A review of breast cancer care and outcomes in 18 countries in Europe, Asia, and Latin America

Associate Prof. Nils Wilking, Karolinska Institutet, Stockholm, Sweden and

Frida Kasteng, i3 Innovus, Stockholm, Sweden

Expert advisors and co-authors:

Prof. Jonas Bergh, Karolinska Institutet and University Hospital, Stockholm, Sweden

Prof. Bengt Jönsson, Stockholm School of Economics, Sweden

Ingrid Kössler, President, Swedish Breast Cancer Organisation BRO, Sweden

Prof. Miguel Martin, Gregorio Marañón University Hospital, Madrid, Spain

Prof. Charles Normand, Trinity College Dublin, Ireland

Liz Reed, Breast Cancer Care, UK

Prof. Guy Widdershoven, VU University Medical Center Amsterdam, The Netherlands

The report is available at: www.comparatorreports.se

Executive Summary

This report aims to give an overview of the burden and cost of breast cancer and of breast cancer care and outcomes in 18 countries in Europe, Asia and Latin America. The primary objective is to present and discuss current evidence-based best practices in breast cancer management and what is necessary for the evaluation of treatment practices and development of optimal breast cancer care in relation to available resources in different settings. The study is based on a review of literature and databases, consultation with clinical experts and a survey administered to previous and current breast cancer patients.

The health and economic burden of breast cancer: The disease burden of breast cancer is high with over 1.2 million women worldwide developing breast cancer every year and with breast cancer being the second most common cancer form; constituting around 25% of all female cancers. Incidence rates are increasing in both developed and developing countries mainly due to lifestyle changes, such as women having fewer children, and ageing populations. The direct costs attributable to breast cancer are considerable, yet vary considerably between study countries in line with inter-country disparities in total healthcare spending. The indirect costs of breast cancer are larger than the direct treatment costs; 55–70% of total costs based on recent assessments in some European countries. One contributing factor to high indirect costs is that most breast cancer cases occur in women under 65 years.

Outcome of breast cancer care: The long-term prognosis for breast cancer patients has improved significantly over the last 50 years. In those countries with the best outcome, 10-year survival rates are now 80% compared to survival rates of just over 50% some 50 years ago. The improvement in survival rates is due to the combination of earlier diagnosis and enhanced treatment. However outcomes differ significantly, also between countries with comparable levels of resources dedicated to healthcare. The quality of life of patients during and after disease and treatment is an important outcome of breast cancer care and is increasingly included as an outcome measure in cancer clinical trials. It is important to evaluate the quality of life in women in all stages of breast cancer as well as in those who are cured, where for some women the cost of cure, i.e. long-term side effects of treatment, can be significant.

Breast cancer treatment patterns: Breast cancer care is complex and a multidisciplinary team approach to diagnosis and treatment is necessary for ensuring best practice outcomes. The use of evidence-based treatment guidelines regularly updated in line with internationally accepted standards is key to promoting the best use of existing services and ensuring equity in access to treatments within a country and/or region. Most of the study countries have published treatment guidelines on the national or regional level that are regularly updated in line with evidence-based international guidelines. Several of the guidelines cover the entire spectrum of breast cancer care from primary and secondary prevention to recovery or palliative care, while other guidelines focus on specific areas, e.g. medical treatment. However, adherence to guidelines is not commonly monitored and many countries do not have an overall process for monitoring compliance and measuring outcome.

The patient perspective: Evidence-based best practices for the design and implementation of patient-focused cancer care are limited. Recommendations for patient involvement include offering patient-centred care with a choice of treatment and care packages, getting systematic feedback from patients through surveys and engaging patients in decision-making regarding the design and development of

cancer care. Well-informed patients are essential for increasing patient involvement in treatment decisions. The patient-physician communication is a very important channel of information for patients and it is also important that health care systems provide relevant information on up-to-date practice outcomes for patients. Patients should be able to compare the outcome, examination, treatment, and standard times for access at their treatment centre with that of other centres so that they know what they can expect in terms of care, and can recognise when a situation may not adhere to standard practices.

Introduction and diffusion of new medical interventions: The introduction of new technology across diagnostics, surgery, radiotherapy and medical treatment is usually slow in relation to the available clinical evidence of their effectiveness. In the countries studied, there are no formal processes for evaluating new technologies except for drugs. New technology should be introduced from the perspective of the total care of the patient, from prevention to palliation, taking into account the cost-effectiveness of alternative options.

Conclusions: It is very important to ensure that regulations, priorities, funding, and the organisation of breast cancer care are coordinated across multidisciplinary teams. In addition, it is essential for quality assessment of breast cancer care to better capture the relationship between treatment patterns and outcomes by means of more detailed registries than what is available today, incorporating also the patient perspective on the care provided by assessing patient satisfaction regarding aspects such as communication, accessibility and continuity. Considering all of these perspectives will help ensure all patients receive the most appropriate cost-effective and evidence-based treatment options with minimal delays. The introduction of new technologies will put pressure on the healthcare system, in all countries, but more so for countries with limited resources. However, with the increasing disease burden and the rapid changes taking place in cancer care today, a broad approach to research is needed in order to make registration more encompassing and relevant across countries with well defined and more patient-focused criteria for outcome assessments.

Acknowledgements

We are greatly thankful to the clinical experts that provided us with valuable input on breast cancer treatment, service configuration and outcomes in their countries: Dr. Simona Borštnar, Medical Oncologist, Department of Medical Oncology, Institute of Oncology, Ljubljana, Slovenia; Prof. Maria M. Konstantinova, Chief Scientist, Deputy Head of Medical Issues and Drug Therapy, Moscow Regional Oncology Dispensary, Moscow, Russia; Prof. Tongyu Lin, Chemotherapy Department, Sun Yat-Sen University Cancer Center, Guangzhou, China; Dr. Flavia Morales-Vásquez, Medical Oncologist, Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico; Associate Prof. Tadeusz Pieńkowski, Medical Oncologist, Head of the Breast Cancer Clinic, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; Dr. Benito Sánchez, Medical Oncologist, Hospital of Obstetrics and Gynaecology, Centro Médico Nacional de Occidente, Guadalajara, Mexico; Prof. Vladimir F. Semiglazov, Head of Surgical Department and Breast Cancer Department, Cancer Research Institute n. a. Prof. N. N. Petrov, St. Petersburg, Russia; and Prof. Elena M. Slonimskaya, Head of the General Oncology Department, Tomsk Cancer Research Institute, Tomsk, Russia.

We would like to thank the following breast cancer patient organisations for their help in collecting input from breast cancer patients: Breast Cancer Care, UK; BRO (Bröstcancerföreningarnas riksorganisation), Sweden; Patientforeningen DBO (Dansk Brystkræft Organisation), Denmark; EUROPA DONNA, Slovenia; FECMA (Federación Española de Cáncer de Mama), Spain; FEMAMA (Federação Brasileira de Instituições Filantrópicas de Apoio à Saúde da Mama), Brazil; FFB (Føreningen for brystkreftopererte), Norway; Fundación Cim*ab, Mexico; Mamazone, Germany; MEMEDER (Meme Sağlığı Derneği), Turkey; and Movement Against Cancer, Russia.

Thanks also to Xuan Wang and Amirbek Musayev, i3 Innovus, Stockholm, Sweden, for help with research and translation of Chinese, Russian and Turkish material, and to Dr. Fernanda Costa-Svedman for preparing the case study on Brazil.

The study was financed by unrestricted grants from Roche and Pierre Fabre.

Table of Contents

1 Introduction

Breast cancer is the most common cancer form in women; in the countries with highest incidence rates, the lifetime risk of developing breast cancer is over 10%. Although breast cancer has a better prognosis than many other cancer forms, with 10-year relative survival rates of up to 80% in some countries, the burden of breast cancer remains considerable. As a result of improved treatments, more and more patients are cured, while others will live on with stable disease for a long time. However, much remains to be done and can be done in a combined approach to increase the early detection and treatment of breast cancer and optimise care organisations to further improve outcomes. For example, survival still differs considerably between countries that appear to have comparable economic and human resources dedicated to healthcare. This highlights a key discrepancy in cancer care and calls for the further assessment of best practices in prevention and treatment and the adaption of such across countries.

Although survival is the most important measure of outcomes in breast cancer, quality of life should also be included as an important marker, as the care the patient experiences impacts greatly on their psychological and physical well being as well as on their socio-economic situation.

Over the last 30 years, major paradigm shifts in the treatment and organisation of breast cancer care include: the implementation of programmes for early detection using mammography; the introduction of adjuvant treatment such as endocrine therapy, chemotherapy and adjuvant radiotherapy following surgical treatment in breast cancer; and the implementation of multidisciplinary care. The change in surgical procedures from mastectomy (total removal of the breast) to more localised excision of tumours complemented by sentenial node biopsy, which makes it possible to fine-tune further treatment, is an important example of how quality of life has been improved without compromising survival. In recent years, targeted biological therapies such as trastuzumab, for the treatment of early as well as metastatic breast cancer, have resulted in further improvement of outcomes.

1.1 Study objective

This report aims to give an overview of the burden and cost of breast cancer and of breast cancer care and outcomes in 18 countries in Europe, Asia and Latin America. The primary objective is to present and discuss current evidence-based best practices in breast cancer management and understand the elements of care that are driving the improvement in outcomes to identify which areas need further enhancement. Using the data available, relationships between care elements such as treatment patterns, care organisation and patient experiences are examined.

The countries covered in the study are: in Asia: China; in Asia/Europe: Russia and Turkey; in Latin America: Brazil and Mexico; in Central/Eastern Europe: Hungary, Poland, Slovenia; and in Western Europe: Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden and the UK (United Kingdom). Countries selected for inclusion in the study were the major countries in respective regions, countries with an availability of good-quality long-term epidemiological data and/or countries that were relevant to include in the analysis for the purpose of illustrating best practices in breast cancer care.

1.2 Materials and methods

The study is based on a review of literature and public databases, consultation with clinical experts and a survey administered to previous and current breast cancer patients. The literature review, focusing specifically on treatment patterns and costs of breast cancer in each study country, was conducted in MEDLINE but included also grey literature, specifically documents from the national (and regional) healthcare organisations in each country, including treatment guidelines, cancer control plans, and documentation on the cost of breast cancer.

Clinical experts in each study country were contacted and asked to participate in the study by providing data on breast cancer care and outcomes in their country. A questionnaire was developed for this purpose. Input from the national clinical experts is presented in different parts of the report, and referenced as such. In many countries statistical estimates on breast cancer treatment patterns and outcomes are not available on a national basis; in cases where estimates provided are based on data available from just one hospital or region, it is clearly stated that the given estimates do not represent the entire country.

In order to capture the patients' perspective on breast cancer care in the study countries, a questionnaire directed to patients was developed. The questionnaire was translated into the national language for each country and a local patient organisation was contacted and asked to participate in the study by distributing the questionnaire to breast cancer patients in different stages of the disease in their network. Due to the limited timeframe of the study, the patient organisations were requested only to include a minimum of 25 survey participants. Two thirds of the patient organisations contacted agreed to participate. Patient responses were received from Brazil, Denmark, Germany, Mexico, Norway, Poland, Russia, Turkey, Slovenia, Spain, Sweden, and the UK. A total of 483 completed patient surveys were included in the analysis; the number of responses per country varied between 9 and 66. Given this limited sample size per country, the patient survey should be considered as explorative; a larger and geographically randomised patient sample would be necessary to draw statistically valid conclusions about the situations in each country, and the results from the patient survey are therefore only presented in aggregated form for all countries together in this report. The results of the patient survey are presented in chapter 5.

A limitation of this study, in relation to the understanding of current treatment patterns, is that treatment patterns in the study countries were not assessed based on patient-level data, such as the review of patient charts, which would allow a more thorough appreciation of treatment patterns in each country. Such observational studies are time consuming and costly and would not likely have been possible for all the study countries. As previously mentioned one of the purposes of this study was to review and discuss what data needs to be systematically collected and made readily available to healthcare professionals and patients in order to better understand the relationship between breast cancer management and outcomes.

2 The health and economic burden of breast cancer

SUMMARY

- ***The disease burden of breast cancer is high; every year over 1.2 million women worldwide get breast cancer. Breast cancer is the second most common cancer form overall and constitutes 25% of all female cancer cases.***
- ***Breast cancer incidence rates have steadily increased in developed countries over the last 50 years and in the last decades increased incidence rates are also being seen in many developing countries. The increased incidence of breast cancer is due to lifestyle changes, such as women having fewer children, and ageing populations.***
- ***Accurate data on breast cancer incidence on the national level is lacking in several of the study countries due to limited cancer registration.***
- ***The economic burden of breast cancer is considerable. The direct costs attributable to breast cancer vary greatly between study countries, in line with the inter-country disparities in total health care spending. The indirect costs of breast cancer are larger than the direct treatment costs; one contributing factor to high indirect costs is that most breast cancer cases occur in women under 65 years.***

2.1 Epidemiology

Breast cancer is the most common cancer form in women; with an estimated 1.2 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. 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; the difference in incidence rates between developed and developing countries is due a combination of demographic, hereditary, environmental and lifestyle risk factors. Incidence rates are rapidly increasing in many newly industrialised countries due to rapidly 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, late menopause, some types of oral contraceptives, post-menopausal hormone-replacement therapy (all of which contribute to higher lifetime exposure to the hormones oestrogen and more critically, progesterone), hereditary genetic mutations, ionizing radiation to the breast region in younger individuals, low physical activity, obesity after menopause and alcohol consumption.

Figures 1 and 2 show the estimated crude and age-adjusted incidence and mortality rates of breast cancer in the study countries for 2002 [1]. The crude incidence is the best measure for assessing the actual health and economic burden of breast cancer in a country. The age-adjusted incidence is of interest as it shows the influence of risk factors other than age in the development of breast cancer country-by-country. The age span of women affected by breast cancer is broad. Although uncommon, breast cancer may affect

women already in their 20s and 30s. The incidence rate increases in conjunction with menopause and remains on this level in later decades of life.

Figure 1 Estimated crude incidence and mortality rates breast cancer, cases per 100,000 women [1]

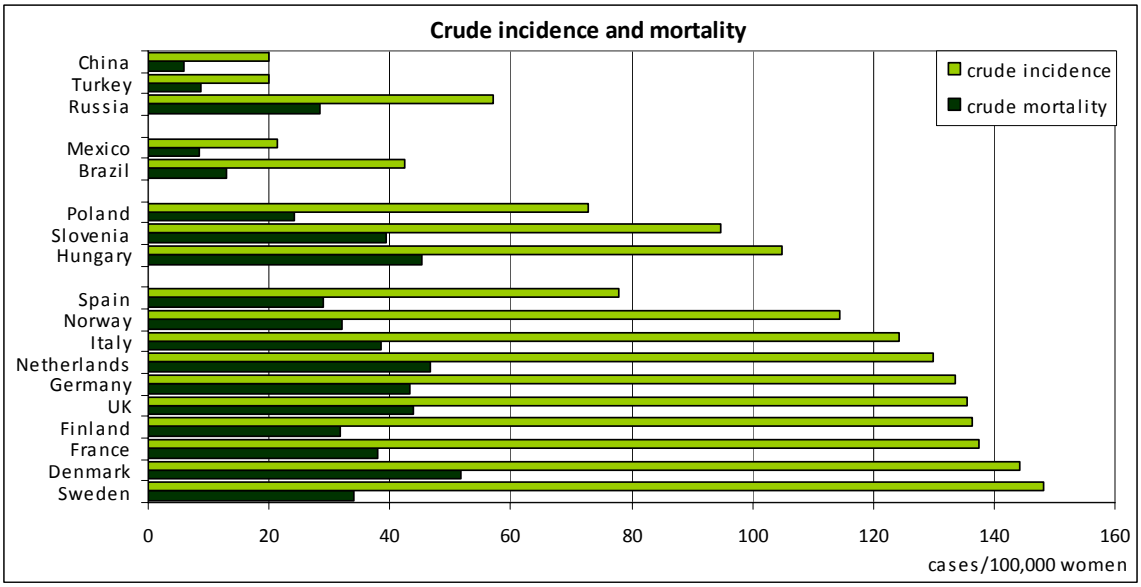
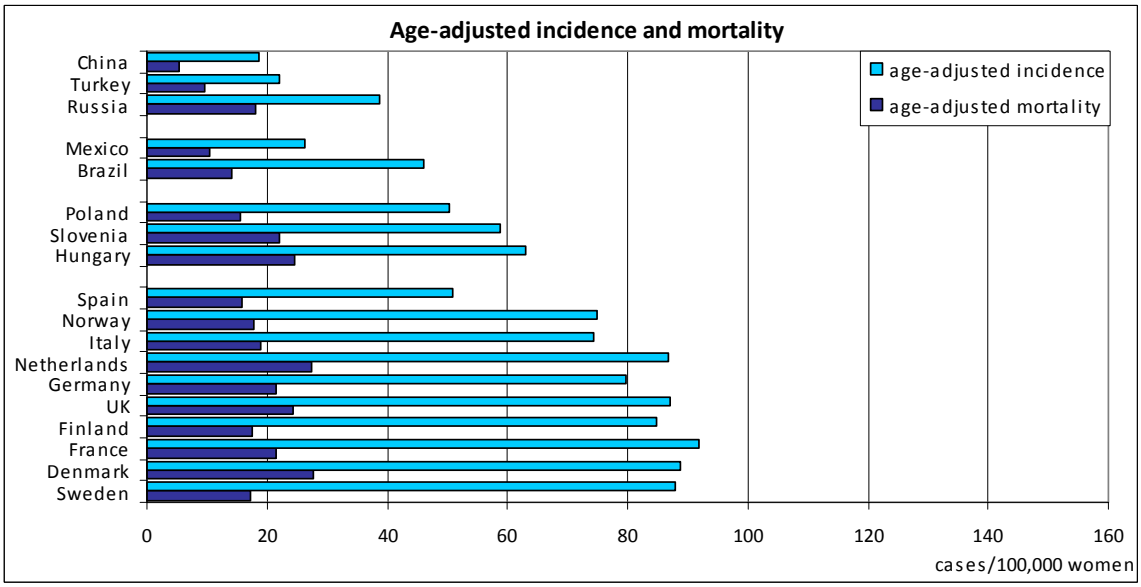


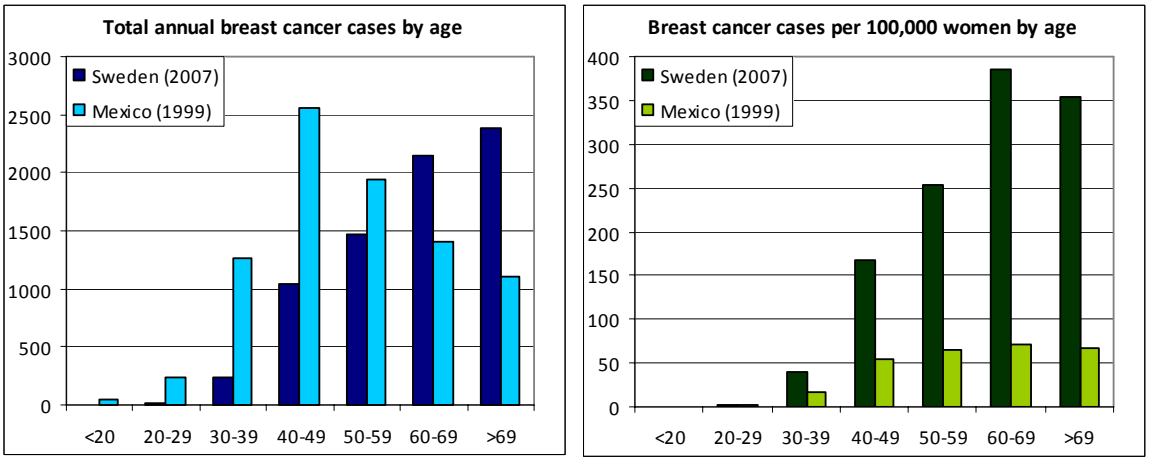
Figure 2 Estimated age-adjusted incidence and mortality rates breast cancer, cases per 100,000 women [1]



As can be seen when comparing the two figures above, 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 3 illustrates the age distribution across the total number of breast cancer cases in

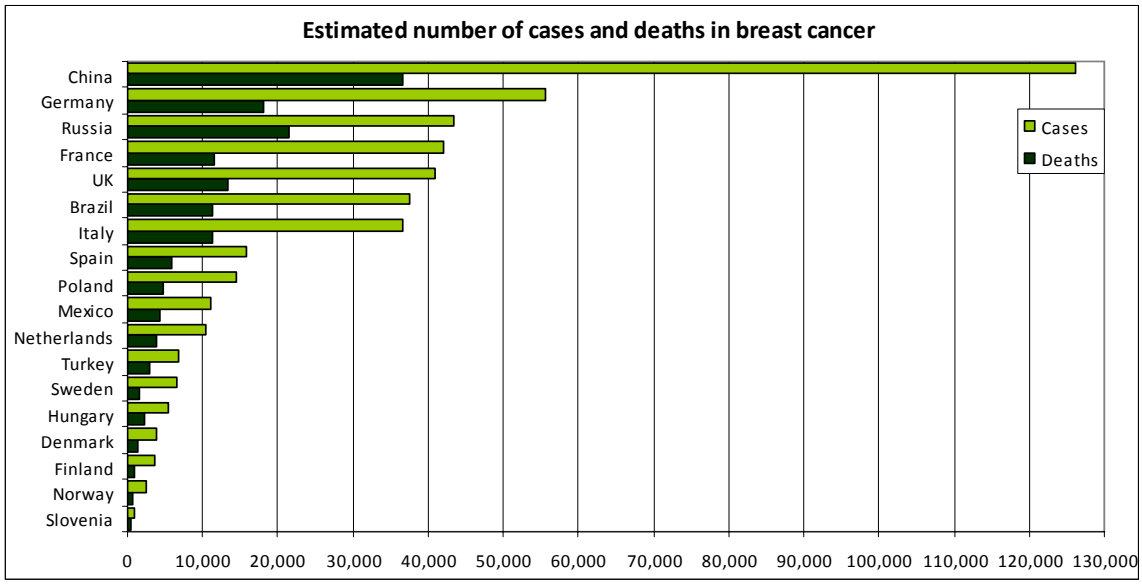
Mexico and Sweden respectively. In Mexico, the average age at diagnosis of breast cancer is approximately 50 years while the average age at diagnosis in Sweden is 60 years due to the younger population on average in Mexico compared to Sweden [2, 3]. In both countries, the large majority of women are under 65 years when they are first affected by breast cancer, which contributes to the large health and economic burden of the disease, as further discussed below.

Figure 3 Breast cancer cases per age group in Mexico and Sweden [3, 4]



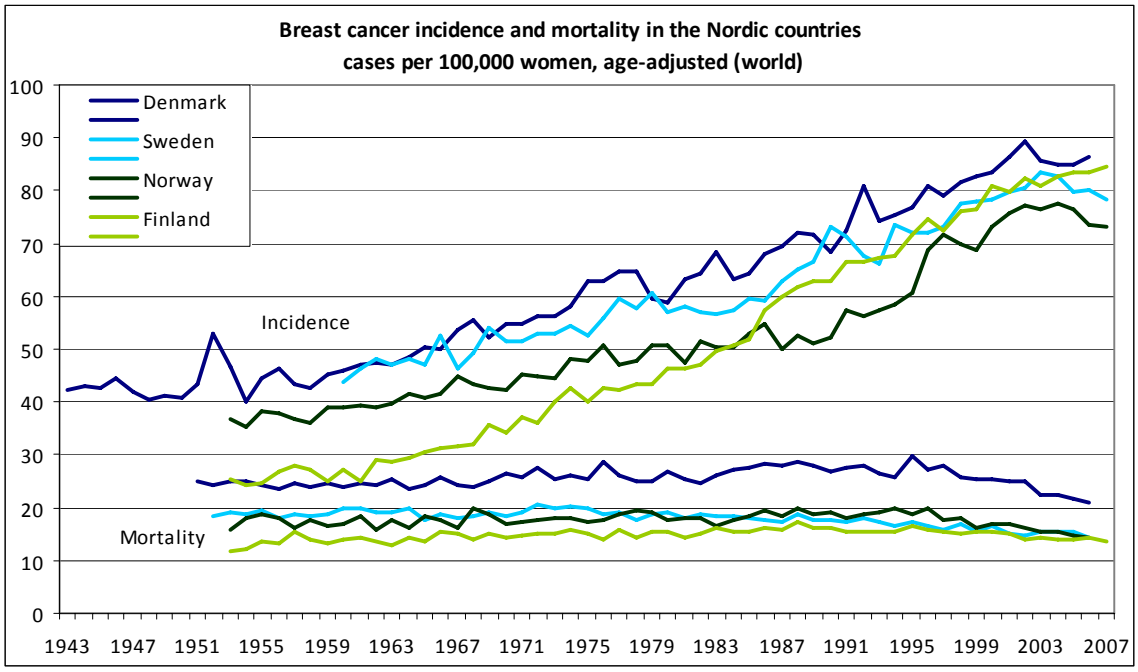
China currently has the lowest age-adjusted incidence of the study countries, but one may expect that the fundamental changes in reproductive patterns in China brought about by the implementation in the 1970s of the one-child policy, as well as current lifestyle changes in China caused by rapid economic 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 [5]. Figure 4 shows the total estimated number of cases and deaths in the study countries.

Figure 4 Estimated number of cases and deaths in breast cancer in 2002 [1]



A barrier to the estimation of global breast-cancer incidence is the limited data availability in many countries. Incidence figures are in many countries 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 in this study do not have a 100% national coverage of cancer registration. However, some of the countries covered in this report introduced national cancer registries some 60 years ago; Denmark being the first of the countries to establish a national cancer registry in 1942. Other Nordic countries and Slovenia initiated cancer registration on a national level in the 1950s and in the UK, cancer registration was coordinated on a national level in the 1960s [6, 7]. Data from such registries can give a comprehensive picture of how breast cancer incidence has developed over time. Figure 5 presents the breast cancer incidence and mortality trends over the last 60 years from the Nordic registries.

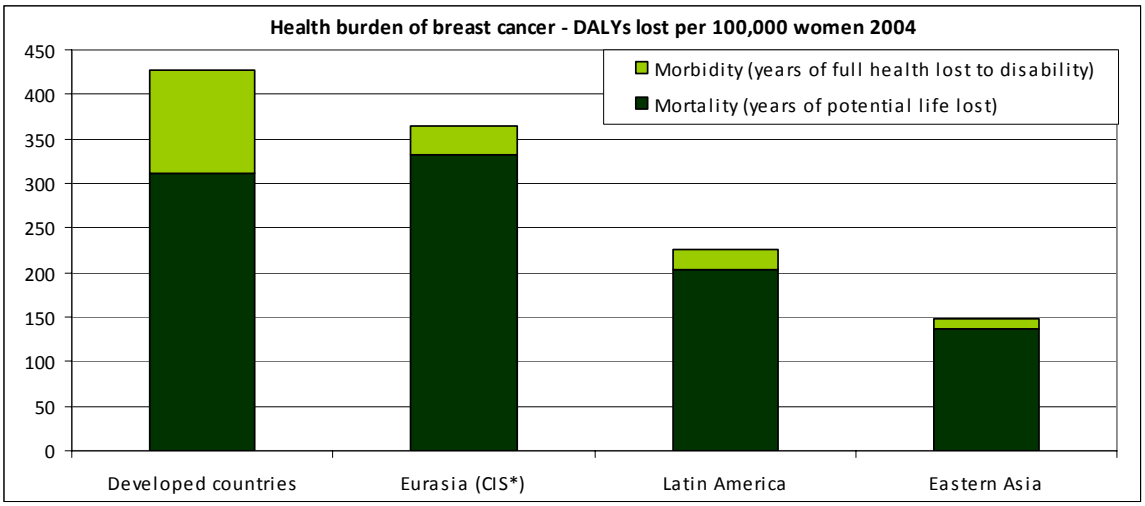
Figure 5 Breast cancer incidence and mortality rates since the 1950s [8]



2.2 Health burden

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 [9]. Figure 6 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 (World Health Organisation Millennium Development Goals) regions as per the study countries. Although the burden per 100,000 women, as presented in figure 6, is highest in developed countries, where incidence rates are largest, it is important to recognise 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.

Figure 6 Disease burden of breast cancer (DALYs lost) [9]



** Commonwealth of Independent States*

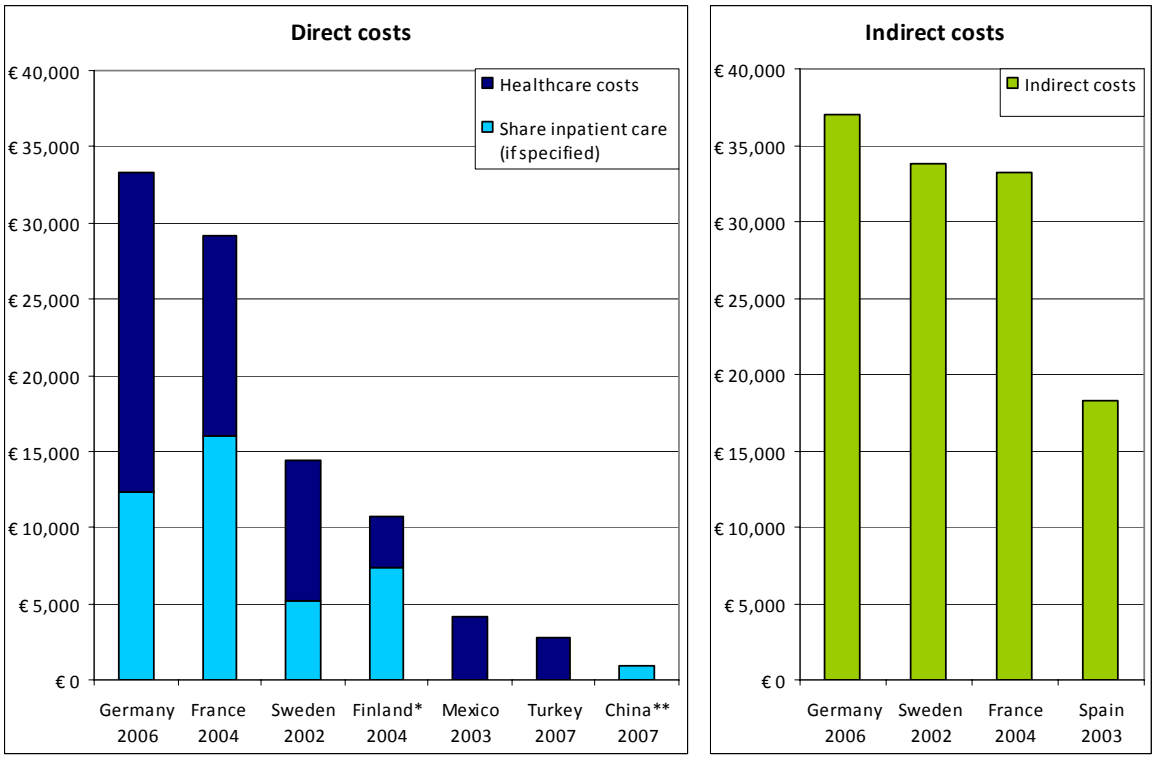
DALYs estimates must be interpreted with some caution, firstly since the incidence and mortality data that serve as input to the DALYs estimates are often based on estimates and extrapolation and secondly because the calculation method in itself is based on a range of assumptions in order to make this kind of assessment possible.

2.3 Economic burden

Breast cancer results in not only a large health burden but also a significant economic burden to society. The economic burden of breast cancer in the study countries 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 (predominantly the cost of lost productivity due to the patients' disability and illness, sometimes also including premature mortality) are more than twice as large as the direct costs. The study estimated the total cost of breast cancer in Sweden in 2002 to be €320 million [10]. This Swedish study was the only burden of illness study, taking into account both direct and indirect costs of breast cancer that was identified in a search of the published literature in major medical databases. The ministries of health in some of the other study countries have estimated the total cost of breast cancer; such estimates were identified for Finland, France and Germany [11, 12]. 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 [13]. In France the total healthcare cost for breast cancer was calculated to be €1,456 million in 2004, of which 55% was 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 [11]. In Germany the total cost of breast cancer in 2006 was estimated to be €1,906 million; indirect costs were estimated to be 52,000 years of lost production annually [12].

In some of the other study countries, cost analyses were identified that estimated either direct costs, hospitalisation costs and/or indirect costs of breast cancer. Figure 7 gives an overview of the cost estimated from identified 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 some caution since the studies have used different methods. The indirect cost per breast cancer case in Germany presented in figure 7 was calculated by multiplying the years of lost productivity due to breast cancer in Germany with the average gross salary in Germany.

Figure 7 Average cost per breast cancer case [10-17]

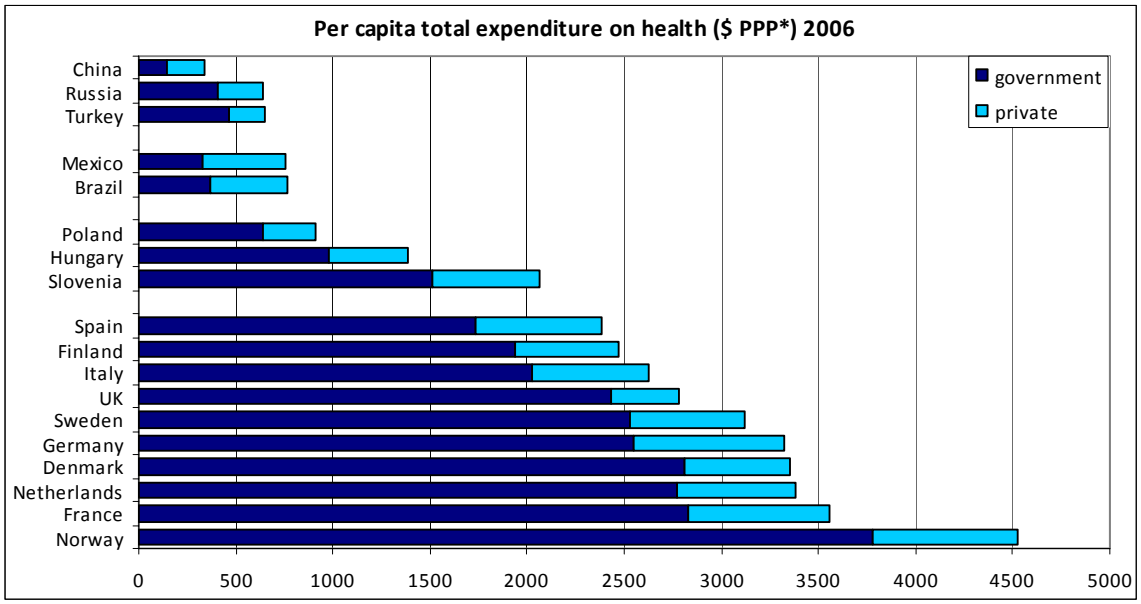


**Not including outpatient specialist care **Not total indirect costs - only inpatient care costs were identified for China*

Most of the 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 total healthcare costs in breast cancer care in the Swedish study based on data from 2002 [10]. 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 [18]. 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 [19, 20] and 25% of total costs in the UK [21]. The treatment of advanced stages of breast cancer is generally more expensive than treatment in earlier stages [19-22].

Even though data on the economic burden of breast cancer is not available from all the study countries, the available cost analyses presented above illustrate 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. Figure 8 below gives an overview of health expenditure per capita in the study countries.

Figure 8 Per capita expenditure on health [23]



**Purchasing Power Parity*

There is no direct link between per capita investments in healthcare and the resources available to the individual patient; one must also take into account how efficiently available resources are utilised in the healthcare system and the different relative costs of, for example, healthcare personnel in different countries.

One critical issue in breast cancer care, where resources are limited, is that 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. Although the WHO recommends that in limited-resource countries medical facilities should initially be concentrated in relatively few places to optimise the use of resources, 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 [24].

3 Outcome of breast cancer care

SUMMARY

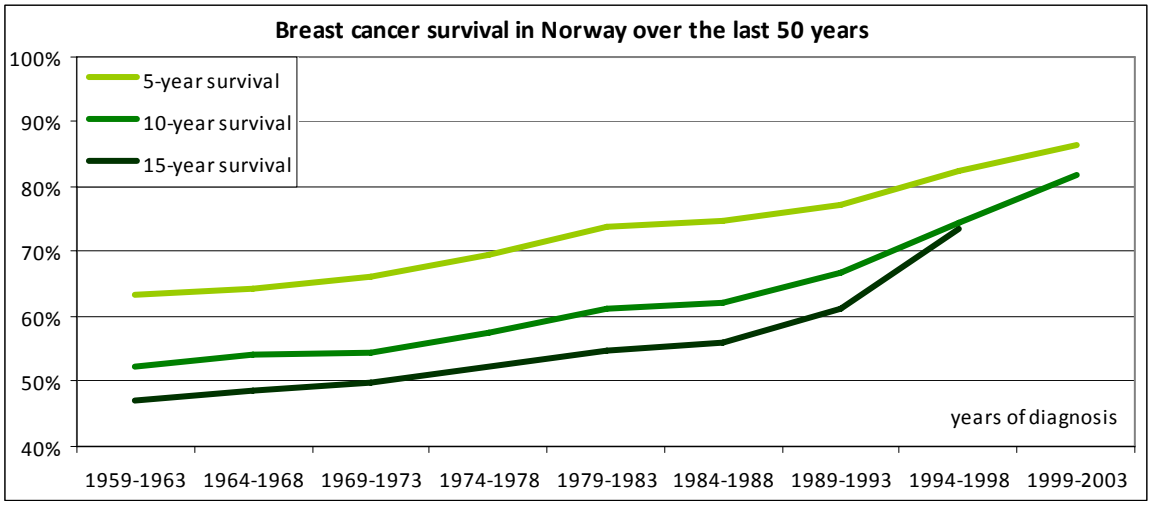
- ***The long-term prognosis for breast cancer patients has improved significantly over the last 50 years, 10-year survival rates are now 80% in those countries with best outcome compared to just over 50% 50 years ago.***
- ***Improved outcome is related to earlier diagnosis, where there is a marked correlation between the stage at diagnosis in a country and overall survival rates in breast cancer.***
- ***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 the introduction of adjuvant treatment.***
- ***An issue that calls for further research on the relationship between treatment patterns and outcome is the fact that in Europe there are significant variations in breast cancer outcomes between countries with comparable levels of resources dedicated to healthcare.***
- ***The lack of detailed 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.***
- ***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.***
- ***Quality of life is more affected in younger women with breast cancer and in women with recurrent and metastatic disease.***

3.1 Survival

The most general health outcome measurement used is survival. For breast cancer as well as other cancers, 5-year survival is often used to evaluate the success of treatment as a surrogate parameter for overall survival. However, a 5-year perspective is not sufficient to estimate the rate of breast cancer patients that are actually cured since some patients may experience relapses after having been disease-free for many years. It is therefore also relevant to look at 10-year or even 15-year survival rates in order to determine the actual outcomes in breast cancer.

Survival trends in breast cancer can be best followed for the last 40 years in those countries that have a long tradition of cancer registration. In Norway and Sweden, 10-year survival has increased from just over 50% at the beginning of the 1960s to up to 80% today [25, 26] and in England the increase has been from 40% at the beginning of the 1970s to slightly more than 70% today [27, 28]. Figure 9 shows the 5-year, 10-year and 15-year survival trends over the last 50 years in Norway.

Figure 9 Breast cancer survival trends Norway [26]

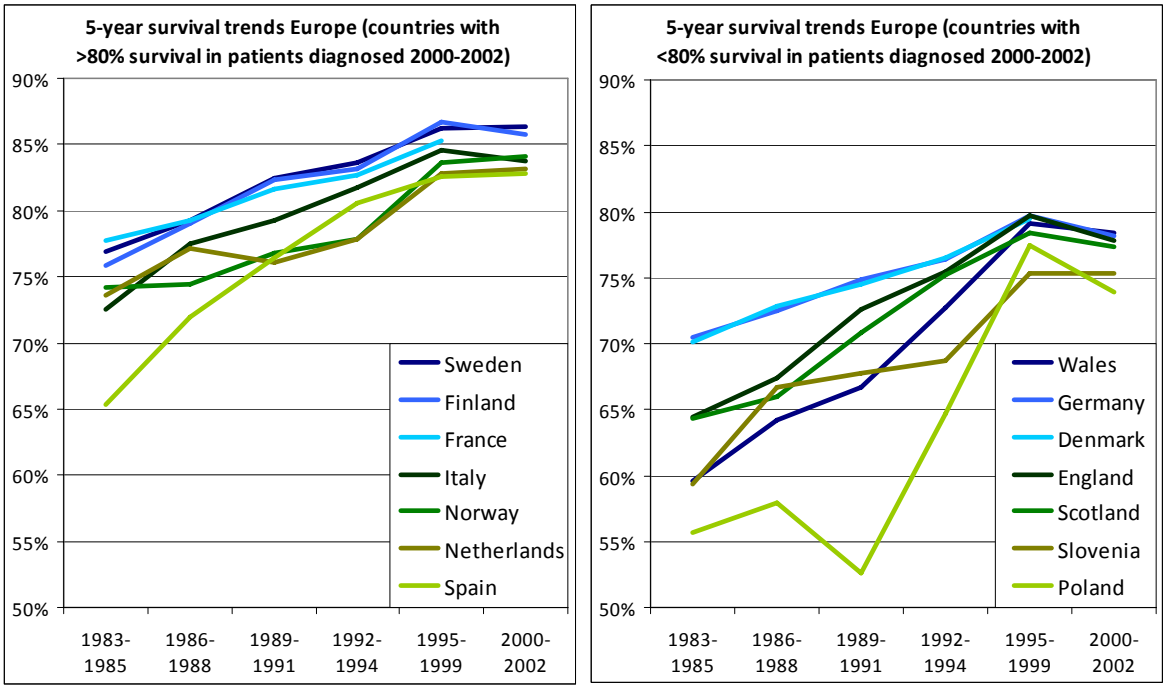


The largest improvements in outcome have been seen during the last 20-30 years and this is mainly due to the introduction of population-based mammography screening leading to earlier diagnosis as well as the introduction of adjuvant systemic chemo- and endocrine therapy. A 25% increase in overall survival and an almost 50% increased survival in women younger than 70 years of age have been reported to be attributable to adjuvant treatment [29]. A number of randomised studies have demonstrated increased breast cancer survival due to earlier diagnosis with screening [30-34]. However, it has also been shown that screening leads to a certain over-diagnosis, e.g. detection of breast cancer that would have remained asymptomatic (cancers in situ), and therefore survival rates are not completely comparable between countries with population-based screening programmes in place and those countries without screening programmes in place [35, 36]. Within countries, there may be a difference in survival rates between different regions, depending on care organisation and access to early diagnosis and treatment. For example in the UK, wide variations in the management of breast cancer patients were reported in the 1990s and efforts have since been put in place to reduce such variations [37, 38]. It has also been demonstrated in several countries, including those that have universal access to healthcare, that survival rates depend on the socio-economic conditions of the patient [39-42].

Europe-wide analyses of cancer survival over the last two decades show a steady improvement of the relative survival from breast cancer in all European countries, but at different rates (figure 10) [7, 43-45]. Finland, France, Sweden, Italy, The Netherlands and Norway have reported the highest survival rates since the 1980s and to the current time. Spain reports a great improvement in breast cancer outcomes in the last two decades, from 65% to over 80% and presents today survival data in line with the countries with best outcomes in Europe (left graph). Germany and Denmark have, despite relatively high survival rates already in the mid-1980s, according to available data not reached survival rates above 80% in the latest assessment available (outcomes for Danish patients diagnosed in 2000-2002 were not available). The UK and Slovenia reported survival trends that have increased from 60-65% in the mid 1980s to 75-80% according to the latest assessment and Poland reports an even higher improvement in survival in the last 10 years (right graph).

However, survival trends over time in Poland are unstable and likely due to the fact the Polish estimates are based on a few registries covering less than 10% of the population in total. It should be noted that the survival data for France, Germany, Italy, The Netherlands and Spain are also based on available regional registries and are thus not a representation of the total population in the countries [45].

Figure 10 Five-year survival rates in the European study countries [43, 44]



Hungary was not included in the European-wide analysis presented above. A study based on data from the national cancer registry in Hungary reported a 5-year breast cancer survival rate of 73% for patients diagnosed between 2001-2005 [46]. This is similar to the survival rates reported in Poland and Slovenia.

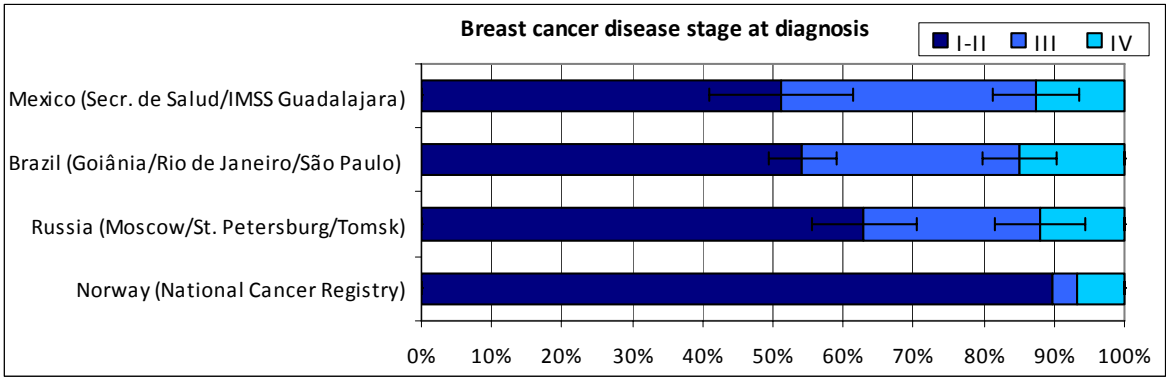
An analysis of breast cancer survival rates in different countries around the world estimated the 5-year survival rate of breast cancer in Brazil to be 58% for patients diagnosed between 1990-94 [47]. Breast cancer survival rates from the other non-European study countries are not available from population-based registries, only from hospital records. A Mexican study calculated a 59% 5-year survival in women admitted between 1990-1999 to a hospital in Mexico City [48]. Statistics from a hospital in Guadalajara, the second biggest city in Mexico, presents a 5-year survival rate of 72% with follow-up until 2009 [49]. In Russia, the cancer centres in Moscow, Tomsk and St Petersburg report 5-year breast cancer survival rates of 58%, 56% and 71% respectively [50-52]. The variation in the estimates from different cities in Mexico and Russia indicate that survival rates based on analyses from just one hospital must be interpreted with caution since they are not based on a representative sample of the population. A Chinese study, also based on data from one hospital and a small sample of patients (<200), presented a 5-year survival rate of 53% [53]. No breast cancer survival rates were identified for Turkey.

The stage at diagnosis of breast cancer is an important predictor for overall survival. Stage I and II is referred to as early breast cancer disease, at which point it is possible to completely remove the tumour and cure rates are high. Stage I disease is defined as a primary tumour less than 2 cm in diameter. In stage

II, the primary tumour is more than 2 cm in diameter but has not spread outside of the breast, or the primary tumour is less than 5 cm but with metastases identified in 1-3 axillar lymph nodes. Stage III is the classification for locally advanced disease when the tumour has spread to lymph nodes and/or to the skin or chest wall and stage IV is advanced disease with distant metastases, most commonly skeletal, liver or lung metastases. In the study countries with the lowest healthcare expenditure per capita, a larger share of breast cancer patients have advanced or metastatic breast cancer at the time of diagnosis compared to those countries with more resources dedicated to healthcare. Since advanced breast cancer has the poorest survival rate and is the most resource-intensive to treat, measures that lead to earlier diagnosis, including greater awareness of the importance of early detection and improved access to mammography, are considered to deliver the greatest overall benefit in terms of survival in relation to cost [54].

Hospitals in Brazil, Mexico and Russia report between 30-60% of cases diagnosed in advanced stages (stage III-IV) [50-52, 55-59] while in Norway - one of the countries with the highest breast cancer survival rates - only 10% of breast cancer patients diagnosed in the early 2000s had stage III-IV disease at diagnosis [26] (Figure 11). The figures from Brazil, Mexico and Russia are not population-based estimates, therefore on the one hand, the data may overestimate the share of patients with advanced disease as it is likely that the most advanced cases are remitted to the major hospitals, while early breast cancer is treated at smaller hospitals, on the other hand the data has come from hospitals in some of the biggest cities in each country and it is possible that awareness of breast cancer and access to care is better in the cities than in the countryside, so data may not be fully representative of true figures.

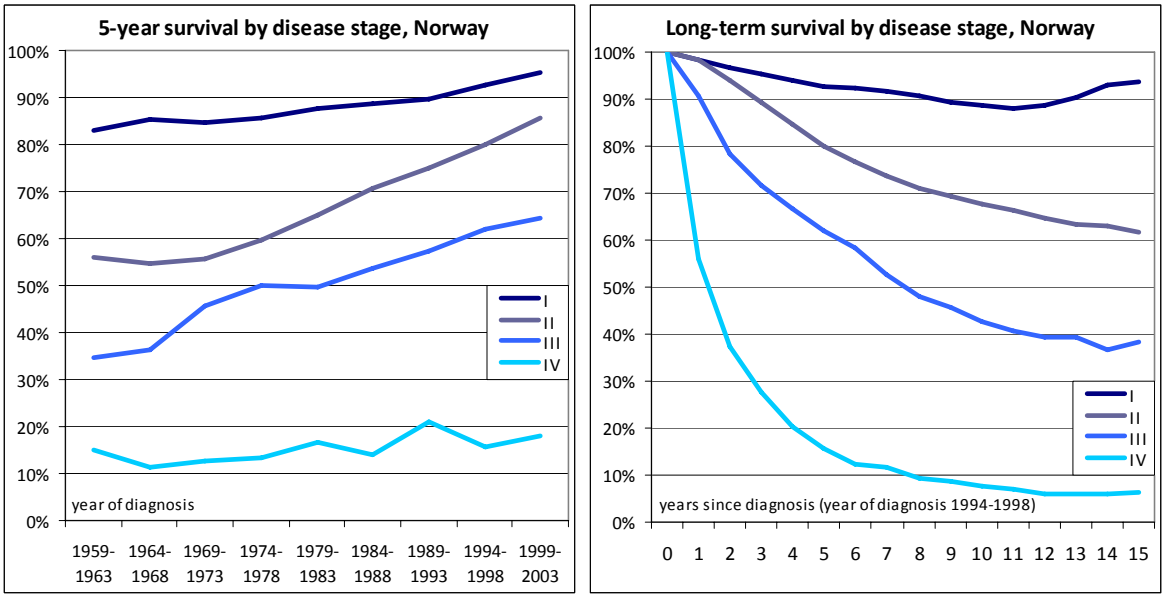
Figure 11 Disease stage at diagnosis



Estimates from Brazil, Mexico and Russia - largely based on hospital records [50-52, 56-58]

The data presented in figure 12 illustrates the relationship between stage of disease at diagnosis and survival. The 5-year relative survival rates for patients in Norway diagnosed in stage II and stage III have improved most since the late 1960s (left graph). Still, the long-term (15-year) survival rates today for stage II and III at diagnosis are considerably lower than the 5-year survival (right graph) since a share of these patients will experience disease relapse at a later time point. For stage IV disease, the 5-year survival is 15%. The data indicate that approximately 5% of patients diagnosed with metastatic breast cancer in Norway are alive 15 years from diagnosis. Although long-term survival rates of patients with stage IV breast cancer are low, the survival of patients with metastatic breast cancer has improved slightly over time, coincident with the widespread availability of newer and more effective systemic therapies [60, 61].

Figure 12 Relative breast cancer survival by stage at diagnosis [26]



There is further potential for improvement, based on better diagnostic tools and more effective treatment, but also through better selection of at-risk groups who would most benefit from medical prevention measures.

3.2 Quality of life

Outcomes research is the study of the net effects of the healthcare process on the health and wellbeing of individuals and populations and has a broad scope, including research on satisfaction with care and measurement of patient preferences and quality of life [62]. The quality of life of patients during and after disease and treatment is an important outcome of breast cancer care and an extensively studied subject. The first instruments to measure cancer patients' performance status and quality of life were physician-rated [63, 64]; quality of life studies based on patient questionnaires did not emerge until the late 1980s and early 1990s [65]. In the last decades a great variety of survey instruments have been developed for the assessment of health-related quality of life in breast cancer - a recent literature review identified over 100 different quality of life instruments used in breast cancer; although only a few of these have become extensively validated and established over time [62, 65]. Due to the complexity of breast cancer care and the heterogeneity in patient populations, one single instrument may not be sufficiently comprehensive and sensitive to determine clinically meaningful changes in outcomes across all phases of care.

Generally, health domains considered in a quality of life assessments are: 1) somatic concerns, such as pain and symptoms; 2) functional ability; 3) family well-being; 4) emotional well-being; 5) spirituality; 6) treatment satisfaction, including financial impact of illness; 7) future orientation; 8) sexuality, intimacy, and body image; 9) social functioning; 10) occupational functioning; and 11) preferences. Published quality of life studies have encompassed the major stages of breast cancer care: screening, local treatment, adjuvant treatment, treatment of metastatic disease, and survivorship and surveillance [62].

Decisions about alternative therapies, in particular in metastatic breast cancer when the objective of treatment is not cure but prolonged survival, often encompass quality of life considerations. Although health-related quality of life is today considered an important endpoint in cancer clinical trials, due to methodological problems with many studies lacking a predefined specific endpoint, quality of life considerations so far have limited impact on the evaluation and approval of drugs. Thus, there is a clear need for expanded research on outcomes measures.

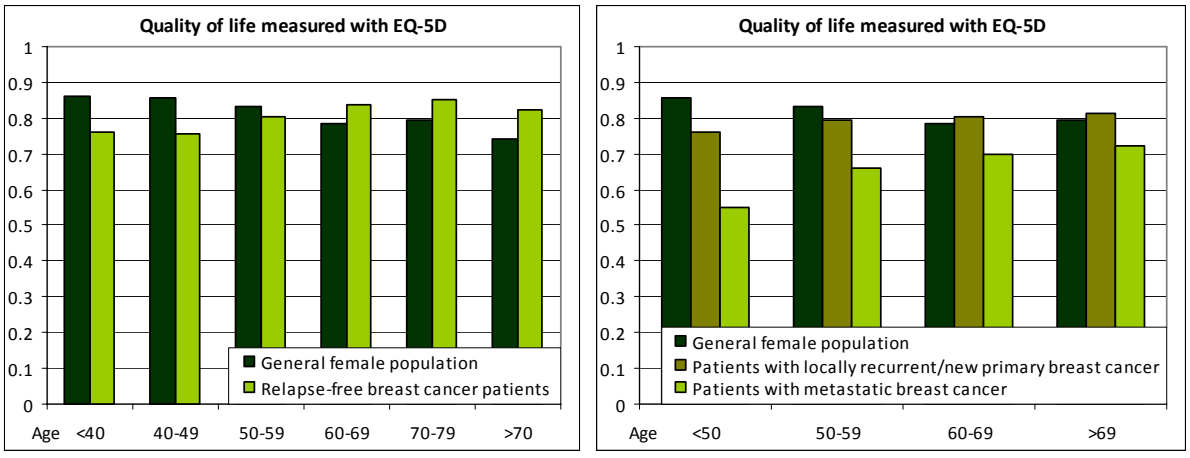
Assessment of the quality of life of breast cancer patients in this report is illustrated by a study conducted in Sweden in 2007. A full study report will be made available as an appendix to this report.

CASE STUDY: Quality of life in Swedish breast cancer patients - a study in a patient advocacy population

Introduction: Health-related quality of life (HRQoL) factors are central to all cancer therapy. Quality of life was investigated in women treated for breast cancer and free of relapse as well as in a breast cancer population having recurrent/new primary or metastatic breast cancer. The participants were all members of the Swedish breast cancer advocacy group BRO. The aim of this study was to evaluate HRQoL in breast cancer patients in relation to age and diagnosis and to compare this with the quality of life of the general Swedish female population of the same age [66].

Methods: Quality of life questionnaires were sent out to members of the Swedish breast cancer advocacy group BRO. One of the instruments used, EuroQol EQ-5D, is a generic HRQoL questionnaire that is used for economic evaluations of health interventions, since it is not disease-specific it allows for comparison of the quality of life of difference diseases. The EQ-5D measures HRQoL in five dimensions and on three levels of response. Using population derived weights, EQ-5D responses are translated to a global index between 0 (death) and 1 (full health). A total of 4,900 women responded (52% response rate), of which 4,027 were free of relapse. Respondents had a mean age of 62 years. Tumour and treatment characteristics reflect the prevalent Swedish breast cancer population.

Figure 13 Quality of life of relapse-free breast cancer patients compared to the general female population (left graph) and patients with locally recurrent/new primary breast cancer, patients with metastatic breast cancer, and the general female population respectively (right graph), in relation to age



Conclusions: The results of the study (figure 13) indicate that women older than 60 years with relapse-free breast cancer have better health status (measured by EQ-5D) than the general female population of this age in Sweden. Women younger than 60 years with relapse-free breast cancer have lower health status than the general female population, and women with recurrent or metastatic breast cancer have lower health status that the general female population regardless of age with the difference most pronounced for younger patients with metastatic disease.

4 Breast cancer treatment patterns

SUMMARY

- ***Evidence-based treatment guidelines - that are regularly updated in line with internationally accepted standards, followed, and audited - are key to promote the rational use of existing resources and equity in access to treatment services within a country and/or region.***
- ***Breast cancer care is complex and a multidisciplinary team approach is recommended.***
- ***Optimal care requires access to (1) diagnostic facilities, including screening and biological characterisation of disease, (2) surgery, radiotherapy and medical treatment, (3) adequate patient follow-up, including psychological support to the patient and their relatives, and (4) adequate care of advanced and incurable disease including palliation and end of life care.***
- ***A process for monitoring best practice compliance and measuring outcomes is lacking in many countries making it challenging to assess spending and investments in relation to outcomes*.**

4.1 Introduction

Breast cancer treatment guidelines on the national or regional level exist in most of the study countries. National/regional treatment guidelines often refer to international guidelines, although with local adaptations according to resource availability and/or how rapidly novel clinical evidence is incorporated. International guidelines in breast cancer are developed by for example the St. Gallen expert consensus meeting (for adjuvant therapy), ESMO (European Society for Medical Oncology) and ESO (European School of Oncology). The guidelines published by NCCN (National Comprehensive Cancer Network) in the United States are also commonly referred to by other countries. Since the internationally referenced treatment guidelines often assume unlimited resources, the BHGI (Breast Health Global Initiative) has recently started to develop treatment guidelines in breast cancer for countries with low- or medium-level resources, which consider how to prioritise between different prevention and treatment options in resource-constrained settings [67-69].

In some of the study countries, breast cancer treatment guidelines are formulated as so called 'care programmes' that include also treatment pathways and organisational aspects of breast cancer care, while in other countries the guidelines are predominantly clinically oriented, focusing on which diagnostic investigations should be performed, and what treatment should be provided depending on diagnostic results. In a few countries, identified guidelines covered only some of the elements in breast cancer care, most commonly medical treatments [70-86].

An important purpose of the establishment of treatment guidelines within a country or region is to create a common standard of care and promote the rational use of existing resources and greater equity in access to treatment services. However, adherence to treatment guidelines appears to vary greatly in the study countries. A Europe-wide survey from 2006 [6] reported that cancer guidelines are well adhered to in the Northern European countries, but only partly followed in the other European study countries. Few

countries have mechanisms in place to audit clinical practice against guidelines; Finland, Poland, Russia, Sweden and the UK reported that certain measures for auditing were in place, while the other European countries included in the survey reported that no control system was in place [6].

4.2 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. Most of the breast cancer risk factors are currently not amenable to primary prevention interventions. The 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 [87]. The more extensive treatment guidelines from some the study countries discuss breast cancer risk factors, but in the majority of guidelines, risk factors are only mentioned briefly or not at all [70-86].

4.2.1 Prevention in high-risk groups

It is estimated that 20–30% of breast cancers are caused by genetic factors that in combination with life-style 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 [88-91]. 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 [92-94]. The most established strategy is preventive removal of the breasts, although the evidence base for this strategy is limited. Recommendations for identification and follow-up of high-risk women were identified in the guidelines of approximately half of the study countries – recommendations included, genetic testing and additional risk-assessment in women with a family history of breast cancer, regular follow-up examinations and ensuring the availability of preventive measures.

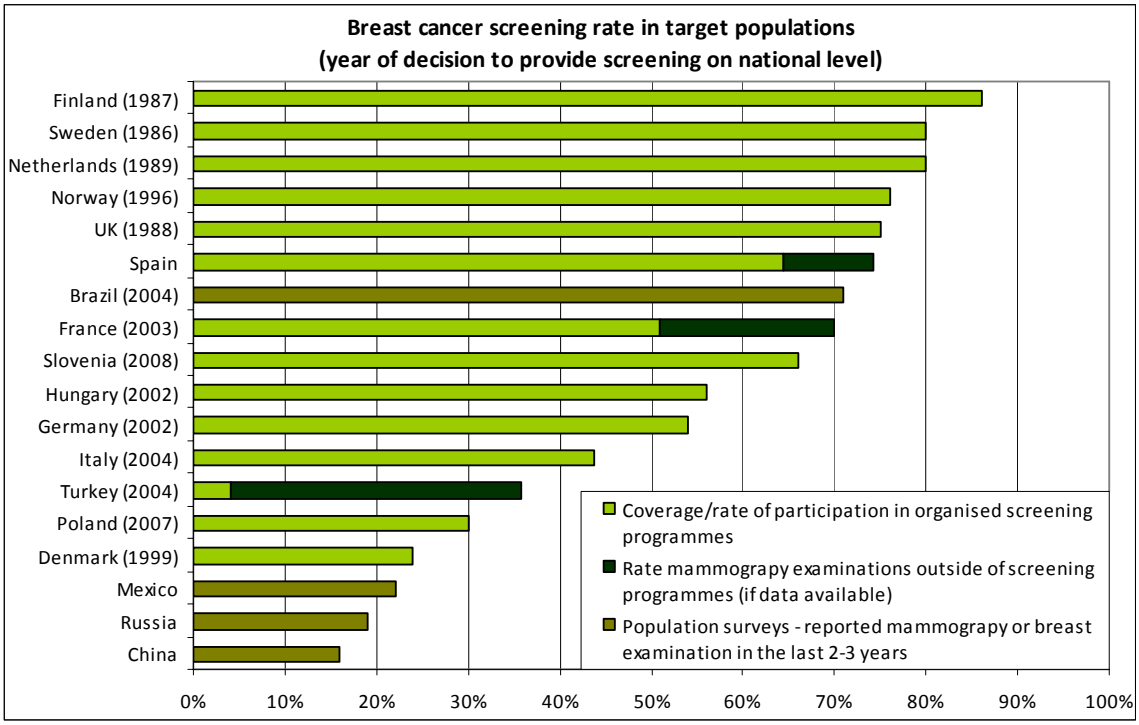
4.3 Secondary prevention/early diagnosis

The aim of secondary prevention is to reduce the severity of disease and the risk of dying from it. As discussed in the previous chapter, outcome is 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 principal secondary prevention measure in breast cancer is population-based mammography which has shown to improve outcomes as it leads to a larger share of breast cancers being diagnosed at an early stage in the screened population [30-34]. 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 [95]. 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 [96, 97], 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 [97].

4.3.1 Mammography screening programmes

Although the outcome of breast cancer screening has been debated by some [98, 99], the increased level of evidence available from the countries that implemented screening programmes in the 1980s [30-34] 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) [100, 101]. Many of the study countries have recently implemented screening programmes on the national level or are in the process of doing so. Extensive guidelines for quality assurance of screening programmes have been developed for example on the EU level [102]. Figure 14 gives an overview of the coverage of screening in the study countries. The target population differs between countries but in most, screening is targeted to 50-69 year old women.

Figure 14 Breast cancer screening implementation



Sources and year of data: Finland 2006/Germany 2006 [103], Sweden 2008 [23, 104], Netherlands [105], Norway [106], UK [107], Brazil 2008 [108], France 2005 [109], Slovenia 2008 [110], Spain 2006 [111, 112], Hungary 2004 [113], Italy 2006 [114], Turkey 2008 [115], Poland 2008 [116], Mexico 2006 [117], Russia 2003/China 2003 [23], Denmark 2006 [23, 118]

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 [119]. Also in countries with a high overall coverage, it has been shown that two groups in particular are under-represented in breast cancer screening programmes; women from lower socio-economic levels and first-generation immigrants [40, 120]. In Mexico, mammography is recommended but there is no national population-base screening programme 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 doing mammography [121, 122]. 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 [123]. 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 [50-52]. 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 [124]. 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 [125]. 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, 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 [126]. The WHO's statement of 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 it is therefore population-based screening is not viable in all countries, but that, although there is insufficient evidence, good clinical breast examinations by specially trained health workers could have an important role when resources are limited [127].

A law was introduced in Denmark in 1999 requiring all counties to offer mammography screening but without a firm deadline for introduction [72, 128]. The value of breast cancer screening has been considerably debated in Denmark [36, 99], 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. A high priority task for future research is to attempt to find methods to sort out such non-malignant lesions from malignant subclinical lesions [35].

4.4 Diagnosis

The recommended diagnostic approach in breast cancer is the so called triple diagnosis with a combination of clinical investigation, radiological investigation and a biopsy, frequently fine needle cytology or a core biopsy, which distinguishes in situ versus invasive lesions. This diagnostic approach is essential in order not to miss small or non-palpable breast lesions.

4.4.1 Tumour classification

Testing for biological markers is recommended in most of the study countries. It provides a basis for the selection of medical therapy. For oestrogen-receptor positive and progesterone-receptor positive patients, endocrine therapy (drugs that interfere with the production of hormones or block their action) is

the recommended treatment option [29]. Advances in molecular medicine in recent years have made it possible to identify genes that provide certain tumour-specific characteristics and in some cases to predict if an individual tumour will respond to certain treatments. Patients with tumours expressing human epidermal growth factor receptor 2 (HER2), previously a subgroup with poorer prognosis than the average breast cancer patient, respond to treatment with trastuzumab which has significantly improved the outcome for these patients [129, 130]. Patients with so called triple negative disease, with oestrogen-receptor, progesterone-receptor and HER2 negative tumours, have been identified as a subgroup that at present have limited treatment options. Further refinement in the classification of breast cancer tumours will most likely take place based on the present development in genomics and proteomics. Already today some subtypes of breast cancer are recognised by this strategy.

4.5 Treatment of early breast cancer

4.5.1 Surgery

Breast tumours in early stages can be completely removed by surgical resection. Surgical procedures include breast-conserving surgery, mastectomy, and axillary lymph node sampling and removal. A mastectomy involves removing all of the breast tissue, sometimes along with other nearby tissues. Breast reconstruction can be performed at the time of tumour resection or later. In breast-conserving surgery, only a part of the affected breast is removed, how much depends on the size and location of the tumour and other factors. For most women with stage I or II breast cancer, breast conservation therapy (lumpectomy/partial mastectomy plus radiation therapy) is as effective as mastectomy [131, 132]. However, breast-conservation surgery requires high-quality breast imaging equipment and is as effective as mastectomy only in combination with radiotherapy thus, in settings with limited resources where this cannot be provided in combination with the breast surgery, modified radical mastectomy is recommended [68].

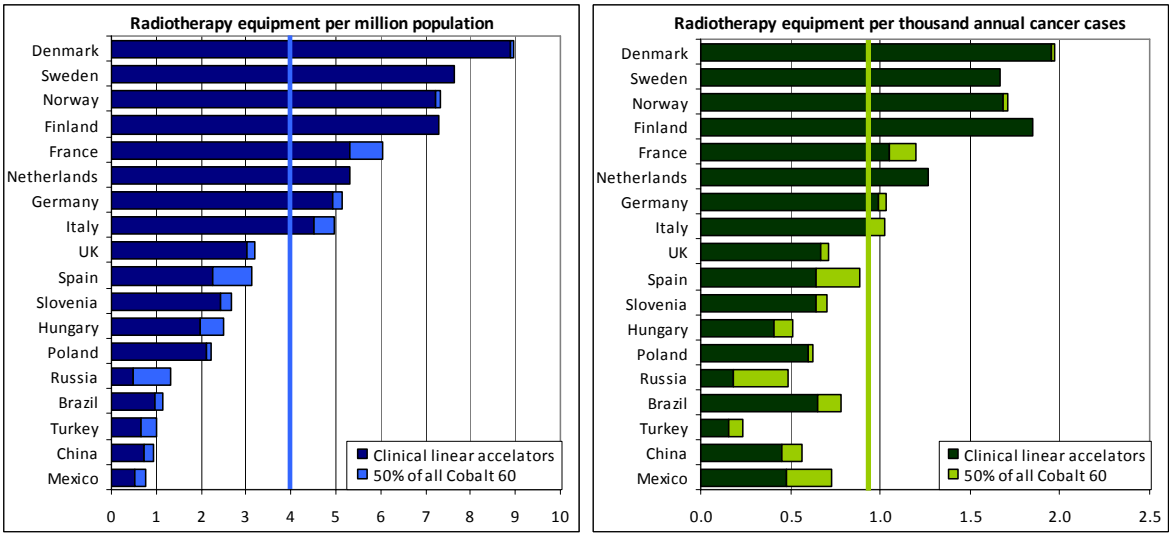
Lymph node dissection is part of the staging process and the results will determine subsequent treatment decisions. A sentinel lymph node biopsy is the identification and removal of the first lymph node(s) into which a tumour drains, which will most likely contain cancer cells if they have started to spread outside of the breast. This procedure requires a great deal of skill and experience. Axillary lymph node dissection is performed as part of the removal of stage II tumours. Anywhere from about 10 to 20 lymph nodes are removed as with these numbers the false negative rate is considered to be acceptable. A possible long-term adverse effect of removing axillary lymph nodes is lymphoedema, which develops in 25% of women who have had underarm lymph nodes removed [133].

4.5.2 Radiotherapy

Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. This treatment may be employed to kill any cancer cells that remain in the breast, chest wall, or lymph node areas after breast-conserving surgery. Radiotherapy has gained an increased importance, and a recent meta-analysis revealed that radiotherapy as a complement to surgery decreased the risk of loco-regional relapse by two-thirds compared to surgery alone [134]. External beam radiation is the most common type of radiation therapy for women with breast cancer. If breast-conservation surgery was performed, the entire

breast receives radiation, and sometimes an extra boost of radiation is given to the area in the breast where the cancer was removed to prevent it from coming back in that area. Depending on the size and extent of the cancer, radiation may include the chest wall and lymph node areas as well. Brachytherapy, also known as internal radiation, is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, radioactive seeds or pellets are placed directly into the breast tissue next to the cancer. It is often used as a way to add an extra boost of radiation to the tumour site along with external radiation to the whole breast. Tumour size, location, and other factors may limit who can get brachytherapy. Linear accelerators are the device principally used for radiation therapy. In some countries cobalt machines are more frequently used; cobalt machines are less efficient than linear accelerators, but also cost less. In Europe, available guidelines for radiotherapy equipment often recommend that the coverage of linear accelerators should be at least four per million inhabitants - cobalt machines are then often counted as having half the value of a linear accelerator - and/or one linear accelerator per 450 patients, although this varies country by country, it has been estimated that 45-55% of new cancer patients would benefit from radiotherapy [135, 136]. Figure 15 depicts the availability of radiotherapy equipment in the study countries in relation to total population and annual new cancer cases [137].

Figure 15 Radiotherapy equipment in the study countries [137]



The lack of sufficient radiotherapy equipment appears to be a bottle-neck that causes waiting times in cancer care in many countries [138, 139]. Other factors that influence patient access to radiotherapy are the rate of appropriately trained personnel [136], the utilisation rate of available equipment, and the geographic dispersion of existing radiotherapy centres.

4.5.3 Medical therapy

Adjuvant treatment is systemic therapy given after surgery to patients with no evidence of cancer spread outside of the breast or the lymph nodes, with the purpose of destroying any microscopic cancer cells that might remain in the body and cause recurrence of the disease. Adjuvant therapy may consist of chemotherapy, endocrine therapy, and/or targeted biological therapies. Chemotherapy inhibits cell growth by different mechanisms and thus reduces the rapid cell proliferation that is a characteristic of

cancer cells. Endocrine therapies (tamoxifen or aromatase inhibitors) block the effect of oestrogen or reduce hormone levels, and have effect in types of breast cancer where tumour growth is stimulated by oestrogen (about two thirds of all cases). Targeted biological therapies selectively attack genetic expression that is typical for cancer cells. Adjuvant treatment is not recommended for all breast cancer patients with early disease; adjuvant treatment decisions are guided by a risk-benefit assessment, weighting a patient's risk of breast cancer recurrence against adverse effects of adjuvant treatment [140, 141]. Adjuvant treatment is an important element in cancer guidelines and is covered in basically all treatment guidelines identified. Clinical guidelines covering adjuvant treatment were not identified for Hungary, Turkey, Russia and Mexico – in these countries clinicians may instead refer to international guidelines [70-86].

Adjuvant medical treatment in breast cancer has evolved over a 30-40 year period. Combination regimens, of two to three drug types, with different mechanisms of action are recommended as adjuvant chemotherapy in breast cancer. The first generation of adjuvant chemotherapy evolved during the 1970s. Better regimens have been developed over time and at present, chemotherapy regimens containing taxanes and anthracyclines have been demonstrated as the most effective [142-145]. Endocrine therapy of breast cancer started with tamoxifen. Launched in 1975 and initially considered a costly treatment with limited effect, tamoxifen has established itself as the most cost-effective cancer treatment to date. Its broad indication in the treatment of advanced disease and as adjuvant treatment (as well as prevention in the USA), represents a major breakthrough in the treatment of breast cancer. Aromatase inhibitors, anastrazole, exemestane and letrozole, are now in part replacing tamoxifen, both in the treatment of advanced disease and in the adjuvant setting. A meta-analysis of data from almost 200,000 women collected over time in order to estimate the value of adjuvant radiotherapy, chemotherapy and endocrine therapy has been an important step in recognising the value of adjuvant therapy. The first results were published in 1988, and follow-up data are regularly published [142, 145-149]. Meta-analyses have demonstrated that adjuvant chemotherapy reduces the relative yearly risk of death by almost 40% for women <50 years and by 20% for women 50-69 years old and that endocrine therapy with tamoxifen in oestrogen-receptor positive patients results in a more than 30% relative risk reduction of mortality [142, 146].

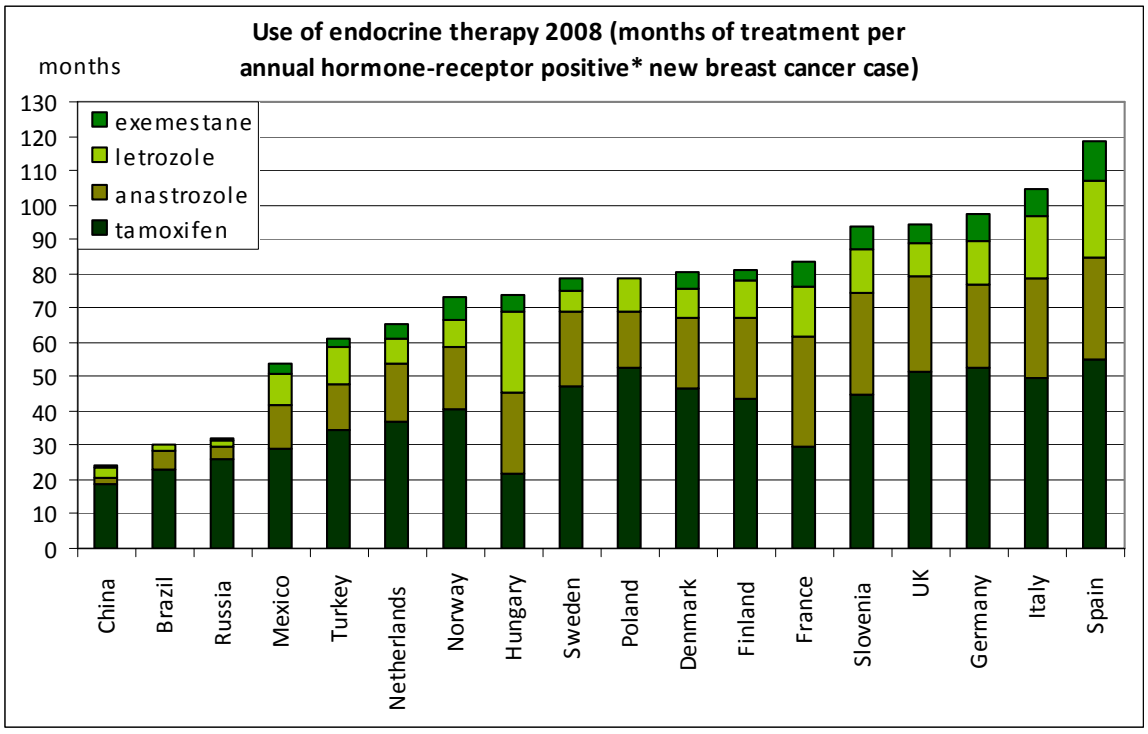
The biological therapy trastuzumab entered breast cancer therapy in the late 1990s and has dramatically changed the outcome for women with HER2 over-expressing breast cancer. Trastuzumab is a monoclonal antibody that attaches to a growth-promoting protein known as HER2/neu which is present in larger than normal amounts on the surface of the breast cancer cells in about 15-20% of women with early breast cancer and 20-30% of women with advanced breast cancer. Trastuzumab can thus suppress HER2 stimulated tumour growth and may also activate the immune system to more effectively attack the cancer. In recent years, studies have shown that 1 year of adjuvant treatment with trastuzumab in women with HER2 positive breast cancer leads to a 50% reduced risk of recurrence, although the follow-up period of these patients is still limited [129, 130].

Adjuvant chemotherapy is commonly given for a period of 6 months, followed by endocrine therapy for 5 years for hormone-sensitive patients, either 5 years of tamoxifen or anastrazole or a sequence of first tamoxifen and then exemestane or letrozole. Some high risk patients may also be subject to prolonged use with tamoxifen followed by letrozole with a total treatment time of up to 10 years. There is not

enough evidence to establish the optimal period of adjuvant treatment with trastuzumab but it is usually given for a period of 1 year in combination with, or subsequent to, chemotherapy and may also be followed by endocrine therapy for 5 years.

Figure 16 illustrates the usage of tamoxifen and aromatase inhibitors (anastrazole, exemestane and letrozole) in the study countries in 2008, based on pharmaceutical sales data [150]. The use is expressed as months of treatment (based on the standard daily dose of respective drug) in relation to the annual incidence of breast cancer, from most recent national data sources if available otherwise from global cancer incidence estimates for 2002 [1]. The data presented is total use of endocrine drugs, both in the adjuvant setting and in advanced breast cancer (treatment of metastatic breast cancer is discussed below); since the usage is based on sales data it is not possible to separate drug use by indication. For some countries, a relatively high usage per case depicted in the figure may reflect an under-registration of new cases of breast cancer. This may be the case in for example Mexico and Turkey, as countries with limited coverage of cancer registration, and could also be the case for Spain for which the latest identified incidence data on the national level is from 2002 while more recent incidence data was available for some other European countries. Parallel trade may also affect the reported sales in a country.

Figure 16 Use of endocrine drugs in the study countries in 2008 per hormone-receptor positive new cancer case [1, 150]

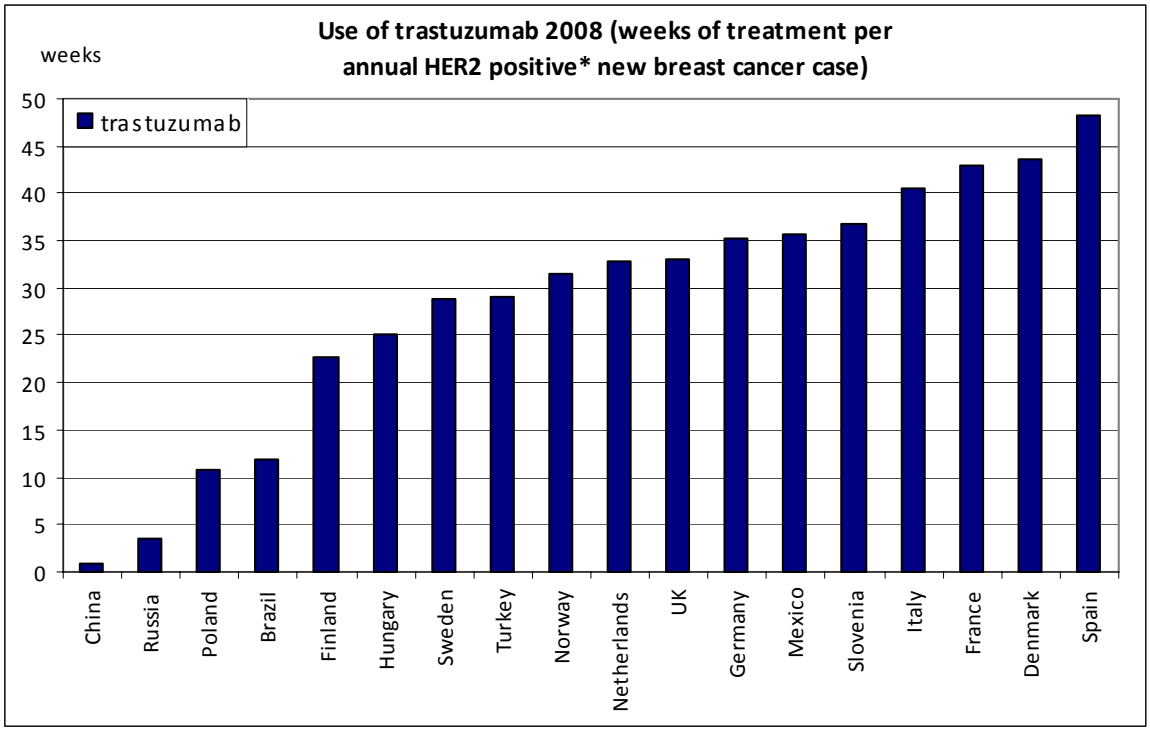


** Assumed two thirds of breast cancer cases overall hormone-receptor positive*

Figure 17 illustrates the usage of trastuzumab in the different study countries in 2008. The use is expressed in weeks of treatment (based on a standard weekly average dose of 150 mg) in relation to the annual incidence of breast cancer, from most recent national data sources if available otherwise from global cancer incidence estimates for 2002 [1]. The data presented is the total use of trastuzumab, both in

the adjuvant setting and in advanced breast cancer (treatment of metastatic breast cancer is discussed below); since the usage is based on sales data it is not possible to separate drug use by indication.

Figure 17 Use of trastuzumab in the study countries in 2008 per HER2 positive new cancer case [1, 150]



**Assumed 20% of breast cancer cases overall HER2 positive*

For some countries, a relatively high usage per case depicted in the figure may reflect an under-registration of new cases of breast cancer. This may be the case in for example Mexico and Turkey, as countries with limited coverage of cancer registration, and could also be the case for Spain for which the latest identified incidence data on the national level is from 2002 while more recent incidence data was available for some other European countries. It should also be noted that the sales data from Germany do not reflect total use in the country. (The sales data used as basis for the analysis cover an estimated 80% of the sales of trastuzumab in Germany). Parallel trade may also affect the reported sales in a country.

Figures 16 and 17 illustrate the difference of uptake between the study countries, even though they must be interpreted with caution due to the lack of solid epidemiological data in some countries, and incomplete sales statistics from other countries. As will be further discussed in chapter 6, the fact that novel drugs due to parallel trade have quite similar prices in all countries leads to reduced patient access to innovative cancer drugs in low- and middle-income countries.

Bisphosphonates, a cornerstone in the treatment of metastatic breast cancer, are a group of drugs that have come into focus also in the adjuvant treatment of breast cancer. A recent study showed a clear reduction in metastatic event in premenopausal women receiving zoledronic acid [151, 152]. However, there are a couple of studies soon to be reported that will give additional information and define the role of bisphosphonates in the adjuvant setting [153].

4.5.4 Alternative medicine

In China, complementary or alternative medicine is commonly used by breast cancer survivors. A recent study reported that over 95% of 5,000 breast cancer survivors in Shanghai used some kind of complementary of alternative medicine and 75% used Chinese herbal medicine as a complement to conventional cancer treatment [154]. Reported reasons for using alternative medicine were the treatment of the cancer and to boost the immune system. Alternative medicine is also used for the treatment of side-effects from endocrine and chemotherapy in breast cancer patients, and discussed in, for example, the Swedish treatment guidelines [80], though it is generally concluded that evidence is limited about the effectiveness and safety of most alternative treatments [155].

4.5.5 Rehabilitation

With improved outcomes of breast cancer treatment the need for rehabilitation - both physical and psychosocial - has increased. In the Nordic countries the Nordic cancer union has supported the development of psychosocial teams [80]. A recent survey indicated that almost all breast cancer units in Denmark can offer a pre-operative rehabilitation programme and physiotherapy for patients with lymph oedema, and that 95% of the units can offer psychosocial support [156]. The German pension fund has developed guidelines for the rehabilitation of breast cancer patients [157, 158]. In some countries patient organisations play an important role in supporting breast cancer patient rehabilitation.

4.5.6 Patient follow-up

Regular follow-up is important in order to identify early signs of recurring disease. Follow-up is also important in order to identify toxicity of treatment, both short- and long-term. A recent systematic review of published evidence concluded that less intensive follow-up strategies based on periodical clinical exam and annual mammography were as effective as more intense surveillance schemes [159]. Only the more extensive national guidelines give recommendations regarding follow-up procedures for patients that have had a breast cancer tumour resected, including the Scandinavian guidelines and some of the Spanish regional guidelines [70-86].

Another area, so far largely neglected, is the evaluation of quality of life both in women that experience recurrent disease and in those who are cured. There is for some women a cost of cure – long-term side effect of treatments – that can be significant [133].

4.6 Treatment of advanced breast cancer

Locally disseminated breast cancer can be surgically removed. The tumour is often pre-treated with neoadjuvant therapy – chemotherapy given before surgery - and radiation with the purpose of shrinking the tumour before surgical resection. Neoadjuvant chemotherapy can also give information on the effect of the selected therapy – around 20% of the patients with a complete pathological response have a significantly better survival compared with those who respond less well. Neoadjuvant chemotherapy has been shown to result in equivalent survival compared with the same adjuvant regimen [160].

Patients with loco-regional relapse of breast cancer are a heterogeneous group. About half of these patients will become disease-free following surgery, radiotherapy and medical adjuvant treatment. In the

remaining group of patients the local relapse is a lead in the development of disseminated metastatic disease and the patient will need treatment accordingly.

In metastatic breast cancer, medical treatment is the most important consideration. The drugs given are to a large extent the same as those given in adjuvant therapy; first-line treatment for pre-menopausal women with hormone-receptor positive metastatic breast cancer is tamoxifen and for post-menopausal women aromatase inhibitors or tamoxifen.

Trastuzumab is indicated as first-line treatment for women with HER2 positive tumours in combination with taxane based chemotherapy or an aromatase inhibitor. Other targeted biological therapies that may be given as secondary options in metastatic breast cancer are bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), which is a protein that helps tumours form new blood vessels, and lapatinib (conditional approval within EU), which like trastuzumab targets the HER2 protein and may be given as third line treatment to women whose tumours progress under treatment with chemotherapy and trastuzumab.

Compared with treatment options for early-stage breast cancer, limited data exist regarding the optimal use of chemotherapy for metastatic breast cancer. Few appropriately powered randomised clinical trials have addressed the question of the sequential use of single cytotoxic agents versus combination chemotherapy. In contrast to adjuvant therapy, for which trials are designed to include thousands of patients to identify small absolute differences in disease-free survival, most studies that address metastatic breast cancer involve smaller numbers of participants and are underpowered to detect potentially meaningful differences in progression-free interval and/or overall survival between combination and sequential approaches [161]. This is also reflected in the treatment guidelines regarding metastatic disease, with less specific recommendation for the treatment of metastatic disease. Some of the guidelines for treatment of metastatic disease discuss the necessity to adjust the treatment to the individual patient by balancing the effect of treatment with adverse events and the patient's overall performance status. The outcomes of treatments for advanced breast cancer should be evaluated from several standpoints together with the patient. For instance, therapeutic strategies may be associated with similar survival but different toxic effects; alternatively, one therapy may yield better survival but more severe side effects, while another may offer poorer survival but better quality of life during the patient's remaining months or years. Thus, decisions about therapy options are often based on quality of life considerations, in addition to survival [162].

4.6.1 Palliative care

In the palliative treatment of metastatic breast cancer, radiotherapy plays a major role. Metastatic bone disease and brain disease are important indications for external palliative radiotherapy. Radiation is effective in locally controlling the tumours and reducing pain. In patients with skeletal metastases, bisphosphonates are also effective in reducing pain and may help to control disease. Bisphosphonates are recommended to be used extensively and early in metastatic disease in order to prevent skeletal complications such as pathological fractures, surgery for fracture or impending fracture, radiation, spinal cord compression as well as hypercalcemia [153, 163, 164]. Dishabilitating symptoms such as pain, fatigue, nausea, physical impairment, and sleeplessness have been found to be persistent problems for

women with advanced breast cancer [165-169]. Breast cancer patients have been found to experience moderate to severe pain with some being unaware that they can have strong analgesia and a reluctance to complain to health professionals [166].

Palliative medicine is slowly being recognised as a fundamental component of the multidisciplinary teaching for medical students (in approximately 50% of European countries). However, the majority of European countries still do not have specialised palliative care facilities, such as hospices, palliative care beds in hospitals, palliative care teams for consultation in hospital and home care, and even in countries that do report them the numbers are very low [170]. Guidelines for palliative care are available in several of the study countries [171, 172].

Below is an overview of breast cancer care in Brazil that presents some critical issues in a large country with unequally distributed health care resources.

CASE STUDY: Breast cancer care in Brazil

Introduction: The Brazilian society is characterised by its heterogeneity in cultural and racial background with immense socio-economical differences. These differences influence directly the access to health care and the quality of healthcare varies considerably within the country. The north and northeast of Brazil are the regions that are the least developed and suffer the most. The Brazilian healthcare system is composed of a large government managed public system which serves the great majority of the population and a complementary private sector, managed by health insurance funds and private entrepreneurs; around 30% of the population in the southeast region has private insurance and 6% in the north region [173].

Screening: The health ministry in Brazil recommends a mammography every other year for women between 50 and 69 years old and a clinical breast examination yearly for women between 40 and 49 years. It is difficult to assess to what extent these guidelines/recommendations are followed in practice. Since 2004, an intervention study in a cohort of women in Southern Brazil is being conducted in order to test the effectiveness and cost-effectiveness of a model for early detection and treatment of breast cancer. The accrual was concluded in 2006 and the study will last for 10 years. The study aims to demonstrate that one can downstage breast cancer in women from underserved communities with a proper screening and early diagnosis programme. More than 4,000 women have been included and are being screened annually with mammography and clinical breast examination. Preliminary results show a very high breast cancer incidence in this population (117/100,000 women/year), despite a low prevalence of the typical risk factors [174].

Diagnosis and access to treatment: In Brazil the diagnostic work is performed in primary care and the referral to other levels of care is their responsibility. A cross-sectional, observational study at a public hospital in Rio de Janeiro in 104 women with breast cancer or suspected breast cancer, indicate a significant time lag - a median time of 6.5 months - from first consultation to confirmation of diagnosis. Around 50% of the patients looked for a private service to have their first medical evaluation [175]. Another descriptive study of breast cancer care in health services covered by the national health system in the state of Rio de Janeiro, from 1999 to 2002, reported that the use of interventions varied between patients with and without health insurance in lower complexity health services; non-insured patients were associated with lower use of interventions. It was also found that there is underutilisation of recommended interventions as well as utilisation of contraindicated interventions [176].

Treatment of early breast cancer: The public health system reimburses surgery, radiotherapy, chemo- and endocrine therapy. The reimbursement levels are higher for neoadjuvant treatment than for adjuvant treatment. It is thus easier to prescribe more expensive drugs like taxanes in the neoadjuvant setting compared to the adjuvant setting. The adjuvant endocrine therapy is usually tamoxifen as first-line and the prescription of aromatase inhibitors is usually restricted to patients with tamoxifen intolerance, formal contra-indications or progressive disease after tamoxifen. The public system usually does not reimburse modern drugs like trastuzumab, bevacizumab or lapatinib which thus are rarely used. Private health insurances reimburse in general similar treatments to those used in Europe and in the

USA, but it is important to mention that, depending on the private insurance a patient has, different drugs will be made available for their treatment. A special problem is oral drugs because some of the private health insurances do not reimburse oral therapy. In these cases the patients must pay themselves or are referred to the public health system.

Treatment of metastatic breast cancer: As mentioned in the treatment for early breast cancer the reimbursement system allows for treatment with radiotherapy, chemotherapy, endocrine therapy and bisphosphonates. Palliative care is most of the time offered by the oncology units and the clinical oncologists will be the ones taking care of the patient from the point of diagnosis of metastatic disease until the end.

Clinical trials: Clinical trial activity in oncology is increasing rapidly in Brazil. Clinical oncologists in general are getting more and more experienced with sending patients to be included in clinical trials where resources are limited. Including a patient in a clinical trial may be the only way to provide a potentially effective treatment to the patient.

Challenges: Implementing an effective national system with high population coverage concerning screening for early breast cancer will be challenging but pivotal in order to improve survival outcomes in breast cancer. Significant investments in public healthcare will be necessary to obtain a more equal access to quality healthcare. Ways for patients to access modern drugs outside clinical trials within the public system also need to be addressed.

4.7 Organisation of breast cancer care

4.7.1 Multidisciplinary teams

Before the mid-1970s, early breast cancer was managed almost exclusively by surgeons, while radiologists and medical oncologists would be involved in the treatment of patients with advanced disease. Since then, the advances in the diagnosis and treatment of breast cancer have made breast cancer care increasingly successful but also more complex. In the process from prevention, diagnosis and treatment to rehabilitation or palliative care, a range of expertise needs to be involved, including surgeons, radiotherapists, medical oncologists, gynaecologists, diagnostic radiologists, pathologists, primary care physicians, specialised nurses, pharmacists, geneticists, psychologists, physiotherapists, and social workers.

Studies in the 1980s and 1990s demonstrated that breast cancer patients managed by specialist surgeons, with a high load of breast cancer cases per year, had better outcomes, since the specialist care resulted in a more holistic treatment approach and the patients were more likely to receive a combination of adjuvant therapies [177-183]. A multidisciplinary treatment approach was something that evolved as it became evident that outcome was improving with the combination of different types of interventions. However as breast cancer care grew increasingly complex it became necessary to formalise the structures for cooperation over disciplines. Today, a multidisciplinary team approach, where specialists of the different disciplines meet regularly, discuss the files of current breast cancer patients at the centre, and together decide on a treatment plan, is the recommended model for breast cancer care as well as for most other forms of cancer. Additionally, it has been demonstrated that decisions made by a multidisciplinary team are more likely to be in accordance with evidence-based guidelines than those made by individual clinicians [178, 183, 184].

Guidelines for multidisciplinary breast cancer care have been developed in some countries. On the European level, the establishment of multidisciplinary breast cancer centres, with a concentration of specialist care and a minimum volume of cancer cases treated every year (an annual hospital volume of

more than 150 newly diagnosed breast cancers and a caseload of at least 50 primary operations per year per breast surgeon) and fulfilling a number of other criteria identified as critical for quality care put forward by EUSOMA (European Society of Breast Cancer Specialists) is recommended by the European Parliament to be established in all member countries by 2016. This, together with nationwide screening programmes, is considered crucial to obtain and improve the overall outcome in breast cancer in Europe and decrease the differences in survival between countries [185-188].

Although it is difficult to find precise data, there appears to be great variations in the share of patients that are cared for by multidisciplinary teams both between and within the study countries. Data from several of the countries indicate that the rate of patients managed in a multidisciplinary team setting is higher in early breast cancer than for patients with metastatic disease [170, 189, 190].

4.7.2 Streamlining the patient pathway

There are many possibilities for delays in the pathway from the time an individual acknowledges the presence of symptoms to warrant a visit to a doctor, until a diagnosis has been made and, if necessary, treatment is initiated. Potential delays include: the individual may hesitate in visiting a general practitioner; the general practitioner may dismiss or misinterpret the symptoms and not conduct the relevant examinations; there can be waiting times for diagnostic tests, the interpretation of the results and for transfer to a specialist for further diagnosis or in initiation of treatment. The different types of delays are referred to as, patient's delay, doctor's delay and system delay respectively [128, 191].

Fragmentation, a lack of continuity, and long waiting times can be particularly evident for cancer patients since the care process is often long and involves different disciplines. Having to wait for the results of a diagnosis or for treatment to be initiated can be a large psychological strain. With ambitions in recent years to offer more patient-focused care, attempts have been made to create a so called seamless care process. Indeed, patients treated by multidisciplinary care teams have reported greater satisfaction, with decreased waiting times from diagnosis to treatment, and reduction in duplication of services [192, 193]. Breast cancer nurses, who often have a coordinating role in the teams and function as care coordinators and contact persons for the patients, seem to have a significant role in this [194, 195]. The aim is to ensure that the patient always knows what and when the next step will be and is not left unattended in the transfer from one medical department to another.

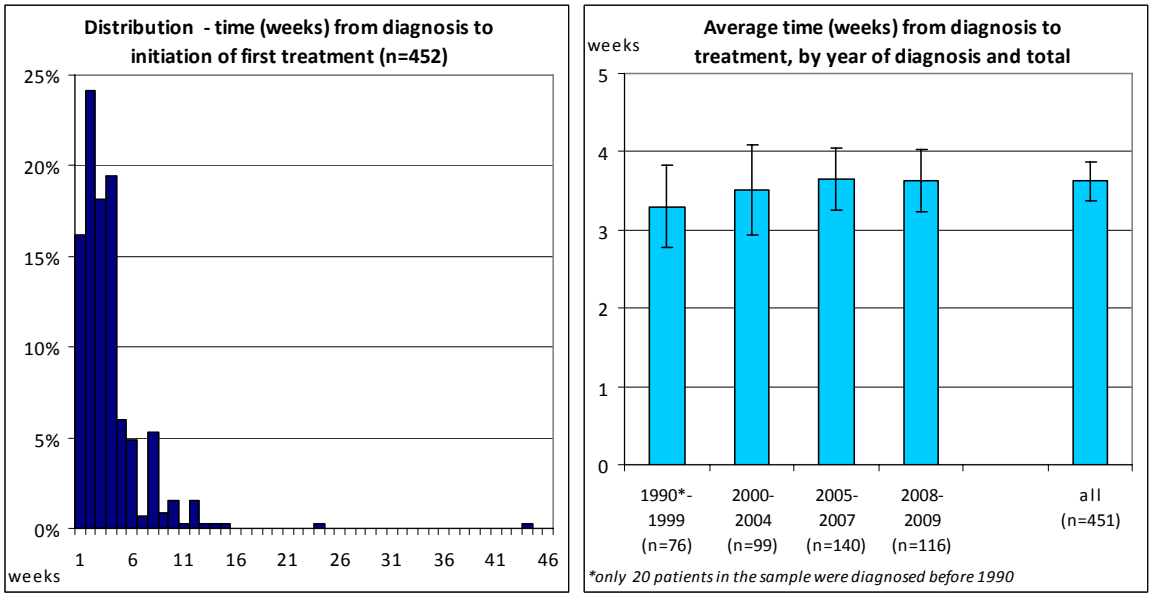
A number of initiatives have been put forward by healthcare organisations in the study countries to shorten lead times in the care process. In for example Denmark and England measures have been put in place to systematically assess the cancer care processes in order to reduce waiting times [107, 128]. England has implemented a 62-day pathway programme for cancer patients, with a maximum 2-week waiting time from urgent general practitioner referral to first hospital assessment, and no more than 1 month from hospital referral to start of treatment, which is reportedly fulfilled in the management of over 95% of urgently referred cancer cases [107]. Denmark introduced a waiting time guarantee for patients with life-threatening cancer in 2001. The national board of health in Denmark has subsequently launched a website where it is possible to check expected waiting times for selected treatments and procedures, including procedures for breast cancer, at public and private hospitals in Denmark [196].

In Mexico, long waiting times are a frequent problem in cancer care, as well as insufficient supply of drugs. Comprehensive data of available resources and access to services do not exist in Mexico, therefore the national institute of public health in Mexico is currently conducting a study to identify and map barriers to breast cancer care [121].

In Sweden, a continuous breast cancer treatment pathway has been established at the two major hospitals in Stockholm that treat breast cancer patients, by mapping the patient pathway through the hospital. Cooperation between departments has increased and waiting times have been reduced. As the mammographic, surgical, oncologic and pathologic/cytologic units are located closely together, the patients can have several diagnostic procedures done during the same visit. According to the scheme, all patients should be offered a contact person, preferably a specialist oncology nurse. One of the responsibilities of the contact person is to follow-up on waiting times, a task that unfortunately generally requires a lot of administration, since the administrative systems from different specialist units are not interlinked [197].

The patient survey that was conducted in 12 of the study countries (see chapter 1 materials and methods) asked the patients about waiting times in breast cancer care. The results showed that for almost 60% of the patients, the waiting time from diagnosis to first treatment was 3 weeks or less (figure 18). The data indicate that average waiting times have not changed noticeably in the last 20 years.

Figure 18 Waiting time from diagnosis to first treatment - patient survey in 12 of the study countries



4.7.3 Quality assurance processes

There may be many barriers to the introduction of clinical evidence into routine clinical practice. A change will often require comprehensive approaches at different levels: the policy environment; the hospital management; the specialist team; the individual physicians. Even if doctors are aware of the new clinical evidence and are willing to change, to alter well-established patterns of care is difficult, especially if the clinical environment is not conducive to change. It has been shown that important factors in order to

improve clinical practice include overall emphasis on quality rather than cost of care, treatment guidelines, awareness-raising through education, monitoring of progress continuously or at regular intervals based on defined indicators for measurement of success and feedback of results [198, 199]. A difficulty with continuous follow-up of outcomes in cancer care is that outcome quality can so far only be measured indirectly by using surrogate parameters under the general assumption that better short- to medium-term structural quality and process quality will result in improved long-term outcome quality.

One important initiative is seen in Germany where, since 2003, a growing number of German hospitals and specialist breast centres with a focus on breast cancer care have chosen to participate in a voluntary, external and independent scientific benchmarking system developed by the major German medical breast cancer societies. Detailed requirements for breast centres have been formulated, based on evidence-based guidelines and the EUSOMA requirements for specialist breast units, and a certification system has been established. The aim is to develop a comprehensive network based on voluntary self declaration of quality assurance data, to develop suitable indicators for benchmarking the quality of care delivered to breast cancer patients, and to demonstrate that the quality of cancer care can be assessed, and subsequently improved, by means of a standardised collection and analysis of such voluntary data. Quality assurance includes both comprehensive documentation of all treatments and external analysis of the data. Certified centres need to demonstrate regularly that they live up to quality requirements [189, 200].

Successful implementation of best practice cancer care throughout a country with support from comprehensive registration of treatment patterns and outcomes has been demonstrated in Sweden for childhood cancers. A so-called care quality registry for childhood cancers was initiated in Sweden in 1982. The registry captures the diagnosis, the treatment provided, and the outcome for each patient, which allows for both comprehensive assessment of the care provided and comparison of the outcomes of different treatment methods. There are today no differences in the survival from childhood cancers between different regions in the country and Sweden has, with 80% survival of childhood cancers, the highest survival rates in Europe. Care quality registries are available in Sweden on the regional level for other cancer forms as well, such as for breast cancer, but these registries are not as comprehensive as the childhood cancer registry [201].

4.7.4 National cancer control strategies

Most of the countries covered in this study have developed strategic plans for cancer control during the last decade as a response to increased cancer prevalence, scattered care and inequalities in access to care, growing possibilities to treat cancer, and a desire to improve outcome. The development of national public health programmes to reduce cancer incidence and mortality and improve quality of life, with evidenced-based strategies to make the best use of available resources, is recommended by the WHO as a means to not only to manage the present burden of cancer but to deal with the expected increased burden of cancer in the future due to changes in the demographic composition and an ageing population. Main action points recurring in many of the cancer control plans of the study countries include: (1) setup and improve registries that report not just cancer incidence and mortality but also more specific parameters that allow outcome measurement; (2) improve primary prevention by increasing awareness among the population of risk factors or by regulation for example banning smoking in public places; (3) increase early diagnosis by increasing awareness of signs and symptoms of early cancer to establish

screening programmes, or if already established, increase its national coverage and/or compliance rates; (4) improve palliative care; (5) increase the cooperation between different specialists in cancer care and streamline the treatment process along the patient pathway through the care system; (6) increase patient influence and the information provided to the patients, empower patients to understand their treatment and be involved in treatment decisions; (7) set-up and validate care quality assurance systems; (8) replace and update technical equipment and assure availability of cost-effective medical treatments; (9) support clinical research; and (10) provide continuous education of healthcare professionals [71, 106, 107, 111, 128, 197, 202-208].

In a recent publication a framework model for analysis of cancer plans was proposed and the cancer plans of European countries were analysed. It was concluded that in most cancer plans the current situation, objectives, and recommended actions were well articulated while specific mechanisms to meet the goals such as financing and resource allocation, measurement of results, and governance issues were less well defined or lacking. Equity, efficiency and patient responsiveness were considered as critical goals that were absent in most national cancer plans [209].

Countries that launched a cancer plan in the beginning of the 2000s, including Denmark, France, Norway and England, have by now had time to evaluate the results of this plan and in some cases presented follow-up plans. In the evaluation of the French cancer plan it was concluded that one of the weak points was the lack of measures to deal with unequal access to care for different socio-economic groups. Positive outcomes included increased participation in screening programmes and the increased coordination of cancer care [210, 211]. Reported successful outcomes of the English cancer plan include the introduction of cancer screening programmes and multidisciplinary teams on the national level and faster delivery of diagnosis and treatment, with the results that survival rates are improving for many cancers in the UK as well as patients' experience of their care [107].

5 The patient perspective

SUMMARY

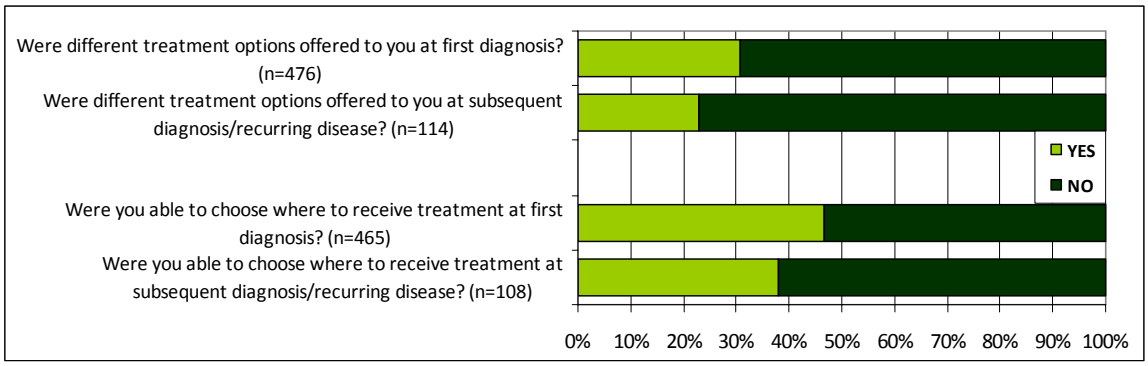
- ***Evidence-based best practices for the design and implementation of patient-focused cancer care are limited. Recommendations include to offer a choice of treatment and care packages, get systematic feedback from the patients through surveys and to engage patients in decision-making regarding the design and development of cancer care.***
- ***Increased patient involvement in treatment decisions requires informed patients. Studies have shown that doctors are inclined to underestimate the information needs of their patients and the value of obtaining the relevant information directly from the treating physician.***
- ***It is important that a healthcare system produces outcome data that are updated and relevant for patients. Patients should be able to compare the outcome in their treatment setting with the outcome of other centres as well as standard times for access, examination and treatment so that they know what they can expect in terms of care, and when a situation is not according to standard practices.***

5.1 Insight and involvement in treatment decisions

There is limited scientific evidence or best practices in the design and implementation of patient-focused care. A recent publication on evidence-based strategies to improve patients' experience of cancer care recommends to give patients information at key points along the care pathway, offer a choice of treatment and care packages, provide support for self-care and self-management, get systematic feedback from the patients through survey and engage patients in decision-making regarding the design and development of cancer care as standard practice [212].

Studies in several countries show that a great majority of breast cancer patients want to be involved in treatment decisions; over half of all patients express that they want the doctor to take the final decision on treatment, but want to feel that their views are taken into account following discussion with their doctor as part of the decision process [213-215]. It has been shown that patients that participate in treatment decisions will have more realistic expectations [197].

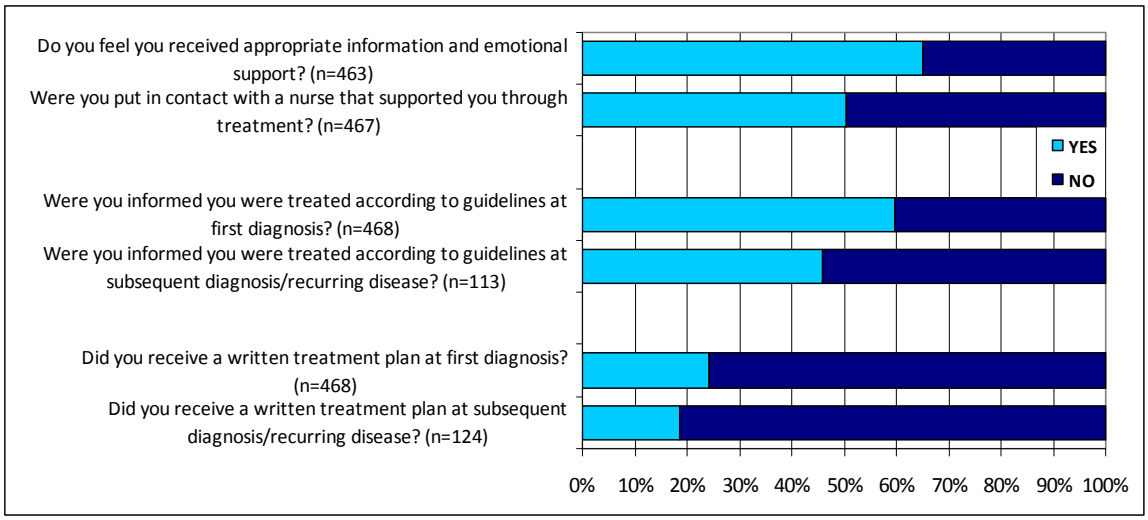
Figure 19 Patient involvement in treatment decisions - patient survey in 12 of the study countries



The patient survey conducted as part of this study, including 483 patients in 12 of the study countries, investigated to what extent patients had been involved in treatment decisions; only 30% of the patients in the survey were offered different treatment options at first diagnosis, and less than 25% of patients upon recurring disease. The majority of patients did not have the opportunity to choose where to receive treatment. This indicated that patient involvement in treatment decisions is not generally practiced, although more in-depth analyses are necessary to understand the specific patient involvement as it can have very different implications for different patients and be on different levels (figure 19).

Well-informed patients are a prerequisite for increased patient involvement in treatment decisions; a number of recent patient surveys have concluded that many patients feel that they are provided insufficient or unclear information about their disease and treatment options [213, 216-218]. Although a general trend in healthcare in many of the study countries is to give the patients more influence, e.g. in selecting care providers and treatment, a patient will in almost all cases have less knowledge and understanding of the disease than the healthcare professionals. This asymmetry of information in combination with the seriousness of a cancer diagnosis can give the patient a feeling of powerlessness in particular when the information provided about the disease and treatment options is felt to be insufficient. Therefore it is important that there is sufficient room for communication to allow the patient to get enough support and information to understand the situation and have the opportunity to plan treatment and care together with their physician. In the survey encompassing breast cancer patients in 12 of the study countries, almost two thirds of the patients felt that they had received appropriate information and emotional support. However only half of the patients were put in contact with a nurse that supported them through treatment, less than 60% of patients in the survey were informed that they were treated in line with guidelines, and no more than 25% of the patients received a written treatment plan (figure 20).

Figure 20 Provision of information and support to patients - patient survey in 12 of the study countries



A study encompassing over 600 breast cancer patients in Germany with early and metastatic disease, reported that, although patients are increasingly turning to the internet as a source of medical information, they find that the most effective and patient-relevant source of information about the

disease and the treatment options is consultation with their physician. 90% of the patients wanted to receive information on and understand the mechanisms of action of the various drugs and radiotherapy [216]. Doctors are inclined to underestimate the information needs of their patients and the value of obtaining the relevant information from the treating physician [218]. Several studies report that most patients want a maximum of detailed information, good or bad [213, 217, 218]. Some of the most frequently suggested areas of improvement from the patients in the survey were that physicians should take more time to explain things and that cooperation between the different physicians treating the patient should be improved.

Many patients express a need for a second opinion with respect to treatment of their disease in order to reduce uncertainty, for example, over 90% of patients in the German survey wanted an independent second opinion but only 20% knew of any such resource [216]. It is important from a societal perspective to address these concerns and provide patients with adequate access to a second opinion about their disease and its treatment. One may assume that this need would be even more pronounced if the patient feels that there is inequity in access to treatment within their region/country, either based on economical factors or lack of information. In line with this, it is also important that the healthcare system is able to produce outcome data that are updated and relevant for patient care. Patients should be able to compare the outcome in their treatment setting with the outcome of other centres in the country as well as outside of the country; this does require fair comparison, given that more specialised centres have a higher risk of negative outcomes due to the complexity of cases. Initiatives to increase patient involvement in care have been seen in for example in The Netherlands, where it is recommended in the national cancer plan that patients are given a more pivotal role in the development of guidelines and best practices as well as standard times for access, examination and treatment so that they know what they can expect in terms of care, and know when a situation is not handled according to standard practices [205]. In the UK cancer plan it is proposed to develop a system of “information prescriptions” at key points in the cancer treatment pathway, which will provide patients with high quality information, tailored to their individual needs [107]. In Sweden, recommendations include that each patient should be assigned a contact person at the cancer clinic upon diagnosis and that each patient should be provided an individual treatment plan. Moreover in order to provide better follow-up on improvement of patient-focused care, it is recommended that health-related quality of life and patient satisfaction are captured in the regional cancer care quality registries, by means of regular patient surveys. Patient satisfaction should cover not only general satisfaction but how the patients value and experience different aspects of their care such as communication, continuity, accessibility and lead times. This would mean it would be possible to inter-relate different dimensions of care quality, and identify a possible correlation between waiting times, patient satisfaction and quality of life [197].

One may expect that current initiatives to increase patient participation in treatment decisions and improve patient information as a means of strengthening patients’ rights will result in new generations of patients that will want to be more actively involved in treatment decision-making [213].

6 Introduction and diffusion of new medical interventions

SUMMARY

- ***Introduction of new technology in diagnostics, surgery, radiotherapy and medical treatment is usually slow in relation to clinical evidence of effectiveness. Budget impact and lack of cost-effectiveness assessment are factors that restrict prompt access to new technologies.***
- ***It is important that new technology is introduced with a perspective on the total care of the patient from prevention to palliation – drugs are subject to the most thorough assessments while there are at present no formal processes for evaluating the cost-effectiveness of other new technologies.***
- ***The prices of new drugs vary little between countries, partly due to parallel trade. This contributes to the unequal access to breast cancer drugs between low-, middle- and high-income countries.***

6.1 Screening

The first scientific evidence indicating that early diagnosis and treatment through breast screening can reduce breast cancer mortality came from a trial in New York initiated in 1964. Five Swedish clinical trials conducted between 1976 and 1984 together provide the most solid evidence regarding the effect of mammography screening on mortality [33, 219]. Early adopters of population-based mammography screening include Sweden, in 1986, and Finland in 1987. The outcome and cost-effectiveness of mammography screening has since then been assessed in a large number of studies. From a patient's perspective it may seem strange that a technology that was developed more than 30 years ago and where the benefit-risk ratio has been known for over 25 years is still not implemented. Critical issues related to mammography screening are: that it is an intervention in the general population, not a treatment of already ill patients; it is costly; and the expertise of involved personnel as well as adherence rates in the target population need to be high to ensure successful outcomes.

The cost effectiveness of mammography screening has been assessed in various European countries over the last 20 years. In a number of analyses identified from Finland, France, Italy, Hungary, The Netherlands, Norway, Slovenia, Spain, Turkey, and the UK, in a brief review of the literature, a common outcome measure has been the cost per year of life gained, which has been estimated to be in the interval of €2,000-€18,000 in identified studies [15, 220-230]. However two recent studies estimated the cost of mammography screening in Chinese women in Hong Kong to be considerably higher per year of life gained, no less than €47,000 (US$ 64,000) [231, 232]. Evidently, the cost-effectiveness of breast cancer screening is clearly related to breast cancer incidence rates in a country and lower incidence rates such as in China will lead to higher cost-effectiveness ratios associated with a screening programme.

The threshold for what is a cost-effective medical intervention is not well defined, an implicit threshold often referred to in European countries is €50,000, however a suggestion from the WHO is that a cost-effective intervention should cost less than 3 times the gross domestic product (GDP) per capita per year of life gained. This would mean a threshold of over €200,000 in for example Norway, €95,000-€100,000 in

France, Germany and the UK, €30,000 in Poland, €26,000 in Russia, €22,000-€23,000 in Mexico and Turkey, €18,000 in Brazil and €7,000 in China based on 2008 GDP levels [233, 234].

6.2 Surgery

Breast cancer surgery has moved towards breast conservation, reconstruction and sentinel node biopsy, as discussed in previous chapters. In contrast to the normal standard for approval of new drugs and some radiotherapy techniques, most of the surgical procedures in breast cancer have not been tested in prospective and randomised studies. The time lag for the introduction of new surgical techniques has differed between countries and in many countries there is no formal process in place to assure patients get access to best surgical practice. However, initiatives like the EUSOMA programme have in Europe resulted in major progress in quality and standardisation of surgical care [187, 188].

6.3 Radiotherapy

Radiotherapy has been used in the treatment of cancer for over a century, and methods have been refined over time. In recent years there has been a rapid development in the field of radiotherapy, but the diffusion of new technology into the clinical setting varies significantly. In many countries there is a shortage of radiation therapy capacity as illustrated previously in this report. The cost-effectiveness of radiotherapy in breast cancer is not as well analysed as the cost-effectiveness of screening, and most published analyses compare different radiotherapy approaches. However, a recent French study assessed the cost-effectiveness of radiotherapy for the most common cancer form to be between €5,000-€25,000 per year of life gained in France [235].

6.4 Medical treatments

As previously discussed in this report, medical treatment options in breast cancer have evolved drastically during the last decades. The introduction of new drugs is subject to the most standardised process for introduction of new technology in the treatment of cancer. Medical treatments are also generally subject to the most thorough assessment in relation to the cost-effectiveness of new interventions.

Authorisation to release a new drug on the market in a country is granted after thorough evaluation of its safety, efficacy and quality. In Europe, there is a centralised procedure for this that covers all EU countries, Iceland, Norway, and Liechtenstein; the manufacturer submits an application to the EMEA (European Medicines Agency). The EMEA evaluates the drug, and submits a recommendation to the European Commission which is the body that formally grants a marketing authorisation. The EMEA authorisation process for the 20 anticancer drugs approved between 1995 and 2005 took an average of 14 months [236]. Some authorisation processes can be significantly shorter; a new indication for trastuzumab in the treatment of early breast cancer was processed by the EMEA in a record time of 2 months in 2006. In the other study countries the decisions are taken by national medicine agencies.

The total cost of cancer drugs, and the share of treatment costs attributable to drugs, has increased significantly in the last decade due to a large number of new drugs entering the market, and is expected to continue to grow [18]. Often a new drug is offered at more or less the same price in all countries; in particular, prices are similar between countries that are open to parallel import, which means that it is possible to export a drug from a country where it is provided at a lower price to a higher-price country.

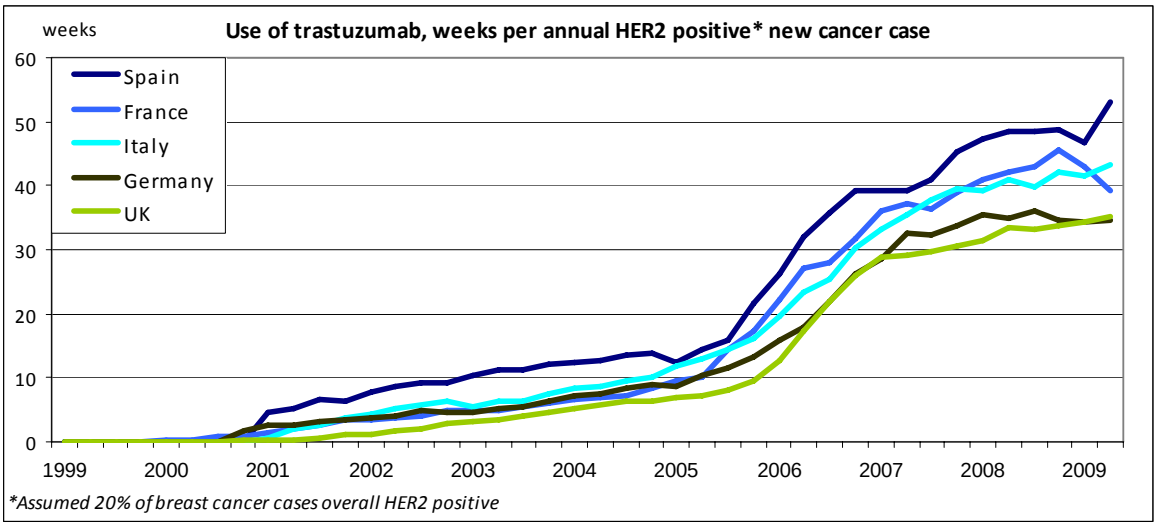
Producers' restrictions on parallel imports are prohibited by EU regulations. A consequence of drugs being offered at a similar price on all national markets is that the relative costs of, for example, new cancer drugs will vary considerably between countries with different levels of income. This leads to unequal access of novel drugs (as illustrated in figures 16 and 17 in chapter 4) since low-income countries cannot afford drugs at the same price as the high-income countries.

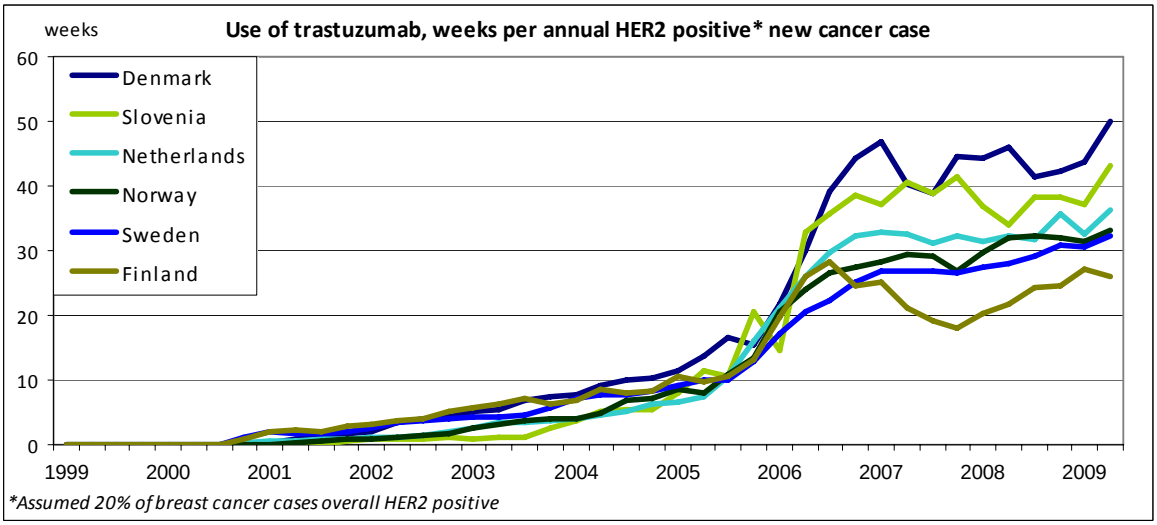
Variations in the use of new drugs in different countries have increased the focus on the development of policies regarding the use of new medical technologies and, in particular, new drugs in many of the high-income countries. Most European countries have formal mechanisms for making reimbursement decisions on the national level for pharmaceuticals. However, since cancer drugs are most often given in the hospital setting, in many countries it is not necessary to apply for reimbursement for cancer drugs. Hospital drugs are covered by the overall hospital budget and not attributed to a specific patient the way prescription drugs are. Finland, The Netherlands and Sweden are examples of countries where no formal economic regulatory approval, regarding neither pricing nor reimbursement, applies for hospital drugs. This means that drugs used in hospitals are in theory immediately available once marketing authorisation by the centralised EMEA procedure (since 1999 the only option for cancer drugs) is granted. It is however up to the regional hospital drug committees and/or the hospital units to decide what drugs will be covered in their budgets. Hospital budgets are more rigid than the budgets for ambulatory care, and it is often necessary to plan years in advance in order to make budgetary space for new treatment alternatives in inpatient care. In order to make innovative drugs accessible to patients, there is a need both for reorganisation of the financing system, so that access to treatments are not hampered by short term budget constraints, and comprehensive economic evaluation in order for long term priorities to be based on the most cost-effective treatment alternatives. There are a number of ways in which different countries have attempted to address the issues of funding new drugs; in some countries (such as France and Germany), separate lists of innovative drugs exist. These may include special funding for the drugs to be accessed outside of the hospital systems or enabling hospitals to apply to get new cancer drugs placed on the list, allowing them to switch to innovative drugs within the restrictions of their hospital budgets.

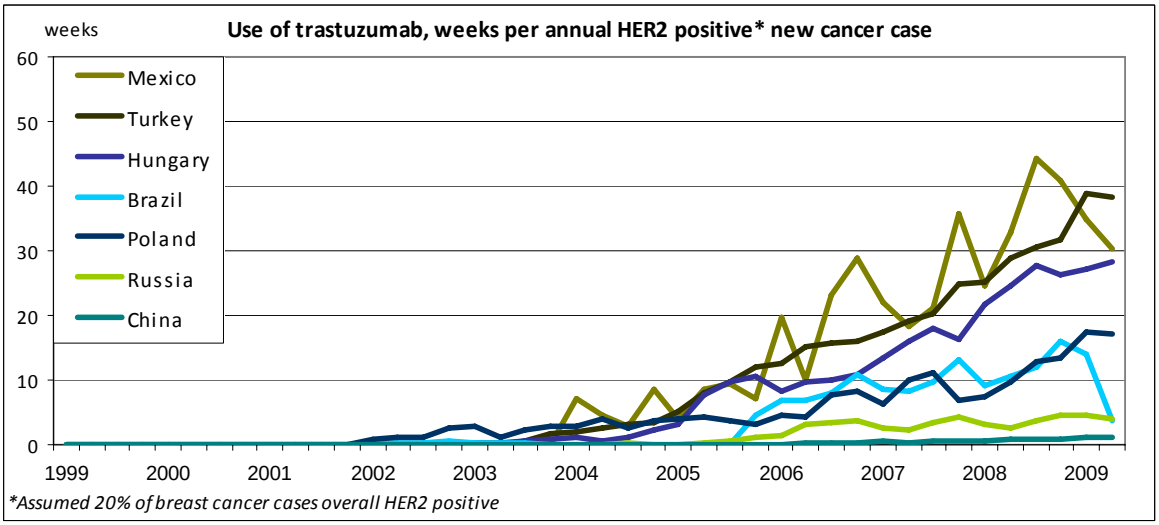
Trastuzumab is an example of an innovative cancer drug where the introduction (uptake and level of use) shows significant variations in the countries studied, specifically with regards to its initial introduction in the metastatic setting. These variations seem to reflect many different factors including: (1) knowledge about the mechanism of action and potential benefit of trastuzumab therapy; (2) differences in the interpretation of the clinical data; (3) differences in diagnostics (capacity/knowledge, etc.); (4) budget impact; (5) lack of treatment facilities; (6) delay in health technology assessment; and (7) differences in the priority of trastuzumab treatment versus other innovations in breast cancer care. The cost-effectiveness of trastuzumab in metastatic breast cancer has been estimated to range from €15,000 to €162,000 per year of life gained [237-240], and as adjuvant treatment in early breast cancer, between €12,000-€36,000 per year of life gained [241-245] in cost-effectiveness analyses conducted in a number of European countries. The introduction of trastuzumab thus illustrates many of the aspect linked to the development and clinical use of new targeted biological therapies in breast cancer, but also in oncology overall. Figure 21 illustrates the adoption of trastuzumab in clinical practice in the study countries. As can been seen the uptake increased significantly when trastuzumab was approved as adjuvant therapy in early breast cancer. The graphs are based on best available sales and incidence data for respective

country, but must be interpreted with caution due to the lack of solid epidemiological data in some countries, and incomplete sales statistics from other countries.

Figure 21 Uptake and level of use of trastuzumab in the study countries [1, 150]







7 Conclusions and recommendations

In this report we have studied the management and organisation of breast cancer care in 18 countries: Brazil, China, Denmark, Finland, France, Germany, Hungary, Italy, Mexico, The Netherlands, Norway, Poland, Russia, Slovenia, Spain, Sweden, Turkey and the UK. We have included data on outcomes of breast cancer care based on 5-year survival rates from the best available data, either from national, regional or hospital registries, in each country. We have analysed initiatives to increase early diagnosis of breast cancer and provide rapid access to evidence-based treatment but also limitations in patient access to the most appropriate diagnostics and treatments.

Breast cancer is the most common form of cancer in women. Approximately 1.2 million women worldwide are affected each year and more than 400,000 women die from the disease. The burden of breast cancer is considerable, both in terms of suffering for patients and their relatives as well as an economic burden to society.

There are large variations between the study countries in terms of incidence and mortality. Among the countries with the lowest incidence we find China, Mexico and Turkey, with an estimated 20 new annual cases per 100,000 women; these countries also have the lowest overall mortality (<10/100,000 women). Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Sweden and the UK have high incidence (>110/ 100,000 women), while the highest mortality is found in Denmark, Germany, Hungary, The Netherlands and the UK (>40/100,000 women). These variations may reflect reality, but could also to some extent relate to insufficient or incomplete cancer registration. Thus, the lack of clinical and epidemiological data in many of the study countries is a limitation when estimating the burden of disease, identifying trends in cancer prevention, care, treatment and outcomes over time as well as when making inter-country comparisons.

The direct costs of breast cancer are high, and vary significantly between the countries in the study in relation to the overall spending on healthcare. Lower overall spending on healthcare means fewer resources available for cancer treatment, limiting the ability to provide the most appropriate treatment to patients. As the majority of women affected with breast cancer are of working age, the indirect costs are considerable, estimated to be as much as twice the direct costs of breast cancer based on recent assessments in some European countries. This could be even higher in developing countries since women are affected on average at a younger age and mortality rates are higher than in developed countries.

In this study, treatment patterns and the organisation of breast cancer care were assessed to the extent possible on the basis of identified observational studies available, clinical expert input, national treatment guidelines and cancer control plans. Outcomes are presented by different levels of detail, depending on what data were available from each country. Overall the lack of available data hampers full assessment of the relationship between breast cancer care practices and disease outcomes. There is a need for registries that capture not only incidence and mortality but also treatment patterns in relation to more specific outcome measurements, including patient-rated outcomes such as quality of life.

There is a long tradition of cancer registration in the Nordic countries; specifically Denmark, Finland and Norway have detailed registration of survival data in relation to the cancer stage at diagnosis. Finland and Norway and Sweden, are also among the most successful countries when it comes to breast cancer

treatment outcome. High adherence to clinical guidelines has been reported from the Nordic countries, where the guidelines are also among the most detailed and comprehensive. Although guidelines for the organisation and treatment of breast cancer are available in almost all countries, guidelines are only monitored in a minority of countries. In order to achieve high quality and equal care it is our strong belief that guidelines need to be evidence-based, regularly updated and monitored.

The fragmented organisation and management of breast cancer care has been acknowledged by many countries and there have been extensive efforts to analyse and re-organise cancer care, resulting in the development of nationally coordinated strategies, for example in the UK. Although there are trends in many countries toward more patient-focused cancer care, as of now the patient perspective is not taken fully into account. Patient satisfaction regarding aspects such as communication, continuity, accessibility and lead times need to be captured and analysed as a lead in the re-organisation of cancer care.

Primary prevention of breast cancer is still an area under debate. Several well-performed prevention trials provide evidence that medical prevention is feasible, although it seems we are still not able to target the right population with those treatment options currently available.

Secondary prevention through the early detection of breast cancer via mammography screening has been in place for more than 20 years in some countries. However, many women still do not have access to screening programmes. As our knowledge about the biology of breast cancer increases, we may be able to improve how we target screening programmes and not just use age as the only criterion for inclusion. There is a strong positive relationship between the stage of cancer at diagnosis and outcome. In some, especially developing, countries many patients are still diagnosed at an advanced stage of disease, resulting in a poor overall outcome. The area of breast cancer diagnosis and sub-typing of the disease is likely to change over the next few years as we increase our understanding of breast cancer biology and widen the use of biological markers.

Surgery has developed significantly over the last decades. With the introduction of guidelines, both national as well as international such as the EUSOMA guidelines, breast cancer surgery has developed into a specialty of its own in many countries. This evolution in breast cancer surgery has lead to the introduction of breast conserving surgery, sentinel node biopsies and an oncoplastic surgical approach. Although these innovations in surgical treatment have not led to an increased cure rate, women with breast cancer have experienced a significantly increased quality of life due to these improvements in surgical care.

Radiotherapy has developed in a similar way as surgery over the last decades. The long-term side-effects of radiotherapy have been reduced with the introduction of new sophisticated dose planning and improved radiotherapy equipment. Thus, toxicity has been lowered for individuals treated although efficacy has not increased. Access to radiotherapy is still a critical issue with a lack of investment in equipment and staffing in many countries (Brazil, China, Hungary, Mexico, Poland, Russia, Slovenia, Spain, Turkey and the UK). This lack of investment is most frequent in countries where fewer resources are spent on healthcare.

A major reason behind the dramatic improvement we have seen in the outcome of breast cancer over the last 20-30 years has been improvements in adjuvant therapy with chemo-, endocrine and now also

targeted biological therapy. Drugs like tamoxifen, the anthracyclines, the taxanes, aromatase inhibitors as well as HER2-interacting drugs, have all contributed to the marked reduction we have seen in breast cancer relapses. However, access to adjuvant therapy varies greatly even many years after the drugs have been approved, although there are evidence-based guidelines about their use.

The follow-up of women treated for breast cancer has been under debate and there is a trend not to follow-up patients as frequently as before. Although there is little scientific evidence showing that close follow-up improves outcome measured in survival terms, one should remember that many women remain on adjuvant endocrine therapy for many years and long-term side-effects of treatment are a common cause of decreased quality of life for women treated for breast cancer. Still, as observed in this report, quality of life seems to improve over time in women cured of breast cancer.

In spite of the advances we have seen in the curative treatment of breast cancer, a significant number of women will suffer a relapse and many will develop metastatic disease. For these women it is extremely important that there is easy access to specialised care. We now have a huge therapeutic arsenal of treatments for palliation of symptoms and supportive therapy. These treatment options include surgery for metastatic complications and palliative radiotherapy but most of all a number of anti-tumour as well as supportive care drugs. Almost all anti-cancer drugs are developed in metastatic breast cancer as first- or second-line interventions and all adjuvant drugs have proven to be of clinical benefit in the metastatic stage before they are developed as adjuvant drugs. Some drugs, like the bisphosphonates, have had a major impact on quality of life of breast cancer patients and these drugs may also have a role in the curative, adjuvant situation.

Introduction of new technology will put pressure on healthcare systems, regardless of which country we are studying, though this is especially true in countries with limited resources. Variations in access that have economic determinants can possibly be addressed in the future through a greater extent of differential pricing of medical interventions between countries with different levels of healthcare resources per capita. Hospital budgets need to be flexible to accommodate new treatments. With the rapid changes in cancer care today, it will be increasingly important to continuously assess the effect of new treatments and medical interventions in clinical practice to be able to link treatment patterns to outcome. Health technology assessments and economic evaluations need to be used to guide decision makers in priorities, and to ensure that new treatments that are cost-effective gain market access quickly. It is also important that such evaluations do not delay the introduction of new treatments more than necessary.

Several patient advocacy groups have supported and provided input to this report. Based on the feedback from these groups we are able to identify some areas of common interest among patients in participating countries. Primarily patients would like to receive more information about their disease and treatment recommendations. A very important channel of information for patients is the communication between patients and physicians. It is also important that healthcare systems provide relevant information on up-to-date practice outcomes for patients, enabling patients to compare the outcome, standard times for access, examination and treatment between treatment centres so that they know what they can expect in terms of care, and can recognise when a situation may not adhere to standard practices. Again there appears to be too little attention on the situation for women with metastatic breast cancer. As pointed

out, metastatic breast cancer constitutes a large part of breast cancer care and is also an area of intensive research. The costs associated with this stage of disease are considerable and therefore a well organised evidenced-based care strategy for these women will have a major impact on the total burden of disease. One should also remember that there still is a social stigma linked to breast cancer in general and specifically to metastatic disease.

In conclusion, it is very important that regulations, priorities, funding, and organisation of breast cancer care are coordinated to provide all patients with the most appropriate, cost-effective and evidence-based treatment with minimal delays.

References

1. Ferlay, J., et al., *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0.* IARCPress, Lyon, 2000.
2. Rodriguez-Cuevas, S., et al., *Breast carcinoma presents a decade earlier in Mexican women than in women in the United States or European countries.* Cancer, 2001. **91**(4): p. 863-8.
3. *Cancer i siffror 2009.* Socialstyrelsen & Cancerfonden, 2009.
4. *Programa de acción para la prevención y control del cáncer mamario.* Programa Nacional de Salud 2001 – 2006, Secretaría de Salud, Mexico, 2001.
5. Fan, L., et al., *Breast cancer in a transitional society over 18 years: trends and present status in Shanghai, China.* Breast Cancer Res Treat, 2009. **117**(2): p. 409-16.
6. *Medical Oncology Serviced in Europe Survey (MOSES) Phase II.* ESMO MOSES Task Force, 2006.
7. Coleman, M.P., et al., *EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century.* Ann Oncol, 2003. **14 Suppl 5**: p. v128-49.
8. Engholm, G., et al., *NORDCAN: Cancer Incidence, Mortality and Prevalence in the Nordic Countries.* Association of Nordic Cancer Registries, Danish Cancer Society [Online at: www.ancr.nu, Accessed August 2009], 2009(Version 3.4).
9. *The global burden of disease: 2004 update.* World Health Organization, 2008.
10. Lidgren, M., N. Wilking, and B. Jonsson, *Cost of breast cancer in Sweden in 2002.* Eur J Health Econ, 2007.
11. *Analyse économique des coûts du cancer en France.* Institute Nacional du Cancer, 2007.
12. *Federal Health Monitoring Germany.* [Online at: www.gbe-bund.de, Accessed August 2009]
13. Mäklin, S. and P. Rissanen, *Kostnader för cancer.* Cancerorganisationernas publikationer 2006, 2006.
14. Cahuana-Hurtado, L., et al., *Análisis del gasto en salud reproductiva en México, 2003.* Rev Panam Salud Publica. 2006;20(5):287–98.
15. Yazihan, N. and H.H. Yilmaz, *Breast Cancer in Turkey: Economic Efficiency and Cost-Effectiveness.* Cancer Control in Turkey, National Cancer Advisory Board of Turkey, 2008.
16. *China Health Care Statistical Yearbook 2008 (in Chinese).* Compiled by Ministry of Health of the People's Republic of China. [Online at: www.moh.gov.cn/publicfiles/business/htmlfiles/zwgkzt/ptjnj/200809/37759.htm. Accessed June 2009], 2008.
17. Oliva, J., et al., *Indirect costs of cervical and breast cancers in Spain.* Eur J Health Econ, 2005. **6**(4): p. 309-13.
18. Jonsson, B. and N. Wilking, *A global comparison regarding patient access to cancer drugs.* Ann Oncol, 2007. **18 Suppl 3**: p. iii1-iii77.
19. Dahlberg, L., J. Lundkvist, and H. Lindman, *Health care costs for treatment of disseminated breast cancer.* Eur J Cancer, 2009. **45**(11): p. 1987-91.
20. Lidgren, M., et al., *Resource use and costs associated with different states of breast cancer.* Int J Technol Assess Health Care, 2007. **23**(2): p. 223-31.
21. Thomas, R.J., et al., *The total hospital and community UK costs of managing patients with relapsed breast cancer.* Br J Cancer, 2009. **100**(4): p. 598-600.
22. Remak, E. and L. Brazil, *Cost of managing women presenting with stage IV breast cancer in the United Kingdom.* Br J Cancer, 2004. **91**(1): p. 77-83.
23. *WHO Statistical Information System (WHOSIS).* 2009.
24. *National Cancer Control Programmes: Policies and Managerial Guidelines.* World Health Organization, Geneva, Switzerland, 2002.
25. *Cancervården i Sverige - kvalitet, struktur och aktuella utmaningar.* Socialstyrelsen, 2007-131-32, 2007.
26. *Kreftregisteret* Institutt for populasjonsbasert kreftforskning, Norway, 2009.
27. Coleman, M., et al., *Cancer Survival Trends in England and Wales 1971– 1995: Deprivation and NHS Region, Series SMPS No. 61. London: The Stationery Office.* 1999.

28. *Long-term Breast Cancer Survival, England and Wales, up to 2003.* Office for National Statistics, 2005.
29. Peto, R., *The worldwide overview: new results for systemic adjuvant therapies. For the Early Breast Cancer Trialists' Collaborative Group* San Antonio Breast Cancer Symposium. , 2007.
30. Duffy, S.W., et al., *The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties.* Cancer, 2002. **95**(3): p. 458-69.
31. Humphrey, L.L., et al., *Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force.* Ann Intern Med, 2002. **137**(5 Part 1): p. 347-60.
32. Nystrom, L., et al., *Long-term effects of mammography screening: updated overview of the Swedish randomised trials.* Lancet, 2002. **359**(9310): p. 909-19.
33. Nystrom, L., et al., *Breast cancer screening with mammography: overview of Swedish randomised trials.* Lancet, 1993. **341**(8851): p. 973-8.
34. Tabar, L., et al., *Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality.* Cancer, 2001. **91**(9): p. 1724-31.
35. Jonsson, H., R. Johansson, and P. Lenner, *Increased incidence of invasive breast cancer after the introduction of service screening with mammography in Sweden.* Int J Cancer, 2005. **117**(5): p. 842-7.
36. Jorgensen, K.J. and P.C. Gotzsche, *Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends.* Bmj, 2009. **339**: p. b2587.
37. Sainsbury, R., et al., *Does it matter where you live? Treatment variation for breast cancer in Yorkshire. The Yorkshire Breast Cancer Group.* Br J Cancer, 1995. **71**(6): p. 1275-8.
38. Chouillet, A.M., C.M. Bell, and J.G. Hiscox, *Management of breast cancer in southeast England.* Bmj, 1994. **308**(6922): p. 168-71.
39. Coleman, M.P., et al., *Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001.* Br J Cancer, 2004. **90**(7): p. 1367-73.
40. Eaker, S., et al., *Social differences in breast cancer survival in relation to patient management within a National Health Care System (Sweden).* Int J Cancer, 2009. **124**(1): p. 180-7.
41. Reyes-Ortiz, C.A., et al., *The impact of education and literacy levels on cancer screening among older Latin American and Caribbean adults.* Cancer Control, 2007. **14**(4): p. 388-95.
42. Zackrisson, S., et al., *Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma.* Int J Cancer, 2004. **108**(5): p. 754-60.
43. *EUROCARE 3/EUROCARE 4 - Survival of cancer patients in Europe* [Online at: www.eurocare.it, Accessed August 2009].
44. Verdecchia, A., et al., *Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data.* Lancet Oncol, 2007. **8**(9): p. 784-96.
45. De Angelis, R., et al., *The EUROCARE-4 database on cancer survival in Europe: data standardisation, quality control and methods of statistical analysis.* Eur J Cancer, 2009. **45**(6): p. 909-30.
46. Gábor, T., et al., *Survival chances of Hungarian cancer patients in the National Cancer Registry.* Magyar Onkológia 52:339–349, 2008, 2008.
47. Coleman, M.P., et al., *Cancer survival in five continents: a worldwide population-based study (CONCORD).* Lancet Oncol, 2008. **9**(8): p. 730-56.
48. Flores-Luna, L., et al., *Factores pronósticos relacionados con la supervivencia del cáncer de mama.* Salud Publica Mex 2008;50:119-125, 2008.
49. *Instituto Méxicano del Seguro Social, UMAE Ginecología y Obstetricia, Guadalaraja, Jalisco, Mexico.* personal communication: Dr Benito Sanchéz, 2009.
50. Merabishvili, V.M. and S. Y A, *Current development of information systems of Oncological Service.* Published in St Petersburg, personal communcation: Prof. Vladimir Fedorovich Semiglazov, General Director of Research Institute Professor N.N.Petrov, St Petersburg, Russia, 2009.
51. *Report Ministry of Health of Moscow region 2008.* Personal communication: Prof. Maria Mikhailovna Konstantinova, Deputy Head of Moscow Region Oncology Hospital, Moscow, Russia, 2009.

52. *Tomsk city and region (annual results) 2008.* Personal communication: Prof. Elena Mikhailovna Slonimskaya, Head of General surgery Department, Tomsk Cancer Research Center, Tomsk, Russia, 2009.
53. Yong, L. and L. Dingl, *Clinical characteristics of 174 breast cancer patients.* Zhonghua Shi Yong Yi Yao Za Zhi, 2005. **21**(5).
54. Anderson, B.O., et al., *Early detection of breast cancer in countries with limited resources.* Breast J, 2003. **9 Suppl 2**: p. S51-9.
55. *Coordinación delegacional de Información en Salud. 2008 Delegación Jalisco.* Personal communication: Dr Benito Sanchéz, 2009.
56. Rodríguez-Cuevas, S., F. Guisa-Hohenstein, and S. Labastida-Alamendaro, *First Breast Cancer Mammography Screening Program in Mexico: Initial Results 2005–2006.* The Breast Journal, 2009. **1**(9).
57. *Fundacão Oncocentro de São Paulo.* Boletim do Registro Hospitala de Câncer [Online at: www.fosp.saude.sp.gov.br/, Accessed September 2009], 2003. **3**(18).
58. Azevedo, G. and S. Mendonça, *A importância dos Estudos longitudinais no Brasil para os serviços de saúde A contribuição dos Registros de Câncer.* (Source: Registro Hospitalar de Câncer, Hospital do Câncer - Unidade I, II e III /INCA/MS) Coordenação de Prevenção e Vigilância, Instituto Nacional de Câncer, ppt-presentation [Online at: www4.ensp.fiocruz.br/eventos_novo/dados/arq401.pdf, Accessed September 2009].
59. Martins, E., et al., *[Temporal evolution of breast cancer stages in a population-based cancer registry in the Brazilian central region].* Rev Bras Ginecol Obstet, 2009. **31**(5): p. 219-23.
60. Giordano, S.H., et al., *Is breast cancer survival improving?* Cancer, 2004. **100**(1): p. 44-52.
61. Chia, S.K., et al., *The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer.* Cancer, 2007. **110**(5): p. 973-9.
62. Mandelblatt, J., et al., *Descriptive review of the literature on breast cancer outcomes: 1990 through 2000.* J Natl Cancer Inst Monogr, 2004(33): p. 8-44.
63. Karnofsky, D.A., et al., *The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma.* Cancer 1948: p. 634-56.
64. Spitzer, W.O., et al., *Measuring the quality of life of cancer patients: a concise QL-index for use by physicians.* J Chronic Dis, 1981. **34**(12): p. 585-97.
65. Montazeri, A., et al., *Quality of life in patients with breast cancer before and after diagnosis: an eighteen months follow-up study.* BMC Cancer, 2008. **8**: p. 330.
66. Burstrom, K., M. Johannesson, and F. Diderichsen, *A comparison of individual and social time trade-off values for health states in the general population.* Health Policy, 2006. **76**(3): p. 359-70.
67. Anderson, B.O., et al., *Overview of breast health care guidelines for countries with limited resources.* Breast J, 2003. **9 Suppl 2**: p. S42-50.
68. Eniu, A., et al., *Breast cancer in limited-resource countries: treatment and allocation of resources.* Breast J, 2006. **12 Suppl 1**: p. S38-53.
69. Eniu, A., et al., *Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation.* Cancer, 2008. **113**(8 Suppl): p. 2269-81.
70. *Advanced breast cancer: diagnosis and treatment; Early and locally advanced breast cancer: diagnosis and treatment.* National Collaborating Centre for Cancer commissioned by NICE,, 2009.
71. *Breast Cancer Treatment Guidelines.* Federal Law dated Oct 9th 2006, Ministry of Health, Russian Federation. [Online at: http://www.garant.ru/ipo/prime/doc/archive/2006/11/23/, Accessed September 2009].
72. *DBCG-retningslinier 2004.* Danish Breast Cancer Cooperative Group, 2004, revised 2009 (Breast Cancer Guidelines Denmark).
73. *Diagnostik, Therapie und Nachsorge des Mammakarzinoms der Frau*. Deutsche Krebsgesellschaft (DKG), Deutche Gesellschaft für Gynäkologie ybd Geuburtshilfe e.V. et al. 2008 (German Breast Cancer Guidelines).
74. *Guía para el diagnóstico y el tratamiento del Cáncer de Mama en el Principado de Asturias.* Servicio de Salud del Principado de Asturias, 2005.

75. *Linee Guida F.O.N.Ca.M. 2005 – Terapia medica.* F.O.N.Ca.M. 2005 (Italian Breast Cancer Guidelines).
76. *Linee Guide Tumore Mammario, Prevenzione - Diagnosi - Terapia, 3 Edizione.* Gruppo Senologico Veronese, 2008.
77. *Mama. Diretrizes para Rastreamento e Detecção Precoce de Câncer; Mama. Tratamento Adjuvante; Mama. Doença Localmente Avançada; Mama. Doença Metastática.* Hospital Sirio Libanês 2008 (Brazilian Breast Cancer Guidelines).
78. *MAMMACARCINOOM Landelijke richtlijn met regionale toevoegingen Versie 1.1 Regio: Landelijk.* NABON, 2008 (Dutch Breast Cancer Guidelines).
79. *Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av pasienter med brystkreft.* Sosial- og helsedirektoratet, 2007 (Breast Cancer Guidelines Norway).
80. *Nationella riktlinjer för bröstcancersjukvård - Medicinskt och hälsoekonomiskt faktadokument.* Socialstyrelsen 2007 (Breast Cancer Guidelines Sweden).
81. *Oncoguía de cáncer de mama - Cominidad Valenciana.* Generalitat Valenciana Conselleria de Sanitat, 2005.
82. *Primera reunión sobre tratamiento médica del cáncer mamario.* Gaceta Mexicana de Oncología, Volumen 6, Suplemento 1, 2007.
83. *Recommandations pour la Pratique Clinique : Saint Paul de Vence 2007 - Cancers du sein.* Groupe de travail Saint Paul de Vence, 2007 (French Breast Cancer Guidelines)
84. *Smernice zdravljenja raka dojk.* Onkoloski Institut Ljubljana, 2004 (Slovenian Treatment Guidelines).
85. *Treatment guidelines for breast cancer by Chinese anti-cancer association.* [Online at: www.cbcs.cn/, Accessed August 2009], 2007.
86. *Zalecenia postepowania diagnostyczno-terapeutycznegow nowotworach zlosliwych - 2009 rok.* Polska Unia Onkologii, 2009 (Polish Breast Cancer Guidelines).
87. Mayo, I., et al., *Epidemiology of breast cancer.* Lancet Oncol. 2001;2:133-140.
88. Lichtenstein, P., et al., *Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland.* N Engl J Med, 2000. **343**(2): p. 78-85.
89. Ford, D., et al., *Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium.* Lancet, 1994. **343**(8899): p. 692-5.
90. Easton, D.F., et al., *Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13.* Am J Hum Genet, 1997. **61**(1): p. 120-8.
91. Claus, E.B., et al., *The genetic attributable risk of breast and ovarian cancer.* Cancer, 1996. **77**(11): p. 2318-24.
92. Fisher, B., et al., *Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.* J Natl Cancer Inst, 1998. **90**(18): p. 1371-88.
93. Freedman, A.N., et al., *Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention.* J Natl Cancer Inst, 2003. **95**(7): p. 526-32.
94. Gail, M.H., *The estimation and use of absolute risk for weighing the risks and benefits of selective estrogen receptor modulators for preventing breast cancer.* Ann N Y Acad Sci, 2001. **949**: p. 286-91.
95. Kosters, J.P. and P.C. Gotzsche, *Regular self-examination or clinical examination for early detection of breast cancer.* Cochrane Database Syst Rev, 2003(2): p. CD003373.
96. López-Carrillo, L., et al., *Identificación de lesiones mamarias malignas en México.* Salud Publica Mexicana, 2001. **43**: p. 199-202.
97. Agarwal, G., et al., *Spectrum of breast cancer in Asian women.* World J Surg, 2007. **31**(5): p. 1031-40.
98. Olsen, O. and P.C. Gotzsche, *Screening for breast cancer with mammography.* Cochrane Database Syst Rev, 2001(4): p. CD001877.
99. Gotzsche, P.C. and O. Olsen, *Is screening for breast cancer with mammography justifiable?* Lancet, 2000. **355**(9198): p. 129-34.

100. *Council recommendation of 2 December 2003 on cancer screening (2003/878/EC).* Official Journal of the European Union, 2003.
101. *IARC Handbook of Cancer Prevention Volume 7 - Breast Cancer Screening.* IARCPress, Lyon, 2002.
102. *European guidelines for quality assurance in breast cancer screening and diagnosis, Fourth Edition.* Health & Consumer Protection, Directorate-General, European Communities, 2006.
103. *OECD Health Data 2009.* Organisation for Economic Co-operation and Development.
104. *Bostadsort avgör tidig upptäckt av bröstcancer* Cancerfonden [Online at: http://www.cancerfonden.se/sv/Om-Cancerfonden/Press/Pressmeddelanden/Bostadsort-avgor-tidig-upptackt-av-brostcancer/, Accessed August 2009], 2008.
105. Verbeek, A.L. and M.J. Broeders, *Evaluation of The Netherlands breast cancer screening programme.* Ann Oncol, 2003. **14**(8): p. 1203-5.
106. *Nasjonal strategi for kreftområdet 2006-2009.* Sosial- og helsedirektoratet, 2006 (National Cancer Plan Norway).
107. *Cancer Reform Strategy* NHS, Department of Health, England, 2007.
108. *VIGITEL BRASIL 2008 - Vigilância de fatores de risco e protecão para doencas crônica por inquérito telefônico.* Ministério da Saúde, 2009.
109. *Baromètre cancer 2005.* Institute national de prévention et d'éducation pour la santé, France.
110. *personal communication: .* Dr. Simona Borštnar, Institute of Oncology, Ljubljana, Slovenia, 2009.
111. *Estrategia en Cáncer del Sistema Nacional de Salud.* Ministerio de Sanidad y Consumo, 2006 (National Cancer Strategy Spain).
112. *Encuesta Nacional de Salud 2006.* Ministerio de Sanidad y Consumo, Gobierno de España.
113. Boncz, I., et al., *The organisation and results of first screening round of the Hungarian nationwide organised breast cancer screening programme.* Ann Oncol, 2007. **18**(4): p. 795-9.
114. Giorgi, D., et al., *Mammography screening in Italy: 2005 survey and 2006 preliminary data.* Epidemiol Prev, 2008. **32**(2 Suppl 1): p. 7-22.
115. *National Cancer Program 2009-2015.* Department of Cancer Control, Ministry of Health, Turkey, 2009.
116. *personal communication:.* Associate Prof. Tadeusz Pienkowski, Centrum Onkologii, Warsawa, 2009.
117. *Encuesta Nacional de Salud y Nutrición - ENSANUT.* Institute Nacional de Salud Pública, Mexico, 2006.
118. Hjulmann, K., H. Vondeling, and M. Bech, *Why did some Danish counties introduce breast cancer screening and others not? An exploratory study of four selected counties.* Int J Technol Assess Health Care, 2008. **24**(3): p. 326-32.
119. Coebergh, J.W., *Early breast cancer in Europe: progress and pitfalls in detection and management at the start of the new century.* Eur J Cancer, 2003. **39**(12): p. 1645-7.
120. Halmin, M., et al., *Long-term inequalities in breast cancer survival--a ten year follow-up study of patients managed within a National Health Care System (Sweden).* Acta Oncol, 2008. **47**(2): p. 216-24.
121. Knaul, F.M., et al., *Breast cancer in Mexico: a pressing priority.* Reprod Health Matters, 2008. **16**(32): p. 113-23.
122. Nigenda, G., M. Caballero, and L. González, *Social process of breast cancer in Mexico. Research protocol.* National Institute of Public Health,Cuernavaca, 2008.
123. Chua, M.S., et al., *Knowledge, perceptions, and attitudes of Hong Kong Chinese women on screening mammography and early breast cancer management.* Breast J, 2005. **11**(1): p. 52-6.
124. *Programa Nacional de Salud 2007-2012 - Por un México sano: construyendo alianzas para una mejor salud.* Secretaria de Salud, 2007 (National Health Plan Mexico)
125. Hujun, L., *The Plight of China's Breast Cancer Screening Program.* China Today - Explaning China to the World, [Online at: www.chinatoday.com.cn, Accessed September 2009], 2009.
126. Wang, S.-m., *Concerns on diagnosis and treatment of breast cancer in China.* Chinese Medical Journal, 2007. **120**(20): p. 1741-1742.

127. *Sceening for Breast Cancer.* WHO, [Online at: http://www.who.int/cancer/detection/breastcancer/en/, Accessed September 2009], Accessed September 2009.
128. *KRÆFTPLAN II.* Sundhedsstyrelsen 2005 (National Cancer Plan II Denmark).
129. Piccart-Gebhart, M.J., et al., *Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.* N Engl J Med, 2005. **353**(16): p. 1659-72.
130. Romond, E.H., et al., *Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.* N Engl J Med, 2005. **353**(16): p. 1673-84.
131. Fisher, B., et al., *Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation.* N Engl J Med, 2002. **347**(8): p. 567-75.
132. Veronesi, U. and S. Zurrida, *Preserving life and conserving the breast.* Lancet Oncol, 2009. **10**(7): p. 736.
133. Tsai, R.J., et al., *The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors.* Ann Surg Oncol, 2009. **16**(7): p. 1959-72.
134. Clarke, M., et al., *Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **366**(9503): p. 2087-106.
135. Bentzen, S.M., et al., *Towards evidence-based guidelines for radiotherapy infrastructure and staffing needs in Europe: the ESTRO QUARTS project.* Radiother Oncol, 2005. **75**(3): p. 355-65.
136. Slotman, B.J., et al., *Overview of national guidelines for infrastructure and staffing of radiotherapy. ESTRO-QUARTS: work package 1.* Radiother Oncol, 2005. **75**(3): p. 349-54.
137. *DIRAC (DIrectory of RAdiotherapy Centres).* International Atomic Energy Agency [Online at: www.iaea.org, Accessed September 2009], 2009.
138. Williams, M.V. and K.J. Drinkwater, *Geographical variation in radiotherapy services across the UK in 2007 and the effect of deprivation.* Clin Oncol (R Coll Radiol), 2009. **21**(6): p. 431-40.
139. Wilking, N., et al., *Benchmarking report of lung cancer care in selected European Countries, Australia, Brazil, Japan, Mexico and New Zealand.* [Online at: www.comparatorreports.se, Accessed September 2009], 2008.
140. Ravdin, P.M., et al., *Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.* J Clin Oncol, 2001. **19**(4): p. 980-91.
141. Siminoff, L.A., et al., *A decision aid to assist in adjuvant therapy choices for breast cancer.* Psychooncology, 2006. **15**(11): p. 1001-13.
142. *Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **365**(9472): p. 1687-717.
143. Henderson, I.C., et al., *Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.* J Clin Oncol, 2003. **21**(6): p. 976-83.
144. Mamounas, E.P., et al., *Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28.* J Clin Oncol, 2005. **23**(16): p. 3686-96.
145. *Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 1998. **352**(9132): p. 930-42.
146. Clarke, M., et al., *Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials.* Lancet, 2008. **371**(9606): p. 29-40.
147. *Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group.* N Engl J Med, 1988. **319**(26): p. 1681-92.
148. *Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 1992. **339**(8785): p. 71-85.

149. *Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 1998. **351**(9114): p. 1451-67.
150. *Pharmaceutical sales data.* IMS health database, 2009.
151. Gnant, M., et al., *Maintaining bone density in patients undergoing treatment for breast cancer: is there an adjuvant benefit?* Clin Breast Cancer, 2009. **9 Suppl 1**: p. S18-27.
152. Gnant, M.F., et al., *Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group.* J Clin Oncol, 2007. **25**(7): p. 820-8.
153. Bedard, P.L., J.J. Body, and M.J. Piccart-Gebhart, *Sowing the soil for cure? Results of the ABCSG-12 trial open a new chapter in the evolving adjuvant bisphosphonate story in early breast cancer.* J Clin Oncol, 2009. **27**(25): p. 4043-6.
154. Chen, Z., et al., *The use of complementary and alternative medicine among Chinese women with breast cancer.* J Altern Complement Med, 2008. **14**(8): p. 1049-55.
155. Zhang, M., et al., *Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients.* Cochrane Database Syst Rev, 2007(2): p. CD004921.
156. *Evaluering af kræftplanens gennemførelse – Status og fremtidig monitorering.* Sundhedsstyrelsen, Center for Evaluering og Medicinsk Teknologivurdering, 2004.
157. Winnefeld, M. and S. Bruggemann, *[Practice guideline for breast cancer rehabilitation from the perspective of the rehabilitation centres: findings of a user survey on acceptance and practicability of the pilot version].* Rehabilitation (Stuttg), 2008. **47**(6): p. 334-42.
158. Weis, J. and U. Domann, *Development of an evidence based clinical guideline for the rehabilitation of breast cancer patients.* Meeting Abstract 27. Deutscher Krebskongress Deutsche Krebsgesellschaft e.V., 2006.
159. Rojas, M.P., et al., *Follow-up strategies for women treated for early breast cancer.* Cochrane Database Syst Rev, 2005(1): p. CD001768.
160. Mieog, J.S., J.A. van der Hage, and C.J. van de Velde, *Preoperative chemotherapy for women with operable breast cancer.* Cochrane Database Syst Rev, 2007(2): p. CD005002.
161. Cardoso, F., et al., *International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy.* J Natl Cancer Inst, 2009. **101**(17): p. 1174-81.
162. Mazur, D.J. and D.H. Hickman, *Patient preferences: survival vs quality-of-life considerations.* J Gen Intern Med, 1993. **8**(7): p. 374-7.
163. Hillner, B.E., et al., *American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer.* J Clin Oncol, 2003. **21**(21): p. 4042-57.
164. Hillner, B.E., et al., *American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel.* J Clin Oncol, 2000. **18**(6): p. 1378-91.
165. Aranda, S., et al., *Mapping the quality of life and unmet needs of urban women with metastatic breast cancer.* Eur J Cancer Care (Engl), 2005. **14**(3): p. 211-22.
166. Arathuzik, D., *Pain experience for metastatic breast cancer patients. Unraveling the mystery.* Cancer Nurs, 1991. **14**(1): p. 41-8.
167. Asola, R., H. Huhtala, and K. Holli, *Intensity of diagnostic and treatment activities during the end of life of patients with advanced breast cancer.* Breast Cancer Res Treat, 2006. **100**(1): p. 77-82.
168. Cheville, A.L., et al., *Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer.* J Clin Oncol, 2008. **26**(16): p. 2621-9.
169. Koopman, C., et al., *Sleep disturbances in women with metastatic breast cancer.* Breast J, 2002. **8**(6): p. 362-70.
170. *Medical Oncology Status in Europe Survey (MOSES) Phase III.* The ESMO MOSES Task Force, 2008.
171. *Improving Supportive and Palliative Care for Adults with Cancer.* National Institute for Clinical Excellence, 2004.

172. *Guía de Práctica Clínica sobre Cuidados Paliativos.* GUÍAS DE PRÁCTICA CLÍNICA EN EL SNS, Ministerio de Sanidad y Consumo, Gobierno de España, 2008.
173. Ribeiro, J.M., *UHS development and hospital services rationing.* Cien Saude Colet, 2009. **14**(3): p. 771-82.
174. Caleffi, M., et al., *A model to optimize public health care and downstage breast cancer in limited-resource populations in southern Brazil. (Porto Alegre Breast Health Intervention Cohort).* BMC Public Health, 2009. **9**: p. 83.
175. Rezende, M.C., et al., *[Factors leading to delay in obtaining definitive diagnosis of suspicious lesions for breast cancer in a dedicated health unit in Rio de Janeiro].* Rev Bras Ginecol Obstet, 2009. **31**(2): p. 75-81.
176. Brito, C., M.C. Portela, and M.T. Vasconcellos, *[Public care for breast cancer women in the state of Rio de Janeiro, Brazil].* Rev Saude Publica, 2005. **39**(6): p. 874-81.
177. Stefoski Mikeljevic, J., et al., *Surgeon workload and survival from breast cancer.* Br J Cancer, 2003. **89**(3): p. 487-91.
178. Sainsbury, R., et al., *Influence of clinician workload and patterns of treatment on survival from breast cancer.* Lancet, 1995. **345**(8960): p. 1265-70.
179. Roohan, P.J., et al., *Hospital volume differences and five-year survival from breast cancer.* Am J Public Health, 1998. **88**(3): p. 454-7.
180. Houssami, N. and R. Sainsbury, *Breast cancer: multidisciplinary care and clinical outcomes.* Eur J Cancer, 2006. **42**(15): p. 2480-91.
181. Hillner, B.E., T.J. Smith, and C.E. Desch, *Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care.* J Clin Oncol, 2000. **18**(11): p. 2327-40.
182. Grilli, R., et al., *Do specialists do it better? The impact of specialization on the processes and outcomes of care for cancer patients.* Ann Oncol, 1998. **9**(4): p. 365-74.
183. Gillis, C.R. and D.J. Hole, *Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland.* Bmj, 1996. **312**(7024): p. 145-8.
184. Chang, J.H., et al., *The impact of a multidisciplinary breast cancer center on recommendations for patient management: the University of Pennsylvania experience.* Cancer, 2001. **91**(7): p. 1231-7.
185. *European Parliament resolution on breast cancer in the European Union (2002/2279(INI)).* P5_TA(2003)0270.
186. *European Parliament resolution on breast cancer in the enlarged European Union.* B6-0528/2006.
187. Blamey, R., *The requirements of a specialist breast unit.* European Journal of Cancer, 2000. **36**: p. 2288-93.
188. Blamey, R. and L. Cataliotti, *The requirements of a specialist Breast Unit, a revised version of the original EUSOMA position paper published in 2000 (European Journal of Cancer 2000; 36: 2288-2293).* EUSOMA, 2004.
189. Brucker, S.Y., et al., *Certification of breast centres in Germany: proof of concept for a prototypical example of quality assurance in multidisciplinary cancer care.* BMC Cancer, 2009. **9**: p. 228.
190. Merck, B., et al., *[Application of the EUSOMA criteria in breast units in countries of the European Union].* Cir Esp, 2005. **77**(2): p. 65-9.
191. Unger-Saldaña, K. and C. Infante-Castañeda, *Delay of medical care for symptomatic breast cancer: A literature review.* Salud Publica Mexicana, 2009. **51** (suppl 2): p. S270-S285.
192. Gabel, M., N.E. Hilton, and S.D. Nathanson, *Multidisciplinary breast cancer clinics. Do they work?* Cancer, 1997. **79**(12): p. 2380-4.
193. *Multidisciplinary meetings for cancer care - a guide for health service providers.* National Breast Cancer Centre, Australian Government, Department of Health and Ageing, 2005.
194. Amir, Z., J. Scully, and C. Borrill, *The professional role of breast cancer nurses in multi-disciplinary breast cancer care teams.* Eur J Oncol Nurs, 2004. **8**(4): p. 306-14.
195. Haward, R., et al., *Breast cancer teams: the impact of constitution, new cancer workload, and methods of operation on their effectiveness.* Br J Cancer, 2003. **89**(1): p. 15-22.
196. *Ventetider.* Sundhedsstyrelsen, [Online at: www.venteinfo.dk/, Accessed September 2009].

197. *En nationell cancerstrategi för framtiden (SOU 2009:11).* Utredningen En nationell cancerstrategi, 2009 (National Cancer Strategy Sweden).
198. Grol, R. and J. Grimshaw, *From best evidence to best practice: effective implementation of change in patients' care.* Lancet, 2003. **362**(9391): p. 1225-30.
199. Grimshaw, J.M. and I.T. Russell, *Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations.* Lancet, 1993. **342**(8883): p. 1317-22.
200. Brucker, S.Y., et al., *Benchmarking the quality of breast cancer care in a nationwide voluntary system: the first five-year results (2003-2007) from Germany as a proof of concept.* BMC Cancer, 2008. **8**: p. 358.
201. Gustafsson, G., M. Heyman, and Å. Vernby, *Childhood Cancer Incidence and Survival in Sweden 1984-2005, Report 2007 From the Swedish Childhood Cancer Registry.* Karolinska Institutet / The Swedish Childhood Cancer Foundation.
202. *Hungarian National Cancer Control Programme.* Government of the Republic of Hungary, 2006
203. *Materiale prodotto dalla Commissione oncologica nazionale (D.M. 26.5.2004) per un Piano Oncologico Nazionale.* Ministero della Salute, 2004.
204. *Narodowy progam zwalczania nowotwórów.* Ministry of Health, 2005 (National Cancer Control Programme Poland)
205. *National Cancer Control Programme - Part I: NPK Vision and Summary 2005-2010.* NPK Steering Group, 2004.
206. *Plan Cancer: 2003-2007.* Mission Interministérielle pour la Lutte contre le Cancer, 2003 (National Cancer Plan France).
207. *PORTARIA Nº 2.439/GM DE 8 DE DEZEMBRO DE 2005 - Política Nacional de Atenção Oncológica.* Ministro de Estado da Saúde, 2005 (National Oncology Policy Brazil).
208. *The Programme of Cancer Prevention and Control in China (2004-2010).* Ministry of Health, 2003.
209. Atun, R., T. Ogava, and J.M. Martin-Moreno, *Analysis of National Cancer Control Programmes in Europe.* Imperial College London Business School, 2009.
210. *Évaluation du plan cancer - Rapport Final.* Haut Conseil de la Santé Publique, France, 2009.
211. *Rapport Public thématique «La mise en oeuvre du plan cancer ».* La cour des comptes, France, 2008.
212. Coulter, A., *Evidence on the effectiveness of strategies to improve patients' experience of cancer care.* Cancer Reform Strategy, Patient Experience Working Group, Macmillian Cancer Support, 2007.
213. Wallberg, B., et al., *Information needs and preferences for participation in treatment decisions among Swedish breast cancer patients.* Acta Oncol, 2000. **39**(4): p. 467-76.
214. Sutherland, H., H. Llewellyn-Thomas, and G. Lockwood, *Cancer patients: their desire for information and participation in treatment decisions.* J R Soc Med, 1989. **82**: p. 260-3.
215. Bilodeau, B. and L. Degner, *Information needs, sources of information and decisional roles in women with breast cancer.* Oncol Nurs Forum 1996. **23**: p. 691-6.
216. Oskay-Ozcelik, G., et al., *Breast cancer patients' expectations in respect of the physician-patient relationship and treatment management results of a survey of 617 patients.* Ann Oncol, 2007. **18**(3): p. 479-84.
217. Jenkinks, V., L. Fallowfield, and J. Saul, *Information needs of patients with cancer: results from a large study in UK cancer centres.* British Journal of Cancer, 2001. **84**(1): p. 48-51.
218. Degner, L.F., et al., *Information needs and decisional preferences in women with breast cancer.* Jama, 1997. **277**(18): p. 1485-92.
219. Andersson, I., *Några glimtar ur mammografins historia: Från preparatröntgen till allmän screening.* Läkartidningen, 1996. **93**(14): p. 1329-1333.
220. de Koning, H.J., et al., *Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors.* Int J Cancer, 1991. **49**(4): p. 531-7.
221. Norum, J., *Breast cancer screening by mammography in Norway. Is it cost-effective?* Ann Oncol, 1999. **10**(2): p. 197-203.

222. De Koning, H.J., *Breast cancer screening; cost-effective in practice?* Eur J Radiol, 2000. **33**(1): p. 32-7.
223. Vanara, F., et al., *[Cost-benefit analysis of a mammography screening program extended to all the national territory].* Epidemiol Prev, 1997. **21**(2): p. 118-28.
224. Plans, P., L. Casademont, and L. Salleras, *Cost-effectiveness of breast cancer screening in Spain.* Int J Technol Assess Health Care, 1996. **12**(1): p. 146-50.
225. Leivo, T., et al., *The cost-effectiveness of nationwide breast carcinoma screening in Finland, 1987-1992.* Cancer, 1999. **86**(4): p. 638-46.
226. Boncz, I., et al., *[Health economics analysis of breast cancer screening].* Magy Onkol, 2003. **47**(2): p. 149-54.
227. van Ineveld, B.M., et al., *How cost-effective is breast cancer screening in different EC countries?* Eur J Cancer, 1993. **29A**(12): p. 1663-8.
228. Wang, H., et al., *Mammography screening in Norway: results from the first screening round in four counties and cost-effectiveness of a modeled nationwide screening.* Cancer Causes Control, 2001. **12**(1): p. 39-45.
229. Rojnik, K., et al., *Probabilistic cost-effectiveness modeling of different breast cancer screening policies in Slovenia.* Value Health, 2008. **11**(2): p. 139-48.
230. *Screening for breast cancer in England: past and future.* J Med Screen, 2006. **13**(2): p. 59-61.
231. Woo, P.P., J.J. Kim, and G.M. Leung, *What is the most cost-effective population-based cancer screening program for Chinese women?* J Clin Oncol, 2007. **25**(6): p. 617-24.
232. Wong, I.O., et al., *Cost effectiveness of mammography screening for Chinese women.* Cancer, 2007. **110**(4): p. 885-95.
233. *WHO Choice (CHOosing Interventions that are Cost Effective): Tables of Costs and Prices used in WHO-CHOICE Analysis.* [Online at:www.who.int/choice/en/, Accessed October 2009].
234. *World Economic Outlook Database, October 2009: Nominal GDP list of countries. Data for the year 2008.* International Monetary Fund.
235. Durand-Zaleski, I., *[Economic evaluation of radiotherapy: methods and results].* Cancer Radiother, 2005. **9**(6-7): p. 449-51.
236. Netzer, T., *European Union centralised procedure for marketing authorisation of oncology drugs: an in-depth review of its efficiency.* Eur J Cancer, 2006. **42**(4): p. 446-55.
237. Lidgren, M., et al., *Cost-effectiveness of HER2 testing and trastuzumab therapy for metastatic breast cancer.* Acta Oncol, 2008. **47**(6): p. 1018-28.
238. Norum, J., T. Risberg, and J.A. Olsen, *A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a model-based cost-effectiveness analysis.* Ann Oncol, 2005. **16**(6): p. 909-14.
239. Perez-Ellis, C., et al., *Cost-Effectiveness Analysis of Trastuzumab (Herceptin) in HER2-Overexpressed Metastatic Breast Cancer.* Am J Clin Oncol, 2009.
240. Poncet, B., et al., *Use of the monoclonal antibody anti-HER2 trastuzumab in the treatment of metastatic breast cancer: a cost-effectiveness analysis.* Am J Clin Oncol, 2008. **31**(4): p. 363-8.
241. Fagnani, F., et al., *[Cost/effectiveness analysis of adjuvant therapy with trastuzumab in patients with HER2 positive early breast cancer].* Bull Cancer, 2007. **94**(7): p. 711-20.
242. Liberato, N.L., M. Marchetti, and G. Barosi, *Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer.* J Clin Oncol, 2007. **25**(6): p. 625-33.
243. Lidgren, M., et al., *Cost-effectiveness of HER2 testing and 1-year adjuvant trastuzumab therapy for early breast cancer.* Ann Oncol, 2008. **19**(3): p. 487-95.
244. Norum, J., et al., *Trastuzumab in adjuvant breast cancer therapy. A model based cost-effectiveness analysis.* Acta Oncol, 2007. **46**(2): p. 153-64.
245. Ward, S., H. Pilgrim, and D. Hind, *Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.* Health Technol Assess, 2009. **13 Suppl 1**: p. 1-6.