Breast cancer screening with mammography of women 40-49 years in Sweden

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Abstract

Background The debate regarding the lower age limit for mammography service screening is old and lively; a product in part of the lower breast cancer risk in younger ages as well as the limited data available for studies of the younger age group. Recently the idea of inviting only high risk groups has gained momentum, however high risk might not be equivalent to greater benefit from screening. Therefore, there is a need for information on effectiveness of screening as it relates to young women and to specific risk groups. To this end, this thesis evaluates mammography screening for the age group – 40 to 49 year old women – in terms of breast cancer mortality reduction in total and in subgroups based on breast cancer risk factors. Overdiagnosis of mammography screening is also evaluated for women 40 to 49 years old. In addition, this thesis presents a statistical method to estimate this effectiveness and to test for differences in effectiveness between subgroups adjusted for non-compliance and contamination.

Methods The studies of this thesis are based on data from the Screening of Young Women (SCRY) database. The SCRY database consists of detailed information on diagnosis, death, screening exposure and risk factors for breast cancer cases and population size by year (between 1986 and 2005) and municipality for women in Sweden between 40 and 49 years old. The material was divided into a study group consisting of the counties that invited women in the age group 40-49 years to mammography screening, and a contemporaneous control group consisting of the counties that did not. Effectiveness was estimated in terms of rate ratios for two different exposures (invitation to and participation in screening), and overdiagnosis for subsequent screening was estimated adjusting for lead time bias. Defining a reference period enabled adjustment for possible underlying differences in breast cancer mortality and incidence. A statistical model for adjusting for non-compliance and contamination in randomised controlled trials was further developed to allow for adjustment in cohort studies using a Poisson model with log-linear structure for exposure and background risk.

Results During the study period (1986-2005), there were 619 and 1205 breast cancer deaths and 6047 and 7790 breast cancer cases in the study group and the control groups, respectively. For women between 40 and 49 years old, the breast cancer mortality reduction was estimated at 26% [95% CI, 17 to 34%] for invited to screening and 29% [95% CI, 20 to 38%] for attending screening. The RR estimates for the high-risk groups based on the risk factors parity, age at birth of first child, and socio-economic status were equal to or higher than that of the low risk groups. The new statistical

method showed that the decrease in effectiveness with parity was not a statistically significant trend. The overdiagnosis from subsequent screening for 40 to 49 year old women was estimated at 1% [95 % CI, -6 to 8 %] (i.e., not statistically significant).

Conclusion Subgroup specific effectiveness was also estimated. The relative effectiveness of screening for breast cancer with mammography for women age 40 to 49 years appears to be comparable to that for older women. These findings and the fact that there was no statistically significant overdiagnosis from subsequent screening speak for inviting women 40 to 49 years old to screening. High-risk screening for nulliparous women aged 40 to 49 years, for example, might be an alternative in countries where population-based screening for all women between 40 and 49 years old is not possible. However, the matter of risk factors and the effect of their combinations is complex and risk group screening presents ethical and practical difficulties. The new statistical model is a useful tool for analysing cohorts with exposed and non-exposed populations where non-compliance and contamination is a potential source of bias.

Abbreviations

BMI	Body Mass Index
NNS	Number Needed to Screen to save a life
RR	Rate Ratio
SCRY	SCReening of Young women
SES	Socio-Economic Status
SNBHW	Swedish National Board of Health and Welfare
SS	Statistics Sweden

Original papers

This thesis is based on the following papers, referred to in the text by their roman numerals

I Hellquist BN, Duffy SW, Abdsaleh S, Bjorneld L, Bordas P, Tabar L, Vitak B, Zackrisson S, Nyström L, Jonsson H. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. Cancer, 2011;117(4):714-22. *Reprinted with permission.*

II Hellquist BN, Czene K, Hjälm A, Nyström L, Jonsson H. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years with high and low risk of breast cancer - socioeconomic status, parity and age at birth of first child. *Submitted.*

III Hellquist BN, Bolin D, Yu J, Jonsson H. Poisson based model for adjusting for non-compliance and contamination in cohort studies. *Manuscript.*

IV Hellquist BN, Duffy SW, Nyström L, Jonsson H. Overdiagnosis in the population-based service screening programme with mammography for women aged 40 to 49 years in Sweden. Journal of Medical Screening, Sage Publication Ltd. 2012;19(1):14-9. *Reprinted with permission.*

Populärvetenskaplig sammanfattning (Summary in Swedish)

I Sverige får årligen ungefär 6600 kvinnor en bröstcancerdiagnos och 1400 kvinnor dör varje år med bröstcancer som orsak. Även globalt är bröstcancer den vanligaste cancern bland kvinnor, 23% av alla cancerfall är bröstcancerfall.

Ett sätt att påverka bröstcancerdödligheten är att hitta bröstcancrarna tidigare, när cancern är lättare att behandla. Svenska och internationella studier har visat att regelbundna mammografiundersökningar (en form av röntgenundersökningar av bröstet) av friska kvinnor i ålder 40-74 år sänker bröstcancerdödligheten i åldergruppen. För den yngsta och äldsta åldergruppen i spannet 40-74 år, det vill säga 40-49 år och 70-74 år, har resultaten från de stora randomiserade studierna varierat och mammografiscreening för kvinnor i dessa åldrar har varit omdebatterade, både i Sverige men framförallt internationellt. Utredningsinstanser i till exempel EU och USA rekommenderar inte mammografiscreening för kvinnor i ålder 40-49 år idag. Däremot rekommenderar Socialstyrelsen i Sverige alla landsting att bjuda in kvinnor i ålder 40-74 år till mammografiundersökningar, vartannat år för äldre och var 18:e månad för yngre kvinnor.

I denna avhandling skattades om och i så fall hur mycket bröstcancerdödligheten minskar med mammografiscreening för åldergruppen 40-49 år med hjälp av ett unikt stort svenskt material kallat SCRY (Screening of Young women). Materialet bygger på att ungefär hälften av Sveriges landsting under perioden 1986-2005 bjöd in kvinnor från 40 år och ungefär hälften av landstingen då hade en högre åldergräns. Materialet inkluderar fler än dubbelt så många bröstcancerdödsfall (med diagnos i ålder 40-49 år) som de stora randomiserade studierna sammanslaget. För kvinnor i ålder 40-49 år skattades att bröstcancerdödligheten är 21% lägre för all inbjudna och 29% lägre för de kvinnor som faktiskt deltar i mammografiscreeningen.

Ett alternativ för länder som inte kan bjuda in alla kvinnor i ålder 40-49 år skulle kunna vara att endast bjuda in de som har högre bröstcancerrisk. I denna avhandling skattas därför med hjälp av SCRY materialet även hur mycket bröstcancerdödligheten minskar med mammografiscreening specifikt för kvinnor med; olika antal barn, olika ålder vid första barnets födelse samt olika socioekonomisk status, tre kända riskfaktorer för bröstcancer. För alla tre riskfaktorer visade det sig att reduktionen för

kvinnor med högre risk inte skiljde sig (med statistisk signifikans) från reduktionen för kvinnor med lägre risk. Detta indikerar att mammografiscreening i högriskgruppen borde rädda fler liv än i lågriskgruppen (bland lika många undersökta kvinnor).

En metod för skattning och jämförelse av till exempel minskning av bröstcancerdödlighet mellan grupper utvecklades även. Fördelen med metoden är att den gör det möjligt att jämföra skattningar gjorda till exempel särskilt för de som faktiskt deltagit samt att testa den statistiska signifikansen hos så kallade trender, det vill säga en stegvis ökad skillnad i till exempel minskning av bröstcancerdödlighet för 0, 1, 2 och 3 eller fler barn.

Ett av argumenten mot mammografiscreening, rent allmänt och för åldergruppen 40-49 år, har varit att vissa bröstcancrar kanske hittas med screening som utan screening inte skulle ha gjort någon skada under hela kvinnans liv, så kallad överdiagnostik. Detta skulle kunna leda till onödig behandling, stress och lidande. Baserat på SCRY materialet skattades i denna avhandling att det inte finns någon statistiskt signifikant överdiagnostik för åldergruppen 40-49 år.

Sammanfattningsvis pekar resultaten i denna avhandling på att åldergruppen 40-49 år bör fortsätta bjudas in till mammografiscreening i Sverige. I länder där det inte är möjligt att bjuda in alla kvinnor i ålder 40-49 år kan mammografiscreening endast för kvinnor med hög risk för bröstcancer vara ett alternativ, men här behövs ytterligare forskning.

Background

Breast cancer in Sweden and worldwide

Although breast cancer is primarily a health problem in high income countries, recently it has emerged as a problem in low and middle income countries as well, probably due both to changes in the pattern of risk factors and increased awareness. Globally, breast cancer is the most common cancer in women, responsible for 23% of all cancer cases and 14% of all cancer deaths[1] (Figure 1). In high income countries, female breast cancer incidence increased in the 1980s and 1990s, but mortality rates have been decreasing over the past 25 years, most likely due to early detection through screening and better treatment[1]. (As male breast cancer corresponds to less than 1% of all breast cancers[2], this thesis deals only with female breast cancer.)

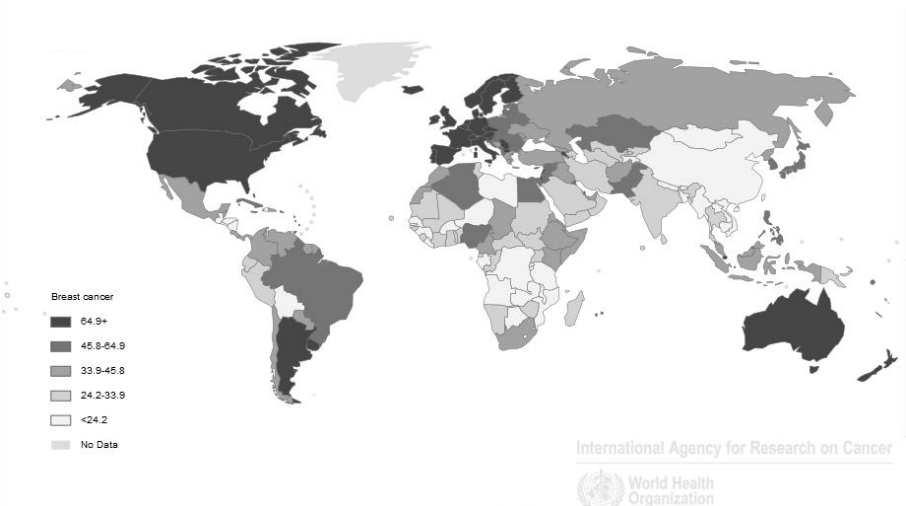

Figure 1. Age standardised breast cancer incidence rate among women in 2012 worldwide. Figure from GLOBOCAN 2012 (IARC) [1].

The general pattern of increasing incidence but decreasing mortality in high income countries is also seen in Sweden (Figure 2a). In Sweden the 5- and 10-year breast cancer survival has improved over the past 30-50 years, both for all ages and specifically for the age group 40 to 49 years [3]. In 2013, about 6600 women were diagnosed with breast cancer in Sweden and 1400 died of breast cancer. Of those, 14% of cases and 6.5% of deaths were between 40 and 49 years old.

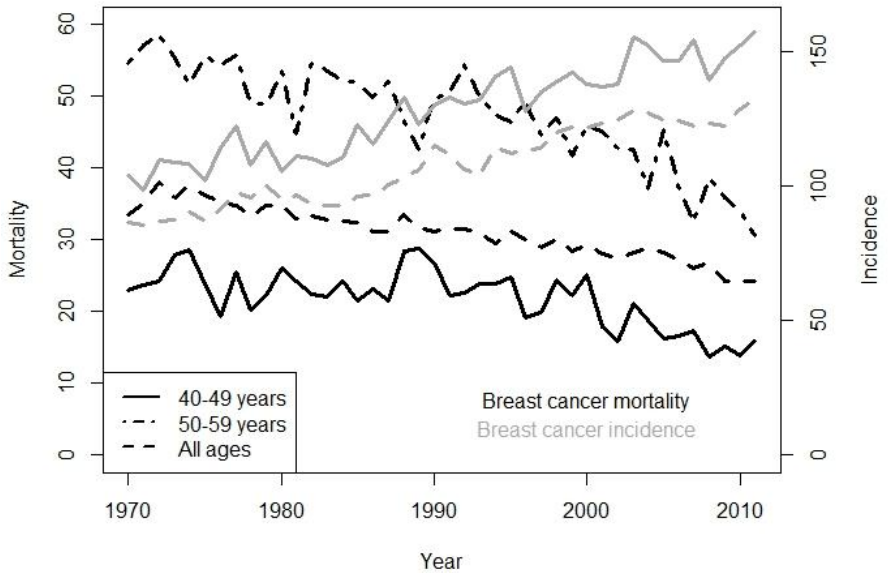

Figure 2a: Breast cancer mortality for all ages and the age groups 40-49 years and 50-59 years, and breast cancer incidence for all ages and age group 40-49 years. Age standardized rates per 100 000 women in Sweden between 1970 and 2011.[4]

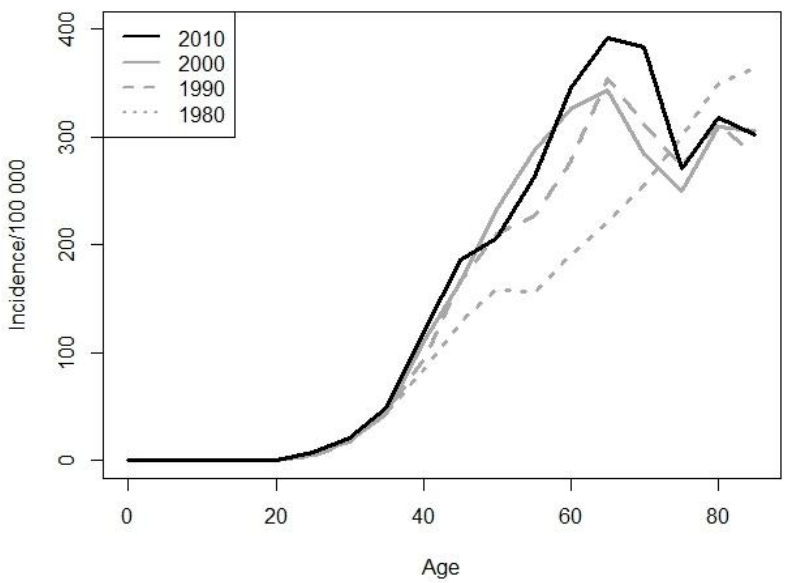

Figure 2b. Breast cancer incidence rate per 100 000 women versus age for the years 1980, 1990, 2000 and 2010 in Sweden.[4]

Risk factors for breast cancer in total and for the age group 40-49 years

The main risk factor of breast cancer is increasing age. Incidence increases with age, particularly between 35 and 65 years of age, but incidence increases less rapidly around the age of menopause (45-55 years), and then drops around the end of screening invitation (70-74 years) (Figure 2b). Breast cancer risk also varies with geographical location, reproductive and hormonal factors, genetic factors, exposure to radiation, socio-economic status (SES) and lifestyle [5].

Table 1 shows risk factors identified for breast cancer for women age 40-49 years old. However it should be emphasised that the identified risk factors are not independent causes of breast cancer but rather are aspects of a complex web of associations. For example, high breast density, low parity, high SES and low body mass index are associated with each other. Also, breast density tends to decrease after menopause. [6-8]

Table 1. Possible direction of association between known breast cancer risk factors for women age 40-49 years and breast cancer risk, survival, and mortality – ↑: higher for higher (or when the risk factor is present for dichotomous risk factors); ↓: lower for lower/absent; →: no association; and ?: association very unclear.

	Breast cancer		
Risk factor	**Risk (age 40-49)** [8]	**Survival**	**Mortality**
Breast density	↑	↑→ [7 10]	↑→ [10 11 12]
BMI*	↓	↑ [13]	↓ [14]
1st and 2nd degree relatives with breast cancer	↑	↑ [15]	? [16]
Parity	↓	↑ [13,17]	↓ [18]
Age at 1st birth	↑	↑→ [13,22]	↑ [18]
Breastfeeding	↓	? [19 22]	? [19]
Oral contraceptive use	↑	→ [13]	? [20,21]
Age at menarche	↓	↑ [22]	? [23]
SES and Education	↑ [24]	↑ [25 9]	↑ [26]

* pre menopause

Less is known of the breast cancer survival and breast cancer mortality for women of high and low (incidence) risk. However, high breast cancer risk does not appear to always indicate high breast cancer mortality or low breast

cancer survival. In some cases, screening attendance may play a part in breast cancer survival and mortality. For example, the results in studies that show better survival for women with high SES could be due to high SES women taking advantage of screening invitations more often than low SES women [9].

Breast cancer screening with mammography

The objective of mammography screening

If breast cancer is found at an earlier stage, the risk of death from breast cancer is smaller [27] (Figure 3). Mammography screening aims to find breast cancers at an earlier stage through regular mammography examinations of populations at risk.

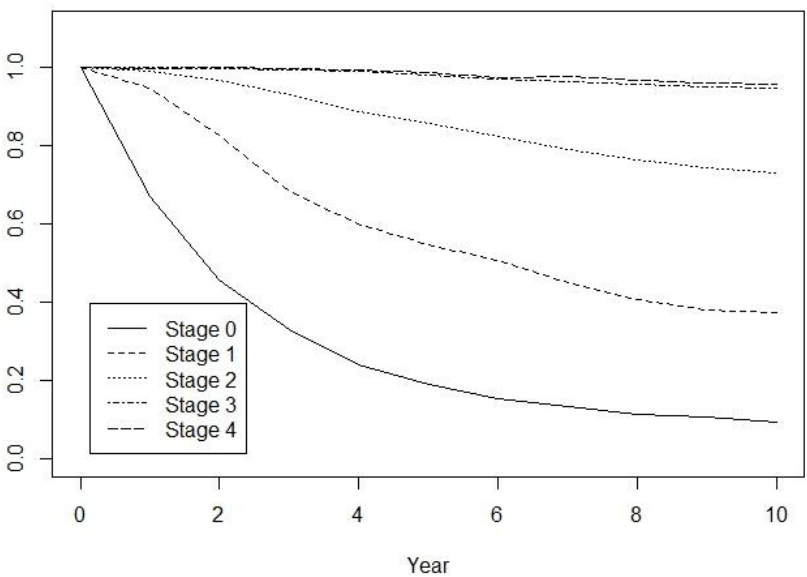

Figure 3. Breast cancer survival by breast cancer stage at diagnosis for women in Sweden 1990-2010 [28].

Screening programs invite all women in a certain age interval, but which age interval remains controversial. Specifically, the invitation of age groups 40-49 and 70-74 years have been questioned; for these, the harms or costs of screening may outweigh the benefits [29].

Harms of mammography screening

Discomfort, radiation exposure and incorrect examination results

Recurrent mammography examinations add to the lifetime radiation exposure, however, exposure from mammography screening is low [30] and the risk of breast cancer death due to radiation exposure from mammography screening from age 40 to age 74 years has been estimated at 1.1 in 100 000 [31]. (It is also worth noting that any increase in breast cancer mortality caused by screening would decrease the observed breast cancer mortality reduction of screening.) Potential pain and anxiety that women may experience in conjunction with the examination is more difficult to quantify, although it does not appear to influence future participation [29].

Incorrectly interpreted mammograms (i.e., false-positive and false-negative tests) are also a potential harm of mammography screening. False-negative tests are rare for all ages. False-positive tests may result in unnecessary treatment and anxiety and are more common in the 40-49 age group than in older women [29]. About 2-4% of women screened in Sweden are recalled (as seen in study I). In Sweden, the most common path to diagnosis for a recalled woman is fine needle biopsy. As very few women need diagnostic surgery, the physical damage to the average recalled woman without breast cancer is small. An important factor regarding the anxiety surrounding a recall is the time spent waiting for diagnosis, which is minimised by mailing informing on recall close in time to the diagnostic examinations and including all examinations and the information on diagnosis on one day[i].

Overdiagnosis

Some breast cancers may not cause any symptoms from the time they are detectable to the time of a woman's death from causes other than breast cancer. No test today can show whether a breast cancer belongs to this category, and once detected such a cancer will most likely be unnecessarily treated. Breast cancers that without screening would not have been detected or caused any problems throughout a woman's lifetime, referred to as overdiagnosis, are considered more common in older women but are a potential harms of mammography screening in all age groups [29].

[i] Moberg, Kerstin; Senior radiologist, personal communication, February 4 , 2014

Breast cancer mortality reduction

Randomised controlled trials

Several randomised controlled trials of mammography screening with breast cancer mortality as outcome have been conducted. Of these, the Swedish, Canadian, New York and Edinburgh randomised trials included women younger than 50 years of age, and the UK trial was exclusively aimed at the age group 40-49 years.

Table 2. Randomised controlled trials (RCTs) for age 40-49 years, estimated rate ratio (RR) with 95% confidence interval (CI) for ages (when not 40-49 years) and recruitment years of trial. HIP = The Health Plan of New York; NBSS = The Canadian National Breast Screening Study.

RCT	Results for age 40-49 years RR [95% CI]	Recruitment years	Age in years (when not 40-49)
The UK trial (AGE)[33]	0.83 [0.66-1.04]	1991-1997	39-41
NBSS [35]	0.97 [0.74-1.27]	1980-1985	
Göteborg[36]	0.56 [0.34-0.91]	1982-1984	39-49
Stockholm[37]	1.52 [0.80-2.88]	1981-1983	39-49
Malmö II[37]	0.65 [0.39-1.08]	1978-1990	43-49
Östergötland[37]	1.05 [0.64-1.71]	1978-1981	38-49
Malmö I[37]	0.87 [0.63-1.20]	1976-1978	45-54
Kopparberg[38]	0.76 [0.42-1.40]	1976-1978	
Edinburgh[39]	0.83 [0.54-1.27]	1978-1982	45-49
HIP [33]	0.77 [0.53-1.11]	1963-1966	

In the UK trial women age 39-41 years were invited at the start, as opposed to the other trials where women age 40-49 years were invited at the start, i.e. where women age 48-49 years (in the study group) were only invited to screening once before age 50 years. At the 10 year follow-up the

breast cancer mortality reduction was estimated to be 17% and when adjusted for invitation 24%, but statistically non-significant [33]. (Both control and study group in the UK trial entered the present screening program at age 50 [34]). In the other randomised trials, results for the age group 40-49 years varied between a 44% statistically significant breast cancer mortality reduction and no effect (Table 2).

Metaanalyses

A number of metaanalyses specifying effect estimates for age 40-49 years have been conducted with estimated rate ratio (RR) varying from 0.71-1.08 (Table 3). The variation may be due to differences in years of follow-up, methods used and trials included.

Regarding total mortality, no statistically significant reduction has been found in the overviews conducted. Assuming mammography screening does not increase or decrease deaths from causes other than breast cancer, the total mortality reduction of mammography screening equals the breast cancer reduction times the proportion of total mortality attributed to breast cancer. In Sweden in 2011 15% of total mortality in the age group 45-54 years were breast cancer deaths [4,40]. (Deaths from breast cancer diagnosed in the age group 40-49 years can be expected to occur approximately between age 45 and 54 years of age.) With an RR_{40-49} of for example 0.8 that would equal a total mortality reduction of 3% (=0.2*0.15) for the age group 40-49 years. In a 2001 overview that includes Malmö and Canada, Olsen and Gotzsche estimated total mortality RR to be 1.03 [95% CI 0.77-1.38] [41]. In 2002, a Swedish overview estimated total mortality RR to be 1.00 [95% CI 0.95-1.06] [37]. In a 2011 overview, the Canadian Task Force, including the Canadian and UK trials, estimated the total mortality RR to be 0.97 [95% CI 0.91–1.04] [42].

Few observational studies have been performed on the age group 40-49 years as few large scale screening programs include women below age 50. A study by Jonsson et al from 2000 based on the Swedish screening program for the years 1986-1996 estimated the RR at 0.91 [95% CI 0.72-1.15] at eight years of follow-up [43]. The study had a similar but not identical design as study I. A more recent study of northern Sweden with 11 years of follow-up estimated the effectiveness of mammography screening at 0.64 [95% CI 0.43–0.97] and 0.62 [95% CI 0.42–0.91] [44] with excess mortality and underlying cause of death as mortality measure respectively. (Excess mortality effectiveness estimates do not rely on cause-of-death data but are based on the difference between expected and observed all cause mortality among breast cancer cases [45].)

Table 3. Results for age 40-49 years from meta-analyses of mammography screening trials. SCS=Swedish Cancer Society; SNBHW= Swedish National Board of Health and Welfare.

Meta-analyses included studies	**Results for age 40-49 years RR [95% CI]**	**Excluding**
14-16 years of follow-up		
Magnus et al, 2011[46]		
6 trials	0.87[0.56- 1.13]	HIP, Malmo(I,II), Edinburgh
Nelson et al, 2009[47]		
9 trials	0.85 [0.75-0.96]	Edinburgh, UK included
Smith et al, 2004[48]		
9 trials	0.85 [0.73-0.98]	
Nyström et al, 2002[37]		
Swedish trials	0.80 [0.63-1.01]	Kopparberg
Humphrey et al, 2002[49]		
8 trials	0.85 [0.73-0.99]	Edinburgh
10-13 years of follow-up		
Gøtzsche and Nielsen, 2011[50]		
9 trials	0.81 [0.74-0.87]	Edinburgh, UK included
Canadian Task Force, 2011[42]		
9 trials	0.85 [0.75–0.96]	Edinburgh, UK included
Larsson et al, 1997[51]		
Swedish trials	0.77 [0.59-1.01]	
Hendrick et al, 1997[52]		
9 trials	0.82 [0.71-0.95]	
Swedish trials	0.71 [0.57-0.89]	
Glasziou and Erwig, 1997[53]		
9 trials	0.85 [0.71-1.01]	

Kerlikowske et al, 1997[54]		
9 trials	0.84 [0.71-0.99]	
SCS and NBHW, 1996[55]		
9 trials	0.85 [0.71-1.01]	
Smart et al, 1995[56]		
9 trials	0.84 [0.69-1.02]	
8 trials	0.76 [0.62-0.95]	NBSS
7-9 years of follow-up		
Kerlikowske et al, 1995[57]		
8 trials	0.93 [0.76-1.13]	
Glasziou et al, 1995[58]		
8 trials	0.95 [0.77-1.18]	
Elwood et al, 1993[59]		
6 trials	1.08 [0.85-1.39]	
Fletcher et al, 1993[60]		
6 trials	1.08 [0.85-1.39]	

Sensitivity and specificity of mammography screening

Sensitivity (i.e. percentage of true positives detected) of mammography screening has been estimated to be 77-95% for all ages [29] and has been estimated to be somewhat lower in younger than older ages [61-63]. Specific estimates for the age group 40-49 years were made based on the UK trial at 90% for invasive and 82% for in situ breast cancers [64].

Specificity (i.e. the percentage of correctly assessed true negative tests), is closly related to the concept of false-positives. For all ages specificity has been estimated to be high, 94% to 97% [29].

Guidelines

Recommendations regarding which age intervals to invite to screening vary, reflecting the lack of consensus regarding the age groups 40-49 and 70-74 years (Table 4). It should be noted, however, that although women age 40-49 years are not included in the recommendations of the European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services (and Council of the EU), several European countries include age 40-49 years or the subset 45-49 years in their screening programs.

Table 4. Recommendations on age limits for mammography screening in the EU, US, Canada, Australia (women age 40-49 years not invited to, but eligible for, free mammography screening) and the Nordic countries according to national/regional guidelines or preventive task forces (US and Canada).

	Screening recommended in 2013 for age group		
Region	**40-49**	**50-69**	**70-74**
US[29], Canada[42] and Australia[65]	No	Yes	Yes
EU[66]	No	Yes	No
Sweden[67]	Yes	Yes	Yes
Finland[68], Norway and Denmark [69]	No	Yes	No
Island[69]	Yes	Yes	No

Practice age 40-49 years

According to a 2012 survey by the International Cancer Screening Network, the age group 40-49 years was invited to mammography screening in Sweden, Iceland and one province in Canada. Japan, Korea and China also had national screening policies that include this age group. In New Zeeland and parts of Portugal (Alentejo and Central region) and parts of Spain (Navarra region), women age 45-49 years were invited [69], and in Australia women age 40-49 years were eligible for free examinations in 2014 [65].

Screening intervals for age 40-49 years

A shorter screening interval is usually recommended for younger women [70-72] due to a higher incidence of more rapidly growing breast tumours [73,74]. However longer intervals have also been suggested [75]; in many countries with screening programs including age 40-49 years the intervals are the same for all age groups [69].

In Sweden the National Board of Health and Welfare recommends shorter intervals for younger women (18 as opposed to 24 months) [69], but the guidelines are not always met and the actual screening intervals at Swedish screening centres for age 40-49 years tended to increase between 1986 and 2005 (as seen in study I).

Digitalisation of mammography screening

Digital mammography has gone from experimental to dominant over the last decade. Unlike film, digital mammography images do not require development or storage other than in the digital form. For young women, premenopausal women and women with dense breasts, digital mammography has been found to have higher detectability of breast cancer [76-78].

Selective screening

Apart from the national screening programs with inclusion criteria based on age, there are specific screening programs for groups with a familial or genetic predisposition for breast cancer. Mammography (but also ultrasound and MRI) have been shown to be effective for screening in such populations [79-82]. Parallel to the debate of whether to screen age 40-49 years or not, the suggestion has been made to limit screening in the age group to subgroups at high risk based on factors other than age [8,83,84]. However, for the absolute effect of screening in terms of e.g. Number Needed to Screen to save a life (NNS) to be superior in these subgroups, the effect of mammography screening must not be too much lower than that of the entire age group 40-49 years.

Aim

The aims of this thesis are, for mammography screening of women aged between 40 to 49 years old

- To estimate the exposure adjusted effectiveness
  - in total and;
  - in subgroups based on the breast cancer risk factors parity, age at birth of first child and socio-economic status.
- To develop a statistical method for analysis of cohorts with a log-linear model that allows comparison of subgroups when non-compliance and contamination are potential sources of bias.
- To estimate the overdiagnosis of subsequent screening.

Materials and methods

The SCRY database

Today, the Swedish National Board of Health and Welfares (SNBHW) recommendation to the county councils is to invite women 40-74 years old to mammography screening. In the mid 1980s, when mammography screening was first initiated, the SNBHW also recommended screening for women 40-74 years, but this recommendation was later modified so that screening for the age group 40-49 and 70-74 was left up to the discretion of the county councils. This strategy resulted in a natural experiment of sorts, where close to half of all Swedish counties invited women to mammography screening from age 40 years and the remaining did not until the 2000s when there was a shift towards more and more counties inviting women in age 40-49 years.

The basic idea of the Screening of Young Women (SCRY) database was to utilize this circumstance and form a study group consisting of the counties that invited women age 40-49 years and a control group of the counties that did not invite the age group, during the years 1986-2005 (Figure 4).

Study and control groups were contemporaneous. During follow-up national guidelines and regional care programs aimed at ensuring equal care in all of Sweden were initialised, and studies show that differences in breast cancer care in Sweden have decreased over time[85]. There was no clear geographical pattern for which counties chose the lower invitation age 40-49 years, both the north and south and more and less densely populated areas were represented in both groups. Although not randomized, the difference between the two groups can be expected to be small, i.e. underlying breast cancer mortality and incidence could be expected to be similar in the study and control group.

In some counties, such as Skåne, invitation age varied between areas within the county. Some counties (or areas) invited women age 40-49 years only during a portion of the follow-up period. When a period of screening for women 40-49 years occurred towards the end of the follow-up, such an area was included in the control group for the earlier years and study group for the latter years. Areas with earlier periods of screening followed by periods of no screening in age 40-49 years were only included in the study group, not the control group, due to the risk of lingering effects of screening. For both the study group and the control group, only follow-up periods of six years or longer were included. The screening examinations of one area, Gävleborg,

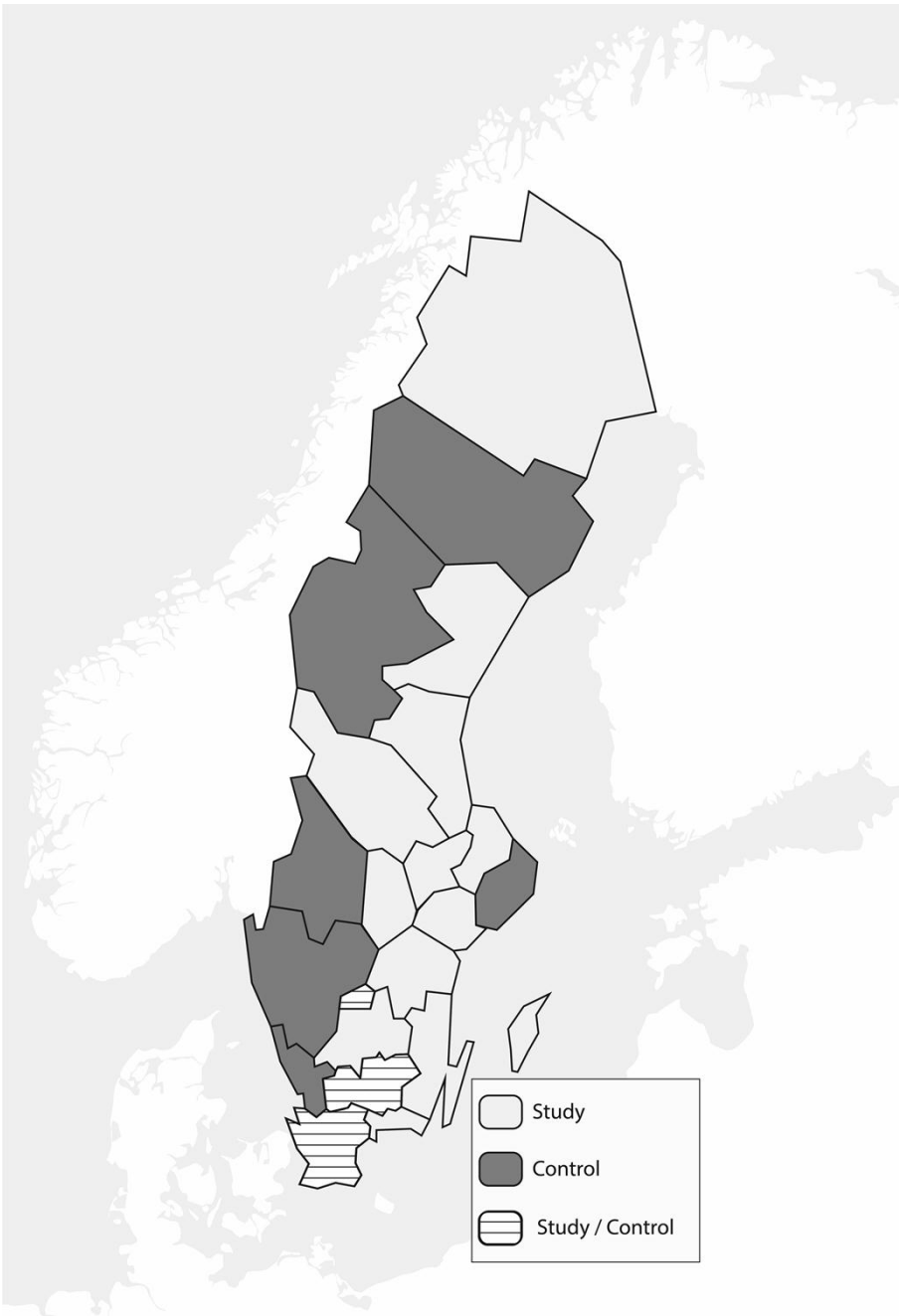

Figure 4: Map of the SCRY control and study group. Control/Study = Counties/Areas including both study and control group, either for different time periods or in different parts of the county. [Map by T. Hellquist]

differed distinctly from all other areas during part of the follow-up, so it was only included in the study group for the years when it was deemed comparable. Another area, Blekinge, only invited women age 45-49 years throughout follow-up, so only women of these ages were included in the study group.

Refined mortality

The SCRY study and control group can be seen as groups of geographical cohorts with start of follow-up at start of exposure in the study group areas and a corresponding start point in control areas. The mortality measure used was refined mortality (i.e., breast cancers with diagnosis in age group 40-49 years and death before end of follow-up, 31 December 2005). The corresponding person-years for each area at follow-up year j was a sum of the population from age 40 to 49+j (j=0 at start years) (Figure 5). The quadrilateral corresponds to area person-years and the arrows show examples of included (black) and not included (grey) breast cancer deaths, with diagnosis at the nock and death at the head of the arrow.

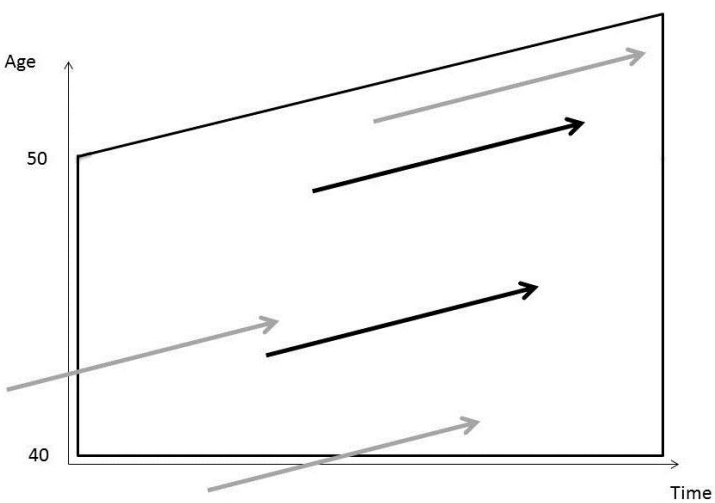

Figure 5: Illustration of refined mortality and corresponding person-years.

Adjusting for exposure

Exposure was defined as invitation to mammography screening and participation in mammography screening respectively, on the last screening occasion before breast cancer diagnosis. There were two potential sources of bias due to misclassification of exposure, non-invited/non-attending in the

study group (i.e. non-compliance), and invited/attending in the control group (i.e. contamination).

At start of screening - for women aged 40-49 years at the start of the screening program and for women turning 40 years - it may take up to two years before invitation. Women who recieve a breast cancer diagnosis after start but before their first invitation are not exposed to screening, and since they on average have a longer follow-up or on average are younger than the rest of the study group their observed breast cancer mortality may differ from the rest of the study group. Throughout screening some women may choose not to partake in screening (self-selection), and these women may have a different underlying breast cancer mortality, due to lifestyle or genetic predisposition, from the rest of the study group [86,87].

In the control group, there were in some areas short periods where women age 40-49 years were invited. The women in the control group who recieved a breast cancer diagnosis during these periods may have been exposed to screening. Periods of screening of 40-49 years in control areas usually took place in later years, and therefore follow-up could be expected to be shorter than for the rest of the control group.

These types of non-compliance and contamination were adjusted for in study I and II utilizing a method by Cuzick et al for randomised controlled trials [88] adapted to adjustment in cohort studies. Underlying breast cancer mortality and proportion of women who would comply if offered screening were assumed to be equal in study and control group. Then, number of person-years could be recalculated to adjust for the potential bias.

In study III the adjustment method by Cuzick et al was further developed to allow for adjustment in cohort studies with subgroups through a log-linear Poisson model, e.g. when estimating the effectiveness of mammography screening in groups based on risk factors. The estimates were made using maximum likelihood estimation and variance estimates for the parameters in the model were made through inverting the negative hessian, i.e. the matrix of second deviates of the likelihood function (Appendix).

There may also have been self-selection in the control group, women who even though they were not invited to screening in age 40-49 years themselves sought out screening (i.e. opportunistic screening). As for women who chose not to attend, there may be a difference in underlying breast cancer mortality related to screening behaviour. This source of contamination was not adjusted for due to lack of data.

Data sources

The data for the SCRY database were supplied by Statistics Sweden (SS), the SNBHW, the Swedish screening centres and the Linnaeus database (Figure 6). The SCRY database includes three levels of detail:

- breast cancer deaths, with individual data on participation in screening and risk factors;
- breast cancer cases, with individual information about diagnosis; and
- population figures by age, year, and screening area.

The SCRY database also includes information on screening programme history for all Swedish screening areas.

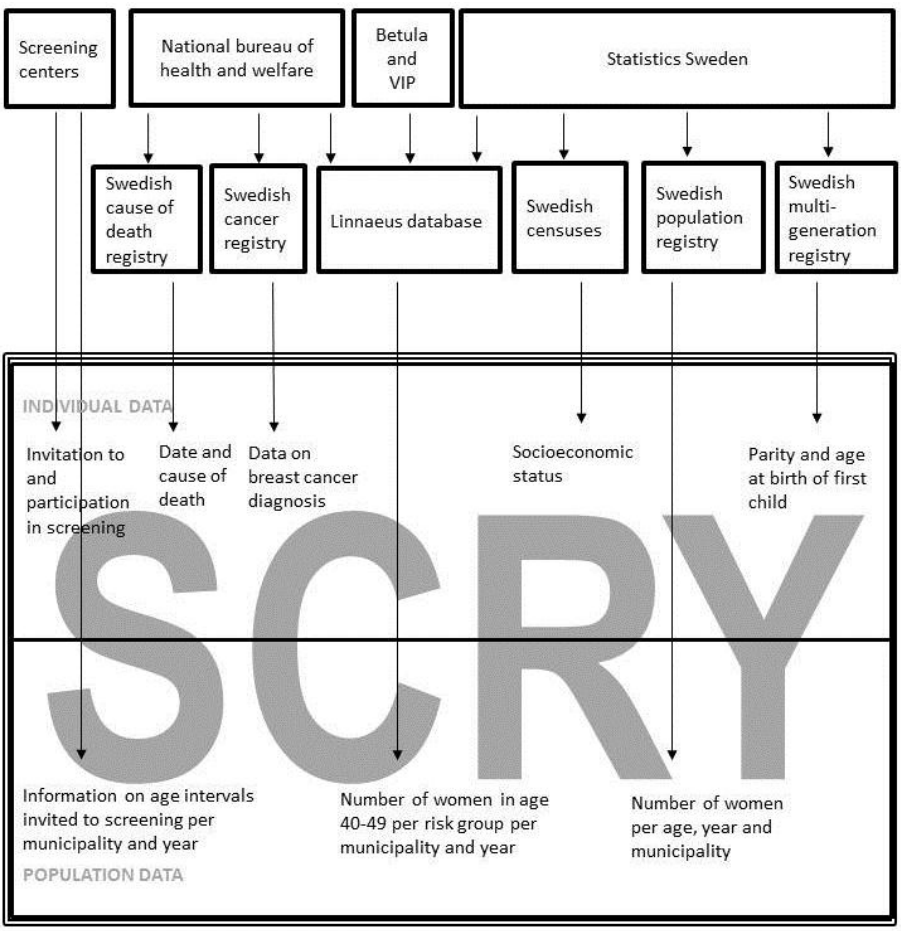

Figure 6: Sources and data level of included data in the SCRY database (VIP =Västerbotten Intervention Programme).

Comparability of study and control group

Contemporaneity

The person-years were similarly distributed over the follow-up in both the control and study group, with a larger proportion in later years, although there was a decrease in the control group in the last few years when more counties began to invite women in the age group 40-49 years (Figure 7). The person-year weighted median follow-up calendar years (1996) and the mean number of follow-up years (16 years) were similar in the control group and the study group.

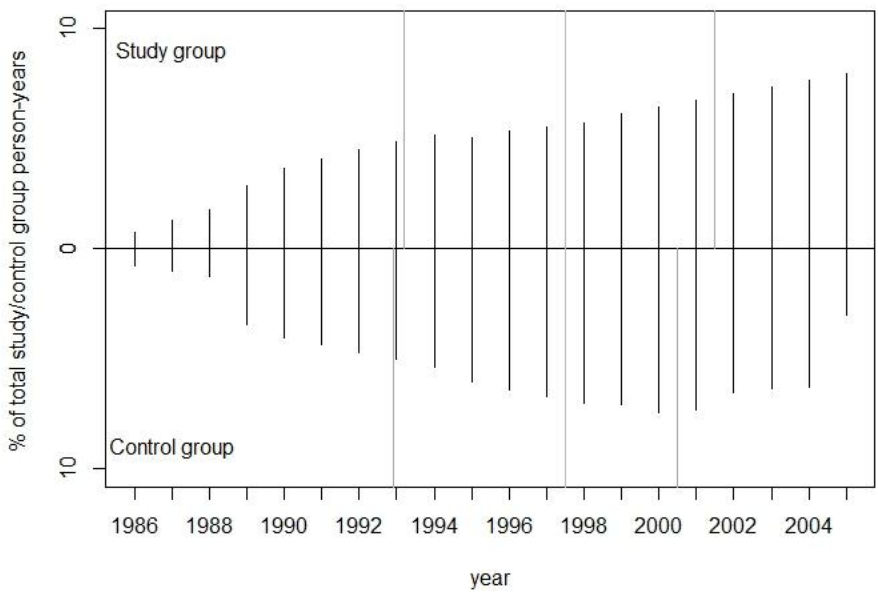

Figure 7: Distribution of person-years over time in control and study group. Grey lines represent 25%, 50% and 75% of cumulative person-year.

Reference period

To further assure the comparability of study and control group, and to allow for adjustment for differences if present, a reference period was defined that included the same areas as the study period but during the period preceding the start of the regional screening programs. The two reference period groups included all women age 40-49 years for the areas in the study and control group between 1970 and 1985. Five areas conducted pre-1986 screening (four randomized controlled trials and one pilot study) and were therefore excluded. Underlying difference in breast cancer

mortality (study I) and breast cancer incidence (study IV) was estimated as RRs for the reference period.

Stockholm

Although both urban and rural areas were represented in study and control group, the largest city in Sweden was included in one of the control areas (Stockholm county). It made out more than a third of the control group person-years. Stockholm may differ from the rest of Sweden both in terms of life style (e.g. higher average age at birth of first child) and screening choises (i.e. opportunistic screening). Effectiveness estimates were made both including and excluding Stockholm.

Lead time for breast cancer cases and deaths

Lead time for breast cancer is the time from detection through screening to the time when the cancer would have started showing symptoms and showed up clinically. The sojourn time is the maximum lead time (Figure 8) [89]. A study based on data from the UK trial estimated mean sojourn time for the age group 40-49 years to be 0.8 years for invasive breast cancer [64]. Estimates for the age group based on Swedish and Canadian trial data and based on Swedish trial data were 1.7 years [90] and 2.4 years [63] respectively. In study IV lead time for the age group 40-49 years was estimated to be 1.2 years.

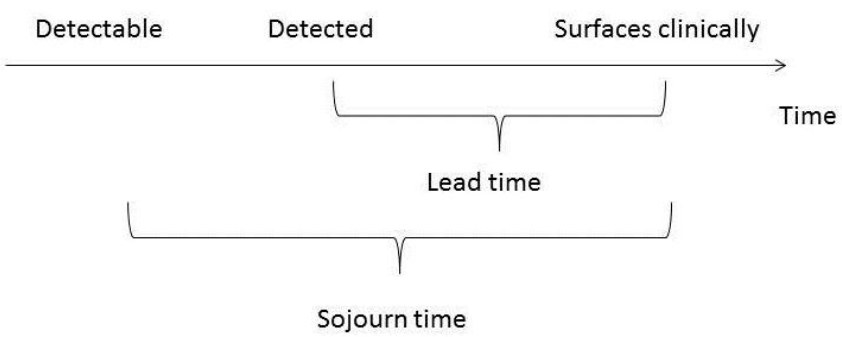

Figure 8. Illustration of sojourn and lead times.

The lead times specifically for breast cancer deaths may be shorter than for all breast cancer cases as a large proportion of the cancers leading to

death may be those not detected in screening or detected late although screened. Based on Swedish trial data the lead time for breast cancer deaths was estimated to be 1 year [91], in study I, it was estimated to be 1 month.

In study I, effectiveness estimates were made adjusted for different lead times in a sensitivity analysis but the main effectiveness estimates were not adjusted for lead time. (Lead time adjustment reduced the estimates.) The subgroup specific effectiveness estimates in study II were not adjusted for lead time since the main aim was to compare estimates between risk groups and since lead time adjustment did not have a great impact in study I. For the overdiagnosis estimates of study IV, lead time adjustment was crucial.

Overdiagnosis of subsequent screening

Overdiagnosis was estimated using breast cancer incidence from the same control and study group as for the effectiveness estimates with a few modifications. Screening areas where only part of the age interval 40-49 years were invited to screening, corresponding to 10% of the original study group (of study I), were not included in the study group in study IV. The person-years for each area was a sum of the population from age 40 to 49 years for all follow-up years. Due to the lead time related accumulation of diagnosis at start of screening, the first years of follow-up and youngest ages (40-41 years) were excluded from both the study and control groups, i.e. overdiagnosis estimates were made for subsequent screening. Lead time bias related to the breast cancer incidence trend was also adjusted for in study IV.

Absolute effectiveness/Number needed to screen

Combining relative effectiveness estimates and breast cancer mortality rates facilitates estimation of absolute effectiveness, e.g. as estimates of Number Needed to Screen to save a life (NNS). NNS can be expressed as the ratio of number of invited women to number of lives saved or equally, the inverse of the difference between the breast cancer mortality without screening (M_g) and the expected breast cancer mortality with screening M_g*RR_g, where RR_g is the relative effectiveness estimate of screening for the group.

Estimates were made of the relationship between the breast cancer mortalities for two groups that would result in equal NNS. NNS is equal in two groups when the ratio of the group specific breast cancer mortalities equals the ratio of the group specific percentage breast cancer mortality reduction ($1-RR_g$) with reverse group order, i.e. $M_1/M_2=(1-RR_2)/(1-RR_1)$.

Results

The SCRY database include 619 and 1205 breast cancer deaths in the control and study group respectively, among those invited in the study group and non-screened in the control group. A large number e.g. compared to the randomised controlled trials. (Figure 9).

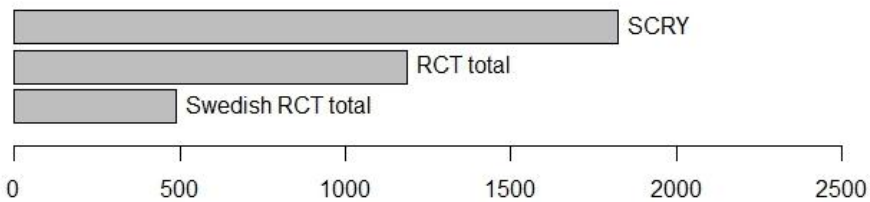

Figure 9: Number of breast cancer deaths for age 40-49 years at diagnosis in SCRY and in the Randomized Controlled Trials (RCT) [33,35-39,59].

For the analysis of effectiveness, there were 6.99 and 8.84 million person-years in total in the study and control groups, respectively (Table 5), and the minimum proportion of person-years in a sub-group was 11% for both study and control group. The total number of breast cancer deaths was 619 for the exposure invitation and 523 for attendance in the study group and 1205 in the control group. No sub-group included less than 10% and 14% of the breast cancer deaths in study and control groups, respectively. (Excluding the SES group self-employed and farmer which was not of key interest.)

For the analysis of overdiagnosis the number of person-years was lower than the effectiveness total (3.8 and 5.2 in study and control group respectively) as only person-years for age 40-49 years were included. The number of breast cancer cases was 6047 and 7790 in the study and control group respectively.

In study III, a statistical method for adjusting for non-compliance and contamination was developed where subgroup differences in effectiveness on dichotomous outcomes can be modelled. Both underlying risk of an outcome (e.g. breast cancer death) and the effectiveness of a treatment on an outcome (e.g. effectiveness of mammography screening) can be estimated using the method.

Table 5. Breast cancer deaths and person-years in age 40-49 years in total and in subgroups (Linneaus database used for subgroup person-year calculations).

	Breast cancer deaths		Person-years	
	Study group (Invited/Attending)	Control group	Study group	Control group
Age				
40-49	619 / 523	1205	6,994,421	8,843,852
40-44	247 / 217	485	5,041,040	6,567,101
45-49	372 / 306	720	5,071,256	6,211,523
SES				
High	276 / 242	582	2,937,657	4,156,610
Low	217 / 192	319	2,657,880	2,741,594
Parity				
0	67 / 51	204	791,931	1,274,075
1	102 / 83	251	1,016,252	1,427,864
≥2	449 / 390	750	5,186,238	6,141,913
Age at birth of first child				
0-19	112 / 87	165	909,275	972,824
20-29	370 / 323	643	4,336,541	5,129,434
≥30	69 / 63	193	1,049,163	1,768,770

Reference period

Reference period breast cancer mortality RR, estimated at 0.94 [95% CI 0.85-1.05] in study I, was not statistically significant but the reference period breast cancer incidence RR was significant, estimated at 0.92 [95% CI 0.88-0.97] in study IV. The main overdiagnosis estimates, but not the main effectiveness estimates, were adjusted for the underlying difference.

Main results

The main results of the thesis are summarised in Table 6. Effectiveness for age 40-49 years was estimated at 26% for women invited to and 29% for women attending mammography screening for age 40-49 years. Effectiveness appeared higher in age 45-49 compared to 40-44 years, similar between subgroups based on SES and age at birth of first child and higher for lower parity. None of the subgroup differences or trends, however, were statistically significant. There was no statistically significant overdiagnosis of subsequent screening for age 40-49 years.

Table 6. Estimates of effectiveness (study I and study II), for invited women and attending women, and overdiagnosis (study IV), for all breast cancer and invasive breast cancer, of mammography screening in age 40-49 years. Rate Ratio (RR) and 95% Confidence Interval (CI). P-values for trend with method developed in study III.

	Effectiveness		Overdiagnosis	
	Invited	**Attending**	**All cancers**	**Invasive cancers**
Age				
40-49	0.74 (0.66-0.83)	0.71 (0.62-0.80)	1.01 (0.94-1.08)	0.95 (0.88-1.02)
40-44	0.83 (0.70-1.00)	0.82 (0.67-1.00)		
45-49	0.68 (0.59-0.78)	0.63 (0.54-0.75)		
SES				
High	0.74 (0.63-0.87)	0.72 (0.60-0.86)		
Low	0.81 (0.66-0.99)	0.79 (0.63-0.99)		
Parity				
0	0.62 (0.45-0.84)	0.55 (0.38-0.79)		
1	0.71 (0.54-0.92)	0.66 (0.49-0.90)		
≥2	0.80 (0.69-0.91)	0.77 (0.66-0.90)		
p-value		*0.14*		
Age at birth of first child				
0-19	0.77 (0.59-1.00)	0.72 (0.52-1.00)		
20-29	0.76 (0.65-0.88)	0.73 (0.62-0.89)		
≥30	0.77 (0.55-1.06)	0.75 (0.53-1.07)		
p-value		*0.97*		

When an adjustment was made for underlying breast cancer mortality difference the estimated RR in study I was 5-6 percentage points higher. When excluding Stockholm from the study group, the estimated RR was 3-4 percentage points lower. Excess mortality based estimates were similar to the main results of study I (which were based on underlying cause of death).

Parity

The estimated effectiveness for different parities in study II was lower for high parities. The method developed in study III gave similar results, both when assuming the relationship to be log-linear and when not (Figure 10). The estimated trend in study III was found to not be statistically significant (Table 6). The effectiveness estimate using the method developed in study III and assuming equal effectiveness for all parities (but still allowing for differences in underlying breast cancer mortality between parities) was similar to the effectiveness estimate of study I for the total age group 40-49 years. All effectiveness estimates made using the method developed in study III were lower than the estimates made in I and II.

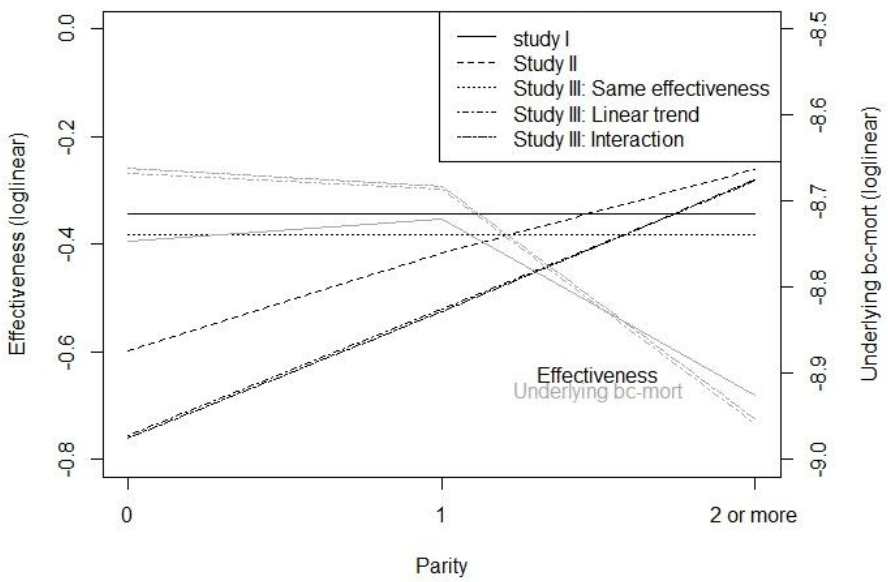

Figure 10. Estimates using the method developed in study III of underlying breast cancer mortality and effectiveness (assuming equal effectiveness, interaction and linear trend for parity, respectively) and effectiveness estimates from study I (total for age 40-49 years) and from study II (per parity). All estimates for women attending screening.

Absolute effectiveness / NNS

In Table 7, the breast cancer mortality ratios for which NNS was estimated to be equal for different age and risk groups are presented. E.g. if nulliparous women in age 40-49 years had a breast cancer mortality of 0.37 of that of women age 50-59 years (or inversely 2.71) the absolute effectiveness of

screening in terms of NNS would be (approximately) equal for the two groups.

The RR estimates for age 50-59 years (0.86 [95% CI 0.75-0.99]) and 60-69 years (0.68 [95% CI 0.54-0.87]) were taken from the overview by Nelson et al from 2009 [47]. The RR estimates for age 40-49 years and 45-49 years are from study I, and the RR for subgroups of age 40-49 years by parity, age at birth of first child and SES are from study II, for women invited to screening.

The presented breast cancer mortality ratios are intended as an illustration of absolute effectiveness, rather than exact estimates.

Table 7. Breast cancer mortality ratio (column:row) that gives equal NNS in groups based on age and subgroups (in age group 40-49 years) at high breast cancer risk.

	40-49				45-49	50-59	60-69
	Total	**Nulli-parous**	**≥30 years at 1st birth**	**High SES**			
40-49							
Total	-	0.68	1.13	1	0.81	1.86	0.81
Nulliparous	1.46	-	1.65	1.46	1.19	2.71	1.19
≥30 years at 1st birth	0.88	0.61	-	0.88	0.72	1.64	0.72
High SES	1	0.68	1.13	-	0.81	1.86	0.81
45-49	1.23	0.84	1.39	1.23	-	2.29	1
50-59	0.54	0.37	0.61	0.54	0.44	-	0.44
60-69	1.23	0.84	1.39	1.23	1	2.29	-

Discussion

In brief, breast cancer mortality was estimated to be 29% lower for women in age 40-49 years who partook in mammography screening and 26% lower for invited compared to the control group for age 40-49 years, i.e. similar to that of women age 50-69 years [29]. In addition, there appeared to be no overdiagnosis of subsequent screening for age 40-49 years. Effectiveness of screening did not differ with statistical significance between subgroups based on parity, age at brith of first child and SES respectively, although there was a tendency towards higher estimated effectiveness in lower parities compared to higher parities. Estimated effectiveness was higher in the age group 45-49 years compared to 40-44 years, but not with statistical significance.

A contemporaneous and comprehensive database

The SCRY database includes a large and recent population of young women in comparison to the randomized controlled trials, most of which took place before the start of the service screening programs in the 1980s. The exception is the UK trial, which included women age 39-41 years in 1991-1997 invited until age 48 (i.e. 2005 at latest) [34].

As SCRY includes relatively recent years, breast cancer care as well as the characteristics of the population are more comparable to the current situation. Breast cancer treatment has continuously improved over the studied period [92]. Regarding screening technology the transition in later years to digital mammography might mean that screening today has higher detectability for women age 40-49 years than it had during the studied period [76-78].

Since the study and control group in SCRY were contemporaneous, changes over time in breast cancer risk factors, care, incidence and mortality should not have affected their comparability. However, although a natural experiment, there may have been differences between the control group and study group. To verify that the study and control group were comparable the underlying breast cancer mortality difference was estimated using a reference period before the start of the screening programs. Screening activities during the reference period disqualified some areas, corresponding to 18 % of the population, from inclusion.

The size of SCRY in combination with the detailed and linkable Swedish registries and databases, allowed for analyses on a subgroup level in study II.

The SCRY cohort does not have the standard cohort design in the sense that for women without a breast cancer diagnosis the information is not actually individual but rather on population sizes (by age, screening area and calendar year). No further information on the general population of women was required to make the estimates in study I. In study II, however, information on the distribution of risk factors among the women in general in the cohort was used, but not on an individual level. The advantage of the SCRY cohort design was its cost-effectiveness since specific estimates could be made given limited data gathering. The workload was low enough for the screening centers to themselves supply the screening exposure information (i.e. for breast cancer deaths in the study group).

Considerations of estimation and adjustment

With the help of screening centers throughout Sweden individual information on exposure was collected. Adjustment for exposure, in terms of invitation and participation, was made in study I and study II, thus avoiding biased estimates. Adjustment for participation is especially advantageous in subgroup analysis based on risk factors such as SES, where compliance may influence screening outcomes. Bias due to opportunistic screening in the control group could not be adjusted for, leading to potentially underestimated effectiveness in study I and study II.

The method used in study I, study II and further developed in study III can be used for exposure adjusted effectiveness adjustment. Both proportion exposed and bias effect is considered. In the SCRY example there are several potential sources of bias related to exposure, not all true self-selection (i.e. when the choice of the woman determines exposure) but necessary to adjust for due to potential differences in underlying breast cancer mortality compared to the rest of the study group (for non-compliance) or control group (for contamination).

The method developed in study III does not allow for modelling of potential differences in non-compliance and contamination between subgroups and this limitation of the method is an area for future development. Compared to the estimates in study I and study II, estimates made using the method developed in study III were overall lower. This may be due to the assumption on non-compliance and contaminaton.

The estimated effectiveness based on excess mortality in study I was very similar to the estimates based on underlying cause of death. Although the accuracy of the Swedish cause of death registry has been evaluated and

confirmed [93], these results further validate the estimates as excess mortality calculations are not dependent on cause of death.

In study I, effectiveness was also estimated both including and excluding Stockholm. Estimated RR was lower when excluding Stockholm from the study group. There may be a higher representation of women of low parity and high age at birth of first child in urban areas such as Stockholm and these are high risk groups for breast cancer, in terms of incidence and possibly also mortality. A higher breast cancer mortality in Stockholm, may lead to higher, but not lower, RR estimates when excluding Stockholm. The potential opportunistic screening in Stockholm, on the other hand, might dilute the effectiveness estimate.

Overdiagnosis was estimated excluding the first screening round, during which the detection of both prevalent and incident breast cancers can be expected to increase the incidence temporarily. The estimated for subsequent screening therefore reflect a potential persisting overdiagnosis that may come of screening, rather than a temporary accumulation.

Overdiagnosis, but not the main effectiveness estimates, were adjusted for underlying difference in breast cancer incidence and mortality, respectively. There is an inconsequence in adjusting for underlying difference in study IV but not the study I, as the two studies are both based on the SCRY database and a difference in incidence may indicate a difference in mortality. However adjusting for a non-significant difference (as in study I) is questionable as well. As there are more breast cancer cases than breast cancer deaths the estimate in study IV has greater power than the estimate in paper I. Adjusting for underlying difference increases the confidence intervals since the uncertainty in the reference period is included.

The main effectiveness measure in study I and study II was the ratio of the refined breast cancer mortality rates in the study and control group, but study I also estimated NNS, at 1252. This estimate however may have been inflated by the limitation on follow-up. In the thesis frame text estimates were made of the breast cancer mortality ratios where NNS was equal in two groups. The formula for these two NNS - the ratio of women invited to lives saved - was the same but the calculations differed in the sense that in study I an exact number was estimated and thus number of screening rounds was taken into consideration. It is worth noting that absolute effectiveness in terms of NNS does not reflect the differences in life years or quality adjusted life years between saving the lives of younger and older women.

Screening women age 40-49 years or not

Younger women have a lower breast cancer incidence and mortality and on average a higher breast density, making mammography images harder to interpret. It is therefore sensible to have a lower age limit for invitation to mammography service screening. The age at which screening should start is less obvious. Although the debate often centres on age 40 or 50 years there is no biological reason to single out these specific ages and screening could just as easily start at some similar age (e.g. 51 years which is the average age of menopause). Some screening programs invite women from age 45 years. In study I the estimated effectiveness for age 45-49 years was higher than for age 40-44 years, although not with statistical significance, and the increase in breast cancer incidence temporarily levels off somewhat around age 45-55 years.

The benefit of mammography screening is usually measured as reduction in breast cancer mortality although some have argued for reduction in total mortality as a better measure of the worth of screening. In study I effectiveness for age 40-49 years was estimated at 26% for invited and 29% for attenders (five to six percentage units lower when adjusted for underlying breast cancer mortality difference). These results agree with the UK trial - the most recent randomized controlled trial on mammography screening, specifically aimed at age 40-49 years - which showed a 17% non-significant breast cancer mortality reduction, and with several of the meta-analyses of the randomized controlled trials estimating screening effect at 15-20 %. The estimate of the UK trial and some meta-analysis are statistically non-significant; however in comparison with SCRY the number of breast cancer deaths included are smaller and so far only results from 10 years of follow-up have been published from the UK trial, which is a short follow-up considering the invitation age (39-41 years).

Regarding the potential harms of mammography screening for age 40-49 years, false-positives can be expected to be more common than in older women. However, in Sweden today caregivers strive to keep the invasiveness of the methods commonly used for diagnosis and waiting times till diagnosis to a minimum. Overdiagnosis is another much debated potential harm. In study IV no statistically significant overdiagnosis of subsequent screening was found for age 40-49 years, a finding that is in accordance with the results of a 2007 systematic review [94] and estimates based on the UK trial [64]. How to interpret overdiagnosis in age 40-49 years is complicated due to the presence of screening from age 50, as dormant breast cancers, unless self-healing, will eventually be detected. However, a lack of statistically significant overdiagnosis in age 40-49 years renders this point moot.

For areas where inviting the entire age group 40-49 years to screening is not possible, screening only women of higher risk in this age interval may be considered. Therefore, screening in these risk groups need be evaluated.

High-risk groups are often identified based on breast cancer incidence risk, although high incidence does not always equate to high mortality. Furthermore, for mortality to be reduced, the screening tool must be effective for the high (mortality) risk group in question. To evaluate screening, absolute effectiveness (i.e. the combination of mortality and mortality reduction) can be estimated. In this thesis, the importance of considering the absolute effectiveness was illustrated through NNS comparisons with age groups 50-59 and 60-69 years. Breast cancer mortality of breast cancer diagnosed in age 40-49 years may be approximated with breast cancer mortality for women in age group 45-55 years. The breast cancer mortality is less than twice as high in age group 60-64 years as in age group 50-54 years in Sweden (Table 8).

Table 8. Breast cancer mortality rate per 100 000 women by 5-year age group (starting with age 40-44 years) in 2009-2012 in Sweden [4].

Age group	Breast cancer mortality
40-44	10.18
45-49	20.08
50-54	30.07
55-59	36.65
60-64	50.44
65-69	59.76
70-74	71.58
75-79	92.78
80-84	119.39
≥85	178.77

Given the effectiveness estimates of study I and Nelson et al [47], NNS appears to be similar or higher for the 40-49 age group compared to the 50-59 year age group (as 36.65 < 1.86*20.08 and 50.44 < 1.86*30.07). Also age group 45-49 year appear to have similar NNS as age group 50-59 years (as 36.65 < 2.29*20.08 and 50.44 < 2.29*30.07). Compared to age group 60-69 years, age group 40-49 years (and 40-45 years) appear to have lower NNS. Nulliparous women in age group 40-49 years would have comparable NNS as women in age group 50-59 years, assuming they have the same breast cancer mortality as women 40-49 in general (as 36.65 < 2.71*20.08 and 50.44 < 2.71*30.07). These approximations are rough, and mainly intended as illustrations.

It has been suggested that women with dense breasts and relatives with breast cancer at an early age would be well suited for high-risk screening and estimating effectiveness of screening for these groups of women is a future area of interest. Another potential area for future study is the intertwined nature of risk factors, since e.g. high parity may be related to low SES and low age at birth of first child, and absolute effectiveness may be different for groups of women with combinations of high risk factors.

Even if absolute effectiveness is estimated to be sufficiently large, screening only certain women based on risk factors may be ethically and practically challenging. Ethical issues to consider include the fundamental concept of equal care for all and how to translate that into the reality of subgroup selection. A practical matter to consider is that the access to mammography screening in many countries is such a sensitive issue that the turnout may not be as intended. (E.g. non-invited women in the age group 40-49 years may choose to seek out screening.)

Conclusion on screening of women in the age group 40-49 years

The findings of this thesis indicates that invitation to mammography screening of women age 40-49 years is justified. For countries where 40 years is not a feasible lower age limit, 45 years may be an alternative. Only inviting women age 40-49 years at higher risk may also be an option, but effectiveness in relation to risk factors and combinations of risk factors requires further research.

Conclusions

- The estimated exposure adjusted relative effectiveness of mammography screening for women in age 40 to 49 years,

    - was for the total age group 40 to 49 years comparable to the age group 50 to 69 years and;

    - did not differ with statistical significance between groups based on the breast cancer risk factors parity, age at birth of first child and socio-economic status for age group 40 to 49 years.

- The new statistical model allows for comparison and testing of differences and trends in estimated effectiveness for subgroups adjusted for noncompliance and contamination.

- There was no statistically significant overdiagnosis from subsequent screening for the age group 40-49 years.

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Appendix

Hessian for interaction and linear model

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\begin{bmatrix}
\frac{\partial^2 L}{\partial \lambda^2} & \frac{\partial^2 L}{\partial \lambda \partial \lambda_1} & \frac{\partial^2 L}{\partial \lambda \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \lambda \partial \beta} & \frac{\partial^2 L}{\partial \lambda \partial \beta_1} & \frac{\partial^2 L}{\partial \lambda \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \lambda \partial \eta} & \frac{\partial^2 L}{\partial \lambda \partial \zeta} \\
\frac{\partial^2 L}{\partial \lambda_1 \partial \lambda} & \frac{\partial^2 L}{\partial \lambda_1^2} & \frac{\partial^2 L}{\partial \lambda_1 \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \lambda_1 \partial \beta} & \frac{\partial^2 L}{\partial \lambda_1 \partial \beta_1} & \frac{\partial^2}{\partial \lambda_1 \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \lambda_1 \partial \eta} & \frac{\partial^2 L}{\partial \lambda_1 \partial \zeta} \\
\frac{\partial^2 L}{\partial \lambda_2 \partial \lambda} & \frac{\partial^2 L}{\partial \lambda_2 \partial \lambda_1} & \frac{\partial^2 L}{\partial \lambda_2^2} & \cdots & \frac{\partial^2 L}{\partial \lambda_2 \partial \beta} & \frac{\partial^2 L}{\partial \lambda_2 \partial \beta_1} & \frac{\partial^2 L}{\partial \lambda_2 \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \lambda_2 \partial \eta} & \frac{\partial^2 L}{\partial \lambda_2 \partial \zeta} \\
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\frac{\partial^2 L}{\partial \beta \partial \lambda} & \frac{\partial^2 L}{\partial \beta \partial \lambda_1} & \frac{\partial^2 L}{\partial \beta \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \beta^2} & \frac{\partial^2 L}{\partial \beta \partial \beta_1} & \frac{\partial^2 L}{\partial \beta \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \beta \partial \eta} & \frac{\partial^2 L}{\partial \beta \partial \zeta} \\
\frac{\partial^2 L}{\partial \beta_1 \partial \lambda} & \frac{\partial^2 L}{\partial \beta_1 \partial \lambda_1} & \frac{\partial^2 L}{\partial \beta_1 \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \beta_1 \partial \beta} & \frac{\partial^2 L}{\partial \beta_1^2} & \frac{\partial^2 L}{\partial \beta_1 \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \beta_1 \partial \eta} & \frac{\partial^2 L}{\partial \beta_1 \partial \zeta} \\
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\frac{\partial^2 L}{\partial \eta \partial \lambda} & \frac{\partial^2 L}{\partial \eta \partial \lambda_1} & \frac{\partial^2 L}{\partial \eta \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \eta \partial \beta} & \frac{\partial^2 L}{\partial \eta \partial \beta_1} & \frac{\partial^2 L}{\partial \eta \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \eta^2} & \frac{\partial^2 L}{\partial \eta \partial \zeta} \\
\frac{\partial^2 L}{\partial \zeta \partial \lambda} & \frac{\partial^2 L}{\partial \zeta \partial \lambda_1} & \frac{\partial^2 L}{\partial \zeta \partial \lambda_2} & \cdots & \frac{\partial^2 L}{\partial \zeta \partial \beta} & \frac{\partial^2 L}{\partial \zeta \partial \beta_1} & \frac{\partial^2 L}{\partial \zeta \partial \beta_2} & \cdots & \frac{\partial^2 L}{\partial \zeta \partial \eta} & \frac{\partial^2 L}{\partial \zeta^2}
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\begin{bmatrix}
\sum_{k=0}^{n} -M_{0k}-M_{1k}-B_{0k}-B_{1k} & -M_{01}-M_{11}-B_{01}-B_{11} & -M_{02}-M_{12}-B_{02}-B_{12} & \dots & \sum_{k=0}^{n} -B_{0k}-B_{1k} & -B_{01}-B_{11} & -B_{02}-B_{12} & \dots & \sum_{k=0}^{n} C_{1k}-D1k & \sum_{k=0}^{n} C_{0k}-D_{0k} \\
-M_{01}-M_{11}-B_{01}-B_{11} & -M_{01}-M_{11}-B_{01}-B_{11} & 0 & \dots & -B_{01}-B_{11} & -B_{01}-B_{11} & 0 & \dots & C_{11}-D_{11} & C_{01}-D_{01} \\
-M_{02}-M_{12}-B_{02}-B_{12} & 0 & -M_{02}-M_{12}-B_{02}-B_{12} & \dots & -B_{02}-B_{12} & 0 & -B_{02}-B_{12} & \dots & C_{12}-D_{12} & C_{02}-D_{02} \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\sum_{k=0}^{n} -B_{0k}-B_{1k} & -B_{01}-B_{11} & -B_{02}-B_{12} & \dots & \sum_{k=0}^{n} -B_{0k}-B_{1k} & -B_{01}-B_{11} & -B_{02}-B_{12} & \dots & \sum_{k=0}^{n} -D_{1k} & \sum_{k=0}^{n} -D_{0k} \\
-B_{01}-B_{11} & -B_{01}-B_{11} & 0 & \dots & -B_{01}-B_{11} & -B_{01}-B_{11} & 0 & \dots & -D_{11} & -D_{01} \\
-B_{02}-B_{12} & 0 & -B_{02}-B_{12} & \dots & -B_{02}-B_{12} & 0 & -B_{02}-B_{12} & \dots & -D_{12} & -D_{02} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\sum_{k=0}^{n} C_{1k}-D1k & C_{11}-D_{11} & C_{12}-D_{12} & \dots & \sum_{k=0}^{n} -D_{1k} & -D_{11} & -D_{12} & \dots & \sum_{k=0}^{n} -\frac{D_{10k}}{(1-\eta)^2}-\frac{D_{11k}}{\eta^2} & 0 \\
\sum_{k=0}^{n} C_{0k}-D0k & C_{01}-D_{01} & C_{02}-D_{02} & \dots & \sum_{k=0}^{n} -D_{0k} & -D_{01} & -D_{02} & \dots & 0 & \sum_{k=0}^{n} -\frac{D_{00k}}{(1-\zeta)^2}-\frac{D_{01k}}{\zeta^2}
\end{bmatrix}
$$

$M_{0k} = exp(\lambda + \lambda_k)(1-\eta)N_{1k}$, $M_{1k} = exp(\lambda + \lambda_k)(1-\zeta)N_{0k}$, $B_{0k} = exp(\lambda + \lambda_k + \beta + \beta_k)\eta N_{1k}$, $B_{1k} = exp(\lambda + \lambda_k + \beta + \beta_k)\zeta N_{0k}$,
$C_{0k} = exp(\lambda + \lambda_k)N_{0k}$, $C_{1k} = exp(\lambda + \lambda_k)N_{1k}$, $D_{0k} = exp(\lambda + \lambda_k + \beta + \beta_k)N_{0k}$, $D_{1k} = exp(\lambda + \lambda_k + \beta + \beta_k)N_{1k}$

$$
\begin{bmatrix}
\sum_{k=0}^{n} -M_{0k}-M_{1k}-B_{0k}-B_{1k} & -M_{01}-M_{11}-B_{01}-B_{11} & -M_{02}-M_{12}-B_{02}-B_{12} & \dots & \sum_{k=0}^{n} -B_{0k}-B_{1k} & \sum_{k=1}^{n} -B_{0k}-B_{1k} & \sum_{k=0}^{n} C_{1k}-D1k & \sum_{k=0}^{n} C_{0k}-D_{0k} \\
-M_{01}-M_{11}-B_{01}-B_{11} & -M_{01}-M_{11}-B_{01}-B_{11} & 0 & \dots & -B_{01}-B_{11} & -B_{01}-B_{11} & C_{11}-D_{11} & C_{01}-D_{01} \\
-M_{02}-M_{12}-B_{02}-B_{12} & 0 & -M_{02}-M_{12}-B_{02}-B_{12} & \dots & -B_{02}-B_{12} & -B_{02}-B_{12} & C_{12}-D_{12} & C_{02}-D_{02} \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\
\sum_{k=0}^{n} -B_{0k}-B_{1k} & -B_{01}-B_{11} & -B_{02}-B_{12} & \dots & \sum_{k=0}^{n} -B_{0k}-B_{1k} & \sum_{k=1}^{n} -B_{0k}-B_{1k} & \sum_{k=0}^{n} -D_{1k} & \sum_{k=0}^{n} -D_{0k} \\
\sum_{k=1}^{n} -B_{0k}-B_{1k} & -B_{01}-B_{11} & -B_{02}-B_{12} & \dots & \sum_{k=1}^{n} -B_{0k}-B_{1k} & \sum_{k=1}^{n} -B_{0k}-B_{1k} & \sum_{k=1}^{n} -D_{1k} & \sum_{k=1}^{n} -D_{0k} \\
\sum_{k=0}^{n} C_{1k}-D1k & C_{11}-D_{11} & C_{12}-D_{12} & \dots & \sum_{k=0}^{n} -D_{1k} & \sum_{k=1}^{n} -D_{1k} & \sum_{k=0}^{n} -\frac{D_{10k}}{(1-\eta)^2}-\frac{D_{11k}}{\eta^2} & 0 \\
\sum_{k=0}^{n} C_{0k}-D0k & C_{01}-D_{01} & C_{02}-D_{02} & \dots & \sum_{k=0}^{n} -D_{0k} & \sum_{k=1}^{n} -D_{0k} & 0 & \sum_{k=0}^{n} -\frac{D_{00k}}{(1-\zeta)^2}-\frac{D_{01k}}{\zeta^2}
\end{bmatrix}
$$

$M_{0k} = exp(\lambda + \lambda_k)(1-\eta)N_{1k}$, $M_{1k} = exp(\lambda + \lambda_k)(1-\zeta)N_{0k}$, $B_{0k} = exp(\lambda + \lambda_k + \beta + \beta_1 X_k)\eta N_{1k}$, $B_{1k} = exp(\lambda + \lambda_k + \beta + \beta_1 X_k)\zeta N_{0k}$,
$C_{0k} = exp(\lambda + \lambda_k)N_{0k}$, $C_{1k} = exp(\lambda + \lambda_k)N_{1k}$, $D_{0k} = exp(\lambda + \lambda_k + \beta + \beta_1 X_k)N_{0k}$, $D_{1k} = exp(\lambda + \lambda_k + \beta + \beta_1 X_k)N_{1k}$

Where, $\exp(\lambda)$ is the underlying risk of the outcome in subgroup 0, $\exp(\lambda + \lambda_k)$ is the underlying risk of the outcome in subgroup k, $\exp(\beta)$ is the effect of treatment in subgroup 0, $\exp(\beta + \beta_k)$ is the effect of treatment in subgroup k, η is the product of the selection bias related to non-compliance and the proportion treated in the study group, ζ is the product of the selection bias related to contamination and the proportion treated in the control group, and X_k is a covariate related to increasing subgroup number so that $\beta_k = \beta_1 X_k$.