after diagnosis. A relative survival rate compares the observed survival with what would be expected for people without the cancer. This helps to correct for the deaths caused by something besides cancer, and as an alternative way to describe the effect of cancer on survival.

Table 4 Five year survival rates for female breast cancer in different countries 2008. Source (3).

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Method</th>
<th>Ages</th>
<th>5-year relative survival (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States of America</td>
<td>2005-2007</td>
<td>Period</td>
<td>All ages</td>
<td>89.2 (89.0-89.5)</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>2000-2006</td>
<td>Cohort</td>
<td>All ages</td>
<td>88.3 (88.0-88.6)</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>2001-2005</td>
<td>Period</td>
<td>15-99</td>
<td>86.9 (86.5-87.3)</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>86.2 (85.9-86.6)</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>85.9 (85.5-86.3)</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>85.2 (84.8-85.7)</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>85.1 (84.7-85.5)</td>
<td></td>
</tr>
<tr>
<td>Cuba</td>
<td>1995-1999</td>
<td>Cohort</td>
<td>15-99</td>
<td>84.9 (84.6-85.1)</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>84.3 (83.9-84.6)</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>84.2 (83.9-84.5)</td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>2000-2005</td>
<td>Cohort</td>
<td>All ages</td>
<td>83.2 (82.9-83.5)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>82.2 (81.7-82.5)</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>2001-2005</td>
<td>Period</td>
<td>15-99</td>
<td>81.9 (81.5-82.2)</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>81.7 (81.4-81.9)</td>
<td></td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>1995-1999</td>
<td>Cohort</td>
<td>15-99</td>
<td>81.4 (81.1-81.6)</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>79.6 (79.3-79.9)</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>79.4 (79.1-79.7)</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>79.2 (78.8-79.6)</td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>79.1 (78.8-79.4)</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>2000-2005</td>
<td>Cohort</td>
<td>15-99</td>
<td>78.3 (78.0-78.5)</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>77.7 (77.4-78.0)</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>77.6 (77.3-77.9)</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>77.5 (77.2-77.8)</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>77.1 (76.7-77.5)</td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>76.8 (76.5-77.2)</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1995-1999</td>
<td>Cohort</td>
<td>15-99</td>
<td>75.7 (75.3-76.1)</td>
<td></td>
</tr>
<tr>
<td>Costa Rica</td>
<td>1995-2000</td>
<td>Period</td>
<td>15-99</td>
<td>75.1 (74.7-75.6)</td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>74.8 (74.5-75.1)</td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1994-1998</td>
<td>Period</td>
<td>15-99</td>
<td>74.0 (73.6-74.4)</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>1990-1994</td>
<td>Cohort</td>
<td>15-99</td>
<td>73.7 (73.3-74.1)</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>2000-2005</td>
<td>Period</td>
<td>15-99</td>
<td>73.6 (73.3-73.9)</td>
<td></td>
</tr>
<tr>
<td>Belarus</td>
<td>1995-1999</td>
<td>Cohort</td>
<td>15-99</td>
<td>73.3 (72.9-73.7)</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>1995-1999</td>
<td>Cohort</td>
<td>15-99</td>
<td>73.2 (72.9-73.6)</td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>1990-1994</td>
<td>Period</td>
<td>15-99</td>
<td>72.8 (72.4-73.2)</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>1991-1997</td>
<td>Cohort</td>
<td>15-99</td>
<td>72.2 (71.8-72.6)</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>1990-1996</td>
<td>Cohort</td>
<td>15-99</td>
<td>72.0 (71.6-72.5)</td>
<td></td>
</tr>
<tr>
<td>The Gambia</td>
<td>1993-1997</td>
<td>Cohort</td>
<td>15-99</td>
<td>71.8 (71.4-72.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Data taken from Refs. [47,68,70,74-78].

b Confidence intervals are not intended for comparative purposes, but rather to indicate the precision of the estimate.

c Country estimates were only provided to integer precision

n.a. = 95% confidence interval not available

Estimates of 5-year relative survival for female breast cancer in selected countries.*

Figure 8 Survival by disease stage in Norway. Source: Kreftregisteret Institutt for populasjonbasert kreftforskning" (Cancer statistics, Institute for population based cancer research), Norway, 2009.

Prevention and the economic burden of breast cancer
Latest five-year relative survival figures from the US shows 100% in stage I, 93% in stage II, 72% in stage III and 22% in stage IV (78).

Early detection and treatment are thus the major strategies for improved survival after diagnosis. We will later discuss strategies for prevention and early detection. The importance of early treatment can be illustrated with the introduction of trastuzumab for HER 2 positive breast cancer. The drug was first introduced for metastatic disease, and in that stage, gave an improved survival corresponding to 0.60–1.00 QALY per treated woman, compared to treatment without trastuzumab, while when used for adjuvant (early) treatment, gave a survival benefit of 0.97–1.22 QALY per treated woman in an estimate for Sweden (29), and 0.56 QALY versus 1.70 QALY in an estimate for the US (30).

Since the cost of early treatment is about the same as the cost of treatment of metastatic disease, (50-60 000 USD), but there is improved effectiveness with early treatment, the cost-effectiveness of early treatment is better than later treatment. But it should also be noted that the estimated survival increases are limited to about one year, which reinforces the point that to have a significant effect on the burden of disease, further improvement in survival from primary and secondary prevention is necessary. New drugs show promise for further improvement in outcome of treatment, but they also come at a significant increase in costs (31-32).

The quality of life of patients during and after disease and treatment is an important outcome of breast cancer care and is considered an essential outcome measure in cancer clinical trials. There is still very limited information on quality of life of breast cancer patients from clinical trials as well as from clinical practice. Quality of life is more affected in younger women with breast cancer and in women with recurrent and metastatic disease (4).

Prevention

Primary prevention

Primary prevention measures aim to reduce the risk factors for a specific disease and/or the individual perceptibility for such risk factors. Primary prevention of breast cancer is more difficult to achieve than for some other cancer forms, for example lung cancer, since most of the breast cancer risk factors are currently not amenable to primary prevention interventions. However it should be noted that a healthy lifestyle reduces the risk for breast cancer as well as many other diseases.

The specific life-style risk factors of breast cancer that are susceptible to primary prevention measures include: breast feeding, obesity after menopause, diet, alcohol, physical activity, oral contraception close to menopause, and post-menopausal hormonal treatment (33). The more extensive treatment guidelines from some countries discuss breast cancer risk factors, but in the majority of guidelines, risk factors are only mentioned briefly or not at all (34).

Primary prevention

Research commissioned by GE Healthcare in eight countries revealed that adults are unaware of the link between bad habits such as smoking, excessive alcohol consumption or physical inactivity and breast cancer. During three consecutive years, GE Healthcare has run #GetFit, an initiative that promotes the adoption of healthy habits to improve health and reduce the likelihood of developing certain cancers. A total of 111 countries took part in the 2013 initiative, with participants adopting and sharing new healthy daily choices via social media and committing to maintaining these long-term.

Prevention in high-risk groups

It is estimated that 20–30% of breast cancers are related to genetic factors that in combination with lifestyle factors can trigger the development of the disease. Around 4–7% of breast cancer cases are directly attributable to certain genetic mutations, most commonly in the BRCA1 and BRCA2 genes, which predispose women to a 60-80% life-time risk of developing breast cancer, often already at a young age. For women with a high genetic predisposition for breast cancer, preventive measures can be taken including; more frequent screening, and at a younger age, or chemoprevention with endocrine therapy. These drugs however, may have limited impact since BRCA1 carriers are frequently endocrine unresponsive. The most established strategy is preventive surgery including removal of the breasts, although the evidence base for this strategy is limited (35).

Tamoxifen and raloxifen have been available for use as preventive agents in the US for many years (36–39). A recent review, confirms
that the prophylactic use of tamoxifen and raloxifen reduces the incidence of invasive breast cancer. Subgroup analyses and decision models suggest that high-risk women, particularly those who have had a hysterectomy, derive the most benefit with the least harm, the researchers report (40).

Both drugs have recently been granted market authorization for this indication from EMA in Europe. Women in England with a family history of cancer will be able to get the drugs tamoxifen and raloxifen on the National Health Service as a protection against breast cancer, under new guidelines from the National Institute of Health and Care Excellence (NICE)(41). It is estimated that about 3% of the female population would be indicated for prevention. However, experience from the US market tells that rather few women use this treatment, mainly due to the side effects involved.

The American Society of Clinical Oncology (ASCO) has recently issued updated guidelines for chemoprevention (42). In women at increased risk of breast cancer age ≥ 35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor (ER)–positive breast cancer. In postmenopausal women, raloxifen (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) should also be discussed as options for breast cancer risk reduction. Those at increased breast cancer risk are defined as individuals with a 5-year projected absolute risk of breast cancer ≥ 1.66% (based on the National Cancer Institute Breast Cancer Risk Assessment Tool or an equivalent measure) or women diagnosed with lobular carcinoma in situ. Use of other selective ER modulators or other aromatase inhibitors to lower breast cancer risk is not recommended outside of a clinical trial. Health care providers are encouraged to discuss the option of chemoprevention among women at increased breast cancer risk. The discussion should include the specific risks and benefits associated with each chemo preventive agent.

Since the drugs are generic, costs and cost-effectiveness are not an issue, but the resources for identification of risk groups and follow up may be a matter for consideration.

**Secondary prevention/early diagnosis**

The aim of secondary prevention is to reduce the severity of disease (risk of recurrent and/or metastatic disease) and the risk of dying from it. As discussed earlier, outcomes are significantly better if the breast cancer is detected before it has spread outside of the breast.

However, early-stage breast cancer is not symptomatic in all patients. The main objective of early detection or secondary prevention through screening is to detect early stage cancers when they can be treated most effectively. Early detection has been shown to be important due to the strong association between stage at diagnosis (or tumor size) and survival (44). For most types of breast cancer the likelihood of lymph node invasion and worsening tumor grade increases as tumor size increases (45), leading to poorer long-term survival. Early detection is only valuable if it leads to timely diagnostic follow-up and effective treatment. The principal secondary prevention measure in breast cancer is population-based mammography, combined with ultrasound examination in dense breasts in some countries, which has been shown to improve outcomes as it leads to a larger share of breast cancers being diagnosed at an early stage in the screened population. Regular self-examination of the breast has also been put forward as a measure for early detection of breast cancer. However, there is no evidence that self-examination has any effect on earlier diagnosis. Nevertheless, in many countries with limited coverage of breast cancer screening, the majority of breast cancer is detected when women seek care after having noticed a breast lump, therefore initiatives to increase the awareness of breast cancer are extremely important so that women are conscious that breast lumps and other changes to the breasts can be a sign of cancer and do not postpone seeking care until the symptoms have reached a critical stage. It is also interesting to note that a recent retrospective ‘failure analysis’ of BC mortality in over 7000 women found that >70% of deaths from breast cancer occurred in women who did not receive regular screening mammograms (46). A critical factor in relation to this is access to well organized breast cancer care, including diagnostic work-up, surgical and non-surgical treatment.

**Mammography screening programs**

Although the outcome of breast cancer screening has been debated, the increased level of evidence available from the countries that implemented screening programs in the 1980s has resulted in breast
cancer screening now being recommended by both the WHO, (in countries where resources are available to ensure effective and reliable screening of at least 70% of the target age group), and the Council of the European Union (EU) (47-49). Screening programs have been implemented for a long time in many countries, while other countries have recently implemented screening programs on the national level or are in the process of doing so. Extensive guidelines for quality assurance of screening programs have been developed for example on the EU level (47). Figure 9 gives an overview of the coverage of screening in a selection of countries. The target population differs between countries but in most, screening is targeted to 50-69 year old women.

![Breast cancer screening rate in target populations](image)

**Figure 9 Breast cancer screening coverage in selected countries. (4).**

Population-based screening is a complex logistical process, from the initial invitation of the target population to further referral of patients with a screen result that requires follow-up. The WHO’s statement on mammography is that it is an expensive test that requires great care and expertise both to perform and in the interpretation of results, and that therefore population-based screening is not viable in all countries. Although there is insufficient evidence, good clinical breast examinations by specially trained health workers could have an important role when resources are limited (45).

The situation in the world regarding access to mammography varies.

In Mexico, mammography is recommended but there is no national population-based screening program and the overall adherence rate to mammography controls is low; a recent survey in Mexico City indicates that many women feel uncomfortable or worried about having mammography (50-51).

A recent survey among 1,000 Hong Kong Chinese women aged 18-69 years reported that almost 60% of the women had never heard of mammography screening (52). These studies indicate that increased communication efforts are needed to promote breast examination in groups with low adherence.

Based on identified data, China, Russia, Mexico, and Denmark have the lowest coverage of breast cancer screening.

In Russia, where mammography screening is managed at the regional level, coverage and adherence varies greatly between regions (53-55).
One of the goals of Mexican healthcare for the period 2007-2012 is to triple the coverage of mammography screening in women 45-64 years old from the reported coverage of 22% in 2006 (56).

In China, the anti-cancer association launched a pilot project called “breast cancer screening for one million women” in 2005, with the objective to offer regular screenings to one million women aged 35-70 years (53). However the project suffered from technical problems and a lack of funding, which meant that the screening could be offered at a reduced price but not free of charge, and by 2006, only 120,000 women had been screened. In 2008, a follow-up project was initiated with the aim to provide screening to women in rural areas and this project has obtained government funding. The ambition is to screen more than half a million women in the next few years. Still this is only a small proportion of the 300 million women that would belong to the target group for mammography screening in China. Some local government schemes have started to offer cancer screening, such as the Beijing government that offers free breast examination for women within a certain age range. One issue with screening in China is that breast cancer is most common in premenopausal women and it is more difficult to detect cancer with mammography in younger women as breast tissue is more dense (57-58).

No national or regional breast screening program exists in India. Mammography is available in all major cities in both private and public hospitals for those who are willing to pay for it. Use of mammography for screening is not considered to be cost-effective, partly because of the lack of high quality treatment facilities (9).

Also in countries with a high overall coverage, it has been shown that two groups in particular are underrepresented in breast cancer screening programs; women from lower socio-economic levels and first generation immigrants.

**Current controversies about screening**

The value of breast cancer screening has been considerably debated, for example in Denmark (59-60), partly with the argument that population-based screening leads to over-diagnosis of cancer in situ that would not have developed into breast cancer, thus incurring unnecessary treatment costs as well as risks and worries for affected women.

Lately a similar debate has started in the US after the U.S. Preventive Services Task Force recommendation in 2009 that there was no evidence that women aged 40-49 benefit from routine screening. While mammography undoubtedly detects early stages of breast cancer, and reduces mortality in breast cancer (61), there is a renewed debate on the balance between benefits and harms, with consequences for the way this technology is applied in an optimal manner. The assessment of pros and cons is complicated by the fact that it is difficult to provide evidence about the outcome in clinical practice. It should be noted that this problem is also increasingly evident for new treatments in cancer, where outcome measures used in clinical trials, such as progression free survival, may not easily be directly translated into improvements in quality of life and overall survival in clinical practice.

Recent important evidence comes from a study of the Norwegian breast-cancer screening program that was started in 1996 and expanded geographically during the subsequent 9 years (62).
Women between the ages of 50 and 69 years were offered screening mammography every 2 years. The study compared the incidence-based rates of death from breast cancer in four groups: two groups of women who from 1996 through 2005 were living in countries with screening (screening group) or without screening (non-screening group); and two historical-comparison groups that from 1986 through 1995 mirrored the current groups. The rate of death was reduced by 7.2 deaths per 100,000 person-years in the screening group as compared with the historical screening group (rate ratio, 0.72; 95% confidence interval [CI], 0.63 to 0.81) and by 4.8 deaths per 100,000 person-years in the non-screening group as compared with the historical non-screening group (rate ratio, 0.82; 95% CI, 0.71 to 0.93; \( P<0.001 \) for both comparisons), for a relative reduction in mortality of 10% in the screening group (\( P = 0.13 \)). Thus, the difference in the reduction in mortality between the current and historical groups that could be attributed to screening alone was 2.4 deaths per 100,000 person-years, or a third of the total reduction of 7.2 deaths. The availability of screening mammography was associated with a reduction in the rate of death from breast cancer, but the screening itself accounted for only about a third of the total reduction.

A recently published paper studied changes in mortality after the introduction of screening guidelines for breast and prostate cancers in the US and UK (67). They used differences in the timing of guideline adoption, which ages are recommended for screening, and which cancers are detectable by screening to identify the effect of guidelines. Their quadruple-differencing strategy finds a moderately sized mortality benefit from mammography and PSA screening guidelines among recommended age groups and little change in mortality rates among age groups not recommended to receive screening. The result can be compared with an earlier US study, which compared screening and adjuvant therapy. The proportion of the total reduction in the rate of death from breast cancer attributed to screening varied in the seven models from 28 to 65 percent (median, 46 percent), with adjuvant treatment contributing the rest (64).

In an attempt to work out the balance between benefits and harm, the EUROSCREEN working group (65) published a “balance sheet” for mammography screening. For every 1000 women screened biennially from age 50–51 until age 68–69 and followed up to age 79, an estimated seven to nine lives are saved, four cases are over-diagnosed, 170 women have at least one recall followed by non-invasive assessment with a negative result and 30 women have at least one recall followed by invasive procedures yielding a negative result. A similar review from the UK estimates that for 10,000 UK women invited to screening from age 50 for 20 years, about 681 cancers will be found of which 129 will represent over-diagnosis, and 43 deaths from breast cancer will be prevented. In round terms, therefore, for each breast cancer death prevented, about three over-diagnosed cases will be identified and treated. Of the 307,000 women aged 50–52 who are invited to screening each year, just 1% would have an over-diagnosed cancer during the next 20 years (66).

These studies conclude that screening for breast cancer has a positive effect on mortality, confirming the results from clinical trials, but that the effect is smaller than the effect from improvement of treatment and other factors. It will thus be even more important to optimize the screening programs. The development of cost-effective screening methods and strategies is particularly important for developing countries, where the potential health benefits are highest, but the available resources the lowest (63).

But also for countries with well-developed screening models, improvements in the technology may change the balance of benefits, harms and costs. A particularly important issue is the improvement in the diagnostic workup to reduce the number of benign biopsies. Early detection of tumors through regular screening mammography biennial as per the United States Preventative Services Task Force recommendations, (USPSTF), has been shown to reduce breast cancer but many women turn out to have false positive results. False positive mammograms have large economic consequences due to the cascade of tests that follow including diagnostic mammography, ultrasound, and biopsy. With an estimated 18 million screening mammograms conducted in the US annually, a false positive rate of 10% amounts to almost $1 billion in unnecessary spending (68). Although the number of diagnostic mammograms and ultrasounds prompted by false-positive screens each year contributes significantly to the economic burden of breast cancer, the most significant cost associated with false-positive mammography screening is the large number of breast biopsies performed, nearly 70% of which result in benign diagnoses (69).

Simulations performed by a research group at the Fred Hutchinson cancer centre in Washington (70), indicate that the consequences of introducing a new diagnostic in order to reduce the number of positive biopsies or as an alternative to diagnostic mammograms and/or ultrasound, are not as clear-cut as may be expected. It comes down to a valuation of the different consequences of a false positive and a false negative result. But it shows the importance of simulation models as a
tool to help to find cost-effective diagnostic and treatment pathways. Surgical biopsies are still performed at many institutions, but can in most instances be replaced by far less expensive percutaneous biopsies (71).

There may be significant opportunities to reduce costs and improve outcomes also with existing methods for breast cancer screening. A Nordic study revealed differences in cost per patient screened between countries; from 34 Euro in Sweden, to 127 in Finland, and with Norway and Denmark in between (15).

Breast MRI and other emerging technologies

Magnetic resonance imaging (MRI) has been shown to detect cancers not visible on mammograms. The chief strength of breast MRI is its very high negative predictive value. A negative MRI can rule out the presence of cancer to a high degree of certainty, making it an excellent tool for screening in patients at high genetic risk or radiographically dense breasts, and for pre-treatment staging where the extent of disease is difficult to determine on mammography and ultrasound. However, breast MRI has long been regarded to have disadvantages. For example, although it is 27–36% more sensitive, it has been claimed to be less specific than mammography (72). As a result, MRI studies may have more false positives (up to 30%), which may have undesirable financial and psychological costs. It is also a relatively expensive procedure, and one which requires the intravenous injection of gadolinium, which has been implicated in a rare reaction called nephrogenic system fibrosis. Another limitation is access to MRI scanners / available capacity for screening linked to the investment required (cost of the MRI equipment).

Proposed indications for using MRI for screening include:

- Strong family history of breast cancer
- Patients with BRCA-1 or BRCA-2 oncogene mutations
- Evaluation of women with breast implants
- History of previous lumpectomy or breast biopsy surgeries
- Axillary metastasis with an unknown primary tumor
- Very dense or scarred breast tissue

In addition, breast MRI may be helpful for screening in women who have had breast augmentation procedures involving intramammary injections of various foreign substances that may mask the appearances of breast cancer on mammography and/or ultrasound. These substances include silicone oil and polyacrylamide gel. German investigators reported at the 2013 Breast Cancer Symposium in San Francisco that an abridged magnetic resonance imaging (MRI) protocol can accurately detect cancers among women whose mammographic screenings were negative. MRI, therefore, may reveal the type of tumor that mammography typically misses, and can do so in a time-efficient fashion, thus making MRI feasible for breast cancer screening (73).

Digital breast tomosynthesis (DBT) (74) is a new breast imaging technology that uses tomography and 3-D reconstruction to improve lesion visibility. The U.S. Food and Drug Administration recently approved DBT equipment, and research on its effectiveness continues around the world. In 2012, the Automated Breast Ultrasound System (ABUS) was approved by the FDA as an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (BI-RADS Assessment Category 1 or 2), with dense breast parenchyma (BI-RADS Composition/Density 3 or 4), and have not had previous clinical breast intervention.

New technological options are welcome, but need to be carefully evaluated in clinical practice, including an assessment of cost-effectiveness in the screening situation. At present these new modalities seems to be very valuable tools in the work-up of women selected through mammographic screening in order to identify false positive cases, as well as mapping the extent of disease in true positive cases.

Cost-effectiveness of breast cancer screening

Cost-effectiveness analyses compare the costs and health effects (outcomes) of an intervention to determine the extent to which it can be regarded as providing value for money. This can be used to help inform decision makers who have to determine where and how to best allocate resources. The cost-effectiveness of breast cancer screening varies by country and depends on many factors e.g. disease epidemiology, health care system, costs and compliance rate. The majority of studies have been conducted in developed countries and cannot be directly translated to low-resource countries. Many of the cost-effectiveness analyses in breast cancer screening have focused on comparing different strategies for screening in high-income countries, e.g. age range, screening test, frequency of screening (75-83).
Assuming that mammography screening reduces mortality in breast cancer by 20%, 43 deaths are avoided per 10,000 screened using figures from the UK screening program (76). The same source gives the estimate of 17 years of life gained per death avoided, which gives 0.073 LYG per screened woman. The costs of screening programs vary between countries, and how the costs are calculated. Ideally, a cost-effectiveness calculation should include all costs for screening and diagnosis and treatment.

Using data from the Nordic study, costs vary from 34 Euro to 127 Euro per woman screened (15). We will use 100 Euro as the base case estimate (15). Let us further assume that over a 20-year period, there are seven screening occasions. This will give a cost per life year gained of 10,000 Euro. This estimate is consistent with, but in the lower range, of earlier studies of cost-effectiveness which have arrived at estimates between 1000 and 30,000 Euro per LYG (75-76). This indicates that screening is a cost-effective method for improving outcomes in breast cancer compared to no screening.

The variation in results between studies is not surprising, taking into account the uncertainties about the clinical outcome of screening. There is also limited data to adjust life years gained to quality adjusted life years gained, taking into account both the fact that all life years gained are not of full quality, and impact of diagnosis and treatment on quality of life. In addition, it is both conceptually and empirically difficult to estimate the incremental costs of screening. How much of treatment costs should be included in the cost of screening. Without a screening program, cancer may have been detected later, with a different stream of costs. Changes in survival also have an impact on costs for treatment of other diseases, and it is debated if changes in costs for treatment of other diseases should be included or not. The inclusion of changes in indirect costs due to reduced morbidity in women who are of working age, and the inclusion of costs in added years of life, will also affect the estimates of cost-effectiveness. Finally, cost-effectiveness is determined by the design of the screening program, and will differ between patient characteristics, such as age.

Performing cost-effectiveness studies of screening programs are thus a complicated task and the results will carry a great degree of uncertainty. However, decisions about the implementation and design of screening programs will be influenced by such estimates. It is therefore better that such studies are performed in a systematic way, with data limits recognized and uncertainties around estimates discussed, than left to speculation. One advantage of this is that systematic studies usually lead to improvements in the data and improved understanding of the drivers of cost-effectiveness, which can make better decisions and thus better outcomes. The increasing number of options for early detection of breast cancer makes it also necessary to use cost-effectiveness to define the detection programs that give most value for money.

Many cost-effectiveness studies of mammography have been performed, but since the determinates of both relative effectiveness and costs changes over time, new studies need to be performed. The development of cost-effective strategies for early detection for countries with low and medium income and health care spending levels should be a priority for reducing the burden of breast cancer globally.

Conclusions and policy implications

• **Accurate data on breast cancer incidence and mortality on the national level is lacking in several countries due to limited cancer registration.** Such data are important for documentation, assessment and communication of the burden of the disease. There is a need for an initiative for collection of such data in a way that makes international comparisons possible, as well as comparisons over time to assess progress and impact of policy development.

• **Available data show that breast cancer incidence rates have steadily increased in developed countries over the last 50 years.** In the last decades increased incidence rates are also being seen in many developing countries, in particular in parts of Asia. The increased incidence of breast cancer is mainly due to increased life expectancy but also relates to lifestyle changes, such as women having fewer children as well as hormonal interventions like post-menopausal hormonal therapy.

• **Data on the economic burden of breast cancer in terms of direct and indirect costs are sparse.** Such data are important as complements to data on health burden, and for decisions about resource allocation for prevention and treatment. They are also necessary for the performance of comparative studies between countries and between regions (populations) within countries. There is a need to learn from such comparisons for the development of best practices for prevention, early detection and treatment.
The economic burden of breast cancer is considerable in terms of both direct and indirect costs. The direct health care costs attributable to breast cancer vary greatly between study countries, reflecting differences in total health care spending. The indirect costs of breast cancer are larger than the direct treatment costs since many breast cancer cases occur in women below 65 years, specifically in new industrialized countries.

Improved outcome is related to earlier diagnosis, where there is a marked correlation between the stage at diagnosis in a country and overall survival rates in breast cancer. Methods for early detection incur costs and potential harms, as well as benefits, and must be designed according to evidence of the balance between costs and improved outcome.

The largest survival improvements over the last decades have been seen in patients diagnosed with stage II or III disease, which is mainly due to early detection and to the introduction of adjuvant treatment. Currently we see a rapid introduction of new effective drugs for treatment of breast cancer that improve survival but also increase the costs of treatment; particularly at the late stages of the disease.

There are significant variations in breast cancer outcomes in countries with comparable levels of resources dedicated to healthcare. This indicates an opportunity to improve outcome through the identification and implementation of best practices in diagnosis and treatment.

The lack of detailed, patient linked, data on outcome in relation to treatment patterns and stage of diagnosis in many countries impedes and limits analyses of how changes in clinical practice affect outcome.

Survival is the main focus in the treatment of breast cancer, but with increasing survival rates more women are living with the disease, making quality of life during and after treatment increasingly important. Data on quality of life at different stages of the disease, and related to different treatment options are still scarce. There is a need for collecting data on quality of life and quality of care routinely in clinical practice, for both monitoring and assessment of outcome.

New data indicate that options for primary prevention with chemotherapy should be considered in all health care systems. Programs for this should be developed, and combined with evaluation to find out optimal strategies for different risk groups.

Screening for early detection of breast cancer with the aim of improving survival is a key component of a strategy for prevention. Such programs must be designed to meet the specific situation in different health care systems, taking into account the need to balance potential benefits and harms, as well as cost-effectiveness and affordability.

There is great uncertainty around estimates of reductions in mortality and the magnitude of over-diagnosis from screening, but it is possible to conclude that breast cancer screening provides important benefits and should be continued. Data on cost-effectiveness of alternative screening strategies are still limited, and both data and methods for evaluation must be improved to provide the basis for evidence-based practices.
References


27. From (2), based on WHO Statistical Information information systems (WHOSIS), 2009.


32. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) (DS253) NICE Guidance (in development, Sept. 2013) http://guidance.nice.org.uk/?action=byID&o=13815


34. See (2) for references


Prevention and the economic burden of breast cancer
systems of Oncological Service. Published in St Petersburg, personal
53. Merabishvili, V.M. and S. Y A, Current development of information
Chinese women on screening mammography and early breast cancer
52. Chua, M.S., et al., Knowledge, perceptions, and attitudes of Hong Kong
health, Cuernavaca, 2008.
51. Nigenda, G., M. Caballero, and L. González, Social process of breast
49. Perry et al European guidelines for quality assurance in breast cancer
Prevention and the economic burden of breast cancer
43. Union, C.o.t.E., Council recommendation of 2 December 2003 on cancer screening
38. Report Ministry of Health of Moscow region 2008. Personal communication: Prof. MariaMikhailova Konstantinova, Deputy Head of Moscow Region Oncology Hospital, Moscow, Russia.
Contact details

For further information visit: newsroom.gehealthcare.com

80. Socialstyrelsen (The National Board of Health and Welfare), Sweden, Cancer statistics
82 Okonkwo et al Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. JNCI 2008; 100:1290