MEPI

MESTRADO EM EPIDEMIOLOGIA

UNIVERSIDADE DO PORTO
FACULDADE DE MEDICINA

Joana Maria Correia Amaro

PATTERNS OF BREAST CANCER MORTALITY TRENDS IN EUROPE

Porto, 2012

MEPI MESTRADO EM EPIDEMIOLOGIA

UNIVERSIDADE DO PORTO
FACULDADE DE MEDICINA

Joana Maria Correia Amaro

PATTERNS OF BREAST CANCER MORTALITY TRENDS IN EUROPE

Dissertação de candidatura ao grau de Mestre em Epidemiologia apresentada à Faculdade de Medicina da Universidade do Porto, sob orientação do Professor Doutor Nuno Lunet

Porto, 2012

Ao abrigo do Art.º 8º do Decreto-Lei nº 288/70 esta dissertação tem como base um manuscrito, no qual colaborei ativamente na operacionalização das hipóteses, recolha, análise e interpretação dos dados e fui responsável pela redação da sua primeira versão:

- Joana Amaro, Milton Severo, Sofia Vilela, Sérgio Fonseca, Filipa Fontes, Carlo La Vecchia, Nuno Lunet. Patterns of breast cancer mortality trends in Europe. [Submetido]

AGRADECIMENTOS

Ao Professor Doutor Nuno Lunet, orientador desta dissertação, pelo seu empenho, espirito critico, incansável disponibilidade e generosidade ao longo de todo o processo de elaboração do presente trabalho.

Aos meus colegas de mestrado, em particular à Sofia e ao Sérgio, pela amizade e pela partilha de conhecimentos e experiências ao longo destes dois anos.

Aos colegas do Departamento de Epidemiologia Clinica, Medicina Preventiva e Saúde Publica e do Instituto de Saúde Pública da Universidade do Porto, em especial à Sandra, Sara e Helena pela amizade, preocupação e apoio constantes.

A todos os meus amigos, pela compreensão e paciência.

À minha família, em particular aos meus pais e irmão, pelo apoio e carinho incondicionais.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

APC – Annual Percent Change

ASIR – Age-Standardized Incidence Rates (world standard population)

ASMR – Age Standardized Mortality Rates (world standard population)

BCE – Breast clinical examination

BIC – Bayesian Information Criterion

BRCA1 – Breast cancer susceptibility gene 1

BRCA2 – Breast cancer susceptibility 2

BSE – Breast self-examination

CI – Confidence interval

DALYs – Disability-Adjusted Life Years

GDP – Gross Domestic Product

HRT – Hormone Replacement Therapy

ICD – International Classification of Diseases

UK – United Kingdom

USD – United States dollar

WHO – World Health Organization

LIST OF FIGURES

INTRODUCTION

MANUSCRIPT

LIST OF TABLES

MANUSCRIPT

LIST OF APPENDIX

MANUSCRIPT

1. RESUMO

Introdução: As taxas de incidência de cancro da mama têm vido a aumentar na maioria dos países e este apresenta-se como a principal causa de morte oncológica entre as mulheres, apesar da diminuição na mortalidade observada nas últimas décadas por toda a Europa. Contudo, é ainda difícil de avaliar o quanto da redução da mortalidade pode ser atribuída a uma maior frequência de diagnóstico precoce, nomeadamente através de rastreio por mamografia, ou ao acesso a tratamentos mais eficazes. A identificação de grupos de países homogéneos quanto às tendências de mortalidade por cancro da mama pode contribuir para compreender o impacto, a nível populacional, das atuais práticas de diagnóstico precoce e de tratamento.

Objectivos: Identificar padrões de tendências temporais de mortalidade por cancro da mama (1980-2010) através de modelos matemáticos.

Métodos: Foram obtidos dados de mortalidade através da base de dados da Organização Mundial de Saúde e estimativas da população através das Nações Unidas; foram obtidas taxas de incidência padronizadas para a idade (população padrão mundial) através da base *Cancer Incidence in Five Continents* (CI5plus). Foram excluídos os países com dados disponíveis para menos de 20 anos civis entre 1980 e 2010. Foram identificados padrões nas tendências temporais das taxas de mortalidade padronizadas para a idade (todas as idades, população padrão mundial) por *model-based clustering*, no período em análise. Foram selecionados os modelos que permitiam um agrupamento mais homogéneo de países no que concerne ao padrão de variação da mortalidade, entre aqueles que apresentavam valores mais baixos do critério de informação Bayesiano (BIC), de acordo com a avaliação das representações gráficas das tendências em cada país.

Resultados: Foram identificados três padrões principais. Os padrões 1 e 2 são caracterizados por uma estabilidade ou ligeiro aumento das taxas de mortalidade na primeira metade do período em análise e, na segunda metade, é observado um declínio marcado das tendências; no entanto, a mediana das taxas de mortalidade padronizadas para a idade é mais elevada nos países do padrão 1, ao longo de todo o período, e as taxas mais altas são atingidas mais precocemente do que no padrão 2. O padrão 3 é caracterizado por um rápido aumento das taxas de mortalidade até 1999, e a partir daí observa-se uma ligeira diminuição.

Conclusão: Este estudo fornece um modelo geral para a descrição e interpretação de padrões globais de variação da mortalidade por cancro da mama na Europa, bem como uma base para previsões mais precisas da carga de mortalidade associada ao cancro da mama.

2. ABSTRACT

Introduction: Breast cancer incidence is increasing in most countries and is the leading cause of oncological death among women, despite a decline in mortality rates that has been observed over the last decades throughout Europe. It is still difficult to assess how much of the mortality reduction can be attributable to early diagnostic, namely through mammography screening, and to improved management. The identification of clusters of countries with homogeneous trends in breast cancer mortality may contribute to understand the impact of early detection and improved disease management at a population level.

Objectives: To identify patterns of variation in breast cancer mortality in Europe (1980-2010), using a model-based approach.

Methods: Breast cancer mortality data were obtained from the World Health Organization (WHO) database and population estimates from the United Nations' World Population Prospects; age-standardized (world standard population) incidence rates (ASIR) were obtained from CI5plus. Countries with data available for less than 20 calendar years between 1980 and 2010 were excluded. Model-based clustering was used to identify the patterns of time trends in age-standardized (all ages, world standard population) mortality rates (ASMR) in this period. The models allowing the most homogeneous grouping of the countries, regarding the patterns of variation in mortality rates, were selected among those with the lowest Bayesian Information Criterion (BIC) by visual inspection of the country-specific trends.

Results: Three main patterns were identified. Patterns 1 and 2 are characterized by stable or slightly increasing trends in ASMR in the first half of the period under analysis, and a clear decline is observed thereafter; however, the median of the ASMR is higher for the countries included in pattern 1, throughout the whole period, and the highest rates are achieved sooner than in pattern 2. Pattern 3 is characterised by a rapid increase in mortality rates until 1999, and a slow decline thereafter.

Conclusion: This study provides a general model for the description and interpretation of the patterns of variation in breast cancer mortality in Europe, as well as a basis for more accurate predictions of the burden associated with breast cancer.

3. INTRODUCTION

3.1. Morbidity and mortality burden associated with breast cancer

Breast cancer is the malignancy most frequently diagnosed among women, both in developed and developing countries, with an estimated 1.4 million new cases in 2008 (23% of all cases of cancer among women) (1). In 2000, it was the most common tumour among females in low-income regions, surpassing invasive cervical cancer that had been the leading cancer in the previous decades (2). Incidence rates are rising in most countries, though a faster pace in developing countries where risk has been historically low compared with industrialized countries (3).

Due to its good prognosis, breast cancer is the fifth cause of oncological death overall (458000 estimated deaths worldwide in 2008) (1, 4). Despite that, it is still the leading cause of oncological death in females worldwide (5). Approximately 59% of the deaths are estimated to occur in developing countries (1).

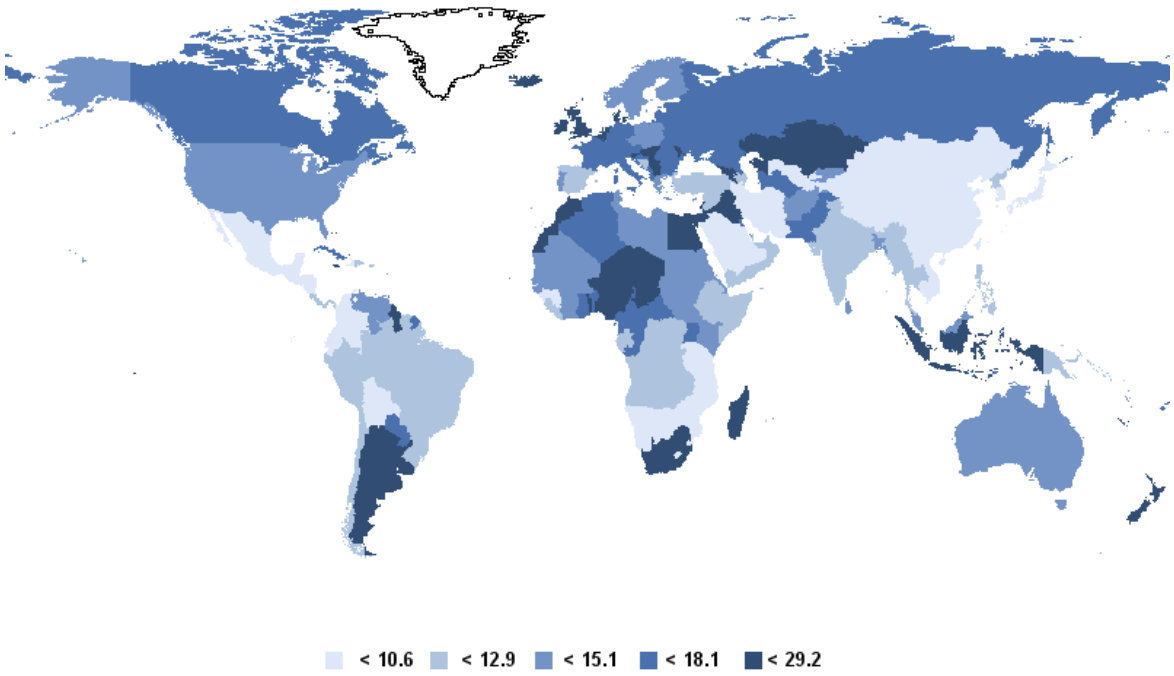


Figure 1. Estimated age-standardised mortality rates (all ages), per 100,000 inhabitants [Source: Globocan 2008 (IARC)].

The range of mortality rates worldwide is much smaller than the range of incidence rates because of the improved survival rates in developed countries (higher incidence), and the less favourable survival observed in developing countries (1, 4).

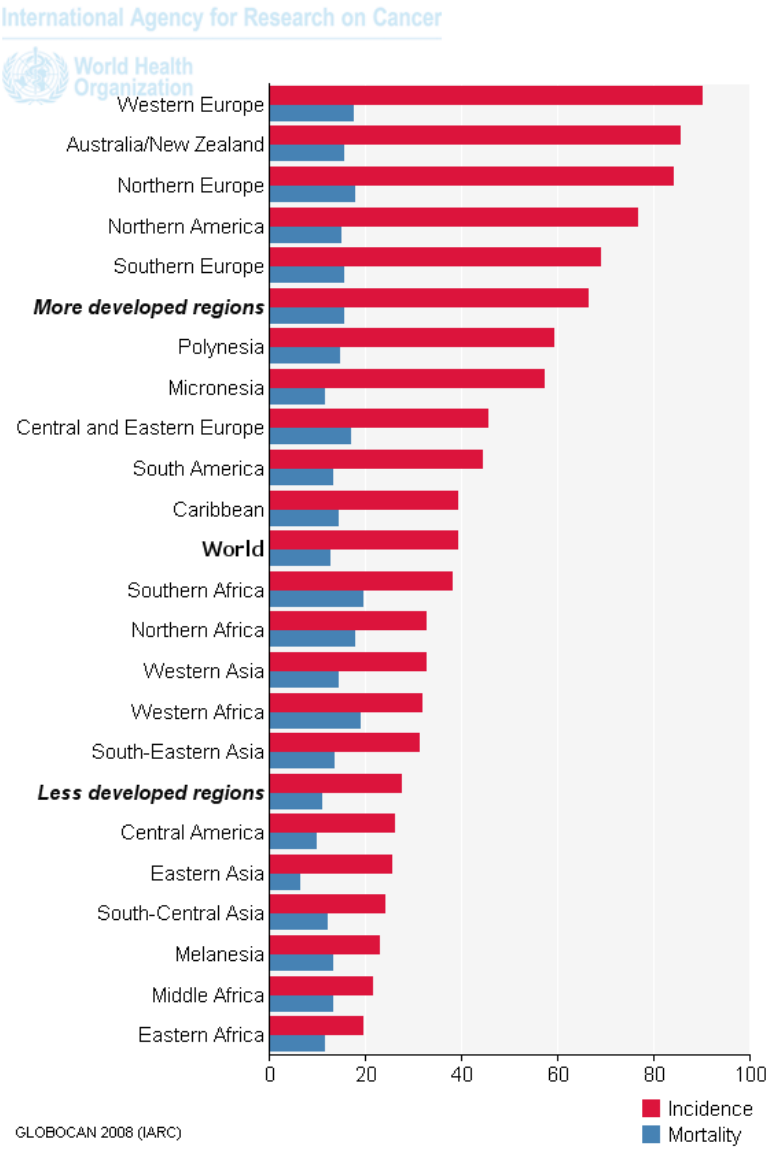


Figure 2. Estimated age-standardized (World population) incidence and mortality rates, per 100,000 inhabitants, in different regions [Source: Globocan 2008 (IARC)].

The European mean survival for breast cancer is fairly high (79.3%) (6) and has been increasing; this has been associated mainly with screening activities and an earlier diagnosis but also with improvements in the organization and delivery of care (7-10).

Breast cancer is one of the three cancers accounting for the highest economic value of disability-adjusted life years (DALYs) at USD 88 billion (9.8%), surpassed only by lung and colon/rectum cancer, for both high-income and upper middle income countries, making breast cancer prevention one of the major priorities in economic and health policy strategy (11).

3.2. Determinants of breast cancer

Incidence rates are highest in most of the developed countries and are lowest in less developed regions and in Japan (12). The international differences in both incidence and mortality rates indicate important differences not only in the endogenous hormonal milieu but also in lifestyle and environmental factors, genetic susceptibility, and mammographic screening activities among countries (13).

Migrant studies indicate that environmental determinants (rather than genetic) have a greater impact on incidence variations (14). For instance, the risk of developing breast cancer in Asian-Americans is considerably higher than the one presented by native Asians, which are at a relatively low risk (15, 16); even in the migrating generation itself there is a substantial increase in risk, particularly if migration occurs early in life (14, 17). This indicates an important role of environmental factors in the aetiology of breast cancer (18).

Age

As for most cancer sites, the incidence of breast cancer increases with age, although up to the age of 40 the increase is steeper than the observed for other cancers, such as lung or colon. The incidence of breast cancer doubles about every 10 years until menopause, when the increase slows substantially; this relation with age has been linked to the high exposure to ovarian hormones from puberty to menopause (12, 13, 18).

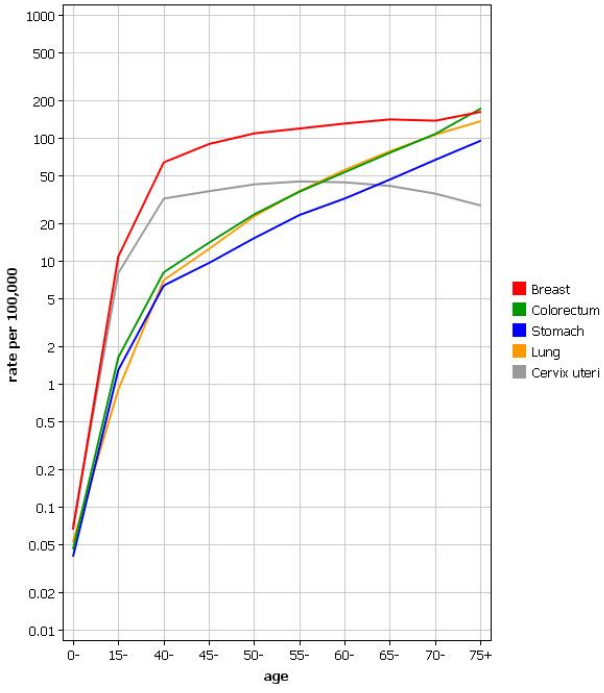


Figure 3. Estimated incidence rates, per 100,000 inhabitants, of breast, colorectum, stomach, lung and cervix uteri cancer [Source: Globocan 2008 (IARC)].

Family history/genetic factors

Family history is a well-established risk factor for breast cancer (13). A woman with a first degree relative who had breast cancer before the age of 50 has a risk at least twice-higher, and the more the relative's age of onset decreases, the higher the risk. If two first degree relatives develop the disease, the risk is increased by four to six times (18).

A positive family history, developing breast cancer at a young age and bilateral disease are strong indicators of inherited breast cancer (19). Although two breast cancer susceptibility genes (BRCA1 and BRCA2) have been already identified and associated to an increased risk of breast cancer, genetic susceptibility accounts for less than 10% of the breast cancer cases in Western countries (18).

Endogenous hormones

Several studies have related serum concentration of oestradiol in postmenopausal women with breast cancer risk; the higher the hormonal levels, the bigger the risk [relative risk=2.3; 95% confidence interval (CI): 1.6 to 3.2] (20).

Age at menarche and menopause. Reproductive factors associated with prolonged exposure to endogenous estrogens are among the most important risk factors for breast cancer; one of the first pieces of evidence suggesting this was te observation that the sooner a bilateral oophorectomy was performed, the greater the risk reduction (18). Both women who experience menarche at a younger age and the ones who stop menstruating later, are at higher risk of breast cancer. Thus, premenopausal women are at higher risk when compared to postmenopausal women of the same age (12) whether the menopause is natural or surgical (13).

Childbearing. The risk of breast cancer is lower in women with at least one full-term pregnancy when compared to nulliparous women, and is further reduced with the increasing number of full-term pregnancies (13). However, the risk increases during and after the pregnancy due to high levels of exposure to estrogen and progesterone (21). The age of first pregnancy has an effect independent of the total number of pregnancies; the older a woman is at her first full-term pregnancy, the higher her risk of breast cancer [relative risk of 2.0; (95%CI 1.1 to 3.7) for women aged 30-<35 and 2.1, (95%CI 0.7 to 6.2) at age 35 or older] (13, 22).

Breastfeeding. There is a protective effect of prolonged breastfeeding on female breast cancer; the relative risk of breast malignancy is reduced by 4.3% (95% CI 2.9 to 5.8) for each year that a woman breastfeeds (23).

Exogenous hormones

Oral contraceptives. While women who are taking combined oral contraceptives or who have stopped its consumption in the previous ten years have a small increase in relative risk of having breast cancer, ten or more years after stopping use, there is no meaningful excess risk (relative risk=1.01; 95%CI, 0.96 to 1.05) (24).

Hormone replacement therapy. As with oral contraceptives, patterns of hormone replacement therapy (HRT) use have changed throughout the last decades. Even so, data suggests that there is a duration-dependent increase in breast cancer risk in HRT users, particularly among non-obese women (25), although the increase in risk is reversible after HRT ceases; there was no significant excess of breast cancer 5 or more years after cessation of use (relative risk=1.07; 95%CI, 0.97 to 1.18) (26).

Previous benign lesions

Severe atypical epithelial hyperplasia increases breast-cancer risk in four to five times; the risk is nine-fold higher in women with these changes and a first degree relative with history of breast cancer (18).

Ionizing radiation

Exposure to radiation is also a known risk factor for breast cancer. Women irradiated for Hodgkin's disease before the age of 30 years are at higher risk for developing breast cancer at a younger age than average, and often before regular breast screening is recommended (27): relative risk of 60.6 (95% CI, 22.1 to 132) if the woman was younger than 16 years when she received radiation therapy; a relative risk of 4.7 (95% CI, 2.9 to 7.3) if she was between 16 and 29 years old, and a relative risk of 1.4 (95% CI, 1.0 to 2.1) if the woman was 30 years or older when receiving radiation therapy (28).

Lifestyle factors

Obesity in postmenopausal women is also thought to influence breast cancer risk through a hormonal mechanism, once obese postmenopausal women have higher serum hormone concentrations via conversion of androstenedione to estrone by adipose tissue (12, 29).

High levels of physical activity are a protective risk factor for postmenopausal breast cancer, with a dose-response relationship, though with some heterogeneity in the results of the different studies on this topic (30). A meta-analysis of cohort studies on the association between recreation physical activity and postmenopausal breast cancer yielded an overall risk estimate of 0.97 (95%CI: 0.95 to 0.99) (30). Similar results were observed in meta-analyses of case-control studies that considered breast cancer and postmenopausal breast cancer as outcome (0.90, 95%CI: 0.88 to 0.93 and 0.97, 95%CI: 0.95 to 1.00, respectively) (30).

There is large evidence addressing the relation of specific food components, such as total fat intake and breast cancer. The report of the World Cancer Research Fund regarding Food, Nutrition, Physical activity and the Prevention of Cancer concluded that the evidence from prospective studies are inconsistent in establishing the high fat intake as a definitive risk factor for neither premenopausal nor postmenopausal breast cancer (30). For breast cancer occurring in the postmenopausal period, case-control studies consistently suggest a significant positive association. A meta-analysis pointed out an overall risk estimate of 1.11 (95% CI: 1.06 to 1.16), without heterogeneity (30). However, when considering only cohort studies, that association was weaker and no longer significant (1.06, 95% CI: 0.99–1.14) (30).

Alcohol consumption is a modifiable risk factor for breast cancer that is associated with a linear increase in incidence. There is an approximately 30% to 40% higher risk in individuals consuming at least 30 g/day of alcohol when compared to nondrinkers (31).

3.3. Breast cancer screening

The early detection of breast cancer may imply mammography testing, breast clinical examination (BCE) by a health professional and breast self-examination (BSE). Film mammography is the standard for breast cancer screening due to its demonstrated effectiveness in randomized trials (32).

Mammography. Either plain film or digital technologies can be used to perform mammography, although the shift to digital is ongoing (33). There is sufficient evidence showing the efficacy of screening women aged 50-69 years by mammography as the sole screening modality in reducing mortality from breast cancer The best estimates of the impact of screening mammography on breast cancer mortality range from 10% on regional mortality data (34), to 20% on trial results (35). Nonetheless, questions have been raised regarding mammography screening pertinence and efficacy both in randomized clinical trials as well as observational studies (36-38).

Breast clinical examination by a health professional. There is no adequate evidence that there are additional effects of BCE beyond mammography on breast cancer mortality (32), although it may be of particular importance in less affluent countries with no sufficient resources for a mammography programme and where disease is often at an advance stage at detection (2).

Breast self-examination. Among women who present with breast cancer clinically, women who perform BSE tend to have smaller tumours and improved survival than those who do not practice self-examination (2). However, there is adequate evidence suggesting that teaching BSE does not reduce breast cancer mortality (32).

Organized programmes for mammography screening were set up for the first time in several Swedish districts in 1986, followed by the Netherlands, several regions of Canada and Finland (39). Breast cancer screening policies are not the same across the different countries in spite of being based in the same scientific evidence (33).

The Council of the European Union recommends the implementation of nationwide screening programmes for women aged 50-69 years (40). However, breast cancer screening in Europe varies between organized and opportunistic, programmes managed at national and regional level, screening every 2 or 3 years, one or two views of the mammogram and the target population varies between 40 to 75 years (2, 41).

Adverse effects of screening

The two major adverse effects of screening are false-positive results and overdiagnosis (2). A previous North American study estimated that 23.8% of women screened had at least one false positive mammogram, during the 10 years of the study (42). False-positive can be defined as an abnormal mammogram that requires further assessment, in a woman without cancer (2). In addition to psychological effects such as anxiety and distress (usually transient effects and are not a barrier to screening), additional testing and invasive procedures, the

estimations of the total costs of evaluating women with false-positive results can range between one fourth and one third of the total costs of performing the screening (2, 32, 42, 43).

Another source of harm associated with screening is overdiagnosis which corresponds to the detection of cancers that would never have become apparent without screening and their detection does not contribute to mortality reduction, once these cancers do not represent a threat to the woman's life (44). In these cases there are no benefits for the participants, and women can only experience the adverse effects of the worry associated with a cancer diagnosis and the complications of therapy (2).

3.4. Treatment of breast cancer

Along with the implementation of screening, there has also been an improvement in treatment. Randomized clinical trials have shown a considerable improvement in survival rates due to adjuvant chemotherapy and tamoxifen (45, 46). Beyond chemotherapy, radiotherapy after local excision for ductal carcinoma in situ, compared with local excision alone, markedly reduced the overall number of both invasive and non-invasive recurrences in the ipsilateral breast (at a median follow-up of 4.25 years) (47).

Breast cancer treatment has changed considerably throughout time. In the early 1960's, when the first mammographic evaluations started to emerge, radical mastectomy was the main treatment option selected (2). Currently, in addition to surgical treatments, the use of adjuvant systemic treatment has substantially increased and it has become more age- and tumour-specific. A study performed in the Netherlands showed that not only age and lymph node status, were determinant in the decision of adjuvant systemic treatment, but also receptor status, tumour size and histologic tumour grade; however, age remained the most important factor when deciding about chemotherapy (48).

At present, treatment for breast cancer often requires a combination of therapies which includes surgery, chemotherapy, hormonal therapy and radiation.

Surgery

Surgical treatment of breast cancer may involve breast-conserving surgery or mastectomy. In 2012, in the United States of America, it was estimated that most women with early stage breast cancer (stage I and II) were treated with breast conserving surgery

(57%), followed by mastectomy (36%), surgical treatments (6%); approximately 1% had no treatment. In contrast, among women with late stage breast cancer (stage III and IV), 13% undergo breast conserving surgery, 60% have mastectomy, 18% do not receive any surgery and 7% do not receive any treatment (49).

Radical mastectomy was the predominant treatment option until the 1970s (2). In the 1980s, large randomised controlled trials found no difference in overall survival between breast conservation therapy (lumpectomy followed by radiation) and mastectomy. Currently, breast conservation is considered as an acceptable surgical treatment (2, 33). Thus, most women diagnosed with early stage disease who undergo breast conserving surgery receive adjuvant treatment: among them, approximately half have radiotherapy alone and a third undergoes both chemo and radiation therapy. In contrast, the majority of women with late stage breast cancer have chemotherapy in addition to surgery and other therapies (49).

Chemotherapy

Adjuvant therapy is recommended when the risk for recurrence is intermediate or high (more than 10% over 10 years) (2). An overview of clinical trials on this topic showed that for women under 50 years old treated with chemotheraphy, an average of 2.3 months of relapse-free survival was gained, as well as 5.4 months of overall survival within 10 years, compared with no chemotherapy group (45).

Hormonal therapy

Hormone-receptor positive tumours ought to be treated with endocrine therapy (50). It is now known that about 5 years of adjuvant tamoxifen is more effective than shorter durations, even if some years of cytotoxic chemotherapy has been given. Additionally, there is now evidence that adjuvant tamoxifen produces substantial benefit, not only for women over 50 years of age but also to women under 50 (46).

Radiation therapy

Post-operative radiotherapy is often used after breast-conserving surgery but can also be used after mastectomy for patients with lymph node metastases or tumours in stage 3 or 4 (2).

According to an overview of several trials, radiotherapy produces a reduction of about two-thirds in local recurrence. Breast cancer mortality was also reduced, however this effect on mortality is offset by an increase in vascular deaths, perhaps attributable to inadvertent irradiation of the coronary, carotid, or other major arteries (51).

4. OBJECTIVES

Breast cancer is still the leading cause of oncological death among women, despite the decline in mortality rates that has been observed over the last decades across Europe. However, it is still difficult to assess how much of the mortality reduction can be attributable to early diagnostic through, namely by mammography screening, and in the access to more effective treatments. The identification of clusters of countries with homogeneous trends in breast cancer mortality may contribute to understand the impact of early detection and improved disease management at a population level. Thus, the general objective of this dissertation is:

- To identify patterns in the time trends of breast cancer mortality across European countries using a model-based approach.

5. MANUSCRIPT

5.1. PATTERNS OF BREAST CANCER MORTALITY TRENDS IN EUROPE

[Article presented in the format required by the journal for which it was submitted]

ABSTRACT

Objectives: To identify patterns of variation in breast cancer mortality in Europe (1980-2010), using a model-based approach.

Methods: Model-based clustering was used to identify clusters of countries with homogeneous variation in age-standardized mortality rates (ASMR); mortality data were obtained from the World Health Organization database.

Results: Three patterns were identified. Patterns 1 and 2 are characterized by stable or slightly increasing trends in ASMR in the first half of the period analysed, and a clear decline is observed thereafter; in pattern 1 the median ASMR is higher, and the highest rates were achieved sooner. Pattern 3 is characterised by a rapid increase in mortality until 1999, declining slowly thereafter.

Conclusion: This study provides a general model for the description and interpretation of the patterns of variation in breast cancer mortality in Europe, as well as a basis for more accurate predictions of the burden associated with breast cancer.

Key-words: Breast Neoplasms; Cluster Analysis; Mortality; Early Detection of Cancer.

INTRODUCTION

Breast cancer is the leading cause of oncological death among women, in both economically developed and developing settings [1]. In Europe, in the last decades the mortality decreased in most countries [2], along with rising incidence rates [3].

An increasing incidence may be explained by trends towards a more frequent exposure to factors that contribute to a higher risk of breast cancer (*e.g.*: delayed childbearing, lower parity, use of postmenopausal hormone therapy, obesity, physical inactivity) [4, 5], while the widespread use of mammographic screening further contributes to higher incidence rates [5, 6].

The decline in mortality rates has been attributed both to an increasing frequency of early diagnosis through mammography screening and access to more efficient treatments, including adjuvant chemotherapy or tamoxifen, besides improved radiotherapy and surgery [7-11]. The identification of clusters of countries with similar trends in breast cancer mortality may contribute to understand the impact, at a population level, of early detection and improved disease management. Previous attempts to describe breast cancer mortality patterns relied on criteria related to geographical [12], social, economic or cultural [13-15] characteristics. Model-based clustering may allow a more meaningful grouping of the different settings with no *a priori* constraints, according to the mortality rates at onset of the observation period, as well as the magnitude and slope of its variation.

Therefore, we aimed to identify patterns of variation in breast cancer mortality, using a model-based approach.

METHODS

Breast cancer mortality data were obtained for 40 countries from the World Health Organization (WHO) database updated in November 24, 2011 [13]. Albania, Bosnia and Herzegovina, Cyprus, Montenegro, The Former Yugoslav Republic of Macedonia, Serbia and Slovakia had data available for less than 20 calendar years between 1980 and 2010, and were excluded from our analyses (Figure 1). In this period, different revisions of the International Classification of Diseases (ICD) were used; we extracted the number of deaths, corresponding to the codes A054 (ICD-8), B113 (ICD-9), C50 (ICD-10).

Mid-year estimates of the resident population were obtained from the 2010 revision of United Nations World Population Prospects [16]. We computed age-standardized mortality rates (ASMR) for all ages, by the direct method, using the world standard population [17] as reference.

Mixed models were used to describe the time trends in the ASMR. All models included random terms by country for the intercept, and slope, quadratic and cubic terms for calendar year. Iceland presented values three times the interquartile range above or below the median for at least one of the above coefficients and was excluded from further analyses (Figure 1). These models were used to estimate the ASMR for the years with missing data, between 1980 and 2010 (Appendix 1), and model-based clustering was used to identify the mortality patterns in this period. According to this method, the clusters are considered to be ellipsoidal, centred at the means, and the covariances determine their other geometric features. Characteristics (orientation, volume and shape) of distributions are estimated from the data, and can be allowed to vary between clusters, or constrained to be the same for all clusters. The most appropriate models were considered those allowing for the most homogeneous grouping the countries regarding their patterns of variation, as assessed by visual inspection of the country-specific trends, selected among those with the lowest

Bayesian Information Criterion (BIC) (Appendix 2). Data analysis was conducted using data from 33 European countries (Figure 1), with the software R *2.14.1*.

The patterns identified through the model-based approach were further characterized according to gross domestic product (GDP) *per capita* in 1995 (the midpoint of the period under analysis); data was obtained from the World Bank database [18].

Data on organized breast cancer screening activities in each country were obtained from published peer reviewed articles or official reports and used in the interpretation of the patterns, along with the trends in breast cancer incidence (Appendix 3). Age-standardized (world standard population) incidence rates (ASIR), and the corresponding standard errors, were abstracted from the Cancer Incidence in Five Continents database CI5plus, after the November 5, 2012 update [19], for all the years with available data in the period 1970-2002; data were available for 18 of the European countries eligible for model-based clustering. We analysed trends in incidence rates for the age groups covered by the breast cancer screening programmes implemented in each country, if applicable, or the age group 50 to 69 years (defined according to European Council's guidelines for breast cancer screening [20]), as well as for the younger and older women than those eligible for screening. The annual percent change (APC), as well as significant changes in the linear trends of age-standardized incidence and mortality rates were assessed using the software Joinpoint Regression Program, version 3.5.3 [21]. The number of joinpoints allowed was limited to a maximum of five (Table 2). For the United Kingdom (UK), incidence data were available only from Scotland and England.

RESULTS

We identified three main patterns of breast cancer mortality trends in Europe, hereafter referred to as patterns 1, 2 and 3.

Patterns 1 and 2 are characterized by stable or slightly increasing trends in ASMR in the first half of the period under analysis, and a clear decline was observed thereafter; however, the median of the ASMR was higher for the countries included in pattern 1, throughout the whole period, and the highest rates were achieved sooner than in pattern 2. Pattern 1 comprises mostly countries from western and northern Europe, and all of them were high income countries [median GDP (USD): 27584, range: 9457-50600], while pattern 2 is more heterogeneous regarding the geographical distribution and GDP [median GDP (USD): 15151, range: 4411-34156] (Figures 1 and 2 and Table 1).

Pattern 3 included 11 countries with GDP lower than 5000 USD, mainly eastern and northern European, and four countries (Finland, France, Greece and Sweden) with GDP higher than 12000 USD (Figure 1). The former were characterized by the lowest median ASMR in 1980, which increased steeply during the first half of the period under analysis, and decreased thereafter, mostly after 1999 and at a slower pace than in patterns 1 and 2 (Figure 2 and Table 1). Finland, France and Greece depicted slightly increasing trends in the first part of the period under study and a marked decline from that point onwards, resembling more closely patterns 1 and 2. However, in these countries the ASMR observed in 1980 were among the lowest in Europe (Appendix 1). Sweden presented a downward trend throughout the whole period, with a steeper decrease in the second half, which is a unique behaviour among all the countries analysed (Appendix 1). Therefore, these four countries were treated separately from all other included in pattern 3, to increase the homogeneity of this cluster.

Over the last three decades there was a levelling of breast cancer mortality across Europe. The difference between pattern 1 and pattern 3 (excluding Finland, France, Greece and Sweden) was about 50% in 1980, but only 10% in 2010.

Most of the countries included in patterns 1 and 2 have organized screening programmes, which were initiated before 1995 in more than half of those grouped in pattern 1 and in more than one third of those in pattern 2. Nearly two-thirds of the countries included in pattern 3 (excluding Finland, France, Greece and Sweden) had no organized screening implemented. Finland, France, Greece and Sweden had organized screening (Figure 3).

In the age groups eligible for screening, among the countries with screening programmes implemented before 2002 (the last year with available date in CI5plus) there was a steep increase in the ASIR close to the year of screening onset, reflecting the increased detection of prevalent cancers, for Finland, Norway, Scotland and Sweden; these countries started organized screening mostly in the 1980's and all have a participation rate of over 70% [22, 23]. A similar increase was observed in Italy after 1995; despite having a screening programme implemented for the first time in 1985, only since 1996 the Italian Ministry of Health issued a nationally agreed protocol [24]. In the remaining countries the ASIR increased with time in all countries considered for this analysis, regardless of the existence of organized screening (Table 2).

DISCUSSION

We identified three patterns that summarize the temporal trends in breast cancer mortality across European countries. Despite an overall downward trend observed in recent years throughout Europe, the patterns differ in the highest rates achieved and the year of inflection in the ASMR trends. A levelling of breast cancer mortality was observed across Europe over the last three decades.

The declines in mortality rates could be explained by earlier diagnosis and mostly access to better management of the cases.

Despite the observations that breast cancer incidence rates are no longer increasing or even declining in some settings and specific age-groups [3, 25], in all the European countries analysed, incidence is still increasing, or not varying significantly, in the age groups with the largest contribution to the overall rates. These trends are largely influenced by diagnosis and screening practices; estimates of excess incidence due to screening range from 11-19% [26] to 15-25% [27, 28]. Furthermore, these trends are also dependent on the frequency and changes of risk factors such as early menarche, delayed childbearing, lower parity, use of postmenopausal hormone therapy and obesity [29, 30]. Most of these risk factors are still more common in more affluent settings and are increasing in the less affluent [31]. This is in accordance with the observation of the highest ASIR in the countries included in pattern 1, the one presenting the highest median GDP, and the lowest ASIR in the less affluent countries from pattern 3.

In pattern 3 (excluding Finland, France, Greece and Sweden), although the inflection in the mortality rates occurred later than in the remaining countries, the ASMR peaked at lower values. Also, in pattern 2 the decline started later and at lower ASMR than the observed for pattern 1. These distinctive features suggest that the implementation of

effective cancer control measures occurred in different moments in settings with different risk profiles for breast cancer.

The best estimate of the impact of screening mammography on breast cancer mortality ranges from 10% on regional mortality data [32], to 20% on trial results [26]. Since the fall in mortality in pattern 1 approached 40%, this indicates that most of the decline is due to improved management and treatment. Most countries included in patterns 1 and 2 and a few of those in pattern 3 have organized screening; however, most of the programmes were implemented after 1995, and in the countries where organized screening started sooner the expected lag of 7 to 12 years [33] between screening onset and the inflection of the mortality trends is not compatible with an important contribution of the programmes to the initial declines, although no inference is possible regarding longer term effects on mortality. Furthermore, these results do not exclude the potential contribution of opportunistic screening for the mortality reduction. In most of the countries from patterns 1 and 3 and in the more affluent from pattern 3, the incidence rates increased more steeply in the age-groups eligible for screening, suggesting that mammography screening was widespread, to higher or lesser extent, even in the absence of screening programmes. In fact, countries with no programmes implemented or with lower participation rates are known to have a considerable volume of "opportunistic" mammography testing, namely Belgium, Czech Republic, France, Germany, Hungary, Italy, Malta and Switzerland [22, 34-36]. Although the balance between benefits and risks of screening is less favourable in opportunistic mammography testing than in organized programmes [37, 38], the former may also have a favourable impact on mortality [39].

There has been a substantial improvement in breast cancer treatments since the 1960's, when radical mastectomy was the predominant treatment option [40]. By the late 1980's, in many developed countries tamoxifen and polychemotherapy were used as adjuvant therapy after surgical treatment for primary breast cancer; therefore, an effect in mortality trends should occur by early 1990's [41], which makes the declining mortality trends experienced in several countries compatible with the increase in use of systemic adjuvant

therapies. The current therapies, more effective and more age- and tumour-specific [8, 11], as well as the integrated organization of the provision of breast cancer care (36) contributed to a sustained decline in mortality rates in the last two decades, especially in countries in patterns 1 and 2.

Between 1980 and 2010, three different revisions of the International Classification of Disease (ICD) were used to code the underlying cause of death. Although changes in coding could induce some variation of rates, it is not likely to compromise the comparability of data over time, once differences between revisions are minor regarding breast cancer; only 0.9% more deaths are classified as breast cancer in ICD-9 than ICD-8 and 1.3% more deaths between ICD-10 and ICD-9 [42, 43].

The reliability of the model-based clustering was evaluated by tenfold cross validation [44]. The sample was divided in ten partitions, and each of the subsets of nine out of the ten partitions was used to fit ten different models (data not shown). The agreement between the predictions from these models and those from the model based on the complete dataset was moderate (kappa=0.55). This, reflects the fact that some countries depict a pattern of variation that does not fit so well in the main patterns, as described for Finland, France, Greece and Sweden, although some misclassification may be anticipated for other countries (e.g. Poland). This, however, does not influence the main patterns described, that reflect quite closely the trends in the majority of the European countries analysed.

We used incidence data obtained from the CI5plus database to ensure some homogeneity of data quality. However, these data are based in a coverage of less than 15% of the country population from Austria, France, Germany, Italy, Netherlands, Poland, Spain and Switzerland [45]. Since incidence data was used mainly to interpret the patterns, this has not compromised the validity of our findings.

In conclusion, this study provides a general model for the description and interpretation of the patterns of variation in breast cancer mortality in Europe, as well as a basis for more accurate predictions of the burden associated with breast cancer.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; **61**(2): 69-90.

2. Bosetti C, Bertuccio P, Levi F, Chatenoud L, Negri E, La Vecchia C. The decline in breast cancer mortality in Europe: an update (to 2009). Breast. 2012; **21**(1): 77-82.

3. Sant M, Francisci S, Capocaccia R, Verdecchia A, Allemani C, Berrino F. Time trends of breast cancer survival in Europe in relation to incidence and mortality. International journal of cancer Journal international du cancer. 2006; **119**(10): 2417-22.

4. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. Maturitas. 2008; **61**(1-2): 203-13; discussion 13.

5. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. The lancet oncology. 2001; **2**(3): 133-40.

6. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol. 2005; **34**(2): 405-12.

7. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. The New England journal of medicine. 2005; **353**(17): 1784-92.

8. Myrthe P.P. Sukel LVvdP-F, Grard A.P. Nieuwenhuijzen, Gerard Vreugdenhil, Ron M.C. Herings, Jan Willem W. Coebergh, Adri C. Voogd. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990–2006 in the southeastern Netherlands. European Journal of Cancer. 2008; **Vol. 44**(Issue 13): 1846–54.

9. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000; **355**(9203): 528-33.

10. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998; **351**(9114): 1451-67.

11. Cole BF, Gelber RD, Gelber S, Coates AS, Goldhirsch A. Polychemotherapy for early breast cancer: an overview of the randomised clinical trials with quality-adjusted survival analysis. Lancet. 2001; **358**(9278): 277-86.

12. Joan Benach YY, Carme Borrell, Elisabeth Rosa, M. Isabel Pasarín, Núria Benach, Esther Español, José Miguel Martínez and Antonio Daponte. Examining geographical patterns of mortality - The Atlas of mortality in small areas in Spain (1987-1995). European Journal of Public Health. 2003; **Vol. 13**(Nr. 2): 115-223.

13. Fukuda Y, Umezaki M, Nakamura K, Takano T. Variations in societal characteristics of spatial disease clusters: examples of colon, lung and breast cancer in Japan. International journal of health geographics. 2005; **4**: 16.

14. Chiehwen Ed Hsu HJ, Francisco Soto Mas. Evaluating the disparity of female breast cancer mortality among racial groups - a spatiotemporal analysis. International journal of health geographics. 2004; **Vol. 3**(4).

15. Nancy Tian JGW, F. Benjamin Zhan. Female breast cancer mortality clusters within racial groups in the United States. Health & Place. 2010; **Vol. 16**(Issue 2): 209–18.

16. United Nations. World Population Prospects: The 2010 Revision - Special Aggregates. [cited 30/05/2012]; Available from: http://esa.un.org/unpd/wpp/index.htm

17. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC scientific publications. 1987; (82): 1-406.

18. The World Bank. World Development Indicators. [cited 31/01/ 2012]; Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD

19. Ferlay J PD, Curado MP, Bray F, Edwards B, Shin HR and Forman D. Cancer Incidence in Five Continents. Volumes I to IX: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://ci5.iarc.fr

20. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--

summary document. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2008; **19**(4): 614-22.

21. Joinpoint Regression Program. Version 3.5 - April 2011 ed: Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program National Cancer Institute.

22. Doris Schopper CdW. Breast cancer screening by mammography: International evidence and the situation in Switzerland. Bern; 2007 June 2007.

23. Information Services Division of Scotland. Scottish Breast Screening Programme. [cited 24/09/2012]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Breast-Screening/

24. Barchielli A, Federico M, De Lisi V, Bucchi L, Ferretti S, Paci E, et al. In situ breast cancer: incidence trend and organised screening programmes in Italy. Eur J Cancer. 2005; **41**(7): 1045-50.

25. J.L. Botha FB, R. Sankila, D.M. Parkin. Breast cancer incidence and mortality trends in 16 European countries. European Journal of Cancer. 2003; **Vol. 39**(Issue 12).

26. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. The Lancet. 2012.

27. La Vecchia C, Negri E, Bruzzi P, Franceschi S, Bucchi L, Parazzini F. The impact of mammography on breast cancer detection. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. 1993; **4**(1): 41-4.

28. Kalager M, Adami HO, Bretthauer M, Tamimi RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. Ann Intern Med. 2012; **156**(7): 491-9.

29. Zahl PH, Maehlen J, Welch HG. The natural history of invasive breast cancers detected by screening mammography. Archives of internal medicine. 2008; **168**(21): 2311-6.

30. Parkin M, Fernández L. Use of Statistics to Assess the Global Burden of Breast Cancer. The breast journal. 2006; **Vol. 12**(Suppl. 1): S70–S80.

31. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006; **24**(14): 2137-50.

32. Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. The New England journal of medicine. 2010; **363**(13): 1203-10.

33. Shapiro S. Screening: Assessment of Current Studies. Cancer. 1994; **74**(1): 231-8.

34. Walter W Holland SS, Cristina Masseria. Policy Brief: Screening in Europe. Copenhagen: World Health Organization 2006.

35. Boncz I, Sebestyen A, Pinter I, Battyany I, Ember I. The effect of an organized, nationwide breast cancer screening programme on non-organized mammography activities. Journal of medical screening. 2008; **15**(1): 14-7.

36. Majek O, Danes J, Skovajsova M, Bartonkova H, Buresova L, Klimes D, et al. Breast cancer screening in the Czech Republic: time trends in performance indicators during the first seven years of the organised programme. BMC public health. 2011; **11**: 288.

37. Zwahlen M, Bopp M, Probst-Hensch NM. Mammography screening in Switzerland: limited evidence from limited data. Swiss Med Wkly. 2004; **134**(21-22): 295-306.

38. Palencia L, Espelt A, Rodriguez-Sanz M, Puigpinos R, Pons-Vigues M, Pasarin MI, et al. Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. Int J Epidemiol. 2010; **39**(3): 757-65.

39. Bulliard JL, Ducros C, Jemelin C, Arzel B, Fioretta G, Levi F. Effectiveness of organised versus opportunistic mammography screening. Ann Oncol, 2009. **20**(7): p. 1199-202.

40. IARC Working Group on the Evaluation of Cancer-Prevention Strategies, IARC Handbooks of Cancer Prevention, Breast Cancer Screening, 2002, IARC Press: Lyon.

41. Ismail Jatoi ABM. Why is breast-cancer mortality declining? The lancet oncology. 2003; **Vol. 4**.

42. Leslie Geran PT, Patricia Wood, Brad Thomas. Comparability of ICD-10 and ICD-9 for Mortality Statistics in Canada. Ottawa: Minister of Industry; 2005.

43. Klebba A. J. and J.H. Scott. Estimates of Selected Comparability Ratios Based on Dual Coding of 1976 Death Certificates by the Eighth and Ninth Revisions of the International Classification of Diseases. Maryland: National Center for Health Statistics; 1980.

44. Efron B, Tibshirani R. Improvements on Cross-Validation: The .632+ Bootstrap Method. J Am Stat Assoc. 1997; **92**: 548-60.

45. Cancer incidence in five continents. Volume IX. IARC scientific publications. 2008; (160): 1-837.

46. Olsen AH, Jensen A, Njor SH, Villadsen E, Schwartz W, Vejborg I, et al. Breast cancer incidence after the start of mammography screening in Denmark. British journal of cancer. 2003; **88**(3): 362-5.

47. Euler-Chelpin Mv. Breast cancer incidence and use of hormone therapy in Denmark 1978-2007. Cancer Causes and Control. 2011; **Volume 22**(Nr. 2): 181-7.

48. Von Karsa L AA, Ronco G, Ponti A, Malila N, Arbyn M, et al. Cancer screening in the European Union, report on the implementation of the Council Recommendation on cancer Screening, First Report. Luxembourg: European Comission; 2008.

49. National Cancer Screening Services [Scotland]. BreastCheck - The National Breast Screening Programme. Programme report 2010/11. Ireland; 2011.

50. National Cancer Screening Services [Scotland]. 2012 [cited 12/10/2012]; Available from: http://www.cancerscreening.ie/screening.html

51. Bastos J, Peleteiro B, Gouveia J, Coleman MP, Lunet N. The state of the art of cancer control in 30 European countries in 2008. International journal of cancer Journal international du cancer. 2010; **126**(11): 2700-15.

52. Elske van den Akker-van Marle HdK, Rob Boer, Paul van der Maas. Reduction in breast cancer mortality due to the introduction of mass screening in the Netherlands: comparison with the United Kingdom. Journal of medical screening. 1999; (6): 30-4.

53. Advisory Committee on Breast Cancer Screening. Screening for breast cancer in England: past and future. Journal of medical screening. 2006; **13**(2): 59-61.

54. P. Wanner LR, C Bouchardy. Geographical disparities in selfreported use of mammography and breast self-examination according to the Swiss Health Survey. Annals of Oncology. 2001; (12): 573-5.

55. Frede TE. Opportunistic breast cancer early detection in Tyrol, Austria 1996-2004. Is a mammography-screening program necessary? Eur J Radiol. 2005; **55**(1): 130-8.

56. Oberaigner W, Buchberger W, Frede T, Knapp R, Marth C, Siebert U. Breast cancer incidence and mortality in Tyrol/Austria after fifteen years of opportunistic mammography screening. BMC public health. 2010; **10**: 86.

57. Biesheuvel C, Weigel S, Heindel W. Mammography Screening: Evidence, History and Current Practice in Germany and Other European Countries. Breast Care (Basel). 2011; **6**(2): 104-9.

58. 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.

59. Giorgi D, Giordano L, Ventura L, Frigerio A, Paci E, Zappa M. Mammography screening in Italy: 2004 survey and 2005 preliminary data. Epidemiologia e prevenzione. 2007; **31**(2-3 Suppl 2): 7-20.

60. Kalager M, Haldorsen T, Bretthauer M, Hoff G, Thoresen SO, Adami HO. Improved breast cancer survival following introduction of an organized mammography screening program among both screened and unscreened women: a population-based cohort study. Breast cancer research: BCR. 2009; **11**(4): R44.

61. Setefilla Luengo-Matos MP-S, Zuleika Saz-Parkinson. Mammography use and factors associated with its use after the introduction of breast cancer screening programmes in Spain. European Journal of Cancer Prevention. 2006; **15**: 242–8.

62. World Health Organization. Strengthening cancer prevention and screening in Belarus. 2012 [cited 12/10/2012]; Available from: http://www.euro.who.int/en/what-we-

do/health-topics/noncommunicable-diseases/cancer/news/news/2011/3/strengthening-cancer-prevention-and-screening-in-belarus

63. Ciraj-Bjelac O, Faj D, Stimac D, Kosutic D, Arandjic D, Brkic H. Good reasons to implement quality assurance in nationwide breast cancer screening programs in Croatia and Serbia: results from a pilot study. Eur J Radiol. 2011; **78**(1): 122-8.

64. Ljubicic N, Ivanda T, Strnad M, Brkljacic B. The Croatian national breast cancer screening program--"mamma". Breast J, 2011. **17**(1): p. 106-8.

65. Institute for Statistical and Epidemiological Cancer Research. Finnish Cancer Registry. [cited 10/10/2012]; Available from: http://www.cancer.fi/syoparekisteri/en/

66. Wait SH, Allemand HM. The French breast cancer screening programme - Epidemiological and economic results of the first round of screening. European Journal of Public Health. 1996; **Vol. 16**(No. 1): 43-8.

67. Simou E, Tsimitselis D, Tsopanlioti M, Anastasakis I, Papatheodorou D, Kourlaba G, et al. Early evaluation of an organised mammography screening program in Greece 2004-2009. Cancer epidemiology. 2011; **35**(4): 375-80.

68. Olsson S, Andersson I, Karlberg I, Bjurstam N, Frodis E, Hakansson S. Olsson. Implementation of service screening with mammography in Sweden: from pilot study to nationwide programme. J Med Screen, 2000. **7**(1): p. 14-8.

Table 1. Characterization of the female breast cancer mortality patterns regarding the estimated age-standardized mortality rates (direct method, world standard population), all ages (ASMR), in 1980, 1995 and 2010, percent changes in rates in the periods 1980-1995 and 1995-2010, and highest rates and corresponding year observed between 1980 and 2010.

	Median (percentile 25 to percentile 75)		
	Pattern 1	Pattern 2	Pattern 3*
ASMR †			
1980	25.5 (24.7 to 26.5)	19.2 (16.8 to 20.0)	12.7 (10.7 to 14.2)
1995	25.5 (23.4 to 26.4)	20.7 (18.2 to 21.4)	16.0 (15.8 to 17.6)
2010	17.4 (15.9 to 18.0)	15.1 (14.1 to 16.1)	15.8 (14.7 to 16.1)
Variation in ASMR (%)‡			
1980-1995	-3.3 (-7.7 to 0.6)	8.0 (4.8 to 14.6)	33.3 (24.9 to 47.9)
1995-2010	-31.3 (-32.6 to -30.4)	-23.9 (-24.9 to -22.7)	-7.2 (-12.8 to -2.2)
ASMR §			
Higher value observed	29.5 (27.3 to 30.0)	22.1 (19.9 to 22.5)	18.2 (16.5 to 19.6)
Year of higher value	1986.5 (1985.5 to 1991.5)	1993 (1991 to 1994)	1999 (1994 to 2002)

ASMR – Age standardized mortality rates (world standard population)

* The results referring to pattern 3 do not include data from Finland, France, Greece or Sweden.

† Model estimates‡ computed from the model estimates

§ Observed data

Table 2. Characterization of countries regarding trends in age-standardized incidence rates by age groups, according to patterns of trends in breast cancer mortality rates.

	Country	Age groups[b] (years)	ASIR[a] 1988	ASIR[a] 2002	Trends in ASIR[a] Period 1 APC (95%CI)	Period 2 APC (95%CI)	Period 3 APC (95%CI)	Period 4 APC (95%CI)	Period 5 APC (95%CI)	Period 6 APC (95%CI)
Pattern 1	Denmark	0-49	32.0	28.4	1970-1988 1.7 (1.1 to 2.3)	1988-2002 -1.1 (-1.8 to -0.4)				
		50-59	210.7	264.6	1970-2002 1.9 (1.7 to 2.1)					
		60+	272.9	378.6	1970-1986 0.9 (0.4 to 1.5)	1986-2002 2.5 (2.0 to 3.0)				
	England (UK)	0-49	27.1	29.5	1985-1992 1.8 (1.0 to 2.6)	1992-2002 0.2 (-0.2 to 0.6)				
		50-64	196.2	288.5	1985-1988 2.3 (-1.3 to 6.0)	1988-1991 12.6 (5.5 to 20.1)	1991-1994 -3.4 (-9.1 to 2.6)	1994-2002 2.2 (1.5 to 2.8)		
		65+	256.1	302.7	1985-2002 1.0 (0.7 to 1.2)					
	Netherlands	0-49	29.2	39.4	1973-2002 1.1 (0.8 to 1.4)					
		50-69	203.8	319.0	1973-1991 0.8 (-0.2 to 1.9)	1991-1995 7.5 (-6.1 to 23.0)	1995-2002 -0.4 (-3.4 to 2.7)			
		70+	296.7	347.2	1973-2002 1.6 (1.0 to 2.1)					
	Scotland (UK)	0-49	26.7	26.8	1975-2002 0.3 (0.1 to 0.5)					
		50-64	188.0	288.1	1975-1988 1.2 (0.5 to 1.9)	1988-1991 12.1 (-0.6 to 26.4)	1991-2002 0.8 (0.1 to 1.6)			
		65+	254.7	271.9	1975-2002 1.0 (0.9 to 1.2)					
	Switzerland	0-49	23.7	26.3	1983-2002 0.6 (0.0 to 1.3)					
		50-70	221.6	298.7	1983-2002 3.1 (2.4 to 3.8)					
		70+	304.5	258.2	1983-2002 -0.9 (-1.6 to -0.3)					
Pattern 2	Austria	0-49	22.0	24.6	1988-2002 0.9 (-0.3 to 2.0)					
		50-69	199.3	244.5	1988-2002 1.9 (1.2 to 2.7)					
		70+	317.6	356.2	1988-2002 -1.0 (-2.5 to 0.7)					
	Czech Republic	0-44	9.9	10.1	1983-2002 0.3 (-0.3 to 0.9)					
		45-69	126.5	182.5	1983-2002 2.4 (2.1 to 2.7)					

	70+	192.7	280.9	1983-1995 3.6 (2.8 to 4.4)	1995-2002 0.7 (-0.8 to 2.2)			
Germany	0-49	25.2	28.1	1970-2002 1.0 (0.7 to 1.4)				
	50-69	202.7	272.1	1970-1987 0.6 (-0.2 to 1.4)	1987-2002 2.9 (2.1 to 3.8)			
	70+	248.9	317.4	1970-2002 1.8 (1.5 to 2.1)				
Italy	0-49	29.1	36.5	1988-2002 2.1 (1.6 to 2.6)				
	50-69	198.3	293.4	1988-1995 2.5 (0.5 to 4.5)	1995-1999 7.5 (0.9 to 14.5)	1999-2002 -2.5 (-8.2 to 3.6)		
	70+	247.1	282.9	1988-1991 -0.7 (-2.8 to 1.6)	1991-1995 3.7 (1.8 to 5.8)	1995-1999 1.8 (0.0 to 3.5)	1999-2002 -2.8 (-4.4 to -1.1)	
Norway	0-49	21.7	23.1	1970-1996 1.3 (0.9 to 1.6)	1996-2002 -2.2 (-4.7 to 0.4)			
	50-69	165.5	287.1	1970-1990 0.8 (0.2 to 1.4)	1990-2002 5.0 (3.9 to 6.0)			
	70+	262.0	233.7	1970-1985 2.2 (1.5 to 2.9)	1985-2002 -0.3 (-0.8 to 0.2)			
Spain	0-49	20.8	26.3*	1985-2000 2.4 (1.8 to 3.1)				
	50-64	120.3	211.0*	1985-2000 3.2 (2.4 to 3.9)				
	65+	157.9	193.4*	1985-2000 2.1 (1.4 to 2.7)				
Slovenia	0-49	18.4	21.8	1970-2002 1.3 (0.9 to 1.6)				
	50-69	152.8	205.7	1970-2002 2.4 (2.2 to 2.7)				
	70+	197.7	259.0	1970-2002 3.1 (2.8 to 3.4)				
Pattern 3								
Estonia	0-49	16.4	21.0	1970-2002 1.7 (1.3 to 2.1)				
	50-59	103.0	154.5	1970-2002 2.2 (1.8 to 2.6)				
	60+	105.6	170.1	1970-2002 2.9 (2.6 to 3.2)				
Finland	0-49	24.1	27.1	1970-1995 2.6 (2.4 to 2.9)	1995-2002 -0.6 (-2.0 to 0.8)			
	50-59	200.7	316.7	1970-1984 2.2 (1.5 to 2.9)	1984-1989 7.7 (3.7 to 11.9)	1989-1993 0.2 (-5.3 to 6.0)	1993-2002 4.4 (3.5 to 5.3)	
	60+	229.7	289.7	1970-2002 1.9 (1.6 to 2.1)				
France	0-49	32.5	32.1	1983-1994 2.6 (1.7 to 3.6)	1994-2002 -2.8 (-4.0 to -1.5)			
	50-74	229.5	361.7	1983-2002 2.9 (2.5 to 3.4)				

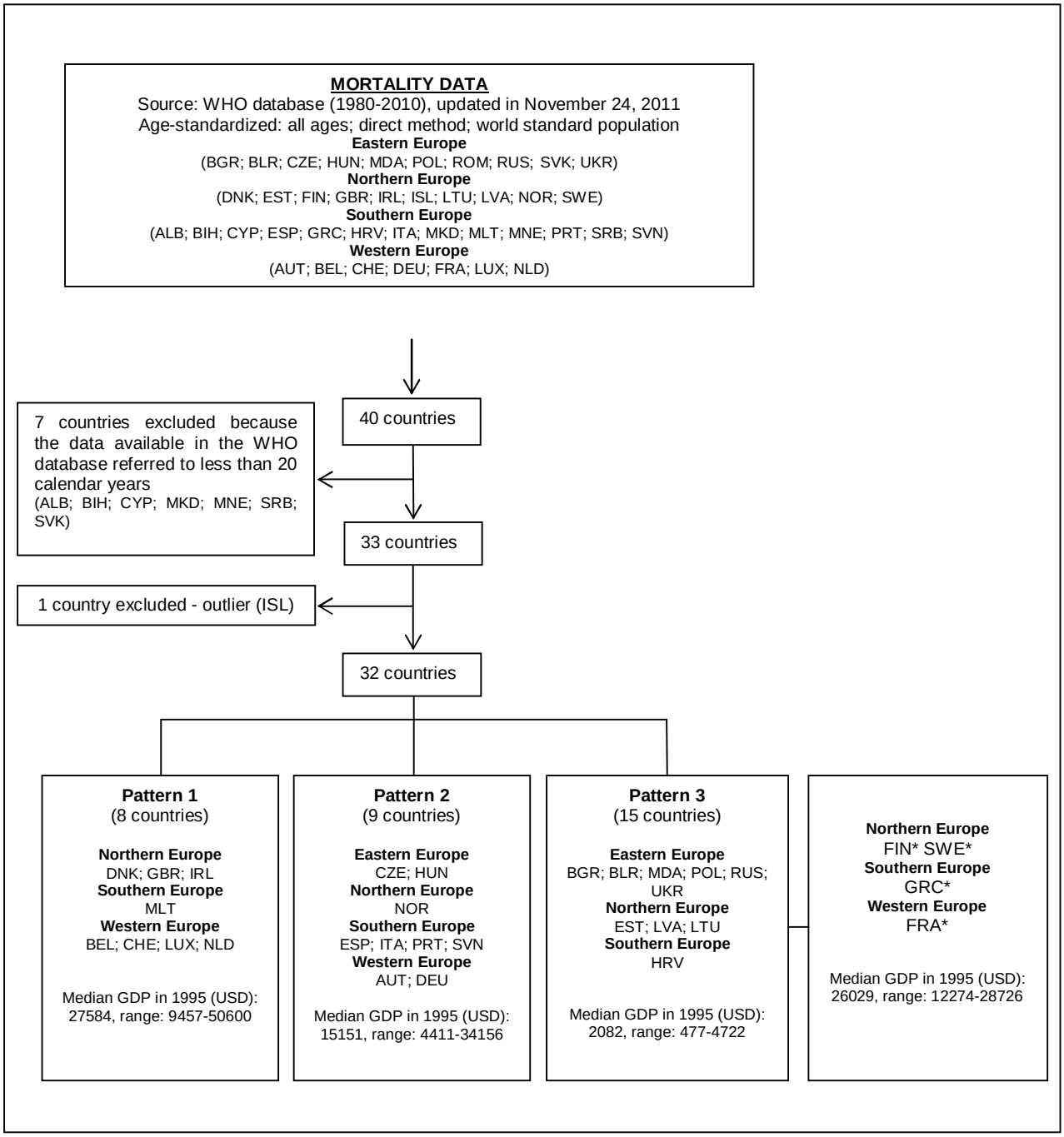
	75+	240.7	277.7	1983-2002 1.2 (0.7 to 1.7)					
Latvia	0-49	16.6	17.3	1988-2002 1.5 (0.2 to 2.8)					
	50-69	111.0	153.8	1988-2002 3.0 (2.4 to 3.6)					
	70+	83.2	153.3	1988-2002 5.4 (3.9 to 6.9)					
Lithuania	0-49	16.3	16.8	1978-2002 1.3 (0.9 to 1.8)					
	50-69	95.8	136.1	1978-2002 2.9 (2.5 to 3.4)					
	70+	83.3	156.6	1978-2002 4.4 (3.8 to 5.0)					
Poland	0-49	18.1	19.6	1988-1995 3.4 (1.1 to 5.8)	1995-2002 -1.6 (-3.6 to 0.5)				
	50-69	130.5	200.2	1988-2002 3.0 (2.3 to 3.7)					
	70+	169.2	209.0	1988-1995 4.9 (1.2 to 8.8)	1995-2002 -1.8 (-4.6 to 1.1)				
Sweden	0-49	25.3	25.9	1970-2002 0.9 (0.8 to 1.1)					
	50-69	209.4	302.6	1970-1978 2.1 (1.3 to 2.8)	1978-1986 0.0 (-0.9 to 0.9)	1986-1990 8.8 (5.5 to 12.3)	1990-1993 -2.4 (-8.0 to 3.5)	1993-2002 3.0 (2.5 to 3.5)	
	70+	288.9	282.5	1970-1973 -2.4 (-6.9 to 2.5)	1973-1979 3.0 (1.0 to 5.0)	1979-1984 -2.4 (-4.9 to 0.1)	1984-1987 3.5 (-4.4 to 12.1)	1987-1995 -1.5 (-2.5 to -0.5)	1995-2002 1.3 (0.2 to 2.3)

[a] ASIR – age-standardized incidence rates (world standard population)

[b] Three groups were considered: age groups covered by the organized breast cancer screening implemented in each country; age groups below the ages eligible for screening; age groups above the ages eligible for screening. In countries with no organized programme(s), the recommendations of the European Council's guidelines were considered as reference (50-69 years)

[c] Age-standardized incidence rates in the last year with data available (2000)

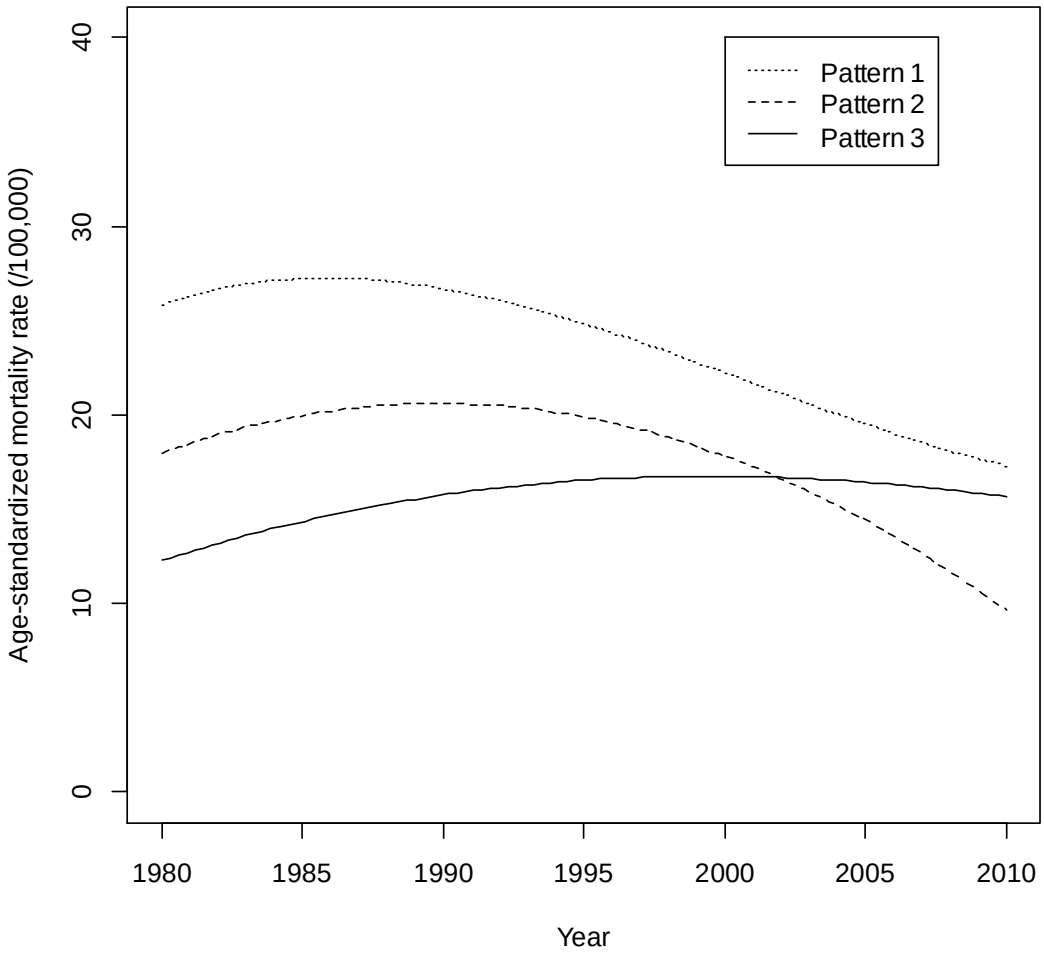
Figure 1. Flowchart of the model-based approach used to identify breast cancer mortality patterns.



*Finland, France, Greece and Sweden had substantially higher GDP than the other countries included in pattern 3, and were treated separately to increase the homogeneity of this cluster

ALB=Albania; AUT=Austria; BEL=Belgium; BIH=Bosnia and Herzegovina; BGR=Bulgaria; BLR=Belarus; CHE=Switzerland; CYP=Cyprus; CZE=Czech Republic; DEU=Germany; DNK=Denmark; ESP=Spain; EST=Estonia; FIN=Finland; FRA=France; GBR=United Kingdom; GRC=Greece; HRV=Croatia; HUN=Hungary; IRL=Ireland; ISL=Island; ITA=Italy; LTU=Lithuania; LUX=Luxembourg; LVA=Latvia; MDA=Republic of Moldova; MNE=Montenegro; MKD=The Former Yugoslav Republic of Macedonia; MLT=Malta; MNE=Montenegro; NLD=The Netherlands; NOR=Norway; POL=Poland; PRT=Portugal; ROM=Romania; RUS=Russian Federation; SRB=Serbia; SVN=Slovenia; SVK=Slovakia; SWE=Sweden; UKR=Ukraine.

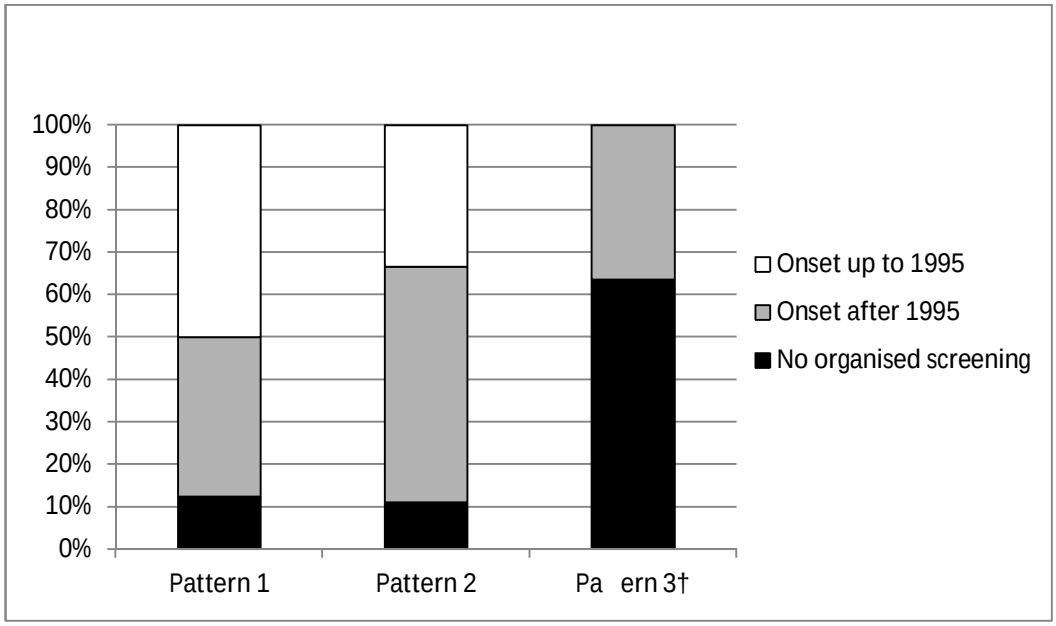
Figure 2. Age-standardized (direct method, world standard population) breast cancer mortality rates *, all ages, for each pattern† identified.



* Mean of the predictions for each of the countries included in the same pattern.

† The results referring to pattern 3 do not include data from Finland, France, Greece or Sweden.

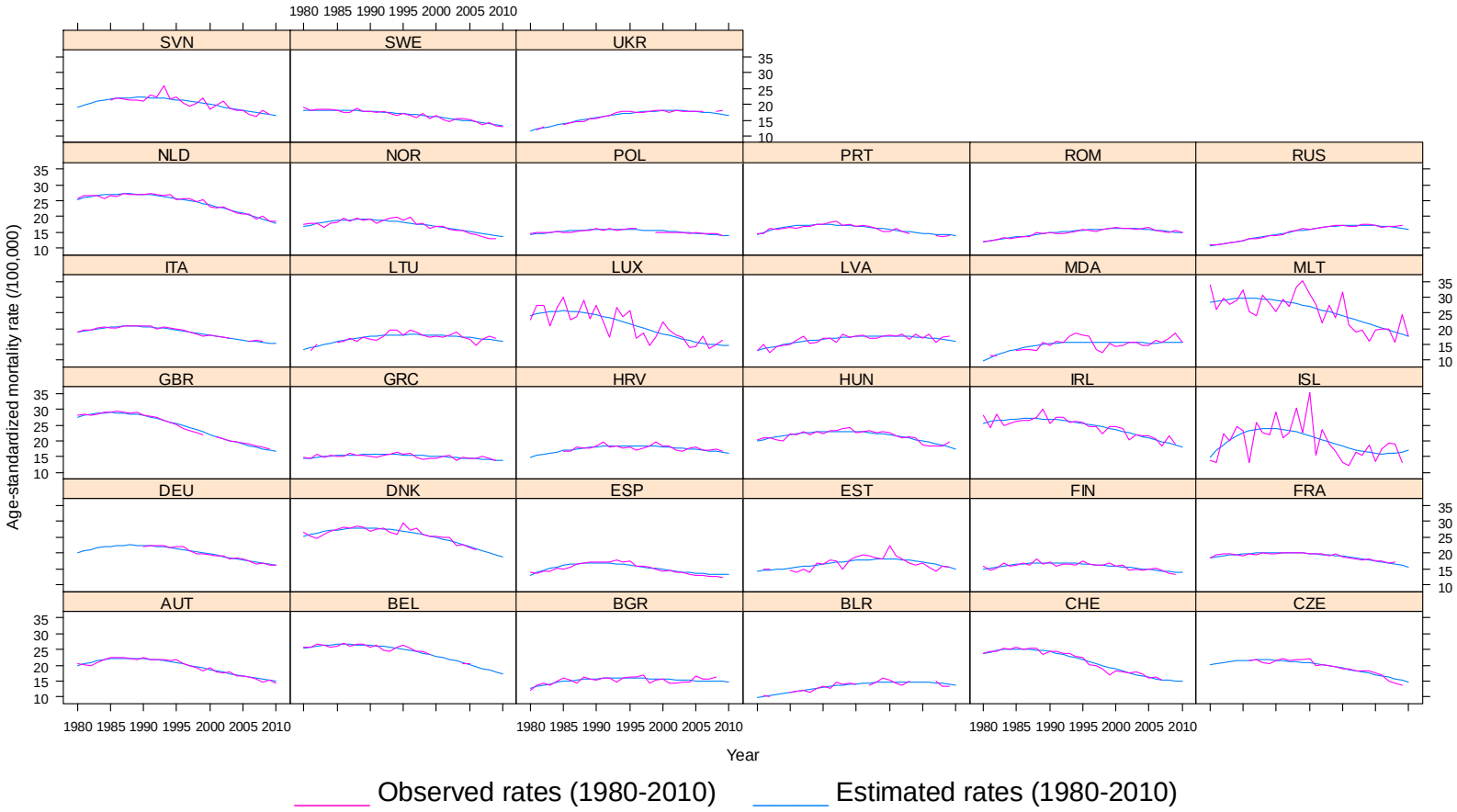
Figure 3. Proportion of countries with no organized breast cancer screening, or screening programmes set up in different time periods*, for each pattern identified.



* We considered the existence of organized screening, regardless of its coverage or participation rates.

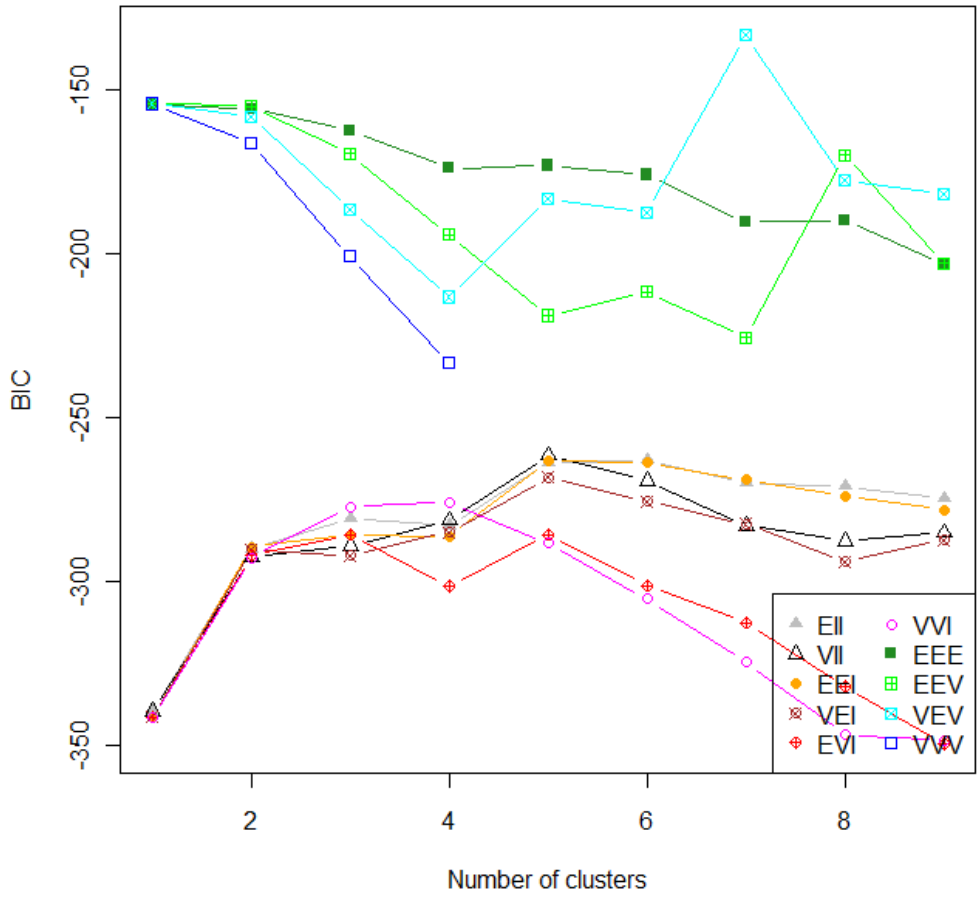
† The results referring to pattern 3 do not include data from Finland, France, Greece or Sweden.

Appendix 1. Observed and predicted breast cancer age standardized mortality rates (direct method, World standard population), all ages.



AUT=Austria; BEL=Belgium; BGR=Bulgaria; BLR=Belarus; CHE=Switzerland; CZE=Czech Republic; DEU=Germany; DNK=Denmark; ESP=Spain; EST=Estonia; FIN=Finland; FRA=France; GBR=United Kingdom; GRC=Greece; HRV=Croatia; HUN=Hungary; IRL=Ireland; ISL=Island; ITA=Italy; LTU=Lithuania; LUX=Luxembourg; LVA=Latvia; MDA=Republic of Moldova; MLT=Malta; NLD=The Netherlands; NOR=Norway; POL=Poland; PRT=Portugal; ROM=Romania; RUS=Russian Federation; SVN=Slovenia; SWE=Sweden; UKR=Ukraine.

Appendix 2. Identification of the patterns by model-based clustering.



BIC – Bayesian Information Criteria (the plot depicts the BIC value multiplied by minus one)

EII – Equal volume, equal shape, non applicable orientation;

VII – Variable volume, equal shape, non applicable orientation;

EEI – Equal volume, equal shape, coordinate axes orientation;

VEI – Variable volume, equal shape, coordinate axes orientation;

EVI – Equal volume, variable shape, coordinate axes orientation;

VVI – Variable volume, variable shape, coordinate axes orientation;

EEE – Equal volume, equal shape, equal orientation;

EEV – Equal volume, equal shape, variable orientation;

VEV – Variable volume, equal shape, variable orientation;

VVV – Variable volume, variable shape, variable orientation.

Appendix 3. Characterization of countries regarding organized screening activities, by patterns of trends in breast cancer mortality rates.

	Country	Organized Screening			References
		Year first programme started	National coverage (year)	Age group (years)	
Pattern 1	Belgium	2001	Yes	50-69	22
	Denmark	1991	No	50-59	22, 46, 47
	Ireland	2000	Yes	50-64	48-50
	Luxembourg	1992	Yes	50-69	22
	Malta	-	No	-	34, 51
	Netherlands	1989	Yes (1997)	50-69/75[a]	22, 52
	Scotland (UK)	1988	Yes (1991)	50-64/70[b]	23
	England (UK)	1988	Yes (1995)	50-64/70[c]	53
	Switzerland	1999[d]	No	50-70	22, 37, 51, 54
Pattern 2	Austria	2008[e]	No	50-69	55, 56
	Czech Republic	2002	Yes	45-69[f]	34, 36, 51
	Germany	2005	2009	50-69	22, 34, 57
	Hungary	2002[g]	Yes	45-65	34, 58
	Italy	1985	No	45/50-69[h]	22, 24, 57, 59
	Norway	1996	2004	50-69	22, 60
	Portugal	1990	No	45-69	22
	Spain	1990	2000	45/50-64/69[i]	61
	Slovenia	-	No	-	33
Pattern 3	Belarus	-	No	-	62
	Bulgaria	-	No	-	23, 29, 32
	Croatia	2006	Yes	50-69	63, 64
	Estonia	2003	Yes	50-59	51
	Finland	1987	Yes	50-59	22, 65
	France	1989	2004	50-74	22, 66
	Greece	2004	No	40-69	22, 67
	Latvia	-	No	-	51
	Lithuania	2006	Yes	50-69	48, 51
	Poland	2007	Yes	50-69	48, 51
	Rep. of Moldova	-	No	-	-
	Romania	-	No	-	51
	Russian Fed.	-	No	-	-
	Sweden	1986	1997	40/50–69/74[j]	22, 48, 68
	Ukraine	-	No	-	-

[a] Women eligible in the Netherlands: 50-69 years; 70-75 included since 1998.

[b] Women eligible in Scotland: 50-64 years; extended to 70 in 2003/04.

[c] Women eligible in the United Kingdom: 50-64 years; by 2005 women aged 50-70 years were being screened.

[d] A pilot programme started in Switzerland in 1993 in canton Vaud.

[e] Tyrol (Austria): spontaneous mammography screening has an overall participation of 75% and was set up around 1993; in 2008 an organized programme started comprising the whole state.

[f] Women eligible in Czech Republic: since 2010 there is no upper age limit.

[g] Hungary: a pilot breast screening programme was established in 1995.

[h] Women eligible in Italy: 50-69 years; several programmes include women over 70 and some invite women 45-49 years.

[i] Women eligible in Spain: 50–65 years; some regions include women up to 69 and some invite women over 45 years.

[j] Women eligible in Sweden: 100% of counties invite 50-69 years; 60-70% start at age 40 and approximately 50% of counties invite age group 70-74.

6. CONCLUSION

In conclusion, the patterns identified summarize the temporal trends in breast cancer mortality across European countries. We can observe an overall downward trend in recent years, as well as a levelling of breast cancer mortality throughout Europe over the last three decades

This study provides a general model for the description and interpretation of the patterns of variation in breast cancer mortality throughout Europe, as well as a basis for more accurate predictions of the burden associated with breast cancer.

REFERENCES

1. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet] [database on the Internet]. [cited 30/06/2012]. Available from: http://globocan.iarc.fr.
2. Strategies IWGotEoC-P. IARC Handbooks of Cancer Prevention, Breast Cancer Screening. Lyon: IARC Press; 2002. Available from: http://www.iarc.fr/en/publications/pdfs-online/prev/handbook7/Handbook7_Breast-0.pdf.
3. Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res. 2004;6(6):229-39. Epub 2004/11/13.
4. Parkin DM, Fernandez LM. Use of statistics to assess the global burden of breast cancer. Breast J. 2006;12 Suppl 1:S70-80. Epub 2006/01/25.
5. Organization WH. The Global Burden of Disease: 2004 Update. Geneva: 2008. Report No.
6. Verdecchia A, Santaquilani M, Sant M. Survival for cancer patients in Europe. Annali dell'Istituto superiore di sanita. 2009;45(3):315-24. Epub 2009/10/29.
7. Lietzen LW, Sorensen GV, Ording AG, Garne JP, Christiansen P, Norgaard M, et al. Survival of women with breast cancer in central and northern Denmark, 1998-2009. Clin Epidemiol. 2011;3 Suppl 1:35-40. Epub 2011/08/05.
8. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011;377(9760):127-38. Epub 2010/12/25.
9. Thomson CS, Brewster DH, Dewar JA, Twelves CJ. Improvements in survival for women with breast cancer in Scotland between 1987 and 1993: impact of earlier diagnosis and changes in treatment. Eur J Cancer. 2004;40(5):743-53. Epub 2004/03/11.
10. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. Eur J Cancer. 2003;39(12):1718-29. Epub 2003/07/31.
11. Rijo M John, Hana Ross. Economic value of disability adjusted life years lost to cancers: 2008. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(15s).
12. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. The lancet oncology. 2001;2(3):133-40. Epub 2002/03/21.
13. Hulka BS, Moorman PG. Breast cancer: hormones and other risk factors. Maturitas. 2008;61(1-2):203-13; discussion 13. Epub 2009/05/13.

14. Valentina A. Andreeva JBU, Mary Ann Pentz. Breast Cancer among Immigrants: A Systematic Review and New Research Directions. J Immigrant Minority Health. 2007(9):307-22. Epub 13 March 2007.

15. Joanne Lee KD, Shou-En Lu, and George G. Rhoads. Cancer Incidence Among Korean-American Immigrants in the United States and Native Koreans in South Korea. Cancer Control. 2007;14(1).

16. Deapen D, Liu LH, Perkins C, Bernstein L, Ross RK. Rapidly rising breast cancer incidence rates among Asian-American women. International Journal of Cancer. 2002;99(5):747-50.

17. H. Shimizu RKR, L. Bernstein, R. Yatani, B. E. Henderson, and T. M. Mack. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Brit J Cancer. 1991(63):963-6.

18. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ. 2000;321(7261):624-8. Epub 2000/09/08.

19. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A. Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. Journal of the National Cancer Institute. 2001;93(16):1215-23. Epub 2001/08/16.

20. Key TJ, Verkasalo PK. Endogenous hormones and the aetiology of breast cancer. Breast Cancer Res. 1999;1(1):18-21. Epub 2001/03/16.

21. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. The New England journal of medicine. 1994;331(1):5-9. Epub 1994/07/07.

22. Tamakoshi K, Yatsuya H, Wakai K, Suzuki S, Nishio K, Lin Y, et al. Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. Cancer science. 2005;96(1):57-62. Epub 2005/01/15.

23. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002;360(9328):187-95. Epub 2002/07/23.

24. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1996;347(9017):1713-27. Epub 1996/06/22.

25. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. International journal of cancer Journal international du cancer. 1999;81(3):339-44. Epub 1999/04/21.

26. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1997;350(9084):1047-59. Epub 1999/04/23.

27. Clemons M, Loijens L, Goss P. Breast cancer risk following irradiation for Hodgkin's disease. Cancer Treat Rev. 2000;26(4):291-302. Epub 2000/07/29.

28. Travis LB, Curtis RE, Boice JD, Jr. Late effects of treatment for childhood Hodgkin's disease. The New England journal of medicine. 1996;335(5):352-3. Epub 1996/08/01.

29. Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. Journal of the National Cancer Institute. 2000;92(14):1126-35. Epub 2000/07/25.

30. World Cancer Research Fund & American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington, DC: IARC, 2007

31. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA : the journal of the American Medical Association. 1998;279(7):535-40. Epub 1998/02/28.

32. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(10):716-26, W-236. Epub 2009/11/19.

33. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan B, Nygren P, et al. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force. Rockville (MD)2009.

34. Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. The New England journal of medicine. 2010;363(13):1203-10. Epub 2010/09/24.

35. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. The Lancet. 2012. Epub 29/10/2012

36. Peter C Gøtzsche OO. Is screening for breast cancer with mammography justifiable? The Lancet. 2000;355:129-34.

37. Puliti D, Miccinesi G, Zappa M, Manneschi G, Crocetti E, Paci E. Balancing harms and benefits of service mammography screening programs: a cohort study. Breast Cancer Res. 2012;14(1):R9. Epub 2012/01/11.

38. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. Lancet. 2001;358(9290):1340-2. Epub 2001/10/31.

39. Schopper D, de Wolf C. How effective are breast cancer screening programmes by mammography? Review of the current evidence. Eur J Cancer. 2009;45(11):1916-23. Epub 2009/04/29.
40. The Council of the European Union. Council Recomendation of 2 December 2003 on cancer screening. Official Journal of the European Union. 2003.
41. Bastos J, Peleteiro B, Gouveia J, Coleman MP, Lunet N. The state of the art of cancer control in 30 European countries in 2008. International journal of cancer Journal international du cancer. 2010;126(11):2700-15. Epub 2009/10/16.
42. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. The New England journal of medicine. 1998;338(16):1089-96. Epub 1998/04/17.
43. Lidbrink E, Elfving J, Frisell J, Jonsson E. Neglected aspects of false positive findings of mammography in breast cancer screening: analysis of false positive cases from the Stockholm trial. BMJ. 1996;312(7026):273-6. Epub 1996/02/03.
44. Heywang-Kobrunner SH, Hacker A, Sedlacek S. Advantages and Disadvantages of Mammography Screening. Breast Care (Basel). 2011;6(3):199-207. Epub 2011/07/23.
45. Cole BF, Gelber RD, Gelber S, Coates AS, Goldhirsch A. Polychemotherapy for early breast cancer: an overview of the randomised clinical trials with quality-adjusted survival analysis. Lancet. 2001;358(9278):277-86. Epub 2001/08/11.
46. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351(9114):1451-67. Epub 1998/05/30.
47. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000;355(9203):528-33. Epub 2000/02/22.
48. Myrthe P.P. Sukel LVvdP-F, Grard A.P. Nieuwenhuijzen, Gerard Vreugdenhil, Ron M.C. Herings, Jan Willem W. Coebergh, Adri C. Voogd. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990–2006 in the southeastern Netherlands. European Journal of Cancer. 2008;Vol. 44(Issue 13):1846–54.
49. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62(4):220-41. Epub 2012/06/16.
50. Aebi S, Davidson T, Gruber G, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2011;22 Suppl 6:vi12-24. Epub 2011/10/20.

51. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 2000;355(9217):1757-70. Epub 2000/06/01.