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The effectiveness of breast cancer screening

Breast cancer screening and the effect on mortality and incidence in 24 European countries

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ABSTRACT

Recommended by the European Union, more and more countries have an organized breast cancer screening program. An X-ray image of the breast (mammogram) is used to detect breast cancer at an early stage with the aim to improve survival and avoid breast cancer mortality. In the literature support is found for decreasing mortality rates after implementing a screening program from 10-30%. Other studies are critical and disprove the reduction or show an increase in mortality. The incidence rate is expected to increase after the implementation of a screening program. The different characteristics of a screening program are showed per country. These characteristics - the starting year of the (pilot) program and age interval - are used to predict breast cancer mortality with OLS and a fixed effects model. Concluded is that the implementation of a screening program leads to a decrease in mortality and increase in incidence rate.

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1. INTRODUCTION

Breast cancer is the most frequent cancer in women, from both a worldwide and European view. In 2006, breast cancer was the most common form of cancer diagnosed in European women with 429.900 cases (28.9%). This percentage means that 28.9% of all diagnosed cancers (long, liver, skin etc.) is diagnosed as breast cancer. Breast cancer was also the leading cause of cancer death for women with 85.300 cases (16.7%). This means that 16.7% of overall cancer mortality is due to breast cancer (Ferlay et al, 2006).. In 2008 worldwide 1.38 million new cases were diagnosed, which is around 23% of the total cancers in women.[1] Breast cancer incidence rates are highest in Western Europe. These numbers show a high incidence and mortality rate. These rates are different between European countries. Differences in incidence- and mortality rates can be caused through differences in the population structure (age-related differences) and anthropometric factors. Risk factors of getting breast cancer can be divided in lifestyle factors such as the use of alcohol or giving breastfeeding, hormonal status and anthropometric factors like height and weight.

Breast cancer screening is a form of preventive care. Generally there are three categories distinguished to categorize preventive care. Primary prevention are activities to reduce the occurrence of the disease (e.g. vaccination campaigns), secondary prevention aims to reduce the health consequences of the disease (cancer screening) and tertiary prevention aims to reduce the disabilities due to chronic illnesses (Jusot et al, 2011). Breast cancer screening can influence breast cancer incidence and mortality rates. The aim of the screening program is to reduce breast cancer mortality by mammographic screening. The high amount of breast cancer incidence and mortality show us the importance of a good and well-developed screening program.

Breast cancer screening can lead to a reduction of breast cancer mortality. This hypothesis is supported through literature. One reason why breast cancer screening reduces mortality is because the cancer is detected earlier. This earlier detection of diagnosed cancers can lead to a more effective treatment (Otten et al, 2008). Several studies have shown a relationship between breast cancer screening and mortality from breast cancer. There is also support for the hypothesis that breast cancer screening will not reduce breast cancer mortality.

This thesis wants to study how screening programs affect mortality an incidence rates. A screening program has different characteristics: start of pilot program, starting year of national program, a

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from http://globocan.iarc.fr. Accessed May 2011.

target group (range of minimum and maximum age), a screening interval (in years) and detection method. The first question is how mortality and incidence rates are influenced after the implementation of a screening program. In other words: are screening programs effective in reducing mortality and what happens with the incidence rate? The second question is how screening possibilities can be used optimally: what is the influence of the specific characteristics of the screening program on mortality and incidence rates.

This brings us to the following research question:

What is the influence of a screening program on the incidence and mortality rates of breast cancer in 24 European countries?

The included countries are Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. These countries are chosen from the OECD Health database. This research is limited to European countries, who all have implemented a screening program. To study the question how effective screening programs are in reducing mortality, it would be better to include countries without a screening program, to compare countries with and without screening. But I have chosen to focus on the question how different characteristics of screening programs influence mortality and incidence rates. Because I want to know how characteristics can be combined to the best screening program.

Mortality and incidence data is collected from the OECD Health data. Mortality of *Malignant neoplasms of female breast* is available in number of female deaths and deaths per 100.000 females (standardized rate) for OECD countries. For this research only the standardized rates of the included European countries are used. The incidence is available in number of female cases and incidence per 100.000 females. Only the standardized rate is used, because this gives the possibility to compare between countries. Characteristics of the screening program per country are collected through literature review.

This thesis starts with a theoretical framework that contains general information about breast cancer screening and guidelines, followed by a literature review about the effect of breast cancer screening on breast cancer mortality and incidence. After that specific program characteristics are summarized. Next to the theoretical information about the effect of breast cancer screening, a statistical analysis is done and described in the sections ‘research design’ and ‘research results’. Limitations are discussed in the ‘discussion’ section and followed by the conclusion of this research.

This thesis wants to identify the effect of breast cancer screening on breast cancer mortality and incidence rates. From the literature is found that most studies show a decrease of mortality and therefore effectiveness of a breast cancer screening program. But there are also studies who criticize this decrease. The incidence rate is expected to be increasing. With breast cancer screening, more breast cancers are detected. From the statistical research is found that with this data and the used models mortality is expected to be decreasing after the implementation of a screening program. The incidence rate is increasing after the implementation of a screening program.

2. THEORETICAL FRAMEWORK

1. Breast cancer screening

In this theoretical framework is described what breast cancer screening is and what the European Union recommends according population based screening. After that the goal and various aspects of a screening program in general, the importance of a high participation rate and different characteristic of the screening program per country are mentioned. This is followed by a literature review about the positive or negative effect of breast cancer screening on breast cancer mortality. The same is done for the effect on breast cancer incidence.

Breast cancer screening means checking a women's breast before there are symptoms of breast cancer. There are different forms of screening; a *mammogram* is an X-ray image of the breast. A radiologist analyzes this image for abnormal findings. A *clinical breast exam* is an examination by a general practitioner or nurse, using their hands to feel for lumps or other changes of the breasts. It is also possible for women to do a *breast self-exam*, checking their own breasts for lumps of changes of the breasts or underarm. Mammograms are the best method to detect breast cancer early, before symptoms appear. This early detection makes it easier to treat breast cancer. Nowadays digital mammography is the most used technique. The X-ray images of the breast can be captured on film or stored directly onto a computer. There are no differences in the interpretation between a mammogram and digital mammogram.

There is a difference between opportunistic screening and population-based screening. Population-based screening (or national screening, organized screening) is the highest level of program organization. Organized screening contains of six characteristics, mentioned in the IARC Handbook for Cancer Prevention. These characteristics are: 1. a policy specifying target population, screening method and interval, 2. a well-defined target population, 3. a team responsible for overseeing screening centers, 4. a decision structure and responsibility for healthcare management, 5. a quality assurance system utilizing relevant data, 6. a system monitoring cancer occurrence in the target population. Opportunistic screening is non-systematic screening outside the national program, or before the national program started. For opportunistic screening there is no invitation sent or a defined target group. This thesis focuses on characteristics 1 and 2: the target population, screening method and screening interval in the given countries.

Guidelines EU

The council of the European Union came with the recommendation for cancer screening on 2 December 2003.[2] First they explain in the recommendation that national policies have the responsibility to prevent human illness and diseases, through health information and education, promoting research and prevention. It is mentioned that cancer is a major cause of death in Europe, with breast cancer as the most prevalent form (29% in 1998). Screening is necessary to detect cancer at an early stage, before it becomes invasive. An indicator for the effectiveness of breast screening is a decrease in breast cancer mortality. Also screening can have a negative effect, so healthcare providers should be aware of both the disadvantages and benefits of screening programs. Quality assurance is important and screening should only be offered to fully informed people.

After this explanation the council recommends to implement evidence-based cancer screening through a systematic population-based approach for women aged 50 to 69 in accordance with European guidelines on quality assurance in mammography.

[2] Council Recommendation 2 December 2003 on cancer screening. Official Journal of the European Union 16-12-2003

2. Literature review

Mammography screening is officially recommended for women between 50-69 years every two years, but here are countries with a wider target group or screening interval than recommended. There is evidence for efficacy of screening women aged 50-69 years, limited evidence for age category 40-49 years and there is no benefit for women with an age lower than 40 or older than 69 (ENCR, 2002). An organized screening program invites women to participate in free mammography screening, offered mostly at a nearby location. There is variation in the exact screening program between countries; this is specified later.

The goal of mammography screening is to detect breast cancer in an early stage, before symptoms appear. Breast cancer develops slowly in contrast to other sorts of cancer and as long as it has not metastasized, the survival rates are higher. If the cancer already has metastasized the survival rate is low. Without metastases the 5-year survival rate is 96% versus 81% when the cancer metastasized to the lymph nodes versus 26% with metastases to other organs (Fang and Wang, 2010). This rate shows the importance of early detection. In a Dutch study the benefit of early detection by mammography is showed with a case-control study (Otto et al, 2011). Women who died from breast cancer where matched to a control group with the same year of birth, first invitation and number of invitations before the diagnose breast cancer. Cases are women who died of breast cancer in the research period, controls are women who were still alive at this date of death and who are free of breast cancer at the date of diagnosis. After controlling for self-selection bias, they conclude that the risk of breast cancer mortality is lower among women who are invited and participate in the screening program. Besides the early detection of breast cancer, there is another advantage. When a government implements a national screening program, the government gives a signal that screening is important and avoids that a woman believes that screening is not necessary (Wübker, 2012).

There are also studies that encounter the decrease of mortality after implementing a breast cancer screening program. Gøtzsche and Jørgensen explain that randomization is very important in the statistical analysis. Randomization means that the program or intervention is randomly assigned to the population, to avoid selection bias. This means that the effect of breast cancer screening must be studied with a group who can attends screening and a control group without screening. Another reason why the mortality decrease is encountered is the possibility of overdiagnosis, which is a disadvantage of screening.

Disadvantages of mammography screening are overtreatment and anxiety associated with false normal results. Overtreatment or overdiagnosis occurs when screening detects breast cancer earlier

while earlier detection will not lead to life extension. Or when screening detects cancerous cells that wouldn't develop into breast cancer. False positive results take place when screening gives positive result (breast cancer) when there is actually no breast cancer.

The process of breast cancer screening can be summarized with the following figure:

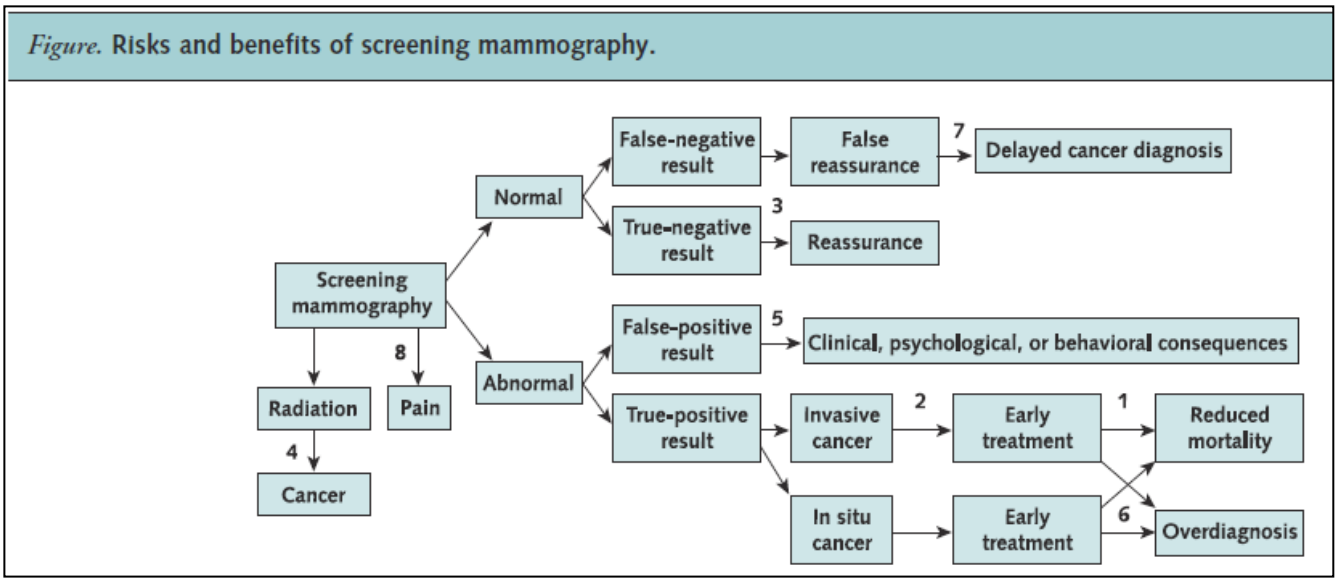


Figure 1 Risks and benefits of screening mammography

Source: Armstrong, K., Moye, E., Williams, S., Berlin, J. A., et al., 2007. Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. *Annals of Internal Medicine,* 146 (7), pp. 516-526.

The effectiveness of the program depends on the quality of individual components. Performance indicators reflect the quality of the program, without contributing directly to reduction in mortality. Examples of performance indicators are coverage, participation rate, proportion of eligible women re-invited within the specified screening interval (+2 of +6 months) and so on. The participation rate is defined as *"the proportion of women attending screening of those personally invited"*.[3] The participation rate is an important indicator. The acceptable level of the participation rate is > 70% and the desirable level is > 75%. This numbers are no indicators of importance, because higher percentages are better in this case. But this numbers are "*the most widely used and generally*

[3] Giordano, L., von Karsa, L., Tomatis, M., Majek, O., et al., 2012. Mammographic screening programmes in Europe: organization, coverage and participation. *Journal of Medical Screening,* 19 (suppl 1), pp. 72-82.

appropriate professionally agreed levels for usage in a Pan-European setting".[4] In the description of the programs per country, we shall see that not all countries reach the acceptable level of 70%. Coverage can be divided into invitation coverage and examination coverage. Invitation coverage is *"the extent to which the screening programme covers the eligible population within the appropriate interval in a given period by invitation"*. Examination coverage is *"the extent to which the screening program covers the eligible population with screening tests".*[5] The term coverage is also used to describe the achievement of the national screening program. Full coverage means that 100% national screening is achieved.

2.1 Mortality

The aim of breast cancer screening is to reduce breast cancer mortality. In The Netherlands, Sweden, England and Wales and Norway most research is done to evaluate breast cancer screening programs. In this paragraph studies that show a negative effect of mortality are first mentioned. There are also studies that show no effect or a positive effect of breast cancer screening programs on mortality. At last: studies have different research methods what will influence the magnitude and sign of the effect.

Screening and decrease of mortality

In 2002 the World Health Organization (WHO) concluded that in areas with a screening attendance of at least 70%, breast cancer mortality may be expected to decrease by 25% for screened women between ages 50-69. The effect on mortality differs per age group. The Agency for Healthcare Research and Quality report in 2009 that breast cancer mortality is reduced by 15% for women aged 39-59 years and around 30% for women aged 60-69 years (Biro, 2012). For women with a higher age (60-69), there is a larger reduction in breast cancer mortality.

The efficacy of screening in reducing breast cancer mortality has been shown in randomized controlled trials (De Koning et al, 2003; Nyström et al, 1993). Research about trends in breast cancer mortality and incidence in relation to the implementation of a national screening program has been done in The Netherlands (Otten et al, 2008; Otto et al, 2003), Sweden (Nyström et al, 1993 and

[4] Perry, N., Broeders, M., De Wolf, C., Törnberg, S., et al., 2006. European guidelines for quality assurance in breast cancer screening and diagnosis Fourth Edition. *Luxembourg Office for Official Publications of the European Communities,* .

[5] Giordano, L., von Karsa, L., Tomatis, M., Majek, O., et al., 2012. Mammographic screening programmes in Europe: organization, coverage and participation. *Journal of Medical Screening,* 19 (suppl 1), pp. 72-82.

2002; Gøtzsche and Olsen, 2000), England and Wales (Quinn et al, 1995; Blanks et al, 2000) and Norway (Kalager et al, 2010).

In The Netherlands mortality rates are decreasing (after approximately 5 years) for the age groups who are invited for screening compared to age groups who are not invited Also a rising incidence rate is the consequence of implementing screening. Screening results in more cancers detected, because of lead time, length-biased sampling and possibly over diagnosis (Otten et al, 2008). Research in The Netherlands confirms that screening initially leads to an increase in the incidence rate, which is temporary. This is followed by a decrease in advanced breast cancers in the women invited for screening. In other words: there is a higher proportion of less severe tumors (Fracheboud et al, 2004).

In Sweden research is done in five trials, to examine the effect of screening in terms of mortality reduction. There is evidence that screening will not decrease mortality. After the different findings about screening and mortality in Sweden, Gøtzsche and Olsen reviewed the methodological quality of the trials in Sweden and their possible sources of bias in the randomized trials. They conclude that only one breast-cancer death is avoided for every 1000 women, screening through 12 years. So the effect of screening programs is small and it is essential that programs are evaluated properly in randomized trials (Gøtzsche and Olsen, 2000). After this criticism, Nyström and colleagues come with a follow-up of their earlier research. In total there is a 21% reduction in breast cancer mortality associated with invitation to screening. The effect of screening depends on the age-groups. The highest effect is measured in women aged 55-69 years and lowest in women aged 50-54 years (Nyström et al, 2002). Fourteen years after the introduction of breast cancer screening is the reduction in breast cancer mortality still visible.

In England and Wales changes in incidence of breast cancer and mortality from breast cancer are measured through comparison of these rates before and after the introduction of screening. In the late 1980s in Britain mortality from breast cancer was among the highest in the world while the incidence rates where similar compared with other western European countries, so survival is worse. In 1988 the NHS breast screening program started. To measure the effects they compare the rates in 1979 with 1992. After the introduction, recorded incidence rates rose steeply in the target group age 50-64 (40% between 1979 and 1992, 25% when 1992 is compared with 1987, 1 year before screening started). Mortality from breast cancer changed little in the target group in the first three years after introduction of the screening program. After this first period they fell steeply (a 12% decrease between 1987 and 1994). Caution is needed when interpreting this numbers, because

these large decreases can also be caused through other factors, such as advancing medical technologies and possibilities to treat breast cancer (Quinn and Allen, 1995).

The Norwegian study of Kalager and colleagues studies both the reduction in mortality between the screening and non-screening group and the historical screening and non-screening group. The historical screening group are women who from 1986 – 1995 live in counties with/without screening and from 1996-2005, after the introduction of population based screening. This comparison with historical control subjects and screened/non-screened subjects makes it possible to know which part of the reduction can be related to the implementation of a program or can be related to chronologic trends, such as more breast cancer awareness and advanced treatments. The mortality rate of women in the screening group compared with the historical group is reduced with 28%. Non-screening compared with historical group shows a reduction of 18%, so the relative reduction among women in the screening group is 10%. The time effect is 18% and the screening effect is 10% reduction in breast cancer mortality. Earlier we have seen that the reduction in mortality is different for different age groups; there is a higher effect in reducing mortality for older women. Mortality reduction is also different for women with a various stage of tumor. There are 4 phases distinguished and a higher stage means a worse prognosis, because the cancer is metastasized to more organs or other parts of the body. The decrease in mortality was highest for women with stage II tumors. Stage II means that the cancer is metastasized locally (more than one organ).

All studies show that the implementation of a screening program affects breast cancer mortality. These results are summarized in table 1. Mortality is an indicator of the effectiveness of a screening program. But the researcher must be aware that it will take a certain amount of years after the implementation of a screening program before mortality is decreasing. Effects can be measured after a period of time.

Table 1 Overview literature studies

Study	Year	Effect	Method	Remarks
Biro et al.	2009	Mortality decreases with 15% for women aged 39-59 and 30% for women aged 60-69	-	From Healthcare Research and Quality (2009)
Otten et al.	2008	Mortality decreases	Joinpoint Poisson regression analysis	
WHO	2002	Mortality decreases with 25% for women aged 50-69	-	With an attendance rate of at least 70%
Gøtzsche and Ølsen	2000	1/1000 deaths is avoided	RCT	

Nystrom et al.	2002	Mortality decreases with 21%	RCT	Decrease depends on age group
Quinn and Allen	1995	Mortality decreases between 1987 and 1994	Comparison of age specific mortality before and after the introduction of screening in the late 1980s.	
Kalager		Mortality decreases with 10%	Comparison of screened and non-screened women and historical control subjects	

Screening and increase of mortality (or no effect)

There are also studies that found no effect of screening on mortality. Gøtzsche and Jørgensen of the Cochrane Centre came recently (June 2013) with an extended review about mammographic screening and the effect on breast cancer mortality. They reviewed only randomized trials, comparing screened women with non-screened women and found 7 trials. Gøtzsche and Jørgensen concluded there is a relationship between the adequacy of randomization and the sign of the effect of screening on mortality. Trials with adequate randomization show no significant decrease in mortality, while fewer adequacies in randomization lead to a significant decrease in breast cancer mortality. So improper statistical research leads to false conclusions that breast cancer screening leads to a reduction in breast cancer mortality.

Also Bleyer and Welch (2012) conclude that screening doesn't have a large impact in reducing mortality. Only at best, there is a small effect on mortality from breast cancer. This study focuses not on the best statistical method, but gives attention to over diagnoses as a result from breast cancer screening. The aim of screening is to come to an earlier diagnosis (in an earlier stage of cancer) and early treatment. In the study of this researchers on the effects of breast cancer screening is mentioned that more early stage cancers are diagnosed and late stage cancers diagnoses are decreased. Early stage cancer increases in 3 decades with 122 cancers per 100.000 women and late stage cancer decreases with 8 cases per 100.000 women. If the burden of disease remains the same (and also in the case of relaxing this assumption), only a small amount of early stage cancer develops into late stage cancer, whereby there is a high over diagnosis. The conclusion is that mortality decrease results from improvements in treatment and not from screening.

Research method

In this paragraph I described the results of mostly randomized controlled trials in different countries. But the results are different when the information is taken from national mortality statistics, which is the case in this thesis. The International Association of Research on Cancer (IARC) mentions different reasons why the reduction in mortality due to screening takes longer to become evident in national mortality statistics than in randomized trials. First it is not always clear when breast cancer is diagnosed. There is dilution due to breast cancer deaths in cases diagnosed before women are invited to screening. In trials pre-existing cases are excluded. Second it takes long time to cover the national population, when a program is started there can be much time between the first invitations and the completion of screening. In a trial woman enter the trial at the time of the first invitation. Third the staff needs learning time to screening, while trials usual have a more experienced staff.

Overall cancer mortality

The report of the Gezondheidsraad[6] paid attention on overall cancer mortality. For a confident analysis of the effect from breast cancer screening on breast cancer mortality, also the effect on overall cancer mortality should be measured. If screening has a negative effect on breast cancer mortality (mortality is decreasing) it should be logical there is also a negative effect on overall cancer mortality. The sign of the effect should be the same, but the magnitude is expected to be smaller for overall cancer mortality.

It is necessary to measure the effect on overall cancer mortality because of the possibility of wrong assignment of cancer sort. When the cancer is metastasized to different organs, it can be assigned to different cancer sorts when the patient is dying. This can affect breast cancer mortality to a lower of higher amount. Another reason to measure the effect on overall cancer mortality is to detect possible dangerous effects of breast cancer screening and to study differences between the effect on breast cancer mortality and overall mortality.

The expectation is that if cancer screening reduces breast cancer mortality, also overall cancer mortality is decreasing. The magnitude of overall cancer mortality depends on the percentage of

[6] Van Veen, W. and Knottnerus, J. 2002. Het nut van bevolkingsonderzoek naar borstkanker; een advies van de gezondheidsraad. *Nederlands Tijdschrift Voor Geneeskunde,* 146 (22), pp. 1023-1025.

breast cancer mortality in overall cancer mortality. This percentage is lower in studies with a randomized control trial, because women who have already breast cancer are excluded of the trial.

2.2 Other determinants of breast cancer incidence and mortality

We already know that the breast cancer incidence rate is high. In 2006 30.9% of all cancer cases in the EU-25 were breast cancer (Ferlay et al, 2006). Worldwide there is variation in the incidence rate, where Europe counts the highest rates. In this paragraph I describe different risk factors and the influence of breast cancer screening on the incidence rate.

Factors to explain the variance in breast cancer incidence are socio-economic differences, hormonal and nutritional factors and also breast cancer screening can affect the incidence rate. The expectation is that there is an increase in incidence of early stage and in situ breast cancers, but a decline in advanced cancer (Bray et al, 2004).

Sweden, Denmark and The Netherland started in the mid to late 1980s with screening and incidence rates were already increasing before screening started. Bray and colleagues observed an increase of 1-3%. This increase was also seen in other countries, which have not implemented a national screening program, or have only pilot programs. The incidence rate varies per age group, increasing incidence occurs from age 35 – 49, 50 – 64 and 65 – 74 year. Also Ferlay under scribed that the introduction of national screening programs increases the incidence rate, which is a short-term consequence.

Measuring the incidence rate, a distinction should be made between the stages of cancer. In the study of Bleyer and Welch we have seen that the amount of early stage cancers increased due to breast cancer screening. But for late stage cancers there is a small decrease. This could be because late stage cancers are already diagnosed before a woman participates in a screening program.

The availability of a screening program does not automatically mean that every woman participates. In most countries the women of the target group are personally invited to utilize the screening program. Countries with a population based program invites all women between the chosen age range. To take advantage of the screening program, screening attendance rates should be as high as possible. There are many factors that can explain the variation in screening attendance. Screening uptake differences occur due to individual factors and institutional factors. Individual factors are for example education, age, income-level and perceived risk. Explicit institutional factors are the health system regulation, financing and provision of the screening program. Implicit institutional factors are

cultural factors such as traditions and norms. The availability of an organized screening program can statistically explain 40% of the between country differences in screening rates (Wübker, 2012). In the literature about attendance rates there is much attention for inequalities between women that attends screening. In this thesis country averages are used and this thesis is not focusing on within country differences. But when participation has an effect on mortality, it is interesting how reducing inequalities women that attend screening can lead to an effect on participation rates and later mortality rates. In the study of Palencia and colleagues (2010) is mentioned that earlier studies show that individual factors have more weight in opportunistic screening than in population based screening. Implementing a population based program can be effective in increasing the participation rate, but is it also effective in reducing inequalities between those women that attends screening? In the study different countries with different type of programs are compared: national screening, pilot or regional screening and opportunistic screening. There are no socio-economic inequalities observed among women who have participated in national screening programs. In pilot/regional or opportunistic programs there are inequalities. The conclusion is that for a woman in a country with national screening it is more likely she had undergo screening compared with a woman in a country without a national screening program. It is relevant to know that national screening programs inequalities and more women will participate compared to pilot or opportunistic programs. It seems that national programs have more magnitude to effect mortality and age range compared to pilot programs.

3. Characteristics screening program

3.1 Characteristics

All countries that are included in this thesis do have a breast cancer screening program. Wübker mentions different explanatory variables regarding the organization of the screening programs:

The share of women who are personally invited (target group): women in the target group, within the age-interval, are invited personally. The advantage of this personal and country-wide approach is that the whole eligible population and range of socioeconomic groups are identified and invited. (IARC)

The screening interval in years: all countries have a screening interval from maximum 24 months. The ideal interval depends on the age of the women, for women aged 40-49 there are lower intervals (maximum 18 months) recommended compared with women aged higher than 50 (maximum 24 months).

The year in which the first screening program started: it will take some time before the effect on mortality can be measured. A program should be started, the data of the population must be available, invitations must be sent and specialists must be trained. When the program is implemented extensively and screening real starts, it will have an effect on mortality rates. So there is a delay of a few years. In my research on time trends, it is important to know the right year in which the first population-bases screening program started. The literature gives us no exact amount of the time lag. Later in this thesis two lags are assumed (2 and 5 year) and the effect on breast cancer mortality is measured.

Whether the screening program is extended to age groups below 50 and up to 69 years: all countries are including women from age 50 to 64 and most include women up to 69. Some countries don't have an upper limit and in some countries the upper limit is extended to age 74 (The Netherlands), but there is little evidence about the benefit of screening women which are older than age 70 (IARC). Among young women (below age 50), breast cancer is less common. IARC mentions that screening of women under age 50 is not recommended. One reason is that it is not cost-effective. Also a Belgian review (Mambourg et al.) concludes that there is no effect of screening on mortality of women between 40 and 49. In practice we see that one-third of the included countries invite women under age 50.

Other variables are the type and geographical spreading of the screening programs, the number of radiologists per million women and the number of mammography units per million women.

3.2 Country-specific characteristics

In the next paragraph I will describe how the breast screening program is structured in different European countries. It contains information about the start of screening and the start of a national population-based screening program, the target group, screening interval in years and other country-specific information. This information is summarized in a table and the most important features are explained. More detailed information about the country-specific characteristics can be found in appendix 1.

In the end of the eighties the first national screening programs are implemented. Finland, Iceland and Sweden where the first countries with a national screening program. In the nineties Denmark, Luxembourg, The Netherlands, Norway, Portugal, Spain and Sweden followed. The other countries implemented their program after 2000, with Slovenia and Slovak Republic lasts in 2008.

The most common age range is age 50-69, with is recommended by the European Council. Some countries have a higher upper limit or a lower minimum age. Two countries have changed the age range during the screening program: in The Netherlands the age range is extended from 69 to 75. In Sweden some counties extended the age range from 70-74 or 40-49. In the Czech Republic there is no upper limit.

The screening interval is for all countries 2 years, except for the United Kingdom. In the United Kingdom the screening interval is 3 years. Sweden distinguishes between age groups. For women aged 50-69 the interval is 2 years, for younger women (age 40-49) the screening interval is 3 years.

In Estonia is participating to screening only possible if the woman has health insurance. In Hungary screening is not allowed for women who have had a(n) (opportunistic) mammography in the last 2 years.

Table 2 Country-specific characteristics of breast cancer screening

Country	**Country_ id**	Year pilot programs began	Year program began	Year 100% national coverage achieved	Detection Method	Age group	Screening interval	Remarks
Austria	1	1998	2006	-	DM	45-69	2 years	
Belgium	2	1980-1990	2001	-	MM, DM	50-69	2 years	
Czech Republic	3	Late 1990's	2002	-	MM, DM, CBE	45-69	2 years	Since 2010 no upper age limit
Denmark	4	1991	-	2010	MM, DM	50-69	2 years	
Estonia	5	1996	2004	-	-	50-59 (since 2007 50-62)	-	Only available for women with health insurance
Finland	6	-	1987		DM	50-64	2 years	
France	7	1989	2003	2004	MM, CBE	50-74	2 years	
Germany	8	2001	2005	-	MM, DM	50-69	2 years	
Greece	9	1989	2004	-	-	40-69	2 years	
Hungary	10	Mid 1990's	2002	-	-	45-65	2 years	Only available if women haven't undergo a(n) (opportunistic) mammogram in the last 2 years
Iceland	11	-	1987	1989	DM, CBE	40-69	2 years	
Ireland	12	-	2000	-	DM	50-64	2 years	
Italy	13	1990	2002	2007	MM	50-69	2 years	
Luxembourg	14	-	1992	1992	DM	50-69	2 years	
The Netherlands	15	1989	1997	1997	DM	50-75	2 years	Age range extended to 75 after 1998

Norway	16	-	1996	2004	DM	50-69	2 years	
Poland	17	-	2007	-	-	50-69	2 years	
Portugal	18	-	1990/1997	-	DM	45-69	2 years	
Slovak Republic	19	2004	2008	-	-	-	-	
Slovenia	20	-	2008	-	-	50-69	2 years	
Spain	21	1990	1995	2003	MM	45-69	2 years	
Sweden	22	1982	1986	1996	-	50-69 in half of the counties extended to 40-49 and 70-74	50-69: 2 years 40-49: 18 months	
Switzerland	23	1993	1999	-	MM, DM	50-69	2 years	
United Kingdom	24	-	1988	1995	MM, DM	50-69	3 years	

- No data available

Abbreviations:
MM: screen-film mammography
DM: digital mammography
CBE: clinical breast exam

Sources:
http://appliedresearch.cancer.gov/icsn/breast/screening.html
Den Engelsman, C.K., 2012. Explaining differences in mammography uptake between European countries
Wübker, A., 2012. *Explaining Variations in Breast Cancer Screening Across European Countries.*
And more country-specific papers, mentioned in reference list.

Summary

In this theoretical framework we have seen that the European Union recommends a national breast screening program, where women between age 50 and 69 years are screened biennial. A national screening program is not opportunistic, but invites women systematically. The goal of the screening program is to detect breast cancer before symptoms appear. Screening characteristics that are important to know for this research are: the year the program started, target group, screening interval, participation rates and the year national coverage is reached. The thirteen different countries all have implemented a screening program at different time and there are differences in detection method and target group. The most important studies to reduction in mortality are done in The Netherlands, Sweden, England and Wales and Norway. Those studies appear that there is a reduction in breast cancer mortality after the implementation of a national screening program. The actual reduction can be different for various age groups or different stages of the tumor. While mortality decreases after the implementation of a national screening program, the theory mentions that the incidence rate will increase. The highest increase is measured for early stage and *in situ* breast cancers. There are also studies that encounter the reduction in mortality because of wrong statistical methods or over diagnosis.

3. RESEARCH DESIGN

3.1 Data

In this research the impact of the implementation of a national breast screening program on mortality and incidence is studied. Mortality and incidence data are collected from the OECD Health database. The other variables are found by literature review. The program STATA version 11 and 13 is used for this research.

Mortality and incidence

Mortality of *Malignant neoplasms of female breast* is available in number of female deaths and deaths per 100.000 females (standardized rate) for OECD countries. The incidence rate is available in number of female cases and incidence per 100.000 females. The aim is to compare countries, so only the standardized rate is used.

In the following table the years available are mentioned. Unfortunately the incidence rate is available for maximum four years, over an age range of ten years. To measure the effect of the implementation of a screening program on incidence, only the countries Belgium, France, Germany, Greece, Italy and Poland can be used, who implemented the national program between the available years. In the other 18 countries the program is implemented before the first year that the incidence rate is available. Also it is a short period to measure the trend of the incidence rate. When this period was longer, a better estimation could be made and might influence the outcome.

Table 3 Data: years available

Country	Mortality	Incidence
Austria	1960-2010	1998, 2000, 2002, 2008
Belgium	1960-1999, 2004-2006	1998, 2000, 2002, 2008
Czech Republic	1986-2010	2002, 2008
Denmark	1960-2006	1998, 2000, 2002, 2008
Estonia	1981-2009	2008
Finland	1960-2011	1998, 2000, 2002, 2008
France	1960-2009	1998, 2000, 2002, 2008
Germany	1990-2010	1998, 2000, 2002, 2008
Greece	1961-2009	1998, 2000, 2002, 2008
Hungary	1960-2011	2002, 2008

Iceland	1960-2009	2002, 2008
Ireland	1960-2010	1998, 2000, 2002, 2008
Italy	1960-2003, 2006-2009	1998, 2000, 2002, 2008
Luxembourg	1967-2011	1998, 2000, 2002, 2008
Netherlands	1960-2010	1998, 2000, 2002, 2008
Norway	1960-2011	2002, 2008
Poland	1960-1996, 1999-2010	2002, 2008
Portugal	1960-2008	1998, 2000, 2002, 2008
Slovak Republic	1992-2010	2002, 2008
Slovenia	1985-2010	2008
Spain	1960-1969, 1971-2010	1998, 2000, 2002, 2008
Sweden	1960-2010	1998, 2000, 2002, 2008
Switzerland	1960-2007	2000, 2002, 2008
United Kingdom	1960-2009	1998, 2000, 2002, 2008

Besides the effect of a screening program on breast cancer mortality, the effect on overall cancer mortality is measured. The variable mortality *malignant neoplasm* per 100.000 females is used and collected from the OECD Health database.

3.2 Method

3.2.1 Variables

The following variables are used:

Breast cancer mortality: deaths of breast cancer per 100.000 women. For mortality long time series are available. The year of implementation of the screening program is covered in the time series. Belgium is an exception, the years 2000 – 2003 are missing, while the program is implemented in 2002. Also Italy has some missing data a few years after the implementation of the program in 2002 (2004-2005). Slovak Republic and Slovenia both started relatively late with the implementation of a national organized program (2008), while data is available until 2010.

Overall cancer mortality: deaths of cancer per 100.000 females.

Incidence: cases of breast cancer per 100.000 females. For most countries the incidence rate is known for 4 years in a period of 10 years. For half of the countries (Belgium, France, Germany, Greece, Ireland, Italy and Poland) the start of the screening program is within the available time interval. The other countries started earlier with the implementation of the program, thus the before and after incidence rate cannot be measured.

Pilot: the year in which pilot programs of screening are started. The variable *pilot* takes value 0 in the years before the pilot program started and takes value 1 in and after the year the pilot program started.

Programme: the year in which the national organized screening program is implemented. For the variable *programme* holds the same values as the variable *pilot*.

Age range: this variable is divided in four dummy variables: *standard* (age 50 – 69) *smallstandard (*age range smaller than 50 – 69 e.g. Estonia with the age range 50-59/62), *extendup* if the maximum age is higher than 69 years and *extendlow* if the minimum age is lower than age 50. The variable takes value 1 if the country has the standard age range and 0 if it has not. Before the implementation of the program the variable takes value 0, because this effect will appear after the implementation of the screening program. In the Czech Republic and The Netherlands the age range is extended up from 2010 and 1998. Sweden has both a lower minimum and a higher maximum age

than the standard range, thus *extendup* and *extendlow* have both value 1. For the Slovak Republic the age range is unknown. Table 4 gives an overview of the age range per country.

Table 4 Age range per country

Small standard	Standard	Extendup	Extendlow
Estonia	Belgium	Czech Republic	Austria
Finland	Denmark	France	Czech Republic
Ireland	Germany	The Netherlands	Greece
	Italy	Sweden	Hungary
	Luxembourg		Iceland
	The Netherlands		Portugal
	Norway		Spain
	Poland		Sweden
	Slovenia		
	Switzerland		
	United Kingdom		

3.2.2 Model

In literature mostly a randomized controlled trial is used to estimate a causal effect between screening and incidence and mortality rates. An important condition to use this method is the availability of a control group. In this thesis there are no countries included without a screening program. First a regression model is used to measure the relationship between the implementation of the screening program and mortality. The same is done for other program characteristics and mortality. Regression is measuring the correlation between the explanatory and dependent variable and not necessary measuring a causal relationship. There can be already a downward or upward trend in mortality before the screening program started or other external factors changed at the same time. So secondly a fixed model is applied, taking advantage of the panel structure of the data it is possible to use a fixed effects model. This model distinguishes time-specific fixed effects (trend) and individual-specific fixed effects. Those are time-invariant characteristic who are correlated with the treatment. Using the fixed effects model, the individual-specific effect captures all variables that are influencing mortality and the screening program that are constant over time. The fixed effects model will give more explanatory power, but there can be factors that influence mortality and screening program that are not constant over time, which are not captured in the model.

Program characteristics

The results-chapter is divided in two paragraphs: descriptive results and the results of the regression analyses and fixed effects model. In the first paragraph the data is described: the mean mortality

and incidence per country. Graphs are plotted to describe the trends over the time period 1960-2011. A vertical line is added in the year the national program is implemented. In addition to this graphs, the effect of the implementation of both the pilot and national program is estimated with the following OLS model:

(1) $mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \varepsilon$

The next characteristic is the age range. The effect of age range on mortality is estimated with the following model:

(2) $mortality = \alpha + \beta * smallstandard + \beta * standard + \beta * extendup + \beta * extendlow + \varepsilon$

For the best estimate of the dependent variable, all relevant independent variables should be included in the model. This will lead to the following full model:

(3) $mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \beta_3 * smallstandard + \beta_4 * standard + \beta_5 * extendup + \beta_6 * extendlow + \varepsilon$

The research question is also referring to the influence of breast cancer screening on incidence rates, so it is obvious to use incidence as dependent variable. But because of the few available observations, we cannot come to trustworthy results.

Time trend

Studying the effect of breast cancer screening on mortality, we have a good reason to suppose that mortality is influenced by other factors than those who are captured in the model. Advancing technologies can influence mortality in a negative relationship, lifestyle factors and increasing cancer incidence rates can influence mortality in a positive way. These factors can be included in the model by a shift of the intercept. This can be done by adding a linear trend, where the time variable has a constant increase in each year. This will give us the following equation:

$mortality = \alpha + \beta_1 * T_t + \beta_x * X + \varepsilon$

I will add the time trend to the first three models. If this coefficient is significant, we can conclude that mortality is influenced by time, in addition to the other variables and is time an important determinant to the dependent variable.

Lags

In the theory is mentioned that after the implementation of the program some time is needed before the program will work. If the breast cancer screening has an effect on mortality, this effect is expected a few years after the implementation of the screening program. To test this assumption, two time lags of 2 year and 5 year are tested. Some countries are omitted because the availability of the data until 2011.

Panel data

Taking advantage of the panel structure of the available data, a random effects and fixed effects regression can be made. It is possible to control for omitted variables, varying between cases but constant over time or varying over time and constant between cases. In other words: we can estimate the between and the within effect.

In the fixed effects model, the assumption is made that the individual specific effect is correlated with the independent variables, while in the random effects model it is not correlated. To test this assumption, a Hausman test is used to identify which model is consistent. First both models are estimated and after that the Hausman test is done. The consistent model is used to interpret the results.

Overall mortality

When breast cancer screening affects breast cancer mortality, the expectation is that also overall cancer mortality is affected. The full model (3) is used to estimate the effect of breast cancer screening on overall cancer mortality.

4 RESEARCH RESULTS

4.1 Descriptive statistics

4.1.1 Mortality

The variable *mortality* is measured as breast cancer deaths per 100.000 females. This standardized rate (table 5) can be compared between countries. Denmark, The Netherlands and United Kingdom have the highest mean, per 100.000 women there are on average 43,8; 43,3 and 42,3 women per year dying from breast cancer. The lowest mean occurs in Greece (22,05), Poland (22,04) and Spain (22,20). The amount of observations varies between countries. In general the countries with fewer observations are missing the observations from the first years of the included years from 1960. If we assume that breast cancer mortality is increasing after 1960 and decreasing after the implementation of a screening program, the mean is overestimated for countries with fewer observations.

Table 5 Mortality descriptive statistics

Country	Observations	Mean mortality	Minimum	Maximum
Austria	52	32.81923	25.4	39.1
Belgium	47	39.89574	34.2	45.1
Czech Republic	26	34.01154	25.5	38.7
Denmark	52	43.78846	34.7	50.9
Estonia	29	26.6931	21.4	34.2
Finland	52	25.87308	19.9	30.5
France	50	31.16	26.4	33.8
Germany	22	24.00455	29.5	38.3
Greece	50	22.054	7.9	29.2
Hungary	52	33.45385	19.5	42.1
Iceland	50	33.774	19.3	60.9
Ireland	51	40.03529	31.3	50.3
Italy	49	30.61224	24.2	35.4
Luxembourg	45	36.10889	25	48.4
Netherlands	52	43.30769	32.8	48.3
Norway	52	29.83077	31.5	34.5
Poland	50	22.036	9.1	26.8

Portugal	49	24.49796	18.1	30.6
Slovak Republic	19	28.86842	26	32.4
Slovenia	26	35.01154	31.5	42.4
Spain	51	22.19804	14	29.5
Sweden	51	30.41756	23.1	36.2
Switzerland	51	39.7902	27	46.3
United Kingdom	50	42.292	30.4	49.8

Time-trends can give more information about the course of mortality. Where the mean gives an average over the 22 - 52 years and can lead to overestimation, information is needed about trends. Figure 2 gives an overview of the time-trend in the deaths per 100.000 females. Globally there can three groups seen: high, medium and low deaths per 100.000 females. The group with the most deaths consists of the countries Belgium, Denmark, The Netherlands and Switzerland. The group in the middle consists of the countries Austria, Czech Republic, France, Germany, Italy and Sweden. The group with less death consists of the countries Greece, Poland, Portugal and Spain. With exception of Greece, in all countries mortality is stable or increasing until the nineties and after this period mortality is decreasing. In Greece mortality is increasing.

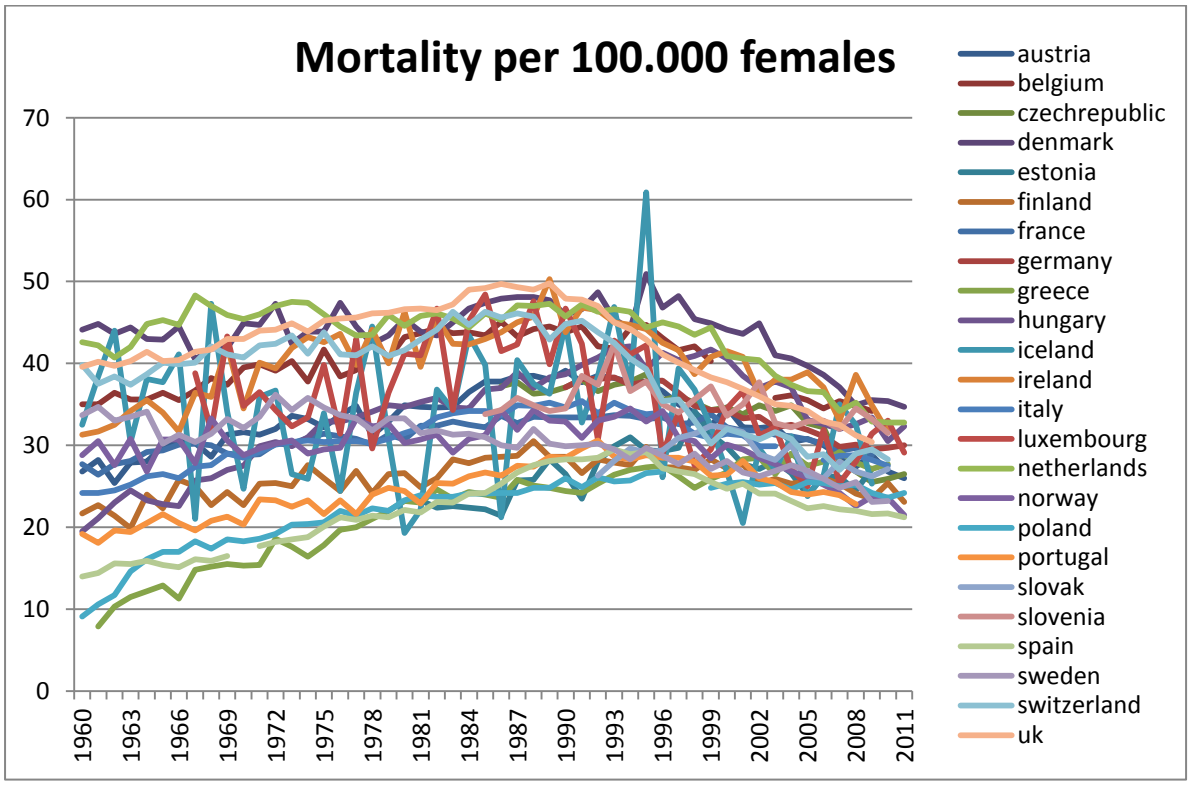
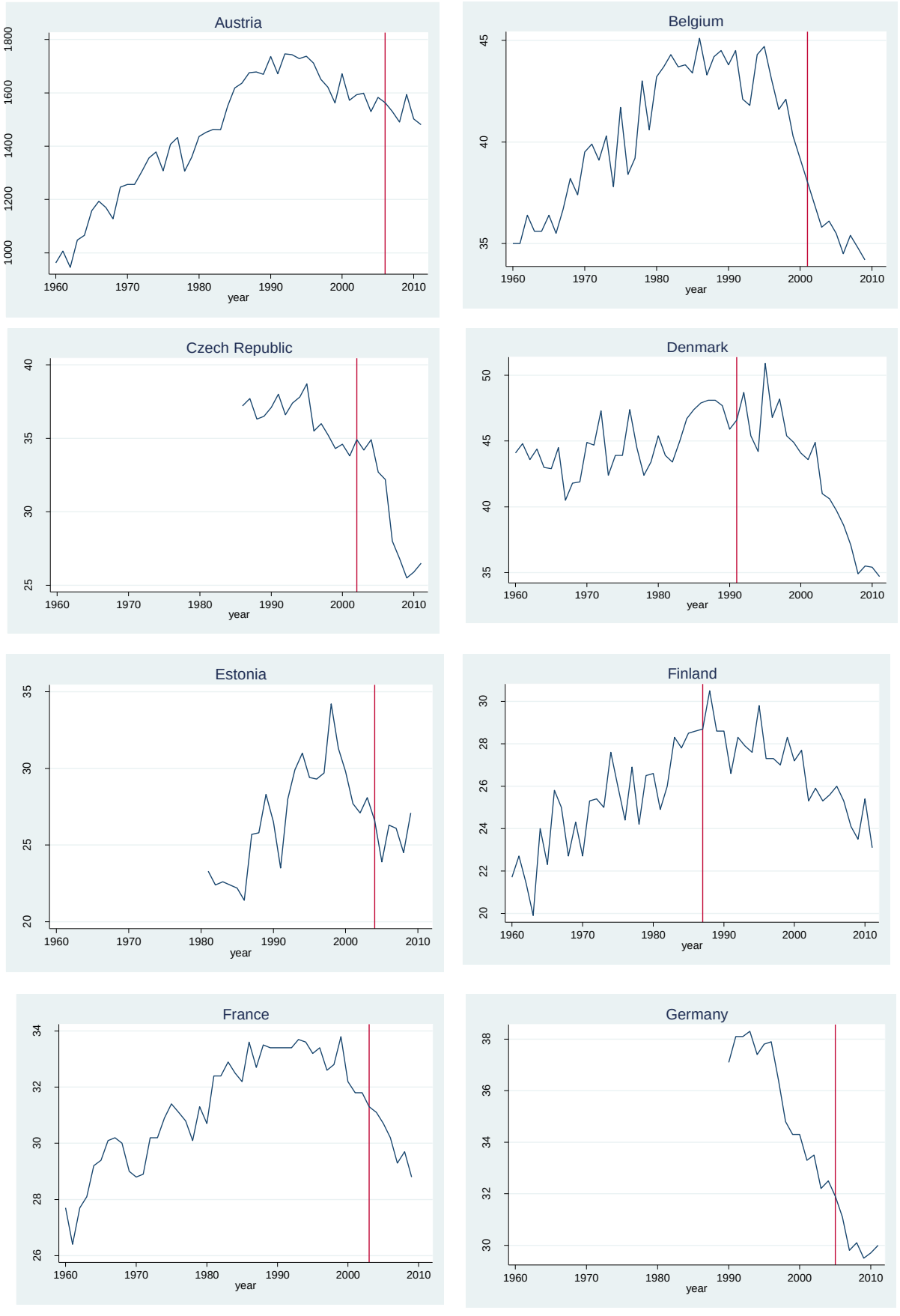


Figure 2 Mortality per 100.000 females

Figure 3 is showing the deaths per 100.000 females per country. A vertical line is added for the year the population based program is implemented in the country.

Estonia, Finland, Iceland, Luxembourg and Slovenia mortality is very variably with very high and very low values. Based on this graphs, it appears that there is no correlation between mortality and the implementation of a screening program. In Greece and Poland there is respectively no and a very low decrease in mortality between 1960 and 2011. The Czech Republic, the Netherlands, Norway, Portugal, Spain and United Kingdom are showing a negative correlation between the implementation of a screening program and mortality. Mortality is decreasing (a few years) after the implementation. In the other countries mortality is already decreasing before the program starts. Based on this graphs, a relationship is lacking.

Figure 3 Mortality per country

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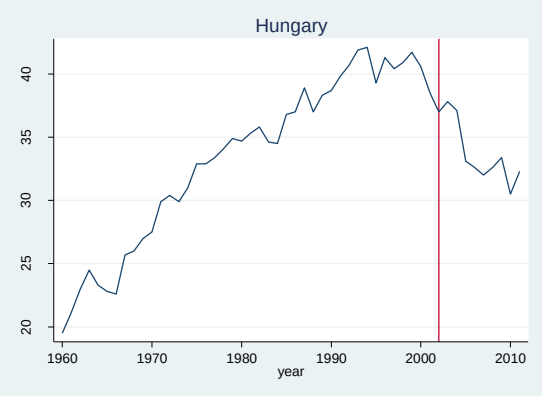
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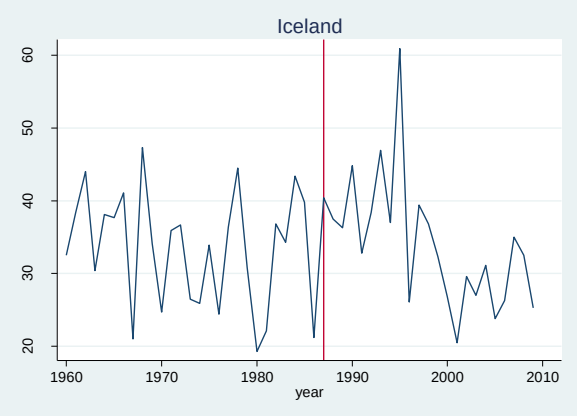
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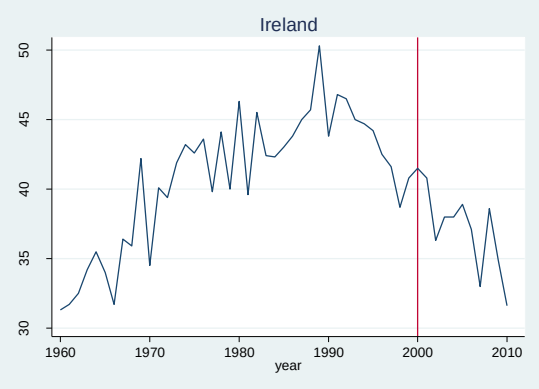
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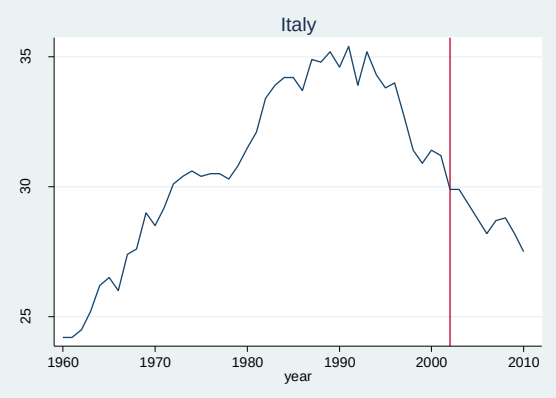
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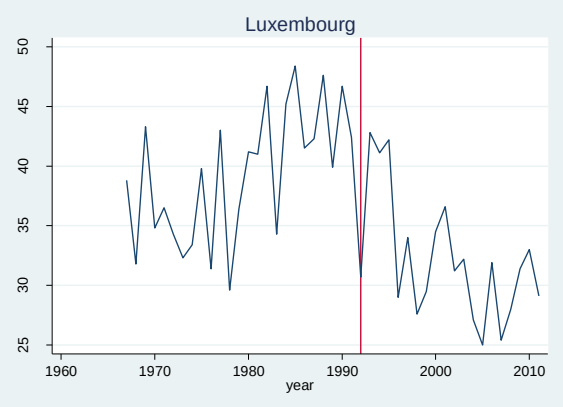
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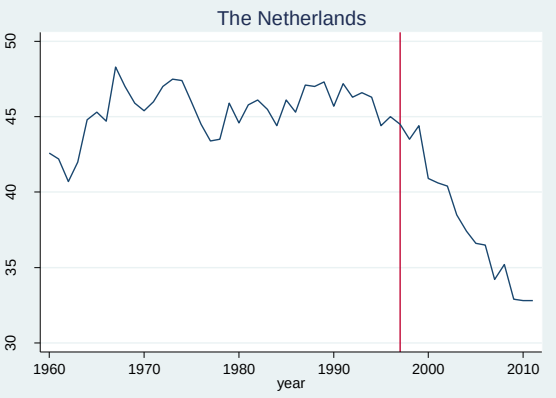
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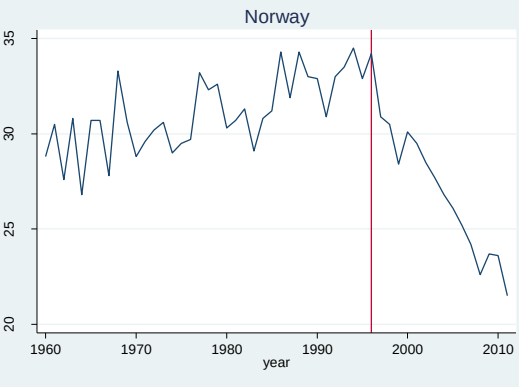
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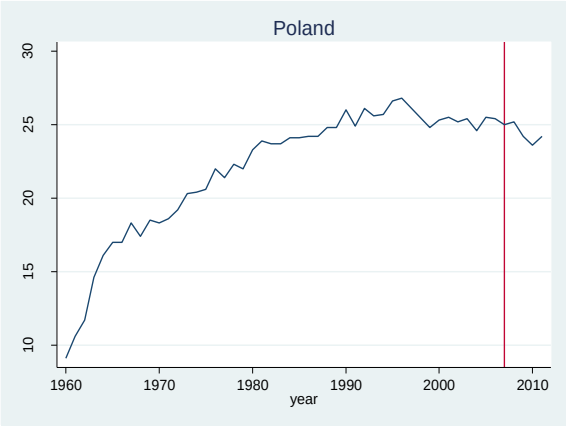
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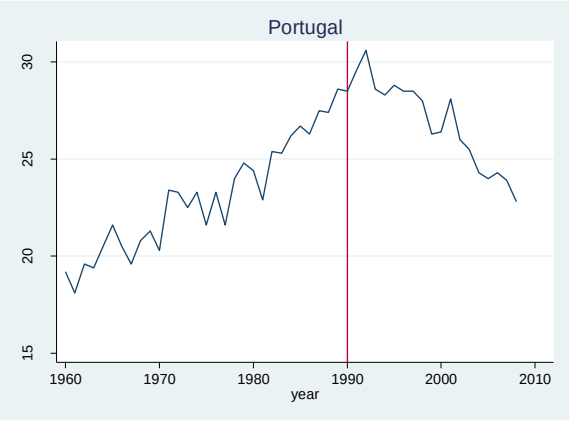
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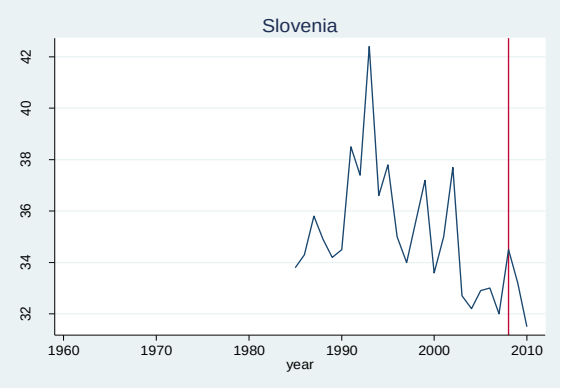
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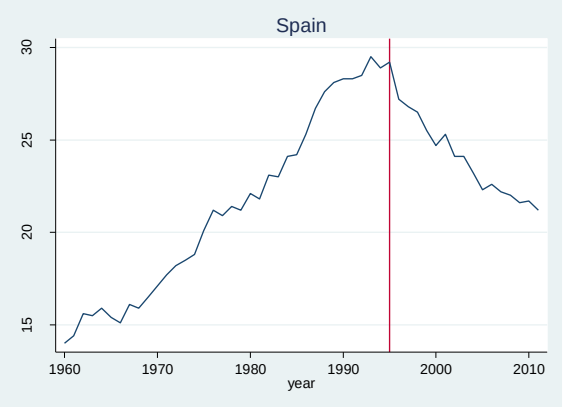
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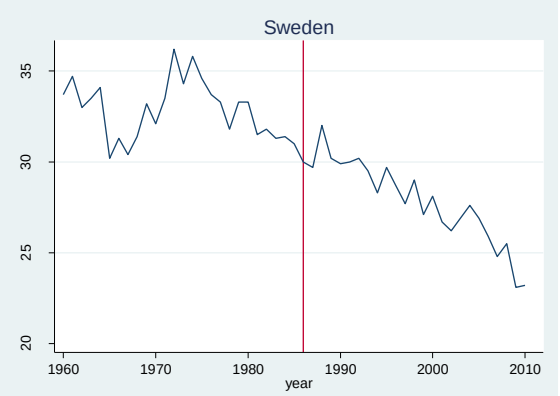
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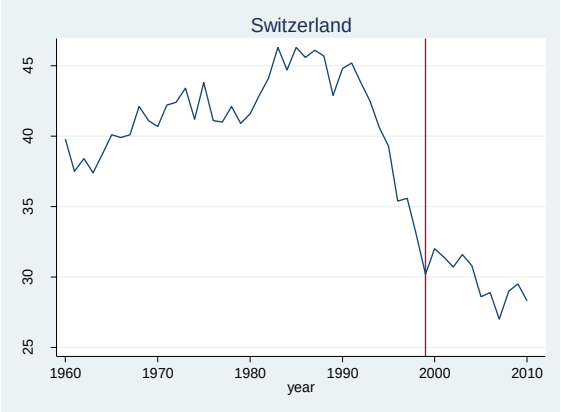
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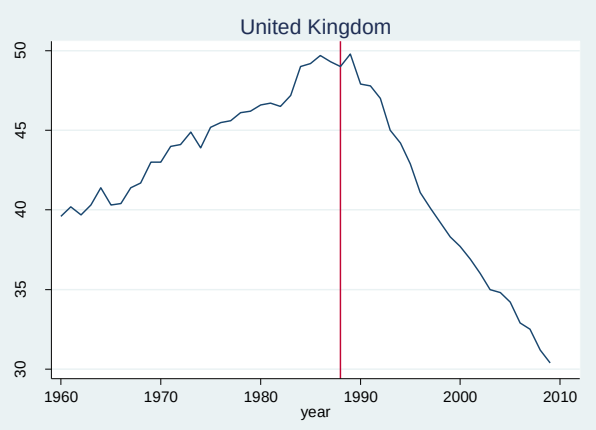
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4.1.2 Incidence

In this paragraph the relation between breast cancer incidence and the implementation of breast cancer screening and age range is described. Furthermore the relation between incidence rate and mortality is showed in a graph. Because of lacking data (maximum 4 years available), it is not possible to come to reliable conclusions using regression analyses. But with the available data it is possible to draw some conclusions about the in influence of screening on the incidence rate of breast cancer.

Table 6 is showing the mean incidence rate per 100.000 females. This average varies from 48.5 (Greece) until 92 (Belgium). It is remarkable that a relatively low mean (48.5 – 67.55) mostly is associated with an age range with lower minimum age. Later in this paragraph is said more about the incidence rate in relation to the age range.

Table 6 Mean incidence rate per 100.000 females

Country	Incidence	Observations
Austria	67.55	4
Belgium	92	4
Czech Republic	63.05	2
Denmark	87	2
Estonia	50.2	1
Finland	81.25	4
France	88.725	4
Germany	75.075	4
Greece	48.5	4
Hungary	60.45	2
Iceland	88.1	2
Ireland	76.7	4
Italy	72.5	4
Luxembourg	74.875	4
Netherlands	89.325	4
Norway	75.5	2
Poland	49.6	2
Portugal	55.775	4
Slovak Republic	50.7	2

Slovenia	65.5	1
Spain	52.35	4
Sweden	83.675	4
Switzerland	80.4	3
United Kingdom	79.7	4

Incidence and implementation program

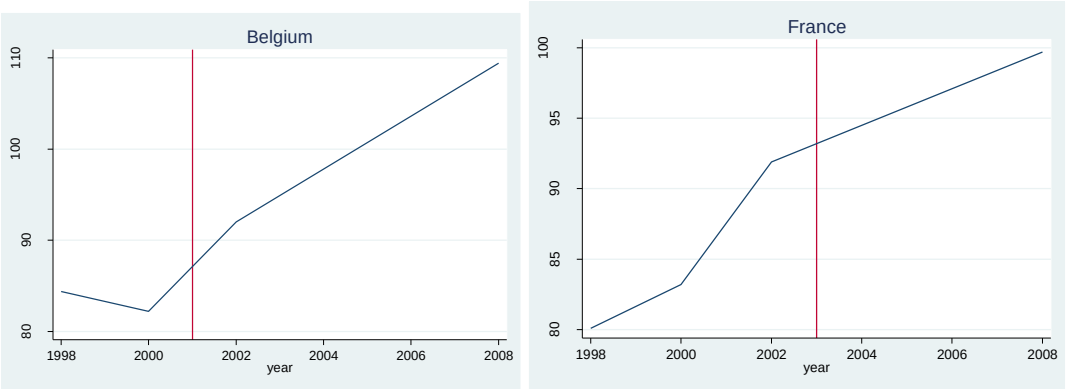
There are 6 countries were the implementation of the national program falls within the available data range; Belgium, France, Germany, Greece, Italy and Poland. For these countries the mean and number of observations is mentioned in table 7. The time trends are showed in figure 4.

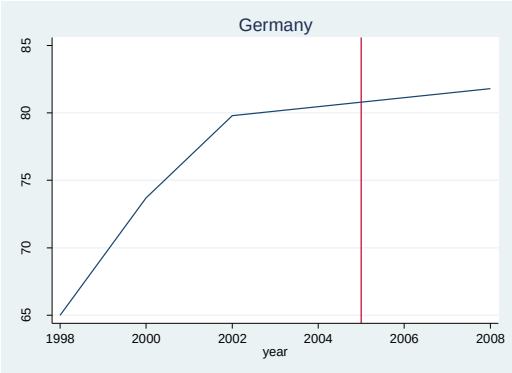
Table 7 Observations and mean incidence rate per country

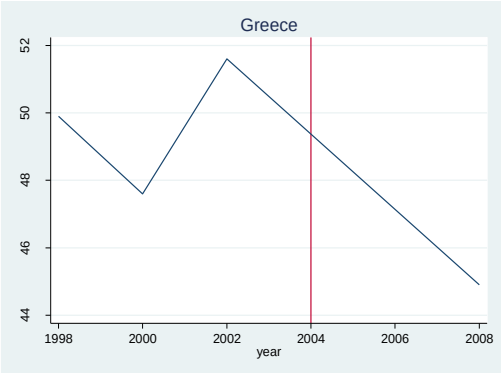
Country	Mean	Observations
Belgium	92	4
France	88.7	4
Germany	75.1	4
Greece	48.5	4
Italy	72.5	4
Poland	49.6	2

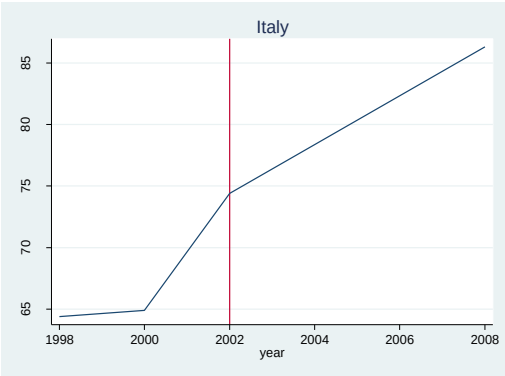
Belgium and France have the highest incidence rate per 100.000 females, followed by Germany and Italy. Greece and Poland have the lowest incidence rate. In the next figures the time trends are showed. The disadvantage is that between 2002 and 2008 no data is available. Between those years there is a straight line, but we can't say anything about the increase between 2002 and 2008.

Figure 4 Incidence rate per 100.000 females









Poland (2007)	2002	2008
Incidence per 100.000 females	50.3	48.9

In Belgium, France, Germany and Italy the incidence rate is increasing before the organized program started and remains increasing after the implementation. In Greece and Poland the incidence rate is decreasing before the program starts and remains decreasing.

Incidence and age range

It is plausible that the incidence rate differs when a wider or narrower age range is used. In table 8 the average incidence is showed before (0) and after (1) the use of a certain age range and thereby the implementation of the screening program. When there are enough observations, the averages can be compared between the different age ranges. The column mean incidence shows the average of the incidence rates of the countries with the given age range, without distinction between before and after.

Table 8 Mean incidence rate per 100.000 females per age range

Age range	Incidence (0)	Obs.	Incidence (1)	Obs.	Mean incidence	Obs.
Smallstandard	72.87	75	50.2	1	69.38333	9
Standard	70.08	59	81.21	17	80.22143	25

Extendup	69.82	64	87.24	12	81.19375	10
Extendlow	76.08	56	62.77	20	61.4025	27

The value 72.87 in the column Incidence(0), is the average incidence rate of all countries who use age range *smallstandard* before the start of the program. The value in column Incidence(1) is lower than 72.87, meaning a decrease in incidence rate after the implementation of the program. But because of one available observation, this cannot be valid. Also for the other age ranges we have to interpret the results with caution because of the limited observations. For the standard and up extended age range, the incidence rate is increased after the implementation of the program. The opposite is true for age range *extendlow.*

The mean incidence (column 6) of *smallstandard* is calculated by counting the average per country with age range *smallstandard* divided by the amount of countries with age range *smallstandard*. The same calculation is made for the other age ranges. When the age range is extended to a higher age, the mean incidence is highest with value 81.19 per 100.000 females. After that follows the standard age range with a mean of 80.22. The mean incidence with an age range with fewer years than the standard age range (*smallstandard*) is 69.38. Extending the age range to a lower age and use age range extendlow, the mean incidence is lowest with 61.40.

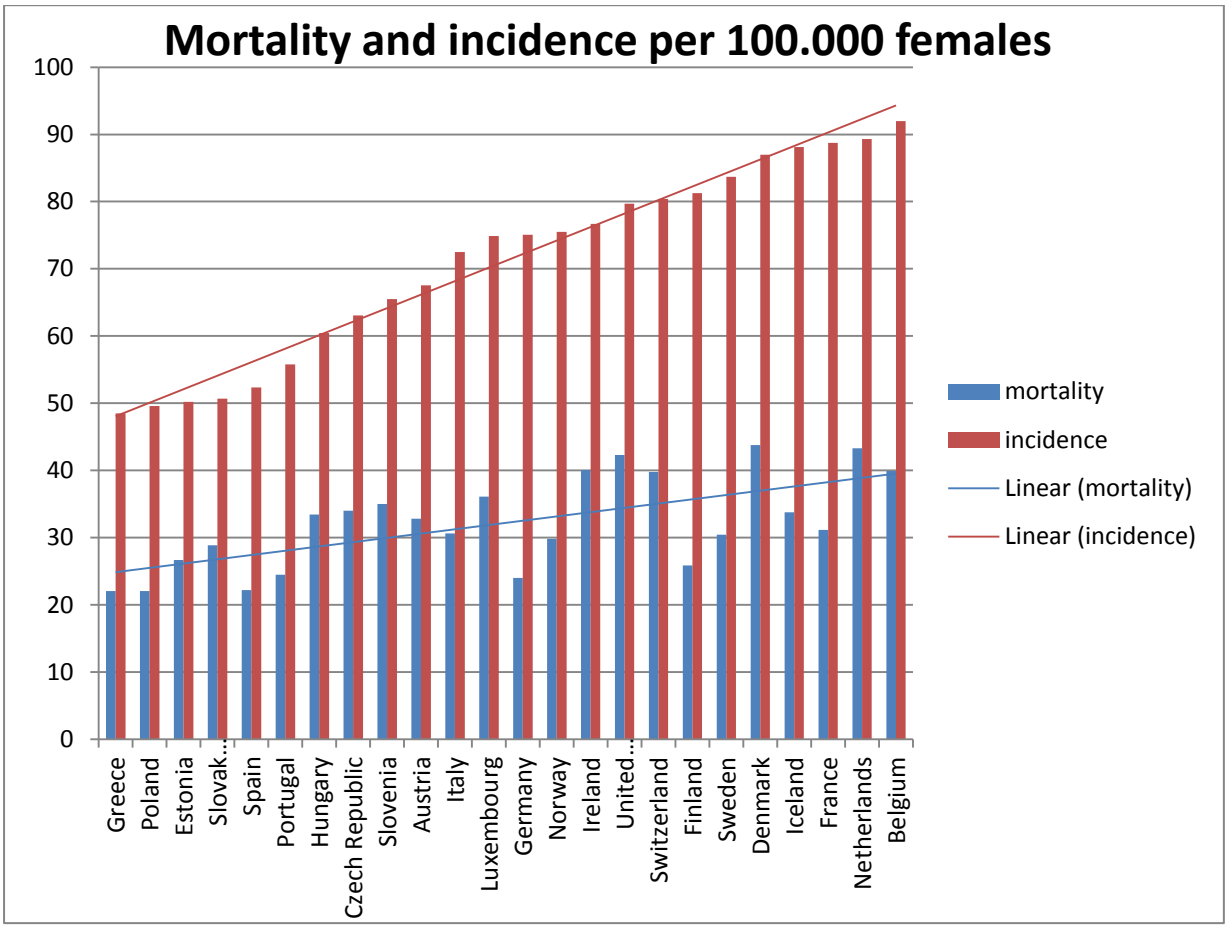
One of the goals of a breast cancer screening program is to identify breast cancer in an early stage. It is plausible to expect a higher incidence range in a good-working program. From this simple analysis we can conclude that extending the age range to a higher maximum age is effective in identifying more breast cancers, leading to a higher incidence rate. Extending the age range to a lower minimum age is less effective in detecting breast cancer compared to using the standard age range and *extendup*. Extending the age range to a higher maximum age is slightly more effective in detecting breast cancer compared to the use of a standard age range.

Incidence rate and mortality

The relationship between incidence and mortality is interesting in the case of breast cancer screening. The aim of a screening program is to reduce mortality. But at the same time is early detection – which is associated with a higher incidence rate – a tool to achieve the goal of decreasing mortality. In figure 5 the mean mortality and incidence rate per 100.000 females is plotted and trend lines are included. The figure shows a positive relationship between mortality and incidence, but gives no answer on the question whether a higher incidence rate causes higher

mortality or higher mortality causes higher incidence rates. It is impossible to control this fact by using an interaction term in a regression analyses because of lacking data.

Figure 5 Mortality and incidence per 100.000 females



Conclusion

From the descriptive results we can conclude that a low incidence rate is associated with age range *extendlow*. This fact is confirmed when the average incidence rate per age range is calculated. The highest incidence rates are measured in age range *extendup* and *standard*, followed by age range *smallstandard* and *extendlow* with the lowest incidence rates. The incidence rate remains increasing in four countries after the implementation of the screening program, and remains decreasing in two countries. Based on a simple comparison of mean mortality and incidence rates per country, it seems there is a positive correlation between incidence and mortality rates.

4.2 Regression analyses

4.2.1 Mortality

In the paragraph 4.1 descriptive statistics, the conclusion is made that mortality in all countries first is increasing until the 1990's and later decreasing. This conclusion is based on the graphs with time trends per country. With the following linear model the effect of the implementation of the pilot program and national program is measured per country. The variable *age range* is deleted, because these are the same within the country.

(1) $mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \varepsilon$

The results are showed in table 9. The variable *pilot* is variably positive and negative. For Belgium, Estonia, France, Greece, Hungary, Italy and Spain the sign is positive. This means that mortality is increasing in the years after the start of the pilot programs. The magnitude differs between 8.7552 (Spain) and 2.5392 (France). For the other 7 countries the sign is negative. Mortality decreases in the years after the start of the pilot programs. For three countries the value is insignificant. The magnitude differs between -1.3342 (Austria) and -4.5061 (Switzerland). The variable *programme* is positive for Finland (1.8545) and Portugal (3.9147), so mortality increases in the years after the implementation of the national program. The similarity between those two countries is that both countries have a relative early implementation of the national program. The variable *programme* is negative for the other countries, implying that mortality is decreasing in the years after the implementation of the national program. The magnitude differs between -8.0676 (Belgium) and -0.8999 (Slovak Republic).

Table 9 Effect pilot and programme on mortality per country

Country	constant	pilot	programme	Adj. R^2
Austria	33.6842	-1.3342	-4.3833*	0.20
Belgium	39.2	4.0533	-8.0676	0.54
Czech Republic	37.45	-1.1786*	-6.1114	0.55
Denmark	44.7032	-2.2651	-	0.08
Estonia	25.4933	4.1567	-3.9	0.29
Finland	24.9815	-	1.8545	0.15
France	30.4967	2.5392	-2.8786	0.37
Germany	36.7727	-3.8977	-2.575	0.84
Greece	18.3036	7.9498	1.8038*	0.53

Hungary	31.96	8.4286	-6.5457	0.19
Iceland	33.3778	-	0.8614*	0.0027
Ireland	40.8275	-	-3.6730	0.11
Italy	30	3.2333	-4.4905	0.21
Luxembourg	39.304	-	-7.189	0.30
Netherlands	45.2414	0.8586*	-8.02	0.62
Norway	31.0472	-	-3.9535	0.34
Poland	21.7689	-	2.6711*	0.04
Portugal	22.98	-	3.9147	0.34
Slovak Republic	29.8333	-2.2333	-0.8999	0.32
Slovenia	35.26	-	-2.1986*	0.05
Spain	19.9449	8.7552	-4.5706	0.40
Sweden	33.1318	-1.7568*	-3.4990	0.64
Switzerland	42.2394	-4.5061	-7.9	0.81
United Kingdom	44.3107	-	-4.5880	0.18

*Insignificant with 5% confidence level

Time trend

A time trend is add to the model to control for the time effect. The following model is used:

$$mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \beta_3 * T_t + \varepsilon$$

The results are showed in table 10. The variable time is significant for 16 countries, meaning that time is an important determinant of the dependent variable. For the other countries the variable is insignificant at a 5% significance level. We can conclude that in those countries there is no time effect on mortality. The sign of the variable time is positive for the majority of the countries, over time breast cancer mortality is increasing. The magnitude of this coefficient is lower than the variables *pilot* and *programme,* so time has less influence on mortality compared with the implementation of a screening program.

The magnitude and sign of the coefficients are different compared with the previous model. The variable *pilot* is positive and significant in one country (Sweden) and both negative and significant for seven countries. The variable *programme* has a negative sign for the majority of the countries. The adjusted R^2 is increased in comparison with the previous model, so this model has more explaining power and the results are more significant.

Table 10 Effect pilot and programme on mortality per country with time trend

Country	constant	pilot	programme	time	Adj. R^2
Austria	27.6893	-8.405133	-6.535353	.3074314	0.81
Belgium	20.99353	-1.54866*	-11.98901	.2800995	0.76
Czech Republic	102.6918	-1.1786*	-.157804*	-.4961353	0.74
Denmark	56.53153	-.477132*	-	-.068769*	0.08
Estonia	-79.74305	-.949739*	-7.008248	.4440354	0.52
Finland	15.04922*	-	.9120408*	.0362491*	0.15
France	-22.20546	-.925954*	-4.570838	.1611682	0.71
Germany	185.1643	-1.11539*	-.534616*	-.3709789	0.94
Greece	-219.264	-3.887323	-4.252373	.5505621	0.93
Hungary	-249.7393	-3.743498	-11.4725	.5796223	0.87
Iceland	252.4387	-	11.11701	-.4102264	0.10
Ireland	-125.5789	-	-10.83475	.2808548	0.47
Italy	-175.1954	-3.504906	-7.997111	.3208685	0.73
Luxembourg	-52.1324*	-	-10.14492	.1313741*	0.30
Netherlands	72.72481*	1.542932*	-7.594617	-.0369898*	0.61
Norway	-16.1824*	-	-5.491318	.0591479*	0.36
Poland	-223.7122	-	-4.975657	.286993	0.78
Portugal	-127.2293	-	-.1765672*	.166992	0.49
Slovak Republic	-167.016*	-3.849334	-1.607*	.202*	0.36
Slovenia	165.5635	-	-.545987*	-.1271203*	0.12
Spain	-316.3846	3.229148	-8.075163	.3185978	0.67
Sweden	212.8756	.360689*	-1.137164*	-.1628852	0.75
Switzerland	-176.9235	-8.187092	-9.598937	.1887708	0.88
United Kingdom	107.7699*	-	-3.277388 *	-.052424*	0.17

Age range and mortality

(2) $mortality = \alpha + \beta * smallstandard + \beta * standard + \beta * extendup + \beta * extendlow + \varepsilon$

The age interval is divided in four categories: the *standard* age interval 50-69, the age interval with fewer years than this standard interval: *smallstandard*, the standard interval extended to 74, 75 or without maximum: *extendup* and the standard interval extended to 40 of 45: *extendlow.* The results are showed in table 11.

Table 11 Mortality and age range

Model 1			
Mortality	**Coefficient**	**P>|t|**	**(Adjusted)R^2**
Standard	5.088679	0.045	0.0331
Constant	32.18932	0.000	
Model 2			
Smallstandard	-4.62835	0.031	0.0448
Standard	4.669079	0.000	
Extendup	0.1346862	0.898	
Extendlow	-2.769228	0.000	
Constant	32.60692	0.000	

First the effect of age interval is measured with *standard* as only explanatory variable for the dependent variable *mortality.* The variable is significant with a significance level of 5%. The magnitude of the effect is 5.088679. Using a standard age range (50-69) will lead to an increase in mortality, compared to countries that don't use the standard age range. But the R^2 has a low value: 3.31% of the variance in mortality can be explained through the variable *standard*.

In the second model with the four categories as explanatory variables, we see that the chosen age interval has little impact on mortality, the adjusted R^2 is 0.0448, and thus 4.5 percent of the variance in mortality is caused by variance in age interval. *Smallstandard* has a negative effect on mortality; *standard* has a positive effect on mortality, both with the same magnitude. *Extendup* has a small positive effect on mortality, but is insignificant with a P-value of 0.898. *Extendlow* has a negative effect on mortality, with half of the magnitude compared with *smallstandard* and *standard.* Because

of the low R^2 we have to be careful with drawing conclusions from this analysis. Another reason to be careful is that mortality-data is aggregated data. It is not possible to distinguish mortality for different age groups. A better way to research the effect of age interval on mortality can be done when mortality per age category is known.

This model is controlled for time effects by adding a time trend with variable T. It seems there is no time effect, because the variable is insignificant (P 0.735>0.05). Mortality is not influenced over time, so the model is measuring the effect of age range on mortality and is not time-biased.

Full model

All the program characteristics are included in the following model (3) and the results are showed in table 12.

(3) $mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \beta_3 * smallstandard + \beta_4 * standard + \beta_5 * extendup + \beta_6 * extendlow + \varepsilon$

Table 12 Mortality full model

Model 1			
Mortality	**Coefficient**	**P>|t|**	**(Adjusted)R^2**
Pilot	0.6191145	0.713	0.0825
Programme	-4.250644	0.006	
Standard	4.840701	0.049	
Constant	32.27337	0.000	
Model 2			
Pilot	2.438853	0.404	0.0973
Programme	-4.512106	0.002	
Smallstandard	-4.799895	0.155	
Standard	3.13349	0.365	
Extendup	1.176487	0.612	
Extendlow	-2.483032	0.405	
Constant	32.27337	0.000	

In model 1, only *standard* is included from the age range variable. This variable is significant at a 5% significance level. Again the sign is positive, meaning that mortality will increase. Also the variable

pilot has a positive sign but is insignificant. The variable *programme* is signigicant and has a negative sign. If a screening program is implemented, mortality will decrease.

When the full model is estimated in model 2, only the constant and the variable *programme* are significant at a 5% significance level (0.000 and 0.002). This will mean that the effect of the variables *pilot, smallstandard, standard, extendup* and *extendlow* is no longer significant and negligible in comparison with the variable *programme*. The variable programme has a negative sign, which means that after implementing the screening program, mortality is decreasing with a magnitude of 4.5121.

The variable T is added to the model to measure the time effect. With a P-value of 0.818 and using a 5% significance level, there is no reason to expect a time effect explaining mortality next to the included explanatory variables.

Fixed effects model

Taking advantage of the panel structure of the data, both the fixed and random effect models are estimated. The Hausman test is used to identify which model fits the best and that model is used to interpret the results. In this case the fixed effects model is used, that controls for unit-specific factors that are constant over time. The coëfficiënt can be interpret as a within-unit change in treatment, the within estimator. In this model each unit serves as its own control group (before and after treatment), so a causal effect can be measured. In this case the countries are the units and the coefficient is the within estimator, measuring the effect when a variable changes from value 0 to 1. The results are showed in table 13.

Table 13 Mortality: fixed effects model

Fixed effects	***model***		
Mortality	**Coefficient**	**P>|t|**	**(Adjusted)R^2**
Pilot	4.411834	0.000	Within: 0.2689
Programme	-5.134027	0.000	Between: 0.2297
Smallstandard	0.2737015	0.874	
Standard	-4.31274	0.000	
Extendup	-4.835599	0.000	
Extendlow	1.678577	0.105	
Constant	32.18833	0.000	

At a 5% significance level, all variables except *smallstandard* and *extendlow* are significant. The variable pilot has a positive sign, meaning that mortality is increasing after a pilot program is implemented. The variable programme has a negative sign, after the implementation of a national screening program, mortality is decreasing. The magnitude is a bit higher compared with the OLS model (-5.1340 vs. -4.5152). Using an age range including less years than the standard age range, has a positive effect on mortality, extending to a lower age also. This effect holds when the value of the variable changes from 0 to 1, at the start of the program. But both variables are insignificant. Using the standard age range and extending this range to a higher age have both a negative effect on mortality, after the program is implemented. Based on this model we can conclude that implementing a screening program, using the standard age range and extending the age range to a higher age are effective in reducing mortality. When a pilot program started, mortality was increasing.

Time lag

In the theory is mentioned a time lag exisits after the implementation of a screening program before the program can have an effect on mortality. It takes time to cover the whole population, there is time between the invitation and the real screening and the staff needs learning time. We know there can be a lag between the implementation and the real effect, but don't know an exact period. The full model is predicted without a lag, a lag of 2 year and a lag of 5 year. With a lag of 0 year the starting year is the real starting year, with a lag of 2 the starting year is assumed to be 2 years later and the same holds for 5 year. The expectation is that a higher lag results in a higher magnitude of the coefficient, because the effect is larger a few years after the implementation of the program.

$$mortality = \alpha + \beta_1 * pilot + \beta_2 * programme + \beta_3 * smallstandard + \beta_4 * standard + \beta_5 * extendup + \beta_6 * extendlow + \varepsilon$$

Table 14 Effect programme on mortality with different lags

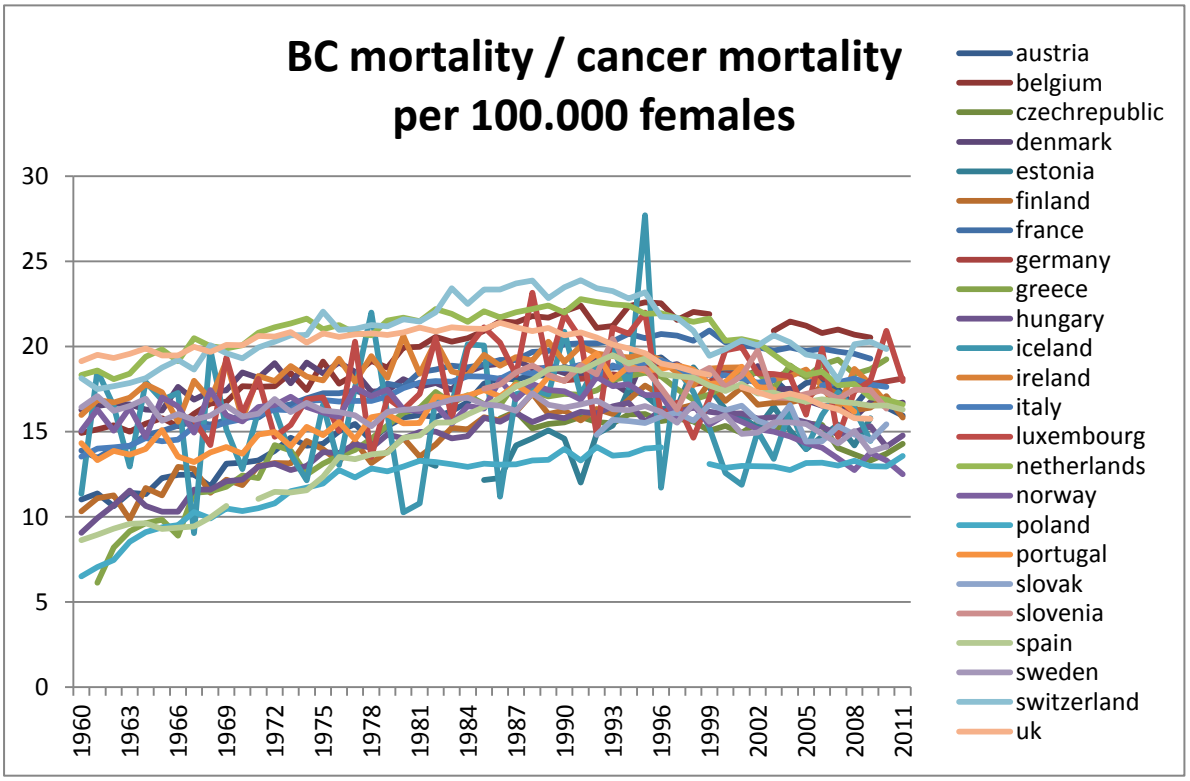
Lag	Coefficient	P-value
0 year	-4.512106	0.002
2 year	-4.4115	0.001
5 year	-4.857562	0.001

From the table we can conclude there is little difference between the coefficient of mortality. The magnitude, compared with the real starting year, is a bit lower with the lag of 2 years and a bit higher with a lag of 5 years. With the available data and with this model we can conclude that the influence of using a lag is negligible. The hypothesis that the effect of the screening program increases after time doesn't hold.

Overall mortality

In the theoretical section is explained that breast cancer mortality and overall cancer mortality are positively correlated. If breast cancer screening affects breast cancer mortality, the expectation is that there is a small effect (with the same sign) on cancer mortality. This effect depends on the percentage of breast cancer mortality compared to overall cancer mortality. To measure this percentage, a new variable is generated where the breast cancer mortality per 100.000 females is divided by overall cancer female mortality per 100.000 females. The results are shown in the following graph:

Figure 6 Percentage of breast cancer mortality per 100.000 females with cancer



The mean percentage of breast cancer mortality per 100.000 female deaths of cancer is 16.85%. In 1960 this percentage is 13.70% and in 2011 15.69%. The graph shows that breast cancer mortality rises untill the nineties and then decreases.

The results of the linear regression are showed in table 15.

Table 15 Overall cancer mortality

OLS cancer mortality			
Mortality	**Coefficient**	**P>|t|**	**(Adjusted)R^2**
Pilot	-13.11417	0.330	0.1117
Programme	-14.58463	0.060	
Smallstandard	-1.192916	0.943	
Standard	-0.3261015	0.984	
Extendup	0.5375408	0.971	
Extendlow	6.421672	0.647	
Constant	196.8932	0.000	

When the full model is ran with overall cancer mortality, the result is that the *variables pilot, programme, smallstandard* and *standard* have a negative sign, which means that mortality is decreasing. Variables *extendup* and *extendlow* have a positive sign. Unfortunetaly all variables are insignificant at a 5% significance level. The most important variable, *programme*, has a P-value of 0.06. As would be expected, the variable has a negative sign, meaning that overall cancer mortality is decreasing when breast cancer screening started. Remarkable is the higher magnitude, -14.58463 vs. -4.512106. Both variables breast cancer mortality and cancer mortality are measured per 100.000 females. From this model we can conclude that the implementation of a breast cancer screening program has more influence on overall cancer mortality than breast cancer mortality.

Conclusion

The results of all analysis are summarized in the next table:

Table 16 Summary of results

Model	Variable	Mortality
1	*Pilot*	+/-
	Programme	-
2	*Smallstandard*	-
	Standard	+
	Extendup	+*
	Extendlow	-
3	*Pilot*	+*
	Programme	-
	Smallstandard	-*
	Standard	+*
	Extendup	+*
	Extendlow	-*
4	*Pilot*	+
	Programme	-
	Smallstandard	+*
	Standard	-
	Extendup	-
	Extendlow	+*

*Insignificant with 5% confidence level

First I will mention the results of the (characteristics of) screening program on mortality. In the graphs – descriptive results – we have seen that there is in 2 countries a very low decrease in mortality after the implementation of a breast cancer screening program. In 6 countries there is a decrease after the starting year of the program and in the other 14 countries mortality was already increasing before the starting year. Variable *pilot* has a positive effect on mortality, so mortality is increasing in the period of a pilot program. Variable *programme* has a negative sign, meaning that mortality decreases after the implementation of a screening program. Using time lags have no appreciably influence on the magnitude of the coefficient. As expected overall cancer mortality is also decreasing after the implementation of a screening program. The variable *smallstandard* is in model 2 and 3 negative and in the random/fixed effect models positive but insignificant. The same

holds for the variable *extendlow*. The variables standard and *extendup* are both positive and insignificant in model 2 and 3. They are negative and significant in the fixed effects model.

Second, about the effect of screening characteristics on incidence, we have only the descriptive results available to draw conclusions. In the graphs we have seen that in two of the six countries the incidence rate is decreasing after the implementation of the program. But for one country only data in 1998 and 2008 are available, we don't know what happened in between. In the other country the incidence rate was increasing before the program started and later decreasing. The incidence rate differs between the used age range. The highest incidence rates are measured in age range *extendup* and *standard*, followed by age range *smallstandard* and *extendlow* with the lowest incidence rates. Notable is that extending the age range to a lower minimum age doesn't affect the incidence rate. When we assume that a good working screening program will lead to high incidence rates, it is not effective to extend the age range below, compared to the standard age range.

5. DISCUSSION

In this section limitations about this research are mentioned. The aim is to measure the effect of breast cancer screening program characteristics on breast cancer mortality and incidence.

The first limitation is about the data. The mortality and incidence data are aggregated per country. There is no distinction between age group, thus the effect on mortality and incidence is an average of all ages. It would be better to estimate the effect on women in- and close to the given age range of the country. The incidence rate counts few observations and can be used for only 6 of the 24 countries. Because of this few observations, incidence could not be included as RHS variable in the models predicting mortality. Without incidence as explanatory variable, the incidence is assumed to be equal. But in reality the incidence rate varies between time and can also affect mortality. In the current models mortality can be underestimated, because it is plausible that the incidence rate increases. On the other hand is it unclear if all newly identified breast cancers, due to screening, will lead to death. Another limitation due to the incidence rate is the short time period (1998 – 2008), while mortality rates are available from 1960. I am assuming that the incidence rate increases over time, so in the latest years the incidence rates are higher because the overall cancer rate (and particularly breast cancer, as mentioned in the introduction of this thesis). Now the implementation of a screening program seems to have a large effect on incidence rates. But if we could correct for the time trend, as is done for mortality, I expect that the time effect would be large. Thus in the current conclusion the effect of screening on incidence rates is overestimated.

One disadvantage is that not all country-specific characteristics of the screening program could be translated into an explanatory variable to estimate mortality or incidence. The screening interval is the same for all countries, except the United Kingdom. Because of the negligible effect, this characteristic is excluded from the comparison to predict mortality or incidence.

Using a long time period is a strength, because many observations can be compared. But a limitation is that there are many time-varying variables that influence breast cancer mortality.. Possible variables - mentioned in the literature - are the increase in advanced screening technology, increasing knowledge about risk factors causing cancer, increasing or decreasing health etc.

6. CONCLUSION

The fact that breast cancer is the most diagnosed form of cancer in women raises the question how breast cancer mortality can be avoided and breast cancer incidence can be reduced. Advanced technical possibilities resulted in using X-ray (mammograms) to detect breast cancer in an early stage, before symptoms appear. Since 1986 European countries have started with (population-based) breast cancer screening. This thesis started with the following research question:

What is the influence of a screening program on the incidence and mortality rates of breast cancer in 24 European countries?

In the literature, Randomized Control Trials show a decrease in mortality after the implementation of a breast cancer screening program. Women participating in the screening program are compared with a control group without screening. Different studies show different reduction in mortality from 10-30%. Gøtzsche and Jørgensen criticize in the Cochrane Review the adequacy of RCT's that approved the negative effect on mortality. They conclude that the adequacy of RCT's influence the outcome and that controlled for this adequacy there is no decrease in mortality. Another study mentions the danger of over diagnosis and concludes that the decrease in mortality must be contributed to improvement in treatment and not to screening.

From the statistical research can be concluded that the implementation of a pilot program has a positive effect on mortality, meaning that mortality increases in the years a pilot program is ran. There can be reverse causality: increasing mortality supports the start of a screening program or running a pilot program can increase mortality. It is logical that increasing mortality supports the start of a screening program. The implementation of a national program has a negative effect on mortality. Two time lags are tested, because of the hypothesis that it will take some time after the implementation of the program before it has an effect on the dependent variable. This hypothesis is rejected because the use of time lags has no appreciably influence on the magnitude of the coefficient. The effect of implementing a screening program on overall cancer mortality is tested, with the expectation that if screening has an effect on breast cancer mortality, there is also an effect on overall cancer mortality. This assumption is true. The variable age range is varying positive and negative. The significant sign is negative, which means that for all age intervals mortality is decreasing, where using the standard age range (50-69) has the highest influence on mortality. For most countries the incidence rate of breast cancer is increasing after the start of breast cancer screening. The highest incidence rates are measured in countries with an age range of 50-69 or with a higher maximum age. Using an age range that is extended to a lower minimum age, will lead to a

lower incidence rate. Assuming that a successful breast cancer screening program will lead to higher incidence rates, because more breast cancers are detected, it seems not effective to extend the age range to a lower minimum age.

Caution is needed with the conclusion of the research results, because of the mentioned limitations in the previous section. But based on this conclusions I should advise policies to implement a national screening program, because screening decreases breast cancer mortality. The invited target group must be between age 50 and 69, extending this age to a higher maximum age is effective in reducing mortality. I would advise a maximum age of 75 and a minimum age of 50, because inviting women with a lower age will not lead to a decrease in mortality or increase in incidence rate.

To give more power to this conclusion, research scan be done to the costs and benefits of extending the maximum age. In this thesis the costs of screening and treatments are disregarded, but including costs in the decision of implementing a screening program, extending the age range and the chosen screening interval lead to an interesting viewpoint.

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8. APPENDIX 1

Appendix 1: country-specific characteristics of breast cancer screening program

Austria

In Austria there was no organized program implemented before 2006. The type of screening in Austria is opportunistic and offered free. There is no active invitation system so there is no controlled screening program. Although spontaneous mammography screening could have been high. In a micro-survey the question was asked if women have had at least one mammography and the result was that 80% of women aged 40-59 years have had at least one mammography and more than 40% have had a mammography in the past year. These percentages can be biased due to self-reporting. In 1998 there is a working group established: Workgroup for Early Breast Cancer Detection for Tyrol and they came with recommendations concerning participation rates. Their aim was to maximize the number of women that participates in screening and early detection due to monthly breast self-examination, yearly examination by a physician and yearly mammography and if necessary with ultrasound. (Frede, 2005)

In 2006 the minister of health decided to implement organized screening programs, first in a pilot region. One of these regions was Tyrol where a state screening program started in 2007 and what's extended to the whole state in 2008. Women are personally invited and screening is offered by radiologists and hospitals. Double reading is not implemented (Oberaigner et al, 2010).

There are plans for renewal of the breast screening program. From October 2013 all women aged 45-69 years will receive an invitation for screening. Women aged between 40-44 and 70-75 years are able to opt in for screening. The coming Austrian National Screening Program will only use digital mammography and in addition they use ultrasound for women with dense breasts. Ultrasound has been used widely for opportunistic screening in the past.

Belgium

Non-organized cancer screening started around 1980-1990, introducing mammography and in some places mammography in combination with ultrasound. Nowadays ultrasound is not recommended because of the low results (higher costs, low benefits) and increasing amount of false extra research.

From 15 June 2001 a national organized screening program started in Flanders and in 2002 in Brussels and Wallonia, following the European quality assurance guidelines. Differences between opportunistic and systematic screening is the double reading in the systematic screening. Double reading is part of the quality criteria. In the organized screening program all women between age 50

and 69 years are once in the two year invited for a mammography. A mammography can be prescribed by the physician. Non-referred women receive an invitation by mail from the Regional Screening Center. The costs of the organized screening program are covered by the federal government.

After the implementation of an organized program, opportunistic screening still exists. In the report 'The performance of the Belgium health system' of the 'FederaalKenniscentrumvoor de Gezondheidszorg' research is done to the coverage of organized versus opportunistic screening. In 2010, the total coverage of screening was 60%, which is below the European average and far below the target (75%). 30% of the total coverage occurred within the organized program. There are large differences between the three regions. Coverage within the organized program is 46% in Flanders and only 11% in Brussels and 7% in Wallonia. A reason could be the higher levels of opportunistic screening in the last two regions before the start of the organized program. Disadvantages of the high coverage in opportunistic screening are the absence of double reading and the unnecessary addition of ultrasound. Also quality is not assured. The aim is that more women will choose for an organized mammography, except those who have medical reasons.

The target group consists of women between age 50 – 69, but there was discussion to extend the age rate to 40 – 49 and 70 – 74. After research they conclude that women aged 40 – 49, without symptoms and without a higher risk for breast cancer, should not be invited for screening. The negative effects of breast cancer screening are explained: false positive results and overdiagnosis and for this age group it is not efficient to invite them for screening. The same argument holds for women aged 70 – 74.

Czech Republic

The Czech Breast Cancer Screening Program (CBCSP) is implemented in September 2002 and at this time an accreditation program was launched by the Ministry of Health. Before 2002, from the late 1990s, mammography was performed at more than 130 facilities and those screening examinations were claimed to be diagnostic. All women have the possibility to undergo a preventive examination by a gynecologist once a year. The Ministry of Health launched the accreditation program, based on the European Guidelines, to minimize the number of preventive examinations at non-accredited centers. Only the centers that met all criteria are allowed to provide screening mammography and are contracted by health insurance companies. In 2011, mammography is performed at 67 accredited centers. The accredited screening centers are monitored and checked by two independent committees: the Breast Cancer Screening Committee at the Ministry of Health and the

Expert Committee on Breast Radiology. The screening program is reimbursed by public health insurance.

In 2002, the target population includes women aged 45-69 years, but since 2010 there is no upper age limit. Women outside the target population can have a mammography, but have to pay the entire costs by themselves. Breast cancer screening is performed at two-year intervals and women are referred by their GP or gynecologist. In the Czech Republic there is no centralized system of direct invitation. Women are achieved through referrals of GP's or gynecologists and media campaigns. The lack of a centralized system of direct invitation results in a low coverage rate of 50%. Because of this reason, in 2007 a pilot project is started where all non-attended women were invited to undergo mammography. The General Health Insurance Company, the provider of health insurance for two-thirds of the Czech population, invited all women between age 45 and 74 that had not undergone mammography during the last three years. Although the low participation rate in this project, the project increases the overall coverage rate, especially in elder women (Majek et al, 2011).

Denmark

Mammography screening is introduced between 1991 and 1994. In Copenhagen the program started in 1991 and Funen county followed in 1993. In 1994 Frederiksberg starts to offer screening, but in 1997 this program was incorporated to the Copenhagen program. Women aged 50-69 years are invited. (Schopper and de Wolf, 2009) Opportunistic mammography screening has remained very limited in Denmark. Non-attenders in organized mammography screening programs do not seek mammography outside the program. The proportion of women seeking diagnostic screening varied between 1-4%, which is very limited (Jensen et al, 2005; Jørgensen et al, 2010).

Estonia

In Estonia pilot programmes started in 1996 and a national program is established since 2004. Estonia is one of the countries with a relatively low age interval. At the start of the program, women between age 50 and age 59 are invited for screening. In 2007 the age range is extended to age 62. Free screening in the national program is only available for women with health insurance.

Finland

Finland is the first country with a national screening program. The program started in 1987. Nowadays digital mammography and film mammography are used techniques to detect (development of) breast cancer. Women between age 50 and age 64 are biennial invited.

France

Regional screening started in 1989 in different pilot areas, where women from age 50 until 69 and affiliated to a sickness funds, could undergo a mammography once in three years (Wait and Allemand, 1996). Six departments initiated a breast screening program and in 1991 four departments followed. In 1994 the Ministry of Health decided to extend the screening program to the remaining districts in 2-5 years. The national program started in 2003. Women aged between 50 and 74 years are screened for free, once in two years. Every two years women receive a voucher from the local health service, offering a mammogram. This voucher must be claimed within six months in one of the nearby centres. There is no referral needed from the GP and health insurance covers the costs. But women outside the target group with a family history of breast cancer can ask for a voucher via their GP. Even when a woman is screened outside the national screening program, it will be reimbursed by the national health insurance (Pivot et al, 2008).

Germany

In June 2002, the German parliament decided to introduce a screening program based on European guidelines. The actual program is implemented in a relative short time: two till three years. Before the national program was implemented in 2005 and completed in 2009, three pilot projects started in Bremen, Wiesbaden and region Weser-Ems in the years 2001-2005. Women in the age range from 50 – 69 years are invited to a mammography examination at 2-year interval by a personal invitation. A fixed appointment is made in the letter that a woman receives. A reminder is send to non-attenders in about six weeks after the missed appointment. Also women are informed by letter about the outcome of the mammography.

Mammography is offered in 94 screening units, which were set up for the program. These centers are specialized in screening by specially trained specialists. There is much attention to quality assurance. The expectation is that opportunistic screening is decreasing and participation is increasing if the national program maintains its high quality performance. In the leaflet that women receive are three quality criteria mentioned: first the mammography is performed by specialists on modern, strictly monitored devices. Second: every mammography image is examined by at least two doctors, who evaluate the mammographies of at least 5000 women annually. Third: abnormal results are clarified by doctors with special advanced training within the early detection program. The Mammography Cooperative is founded to monitor the quality and the continuous training of doctors and radiographers. The costs of the screening are covered by the statutory health insurance. Most screening units used digital techniques from the implementation in 2005 and by the end of 2008 all screening units used digital screening.

Greece

In Greece there was for a long time no national screening program implemented, because screening was opportunistic. Although some pilot projects started in rural areas. The Hellenic Society of Oncologic Screening Program (HSO) began in 1989 with the objective to investigate the feasibility of developing a breast screening program in Greece. They want to apply screening programs throughout Greece. The European Union funded the implementation of a 10-year screening program under the direction and supervision of the HSO. The HSO is using mobile units to screen women aged 40-64. Once a woman enters the screening program, she can be screened irrespective of age. The screening interval is 2 years and in the case of presence of risk factors the interval is 1 year. After a pilot in one prefecture from September 1989 to July 1990 with significant results, the program was extended to two neighboring prefectures. In 1992 the HSO developed its own screening program, named Greece Against Cancer, funded by the Ministry of Health, the Hellenic Cancer Institute and wealthy individuals. This screening program reached 15 prefectures. (Mousiama et al, 2001.

In the north of Greece another program started in 1992, using both mammography centers and general radiology departments to screen women. This program is financed by Europe Against Cancer (Shapiro, 1998) and is operating in about the same way as the HSO program.

The participation rate in Greece is relatively low, around 60% (Shapiro). Dimitrakaki and colleagues come to a lower rate, only 53.8% of the Greek women between 50-69 years were reported as having a mammography done during the last 3 years, where women of 50-54 and 55-59 years had a higher probability to undertake a mammography than 60-69 year old women. The European Guidelines propose a participation rate of at least 70%. A reason for the low participation rate could be that the incidence rate of breast cancer is relatively low and therefore there is less attention for breast cancer screening. Cancer screening is negatively correlated with lower socioeconomic background, educational status, immigration, access to healthcare (lack of invitational system, lack of physician recommendation and lack of insurance coverage).

Next to the regional screening programs, women are screened opportunistic. They need a referral from the gynecologist or undergo a clinical breast examination (CBE) in a hospital. Medical practice guidelines with indications for mammography are set by the First Surgical Clinic of the University of Athens. Women with suspicious findings in the CBE are eligible for a mammography. Screening is annually possible for women over age 50 exposed to a risk factor. Below age 50, women with a history of (breast) cancer or having a mother or sister with breast cancer are eligible for a

mammography. Costs are partially covered by health insurance, reimbursing $10 for every mammography (Mousiama et al., 2001).

In 2008 there is a new plan presented, along with other national action plans in the field of public health: National Action Plan against Cancer.

Hungary

Participation in the national breast cancer screening program is only possible for women who haven't undergo an opportunistic mammogram, or a mammogram in the last 2 years. Pilot programmes started in the mid nineties, national screening started in 2002. Women between 45-65 are invited once in two years.

Iceland

Iceland started relatively early with a national screening program. This program was started in 1987 and 100% coverage was achieved two years later. Used methods are digital mammography and clinical breast exams. Women will receive the first invitation when they are age 40 and until age 69 they are invited biennially, so there is a relatively large target group.

Ireland

The national screening program of Ireland started in 2000. The maximum age range is relatively low, women aged between 50 and 64 are invited to participate in the screening program. The screening interval is 2 years.

Italy

Regional screening programs started in the early 1990s. In Florence were invitations sent to women aged 50-69 years, starting in September 1990. The screening rounds ended in 1993, resulting in an average screening interval of 2.3 years (Damiani et al, 2012). Years later when the program was evaluated, they conclude there was no substantial effect on breast cancer mortality. This was attributed to the relatively low coverage of the program, just 60% (Hakema and Auvinen, 2008). More screening programs started and in 1995 nine areas have implemented a screening program.

Since 2001 screening programs have been included in the Basic Healthcare Parameters. In this year the GISMa (Italian Breast Cancer Screening Group) structured the 60 different programs to a national consensus. Italy has in contrast to most other countries a National screening policy with state/provincial/regional screening program implementation, instead of national implementation. Breast screening programs are developed at regional level. This started in 2002 and in 2007 100%

national coverage was achieved (International Cancer Screening Network). The costs of breast cancer screening are covered by the National Health System.

Luxembourg

Luxembourg started in 1992 with a national screening program and in the same year 100% national coverage was reached, which is very fast. Luxembourg uses the standard age range (age 50-69) and standard interval (2 years).

The Netherlands

The Dutch screening program started in 1989 for women between age 50-70. This age range is extended to age 75 in 1998. The screening service covers the whole country. The implementation of the program has lasted until 1997 and the age shift until 2001. In general there are four phases in the Dutch screening program.: the implementation phase 1990 -1997, extension phase 1998-2001 (to age 75), steady-state phase 2002-2004 (after extension) and the start of digital screening after 2005 (LETB, Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 1990–2007). The Netherlands have one of the highest participation rates, more than 80% of the target group attends to the screening. Especially for age 70-74 the participation rates are increasing. Also there is a low recall rate, lower than other organized population-based programs. The recall rate is the rate at which screened women are recalled for further diagnostic work-up, in case of a positive mammography. This rate is consistent between 1 and 2%. The screening interval is on average 24-24.5 months. For screening X-ray mammography is used, with the aim to detect breast cancer in an early stage in order to reduce breast cancer mortality. Screening is offered in 14 fixed units and 52 mobile screening units. The screening service falls outside the health insurance schemes and is financed directly from taxes and the government asks for a standard of quality which screening organizations have to fulfill. (Nationwide breast cancer screening in TN, 2009)

Digital screening is started after 2005 in three pilots (Utrecht, Heerenveen and Dordrecht). The process is the same as the analog mammogram, but it takes less time. The digital mammogram allows the image to be viewed on a monitor or printed in high resolution. This implementation of digital mammography has led to a temporary increase in the referral rate and increase in detection rate, so detection improved. In 2008 the use of digital screening is increased with the aim that in 2010 only digital screening is offered. In June 2010, the full digitalization has been achieved. (LETB, 2012)

Norway

Norway started in 1996 with a national breast cancer screening program. Full coverage was reached eight years later in 2004. The standard age range (50-69) and screening interval (2 years) are used.

Poland

A nationwide program was introduced in 2007 by the Polish National Health Fund. The target group consists of women aged 50-69 years. The invitations are regulated by the National Health Fund. Females undergoing treatment or being followed-up due to breast cancer are excluded from invitation. In the media awareness is created about breast cancer and breast screening, through general practitioners, health professionals, advertisement, websites, phone lines, text messages via mobile phone and emails. The screening interval is two years.

The screening method is two-view screen-film mammography without clinical examination. Mammography is evaluated with single reading because of limited budget (Matkowski and Szynglarewicz, 2011).

Portugal

In Portugal breast cancer screening programs started in 1990 and 1997. The invited target group is relatively high, women are biennially invited from age 45 to age 69.

Slovak Republic

There is limited information about the breast cancer screening program in the Slovak Republic. We know that pilot programmes started in 2004 and a national program in 2008. There is no information found about the age group and screening interval. The participation rate is lowest for all European countries: 1.2% is invited for a mammography by the program and 98.9% by another initiative (Eurostat). This website also mentions that since 2008 just the preparations are started for a national screening program.

Slovenia

In Slovenia the national screening program started in 2008, with the standard age range and screening interval.

Spain

Population-based breast cancer screening started in 1990 in the province Navarra for women aged 45 - 65 years (Shapiro, 1998). Nowadays the target group covers women aged 45-69 years. In

Catalonia screening started in 1995 for women aged 50-69 years. National coverage is reached in 2003 (International Cancer Screening Network, 2012). Women will receive a personalized letter with the invitation for a free mammography once in two years. Women under age 50 with a family history of breast cancer can ask the GP for inclusion in the screening program. Ascune and his colleagues mention the high acceptability of screening, what is shown by a high participation and degree of adherence (Ascune et al, 2010). Especially the province Navarra counts a high participation rate of 87% in 2010 (International Cancer Screening Network, 2012).

Sweden

Sweden started as first European country with organized screening. In 1982 pilot projects were started and in 1986 the National Board of Health recommended to start screening women aged 40-74 years with two-view mammography in all Swedish counties. The target group differs between the counties. In all counties women aged 50-69 years are invited. This target group is extended to 40 – 49 years in 11 of the 21 counties and to 70 – 74 years in 10 of 21 counties (American Association for Cancer Research, 2006. The screening interval is different per age group. For women aged 40 - 49 years the interval is 18 months and for women older than 50 years the interval is 2 years.

Switzerland

Between October 1993 and January 1999, a pilot program was conducted in the canton Vaud. Every two years, women aged 50 -69 were invited by a personal letter and leaflet to undergo a free mammography. Non-attenders got two reminders (Bulliard et al, 2004). The results from the pilot programs supported an organized screening program. Both opportunistic and organized screening exists, depending on the canton. In 1999 the pilot program was extended to the whole canton Vaud and also to cantons Geneva and Valais.

United Kingdom

In the United Kingdom the national screening program was implemented in 1988. Full coverage was reached in 1995. The United Kingdom is the only country with a screening interval of 3 years.
Women between age 50 and 69 are invited triennial.