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Original papers

I. **Bordás P, Jonsson H, Nyström L, Lenner P.** Interval cancer incidence and episode sensitivity in the Norrbotten Mammography Screening Programme. *J Med Screen* 2009; 16: 39-45.

II. **Bordás P, Jonsson H, Nyström L, Péntek Z, Lenner P.** Radiological review of interval cancer in the Norrbotten Mammography Screening Programme, Sweden. *In manuscript*.

III. **Bordás P, Jonsson H, Nyström L, Cajander S, Lenner P.** Early breast cancer deaths in women aged 40-74 years diagnosed during the first five years of organised mammography service screening in north Sweden. *Breast* 2004; 13:276-283.

IV. **Bordás P, Jonsson H, Nyström L, Lenner P.** Survival from invasive breast cancer among interval cases in the mammography screening programmes of northern Sweden. *Breast* 2007; 16:47-54.

V. **Jonsson H, Bordás P, Wallin H, Nyström L, Lenner P.** Service screening with mammography in northern Sweden. Effects on breast cancer mortality - an update. *J Med Screen* 2007; 14: 84-93.

Abbreviations

ACR	American College of Radiology
ACS	American Cancer Society
BI-RADS	Breast imaging and reporting data system
BC	Breast cancer
BSE	Breast self-examination
CBE	Clinical breast examination
EM	Excess mortality
HR	Hazard ratio
IARC	International Agency for Research on Cancer
IC	Interval cancer
MLT	Mean lead time
MQSA	Mammography Quality Standards Act
MST	Mean sojourn time
NBHW	National Board of Health and Welfare
NCI	National Cancer Institute
NSBCG	Northern Sweden Breast Cancer Group
NMSP	Norrbotten Mammography Screening Programme
NNS	Number needed to screen
NORMA	Northern Sweden Mammography Screening Group
RR	Relative risk

SDC	Screen-detected cancer
UCD	Underlying cause of death
USPSTF	U.S. Preventive Services Task Force
WHO	World Health Organization

Abstract

Service screening with mammography was implemented in Northern Sweden between 1989 and 1998, covering 190,000 women aged 40-74 years constituting the target population in the area.

The aim of our thesis was the evaluation of mammography screening in Northern Sweden with special focus on selected screening performance indicators and on the disease outcome

We analysed interval cancer (IC) incidence and episode sensitivity in the Norrbotten Mammo-graphy Screening Programme (NMSP) for the period 1989-2002. An overall IC rate at 11/10,000 and IC rate ratio at 38% was found and an episode sensitivity was estimated at 62-73%, in concert with reference values of the European guidelines.

Radiological classification of the IC cases in three rounds of the NMSP showed that true, occult, missed and minimal signs IC, were present in 48%, 10%, 14% and 28% of the cases. Our results are within the range of published data.

We analysed early death from breast cancer (n=342) in Northern Sweden during the first five years of service screening. Most fatal cases were advanced and incurable on diagnosis. In a few screen-detected cases with favourable prognostic factors the fatal outcome was unexpected.

We estimated breast cancer survival by detection mode in 5120 women diagnosed with invasive breast cancer. We found a significantly favourable survival among IC cases compared to cases among uninvited.

We studied breast cancer mortality in relation to mammography screening. Our findings indicated a long-term reduction of breast cancer mortality by 26-30% among women invited to screening and by 31-35% among women screened compared to not screened.

We conclude from our evaluation of the mammography screening in Northern Sweden that women benefited from this public health intervention in form of improved survival and reduced mortality.

Keywords

Mammography, screening, sensitivity, interval cancer, survival, mortality

Sammanfattning (Abstract in Swedish)

Hälsokontroll med mammografi (service screening) implementerades i Norra regionen mellan 1989 och 1998 då den blivit helteckande för målgruppen bestående av 190,000 kvinnor 40-74 år bosatta i regionen.

Syftet med vår avhandling var utvärederingen av mammografiscreeningens effekt i Norra regionen med fokus på utvalda prestationsindikatorer och sjukdomsutfall.

Vi har analyserat intervallcancer incidens (förekomst av cancerfall mellan två hälsokontroller bland screeningdeltagare) och episod sensitivitet (känslighet) i Norrbottens mammografiscreening program (NMSP) för perioden 1989-2002. Den totala intervallcancer frekvensen blev 11/10,000 och kvoten mellan intervallcancer och alla cancerfall upptäckta bland screeningdeltagare blev 0.38. Episod sensitiviteten skattades till mellan 62-73%. Våra resultat överensstämmer med de Europeiska rekommendationerna för mammografiscreening.

Vi har gjort en eftergranskning av röntgenbilderna av intervallcancer fallen i tre screeningomgångar av NMSP. Äkta (nytillkomna), ockult (fördolda), missade (felbedömda) och minimaltecken (ospecifikt utseende) intervallcancer fallen förekom i 48%, 10%, 14% och 28%.

Vi har analyserat tidig död på grund av bröstcancer (n=342) under hälsokontrollens första fem år. De flästa dödsfallen befann sig ett avancerat och obotbart skede vid diagnostillfället. I ett fåtal screeningupptäckta fall med gynsamma prognostiska faktorer den dödliga utgången var oväntat.

Vi har skattat överlevand enligt upptäcktssätt hos 5120 kvinnor med invasiv bröstcancer. Vi har konstaterat betydligt gynnsammare överlevnad hos intervallcancer fall jämfört med överlevnad bland icke-inbjudna kvinnor.

Vi har studerat bröstcancer dödlighet i relation till mammografiscreening. I studiegruppen ingick 109,000 kvinnor och i kontrollgruppen 77,000 kvinnor med en uppföljningstid om 11 år. Våra resultat tyder på en långsiktig minskning av dödligheten på grund av bröstcancer med 26-30% bland inbjudna och med 31-35% bland deltagare, jämfört med icke-screenade.

Sammanfattningsvis tyder vår utvärdering på nyttan av hälsokontrollen med mammografi i Norra reegionen i form av förbättrad överlevnad och minskad dödlighet.

Introduction

Screening principles

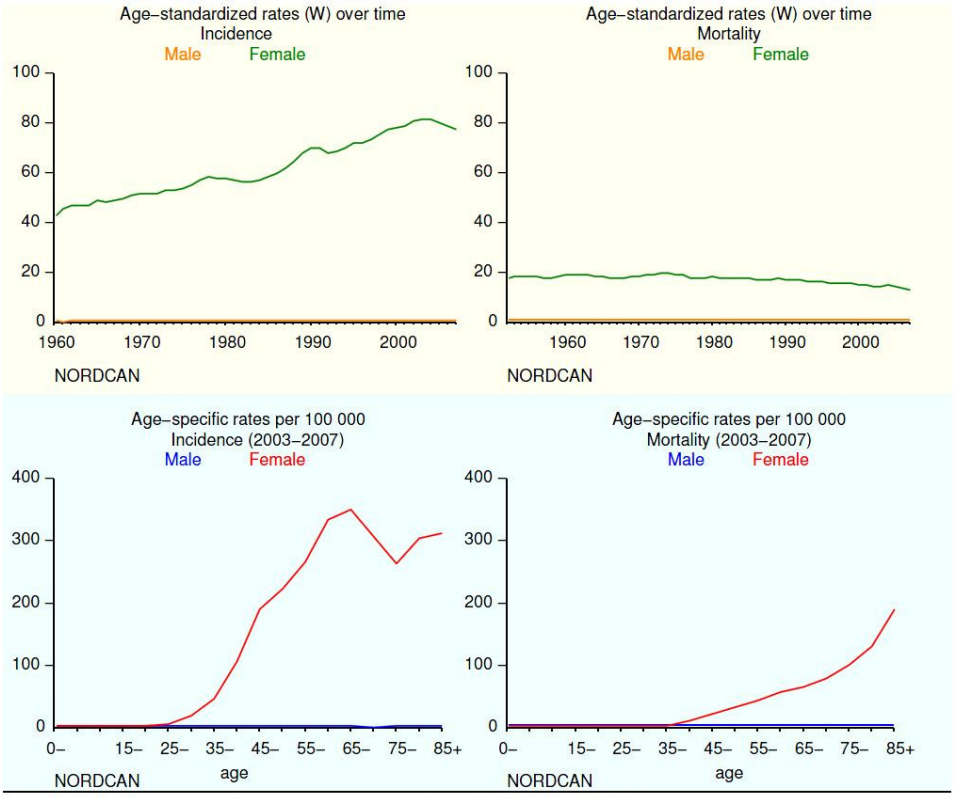
Screening is the systematic testing of a large number of asymptomatic individuals for the presence of risk factors, genetic predisposition, precursors or early evidence of chronic diseases not yet under medical care (1). The initiative for screening usually comes from the professionals, authorities or agencies providing healthcare. A screening test is not a diagnostic test. Persons with suspicious findings must be referred for diagnosis and treatment. Both the disease and the screening test must conform to a number of conventional criteria to be applicable as a public health intervention. The disease must be an important health problem. There should be an asymptomatic period in its natural history when the disease is detectable at an early stage. Treatment at an early stage should offer better outcome than treatment at an advanced stage. The screening test must be secure, reliable (reproducible), accurate (high sensitivity, specificity and predictive value), cost-effective, acceptable for the target population and it must be applied repeatedly according to a screening protocol. Cancer screening is a form of secondary prevention, a second best strategy to be implemented when the initiation of cancer cannot be controlled otherwise and when it is impossible to foresee who will develop the disease (2, 3).

Disease burden

Breast cancer is the leading malignancy of the female population in terms of incidence and mortality in most industrialised countries.

European patients have generally high 5-year relative survival rates, and the Nordic countries, except Denmark, have among the highest. A study of the 5-year and 10-year relative survival from invasive breast cancer in the Nordic countries for the period 1964-2003 and followed up through 2006 showed that both the 5-year and the 10-year survival rates increased by 20-30% in all Nordic countries (4). For Sweden the 5-year and 10-year survival estimates were 85% and 75%, respectively for the years 1999-2003 (4). Figure 1 shows the age-standardised breast cancer incidence and mortality 1960-2006 and the age-specific incidence and mortality rates 2003-2007 for Sweden.

Figure 1. The age standardised breast cancer incidence and mortality (1960-2006) and age-specific incidence and mortality rates (2003-2007) for Sweden



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17.7.2010

Breast cancer is a chronic progressive disease with a lot of intrinsic heterogeneity. Its natural history can be divided into three phases by time: present but not detectable, asymptomatic and detectable by mammography screening, and symptomatic and detectable by clinical methods. *Sojourn time* is the estimated time period for the occult disease when it is detectable by a screening test (5-7). *Lead time* is the actual time gained by screening before the expected onset of symptoms. Sojourn time thus represents the upper limit of lead time that might be gained by screening and that could be beneficial for most individuals participating in a screening programme. The mean sojourn time (MST) and mean lead time (MLT) vary by age. The MST of breast cancer was estimated to be 2.0 to 2.4 years in ages 40-49, 2.5 to 3.7 in ages 50-59, 3.5 to 4.2 in ages 60-69 and 4.0 to 4.1 in ages 70-74 (8). The overall MST in ages 40-74 was estimated at 3.2-3.9 according to the method of calcula-

tion (8). Thus, the MST for different age groups should be considered when planning the length of the screening interval.

Mammography

Mammography as a screening tool proved to comply well with the conventional criteria of a screening test. The benefit of mammography overweighs its harm. It is generally well tolerated by the women. It is secure with built-in security functions, for example against excessive breast compression. It is a standardised, quick, simple to do and relatively cheep method and as such it is reproducible in large populations. The sensitivity and specificity of mammography screening can be high in well functioning screening programmes. An NCI-funded breast cancer surveillance based on 3.6 million screening examinations in the US between 1996-2006 reports on an overall sensitivity of 80% (range 71-85%) and a specificity of 91% (range 90-94%) for ages 40-89 at a 9% overall recall rate (9).

Technique. The mammograph developed during the 1960-ties is low-energy (25-32 kV) x-ray equipment dedicated to the examination of the breast (10). The material of the x-ray source (anode) is molybdenum or wolfram. The breast is compressed between a compression plate and an image receptor (film-screen or digital detector) to reduce thickness and radiation dose, to minimize motion artefacts and thus improve image quality. On exposure, the x-rays will be differently absorbed by the different tissues of the breast and the photons that pass through it expose the detector that is necessary to produce a grey-scale image. Tissues that absorb a lot of x-rays will appear as white areas on the mammogram and tissues that absorb little x-rays appear as dark areas on the mammogram.

Diagnostic mammography. From the nineteen thirties the x-ray examinations of the breast have been increasingly used in the clinical practice of symptomatic patients. It helped the clinician to more accurately characterise a palpable lesion, to do a surgical biopsy, a lumpectomy or a mastectomy (10). Diagnostic mammography, both technology and interpretation, went through an impressive development beginning with the nineteen sixties due to the introduction of mammography screening in the industrialised countries. Diagnostic mammography is still the first choice method in the assessment of breast diseases (11) complemented lately by several modern techniques (digital mammography, ultrasound, magnetic resonance imaging, image-guided biopsy).

In Sweden, where imaging of the breast has earned a strong position within the multidisciplinary breast-team, it is the task of the mammography department, in collaboration with the pathology department, to do the work-up (imaging and biopsy) and present the diagnosis for the surgeon and oncologist. In the Swedish public healthcare system the breast diagnostic centres function as screening centres too. Thus, in the breast imaging centres the assessment and the follow-up of the clinical patients and screen-detected

cases is done by the same personnel and this concept of working generates a vast experience for the benefit of the patients.

Screening mammography. The aim of breast cancer screening with mammography is to identify women with breast abnormalities and refer them for further diagnostic work-up to confirm or reject the presumed presence of the disease. The vast majority of screening decisions will be accurate but some women will be identified as probably having the disease while they do not (false positives) and screening will fail to identify the disease in some women who actually have it (false negatives). *False positives* and *false negatives* are intrinsic and inevitable elements within a screening process, just like *true negatives* and *true positives*.

Coverage means how much of the target population within a geographic area is actually invited to screening. At the start of a screening programme coverage is minimal and it increases stepwise as screening proceeds within the area until finally the whole target population is invited to screening.

Screening of the general population for sporadic breast cancer is age-related and it focuses on the *age groups* in which the incidence of breast cancer is high enough. However, a great variety of age limits can be seen worldwide, anything between 40 to 74 years of age (12). The choice of the length of the *screening interval* should be based on the knowledge of the mean sojourn time for the actual age groups to be screened. Interval length also presents a worldwide variation between one to three years(12). The vast majority of the screening programmes follows the EU guidelines and invite women 50-69 years every second year. The UK started with 3-year interval (13) and the US recommended from the beginning 1-year interval but have now changed to 2-year interval (14).

Compliance or participation rate is an important element of screening. It should be high, preferably over 70 %, for a screening intervention to produce effect in the invited target population (15).

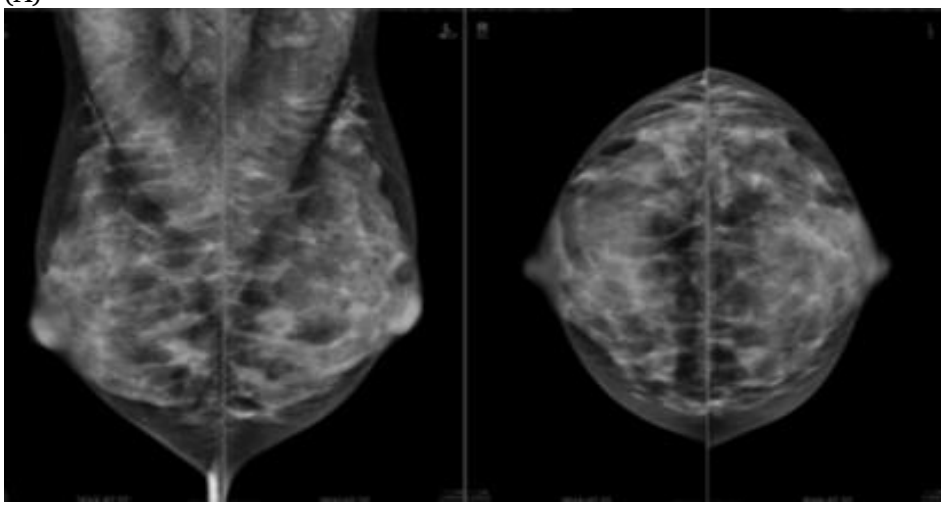
Recall rate, the number of individuals to be recalled for further evaluation per one hundred screened, is also important for the screening programme to be effective. The proper recall rate keeps the right balance between the false positives and false negatives. The recall rate varies between 1% and 5%, except for the US where the recall rate can be as high as 15% (12).

Cancer detection rate is dependent on the background incidence of breast cancer and on all previously mentioned screening elements and it presents a worldwide variation by between 1 and 12 breast cancer cases per 1,000 screened (12). In Sweden on average out of 1,000 screened, 20 are recalled, 4 need tissue diagnosis (biopsy/surgery), and 3 breast cancer cases are diagnosed (16) while in the US out of 1,000 screened, 80 are recalled, 10 undergo tissue diagnosis and 3 breast cancers are diagnosed (17), thus in the US the recall rates and the biopsy rates are higher than in Sweden.

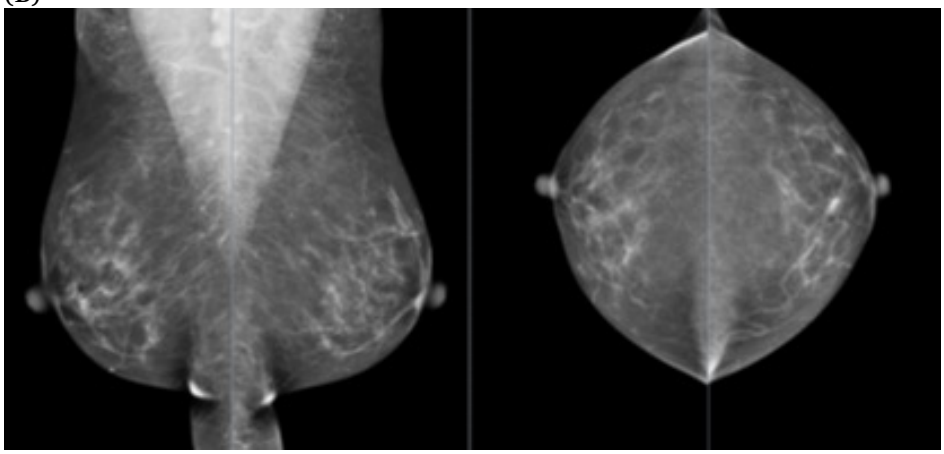
The *interpretation of the screening mammogram* has two phases: perception and analysis. First, the radiologist has to perceive on the image the difference between the normal and the abnormal. Once an abnormality has been identified on the image it has to be analysed and decided upon recall for assessment or not. This type of decision making is done hundreds of times a day and thousand of time a week by a fulltime working radiologist. The proper interpretation of the mammogram supposes the knowledge of the histopathology and its association with the features of breast lesions on the image (18).

Figure 2. Normal mammograms of (A) dense and (B) transparent breasts

(A)



(B)



The normal mammogram is a harmonic image of the breast tissue where the dark shades of the fatty tissue contrast with the light shades of the fibro-glandular tissue. These two basic components together with the visible mammary ducts, blood vessels, lymph nodes give the character of the normal mammogram (19).

Breast density is determined by the quality, quantity and distribution of fibro glandular tissue and fatty tissue in the organ. On the grey-scale image the breast appears as a pattern of light and dark shades which can reflect the grade of difficulty in the interpretation of mammograms and in finding a lesion (Figure 2).

From the radiological point of view one can differentiate between the easy-to-examine, radiolucent, transparent breast and the difficult-to-examine radio-opaque, dense breast. Several density classification concepts (18, 20-25) have been developed during the years as shown in Table 1. Wolf and Tabár attributed different risk for developing breast cancer to the different density patterns. According to Tabár (18) "These small differences in the relative risk of developing breast cancer that are related to the mammographic parenchyma patterns are not of major importance in comparison to the ever-increasing risk every woman encounters as she ages." Tabár concludes that the vast majority of women in the asymptomatic population have low-risk mammographic density patterns of the breast and most breast cancers (72% in the Kopparberg material) will be found in this group (18).

Table 1. Mammographic density pattern concepts

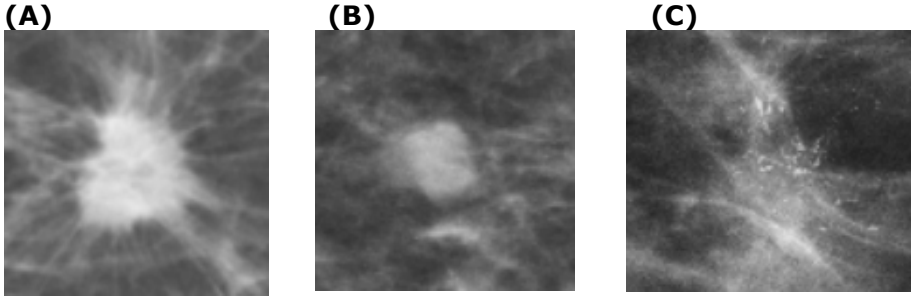
Time period	*Classification*	*Scale*	*Base*
1960ies	Wolfe	4	Density pattern
1980ies	Tabár	5	Density & histology
1990ies	ACR (BI-RADS)	4	Percentage density

Breast lesions on the mammogram can appear as solitary or multiple opacities (shades), micro-calcifications (calcium deposits) or a combination of these two. Masses (densities) can be stellate/spiculated or nodular/round and calcium can be powder-like, granular or casting-type (Figure 3). Masses are easier to find in fatty breasts. Calcium is often well seen in both dense and fatty breasts.

The perception and analysis of small lesions is sometimes difficult even for experienced radiologists. Variation in the performance between readers of screening mammography exists. The main factors that can influence reading performance are the radiologist's expertise, reading time, double reading and

recall rate. Double film reading, when two readers independently from each other interpret the mammograms, is widely practised to decrease the number of lesions overlooked by a single reader. However, this method can improve sensitivity but often at the cost of higher recall rate and lower specificity. Computer aided detection (CAD) has become a practice with the computer acting as a second reader in the era of digital imaging.

Figure 3. Typical breast lesions on the mammogram: (A) spiculated mass, (B) nodular mass, (C) microcalcifications.



Evaluation of mammography screening

Randomised controlled trials. Historically the evaluation of mammography screening for the early detection of breast cancer started with randomised controlled trials (RCT). The most important RCTs were (12): the New York H.I.P. study (1963-69), the Malmö I (1976-78) and Malmö II (1978-90) studies, the Swedish Two-county or WE-study (1977-85), the Edinburgh trial (1979-88); the Canada I and II. trial (1980-87), the Stockholm trial (1981-85) and the Gothenburg study (1982-88).The overall results of efficacy of RCTs showed relative risks <1.0 except for the Canadian trials.

An overview of the long-term effects of the Swedish RCTs with a median trial time of 6.5 years and a median follow-up time of 15.8 years showed a significant 21 % reduction in the breast cancer mortality, RR=0.79 (95% CI 0.70-0.89) in women 40-74 year old at invitation and a borderline significant reduction in the breast cancer mortality by 0.80 (95% CI 0.63-1.01) in women 40-49 year old (26).

The efficacy of inviting women aged 40-49 to screening has been evaluated in the UK Age trial that invited women aged 40-49 to yearly screening until they became 50. The evaluation based on an 10 year follow-up showed a non-significant 17% in the breast cancer mortality in invited women (27).

The Gothenburg trial which invited women aged 39-49 at entry to screening at an 18 months interval, showed a 44% significant reduction in breast cancer mortality in the intervention group at 14 years follow-up (28).

Meta-analysis was originally used to overcome the limitations of small sample sizes in the estimation of age-specific results of RCTs (29). Meta-analyses showed considerable variation in their quality and the size of the benefit for combined studies was less than for individual studies. Age specific analyses have led to "...presume that the true benefit of mammography was best estimated by combining the RCT results even when statistical power was adequate... This pattern has led to mistaken summary conclusions, estimated from meta-analyses, that the true benefit of mammography is less than was estimated by the same individual studies." (29). Hence, the criticism of mammography screening is often based on the meta-analyses of RCTs (30-32).

Clinical studies. In Sweden, the Gävle-Sandviken single-view mammography screening study (1974) proved that this method provided good quality screening at reduced radiation dose and increased patient flow at acceptable costs (33-36).

In 1973 the American Cancer Society (ACS) and the National Cancer Institute (NCI) initiated the Breast Cancer Detection and Demonstration Project to prove the feasibility of large scale breast cancer screening with annual two-view mammography, clinical examination and thermography. Nine years after entry the cumulative breast cancer incidence among participants was 1.4 times larger than expected but the cumulative breast cancer mortality was 80% of that expected in the controls (37).

In the Netherlands a cohort study was set up 1974 in Utrecht (38, 39) and 1975 in Nijmegen (40, 41). Both studies evaluated as case-control studies showed a reduction in mortality for women ever screened compared with those never screened.

The UK Trial of early Detection of Breast Cancer was a non-randomised study (1979-1986) to investigate the effect of screening and breast self-examination on breast cancer mortality in women aged 45-64 at entry (42). The 16-year mortality reduction observed in screening centres was 35% across age groups. No reduction in mortality was observed in the breast self-examination centres.

Finland was the first country to introduce 1987 nationwide biannual screening programme for women aged 50-59 that could be continued up to age 64 (43). The rate ratio of breast cancer deaths after a 5-year follow-up was 0.76 (95%CI 0.52-1.09) in the invited compared to not invited. It was estimated that one .death was prevented per 10.000 screens. The effect of the programme, according to the authors, was similar to that of RCTs and concluded that the introduction of screening as a public health policy could be justified (43).

Guidelines for mammography screening

Swedish guidelines. The results from the WE trial constituted the base for the first guidelines in Sweden issued by the National Board of Health and Welfare (NBHW) in 1986. The NBHW recommended the county councils to invite women 40-74 years to screening, women aged 55-74 every 2nd year and women aged 40-54 every 18 months (16). The NBHW has during the last two decades published several reports advocating mammography screening (44-47). The implementation of mammography screening for women aged 50-69 years took a decade to reach nationwide coverage by 1997. Today about 65% of the counties also invite to screening women 40-49 years and 70% invite women 70-74 years (48).

European guidelines. The European Union decided 1985 to launch an action against cancer (Europe Against Cancer Programme) in its member states. The European Committee of Cancer Experts then built a Screening Subcommittee to promote, finance and monitor pilot studies in the member states. Experts from non-member countries (Sweden, UK, The Netherlands, and Italy) that had already accumulated experience with mammography screening were affiliated to the Screening Subcommittee.

The international experts developed guidelines to assist health professionals and project leaders in their work, as screening was a new undertaking that required special training, accreditation, quality assurance and evaluation, including audits by outside teams.

The first edition of the European Guidelines for Quality Assurance in Mammography was published in 1993 (49) and it contributed to the accomplishment of screening projects in different EU countries and to the improvement of not only the screening quality but also of the diagnosis and treatment of breast cancer. The guidelines have reduced the differences in the quality of breast cancer care among EU countries. The EU guidelines have been further developed; the 2nd edition was issued in 1996, the 3rd edition in 2001 and the 4th edition in 2006 which also included the multidisciplinary aspects of diagnosis and treatment(11).

US guidelines. In the US there are several professional (ACS, ACR) and governmental bodies (NCI, USPSTF) that publish and periodically review their own mammography screening guidelines. These guidelines recommended until recently that the average risk population be invited to annual mammography screening and clinical breast examination (CBE) at age 40 and the upper age limit was not addressed. The USPSTF, however, raised the recommended lower age limit for screening to 50 years and a screening interval from one to two years (14).

A USA federal law (MQSA) regulates mammographic equipment, quality control, technologists and interpreting physicians. A written report of mammography results to patients is required of the interpreting physician. In the

US a Breast Imaging and Reporting Data System (BI-RADS) has been developed to improve quality of work and communication between radiologists, referring physicians and patients (50).

World Health Organization guidelines. In 2002 a review of the evidence on screening was performed under the auspices of the International Agency for Research on Cancer (IARC), a WHO agency (12). The IARC international expert working group confirmed that mammography screening every second year should be offered to women 50-69 years of age as a public health intervention. Their conclusion was consistent with the EU Council Recommendations on Cancer Screening.

Evaluation of service screening with mammography

The aim of a population-based service screening programme with mammography is to detect breast cancer as early as possible, to facilitate effective treatment and thereby reduce morbidity and mortality from the disease (11, 12). Nevertheless, the study of the impact of screening on breast cancer mortality reduction, the ultimate outcome measure of the effectiveness of service screening, is an important and complicated issue. It remains the task of the researchers to estimate the impact of screening and that of other factors (e.g. treatment) on the breast cancer mortality. The aim of the evaluation of service screening is to be able to prove its expected effectiveness. The process indicators can be grouped into performance indicators specific of the screening process and into impact indicators.

Performance indicators refer to the quality aspects of the screening process that contribute indirectly to the reduction of mortality (11, 12). There are a number of performance indicators reflecting different stages of the screening process e.g. coverage, participation rate, recall rate, cancer detection rate, rate of invasive investigations, positive predictive value of the test, cytology or biopsy, benign to malignant biopsy ratio, type of surgery, time interval between the screening test and final assessment, proportion of women recalled for six-months check-up and many more.

Early and late impact indicators are direct markers of the effect of screening on the disease, its clinical picture, incidence, mortality (11, 12). Early impact indicators, also called intermediate or surrogate measures, are necessary but not sufficient for the thorough evaluation of the screening process. Examples of this type of measures are cancer detection rate, interval cancer rate, sensitivity, the distribution of prognostic factors like stage, tumour size, node-status, histological grade. Their common characteristic is that they can be measured shortly after the implementation of screening (11, 12).

The major late impact indicators and outcome measures of the effectiveness of service screening are breast cancer mortality and total mortality. Mortality measures are considered necessary and sufficient measures that cover the

entire process of screening. Comparing them to the golden standards of the RCTs and European guidelines one can assess if they reach an acceptable or a desirable level. Their common characteristic is that they can be first measured many years after the implementation of screening in order to be able to see a difference (11, 12).

The most accurate indicator of the two is the *breast cancer mortality* reduction. Its calculation based on breast cancer as the underlying cause of death (UCD) implies the existence and linkage of the cause-of-death register to the cancer register and screening register for the study population in order to calculate breast cancer deaths in relation to invitation to or participation in screening. This method has been developed and refined ever since the early days of breast cancer screening (51-53).

In countries where cause of death is not available the excess mortality can be used to estimate effectiveness (54). This method implies the existence and linkage of a death register, a cancer register and a screening register for the study population. The difference between the observed number of death in the breast cancer cohort and the expected number of death based on background mortality of the matched healthy population gives the excess number of death due to breast cancer. This method can also be applied to two breast cancer cohorts with and without screening, respectively, to measure the effect of the intervention (55).

The other measure requires only a death register and a screening register to be able to calculate the *total mortality* difference between a screened and an unscreened population, respectively. To be able to detect an effect of screening on the total mortality a huge study population is required as cancer mortality constitutes a minor proportion of the total mortality, e.g. 23% in Sweden (56).

Mortality studies are based either on temporal (before/after) or geographical comparison. However, the widespread screening activity has made it difficult, in Sweden at least, to find contemporary non-screened control group for the purpose.

Alternative measures for the evaluation of the effect of screening on breast cancer mortality have also been developed. These include the number of breast cancer deaths prevented per screen, the lifespan gained per breast cancer death prevented, per patient with screen-detected breast cancer, per one screen and per invitation to screening, respectively (57).

Risks (hazards) of screening

The average risk population invited to mammography screening will be healthy on examination and cannot benefit from the intervention; they can only be harmed of it. However, there are some unavoidable risks of mam-

mography screening that should be kept as low as possible. The main sources of harm can be the false positive test result, overdiagnosis and radiation induced breast cancer.

A *false positive test result* occur when a woman is recalled from the screening because of an abnormal finding on the mammogram and on assessment there is not any evidence of cancer (12). The harm of a false positive test result is transient, it affects women without breast cancer and it consists of additional imaging, eventually invasive procedures that cause anxiety.

Overdiagnosis refers to asymptomatic women recalled from screening and diagnosed with breast cancer that would never have caused symptoms (12). The harm of overdiagnosis is life-long and it consists of anxiety and unnecessary treatment. Practically it is impossible to identify a case that is over diagnosed because all detected cancers are treated. Theoretically however, there are studies that have demonstrated different levels of overdiagnosis in RCTs and observational studies. Initial studies of overdiagnosis estimated it to be of minor significance (58-66). However, lately the issue of overdiagnosis has become the subject of debate with the publication of studies that present this issue as a substantial problem of screening (67-69).

The issue of *radiation induced breast cancer* has been studied extensively internationally and in Sweden (70-78). The results are consistent in showing that using state of the art modern equipment and technique only a few breast cancer cases can be expected to be induced by repeated mammography screening over a long period. The glandular tissue of the breast is the most sensitive to radiation and this sensitivity is age-related. After the menopause the exposure to radiation of the breast is associated with low breast cancer risk. In a Swedish study of radiation induced breast cancer risk and mammography screening in a hypothetical cohort of 100,000 women who entered screening at age 40 and continued it until age 49 with 18 months interval and followed-up until age 100 (74) it was concluded with reasonable assumptions that the group will get a relatively large benefit from screening in terms of years of life gained and breast cancer deaths avoided in spite of the risk of radiation induced cases.

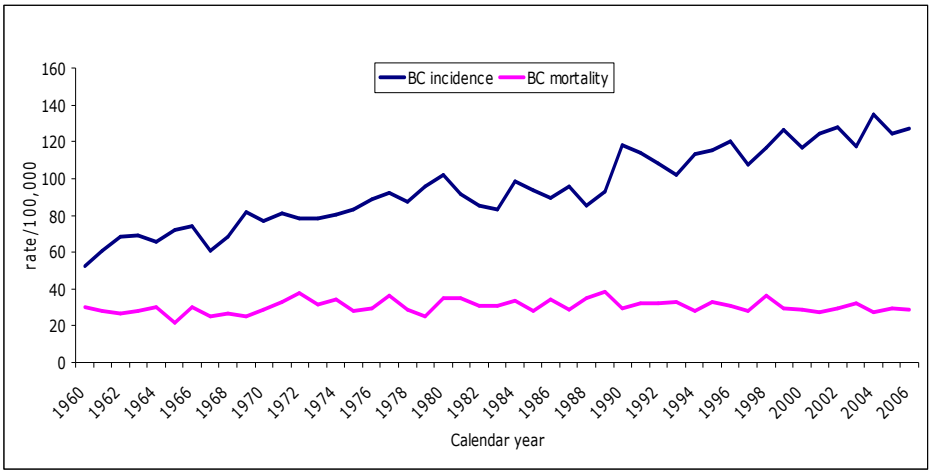
Breast cancer in Sweden

In Sweden 2007 the proportion of breast cancer of all cancers was 29% and the number of new cases was 7049. Breast cancer incidence rate was 153 per 100,000. The number of persons living with breast cancer at the end of 2007 was 84,185 (79). The estimated annual change in breast cancer incidence for the latest 20 years (1989-2008) was 1.2% (80). In 2008 there were 1512 breast cancer deaths in Sweden that corresponded to a mortality rate at 29 per 100,000 (56). The estimated annual change in breast cancer mortality rate over the latest 18 years (1992-2008) was -0.3% (56).

In Northern Sweden the number of new breast cancer cases varies between 600 and 700 per year, which is about 10% of the Swedish national breast cancer incidence. The number of new cases has increased from 193 cases in 1960 to 681 cases in 2007. This rising incidence of breast cancer can partly be explained by the rise in the proportion of the elderly women in the population. The risk for breast cancer rises by age up to 60 years and the mean age at diagnosis is 63 years.

The most obvious geographical difference in breast cancer incidence in Northern Sweden was that Norrbotten County had a lower incidence compared to the rest of the region until the nineteen eighties. During the nineteen nineties there were big variations in breast cancer incidence because of the gradual implementation of mammography service screening (81).

Figure 4. Age-standardised breast cancer incidence and mortality in Northern Sweden 1960-2006

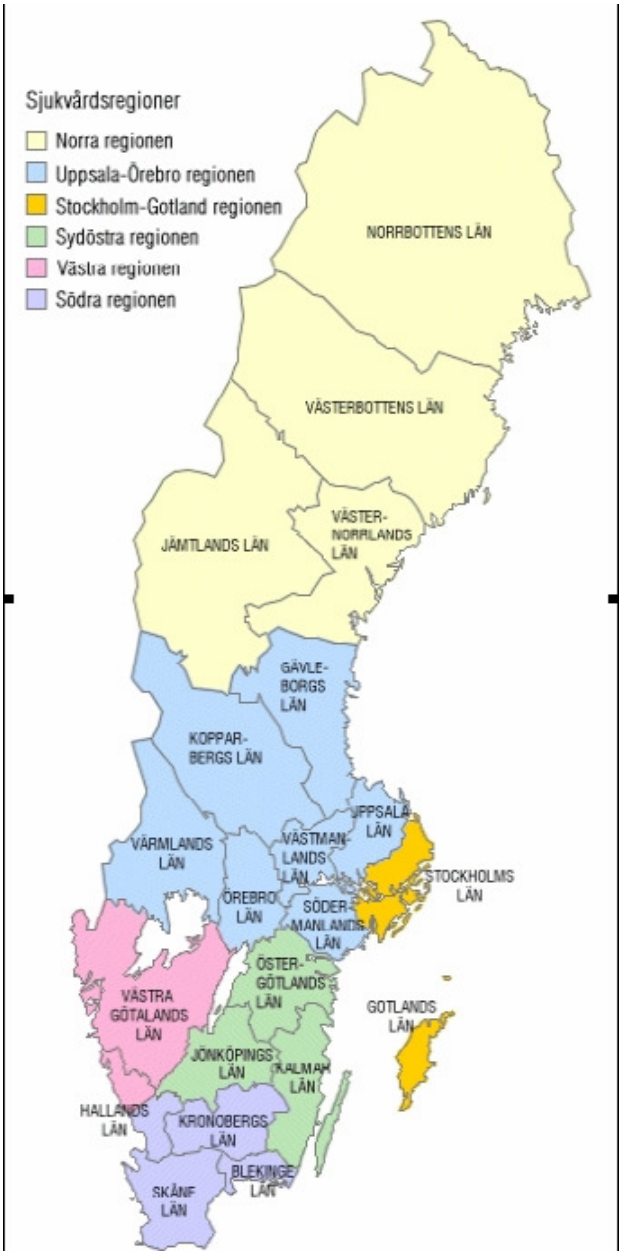


Breast cancer mortality has been relatively constant during these decades in spite of the rising breast cancer incidence (Figure 4). There can be several explanations to that. Two major ones are the improved survival due to more effective treatment methods and the implementation of mass screening with mammography and better quality of the clinical diagnostics that allow for earlier detection and more effective therapy (81). The introduction of adjuvant systemic therapy of breast cancer coincided with that of mammography screening in Northern Sweden. Because of this coincidence it is difficult to specify how much of the mortality reduction can be explained by screening and treatment, respectively. The use of systemic treatment was infrequent during the eighties and it became generally accepted after 1985 following the recommendations of the NIH/NCI Consensus Development Conference on the routine use of adjuvant chemotherapy and tamoxifen. During the nineteen nineties the use of adjuvant systemic chemotherapy and tamoxifen increased successively over time in the ages 40-74 years (82). Screening might have not only resulted in down staging of breast cancer (83) but also influenced the amount and type of therapy (82).

Northern Sweden: population, health care

Northern Sweden comprises about 55% of Sweden's territory (226,000 km^2) and about 10% (900,000) of the Swedish population. This sparsely populated region has 13 hospitals and hospital services at town level, at county level and at University hospital or regional level. Some selected, highly specialised services (e.g. organ transplantation) are provided at the national level outside the borders of Northern Sweden. From the public healthcare point of view Northern Sweden is an organizational and functional entity. It is composed of four Counties with their own political-administrative and economical infrastructure, counties that deliver health services to their citizens and that cooperate with each other over the county borders at the level of the sophisticated hospital care (Figure 5). Within the Northern Sweden Health Care Region breast cancer care is provided at county level except for the oncology and radiation therapy services that are centralised to two hospitals to which patients are admitted over the County borders. The Northern Sweden Breast Cancer Collaboration Group is a multidisciplinary professional working group that edits and regularly updates the Northern Sweden Breast Cancer Care Programme (81) to guarantee a high standard and the uniformity of the diagnostics and treatment of breast cancer patients. The target population for mammography screening consists of women aged 40-74 years accounting for 75% of the incident breast cancer cases in Northern Sweden for the period 1995-2004 (84).

Figure 5. Healthcare regions/Counties of Sweden



Mammography in Northern Sweden

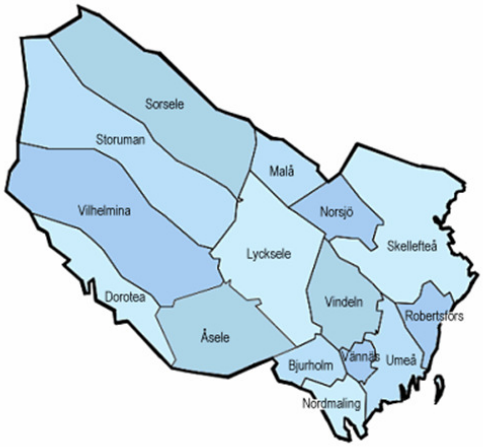
Before the screening era breast cancer diagnostics and treatment was practised according to local routines and rules at most hospitals without too much communication or co-operation between hospitals. Breast cancer patients could seek medical care at general practitioners, surgeons or gynaecologists, as they pleased. Many health professionals dealt with breast cancer patients but few patients in each treating unit did not contribute optimally to the development. A paradigm shift in breast cancer care started in the early nineteen nineties by the centralisation of the breast cancer care to a few expert centres and the establishment of four comprehensive diagnostic and screening centres, one in each of the four counties of Northern Sweden. The length of this process took different time in the different counties. The screening settings are shown in Table 2.

Norrbotten County was first out in the autumn of 1988 to start with breast cancer care centralised to one hospital in Luleå municipality for the whole County. This breast assessment centre was complemented by a mammography screening programme with start 8th March 1989 in the municipality and extended to the whole County beginning with January 1990. A continuous screening service has been delivered to the citizens of the county at multiple places simultaneously by two mobile and one or two stationary screening facilities ever since. The large geographical area, 100,000 km², made it necessary to deliver the service where people live and thus move around in the county with two mobile units and a total number of 13 spots in the thirteen political-administrative communities (Figure 6).

Figure 6. Map over the screening spots in Norrbotten

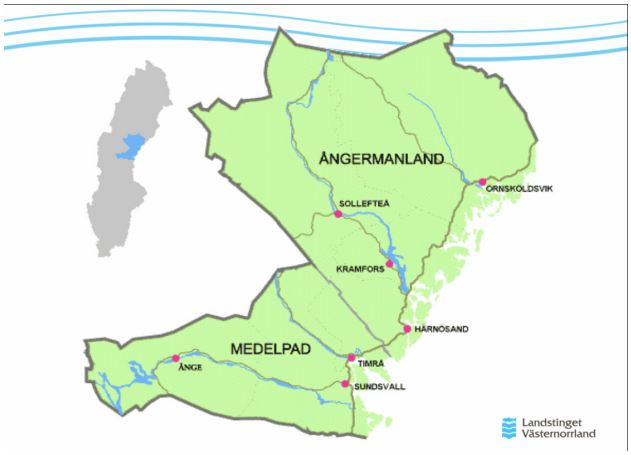
Västerbotten County has the youngest population in the region over a geographical area of about 55.000 km². There are two breast assessment and cancer care centres in the county. One is situated in the University Hospital in Umeå municipality and one in the Skellefteå Hospital. Also, two stationary screening units deliver the service in the municipality of Umeå, one in Skellefteå and two mobile units cover the 16 screening spots in the county.

Figure 7. Map over the screening spots in Västerbotten



Västernorrland County has a smaller surface of about 22,000 km² but as big a population as its two other northern neighbours. The breast assessment centre is localised in the County Hospital in Sundsvall municipality. Simultaneous screening of women has been delivered non-stop since 1990 by one stationary and two mobile units covering 14 screening spots.

Figure 8. Map over some screening spots in Västernorrland



Jämtland County is a sparsely populated territory of about 34,000 km² with the County Hospital and breast assessment centre in the municipality of Östersund. Screening is delivered by one stationary and one mobile unit.

Figure 9. Map over the screening spots in Jämtland

The *Oncology Department and Clinic* of the Northern Sweden University Hospital (www.onkologi.umu.se) is responsible for the uniformity and high standard of breast cancer care in the region.

There is a regional cancer registry called the *Oncologic Centre* (OC) functioning within the University Hospital in Umeå municipality. All clinical data on breast cancer patients are reported to them from all hospitals of the region. It is the task of the OC to collect, organises, analyse and publish cancer statistics and screening statistics for Northern Sweden. Data collected by the OC are regularly transferred to the Swedish NBHW databases.

During the nineteen-nineties, meanwhile mammography service screening programmes were gradually introduced into the public health care system in Northern Sweden; research addressing different aspects of mammography screening was also initiated in the same time. The *Northern Sweden Mammography Screening* (NORMA) forum is the evaluation working group of the mammography service screening in the region where researchers, clinicians and screeners meet, work and discuss quality control issues, evaluate screening results and formulate research projects within the field.

Table 2. Screening setting in Northern Sweden 1989 through 2002

County	***Norrbotten***	***Västerbotten***	***Västernorrland***	***Jämtland***
Start of screening	1989	1995	1990	1996
Screening population	55,000	55,000	55,000	16,000
Screening ages (year)	40-74	40-74	40-74	50-69
Interval length (year)	2	2	2	2
Participation rate (%)	82	83	85	>80
Recall rate (%)	2.0	2.0	2.5	2-3
Detection rate (‰)	3.0	2-4	4.3	3-4

Aims

The general aim of this thesis was to contribute with new data to the evaluation of the population-based organised service screening with mammography through studies of the screening activity in Northern Sweden during 1990-2002.

PAPER I. The aim of this study was to estimate the interval cancer incidence and its determinants and also to estimate the episode sensitivity of the NMSP.

PAPER II. The aim of this study was to identify and describe interval cancer types and to investigate the relationship between interval cancer types, time to diagnosis, mammographic features, breast density and age distribution.

PAPER III. The aim of this study was to analyse individual cases of lethal breast cancer among women 40-74 years of age by mode of detection and prognostic factors during the first five years of service screening.

PAPER IV. The aim of this study was to estimate breast cancer survival by detection mode for women 40-74 years of age, in particular for those detected in the screening intervals, in Northern Sweden between 1988 and 2001.

PAPER V. The aim of this study was to evaluate the effectiveness of service screening in Northern Sweden by breast cancer mortality, the ultimate outcome measure for screening.

Table 3. Main characteristics of the studies included in this thesis on women of ages 40-74 years

Study no.	*Study aim*	*Study population*	*Study period*	*No. cases*	*Main outcome measures*
I	IC incidence and episode sensitivity	Norrbotten	1989-2002	172	Interval cancer rates, rate ratios
II	IC radiological review	Norrbotten	1994-2002	279	Proportions of true, occult and iatrogenic interval cancers
III	Early deaths from breast cancer	Northern Sweden	1989-1998	342	Breast cancer death in numbers and proportions
IV	Survival from breast cancer	Northern Sweden	1988-2001	5120	5-year and 10-year survival rates,
V	Breast cancer mortality	Northern Sweden	1988-2001	2708	Relative risk for underlying cause of death and excess mortality

Methods

Table 3 shows the main characteristics of the studies included in the thesis on women of screening ages 40-74 years.

Data generation process

The data for this thesis were generated from registers at the Oncologic Centre in Umeå using record linkage. Data were extracted from the population register, the cause-of-death register, the tumour register and the screening registers of Northern Sweden.

For papers I and II, the ethical approval of the Regional Ethical Review Board at Umeå University was received to do the epidemiological and radiological analysis of interval cancer. In paper III individual data of deceased persons were used as such for the evaluation of cases that presented early death because of breast cancer. In papers IV and V register data were used in aggregated form.

Interval cancer incidence and episode sensitivity

Interval cancer is by definition a clinically diagnosed breast cancer during the time period between two screening episodes in a participant after a negative test result and before the next screening event (11, 13). Interval cancer incidence and episode sensitivity are two inter-related screening performance indicators. Interval cancer cases are inevitable in a screening process but their incidence should be kept as low as possible (85). The European guidelines for quality assurance in breast cancer screening and diagnosis recommend both epidemiological and radiological monitoring of interval cancer (11). Interval cancer identification and classification can be done at the level of register data only, at the level of register data and film review combined or at the level of register data, film review and medical history. We know from the literature that the quality of data registers the operational definition, the quantification and the level of interval cancer review have great effect on the interval cancer rate (85-87).

Sensitivity is a measure to describe the capability of an intervention to select the cases from a population. In cancer screening three entities of sensitivity have been defined, test sensitivity, episode sensitivity and programme sensitivity (88). All three concepts of sensitivity serve different purposes. Test sensitivity measures the test method's ability to find breast cancer in its detectable asymptomatic phase. Episode sensitivity applies to screening participants alone and indicates the ability of the full diagnostic process (test and histological confirmation) to detect breast cancer. Programme sensitivity indicates the proportion of breast cancer cases detected by the screening programme in the target population. Programme sensitivity depends, beside

the sensitivity of the screening process, on the programme coverage and compliance of the target population.

In paper I an epidemiological review of interval cancers was carried out on the material over six screening rounds of the NMSP. Overall and age-specific screen-detected cancer rates and interval cancer rates in the NMSP were estimated relative to the number of women screened. Early (≤1 year) and late (>1 year) interval cancer rates by screening round were also estimated. Interval cancer rate ratios (RR) were estimated relative to the expected annual number of breast cancer and length of interval. Episode sensitivity in the NMSP was calculated according to the detection method [SDC/(SDC+IC)] and the incidence method (1-RR) (88). The association between age, screening round, recall rate, interval cancer rate and screen-detected cancer rate was analysed in a Poisson model.

Radiological review of interval cancers

Radiological review, incidental or continuous (surveillance), is needed to provide information on the type of interval cancer (e.g. true, missed) and to identify methods to control their incidence (85). Epidemiological review of interval cancer alone does not provide this information. *Radiological review* is the process of reviewing mammograms at the time of the clinical diagnosis and comparing them with the mammograms taken at the previous screen. Radiological reviews of interval cancer should be part of the quality assurance process of screening programmes and should be used to facilitate training in film reading. The classification of interval cancer cases is the responsibility of the reviewing panel and is not part of the routinely submitted information for the evaluation of screening. Interval cancers can present "de novo" (true), as a consequence of the screening process (e.g. interval length) or as a consequence of the assessment process (e.g. reading error).

Research showed that the radiological review design applied to interval cancer affects the detection rate and classification of cases into true, occult and false negative (89-91). The main elements of the review design are the number and experience of readers, the blinded review or not, the mixing of mammograms of cases with films of healthy or not. In one study the proportion of interval cancers regarded as missed varied between 7% and34% depending on the review method (90). In an other study the frequency of missed interval cancers ranged between 1.3% and 35.9% depending on review design (91).

In paper II the radiological review of interval cancer cases from the NMSP was done in 2004 with the involvement of an internal (PB) and an external reviewer (ZP) to cover index rounds 4-6. We classified interval cancer cases into true, occult, missed, minimal signs and not classifiable and by their radiological characteristics into spiculated density, nodular density and microcalcifications alone. The interval cancer is considered *true* if at review the screening mammograms are negative but the diagnostic mammograms are

positive for cancer. The interval cancer is considered *occult* if both the screening and the diagnostic mammograms are negative for cancer at review. We consider the occult interval cancer as a special form of the true interval cancer. The interval cancer is considered *missed* due to reading error whenever the lesion is seen on both the screening and the diagnostic mammograms at review. *Minimal signs* are subtle, non-specific abnormalities on the screening mammogram that were not considered suspect for recall but that turned out to be positive for breast cancer on assessment. The missed and minimal signs interval cancers together constitute the so called iatrogenic type of interval cancer. An interval cancer is *unclassifiable* whenever the interpretation of the case is not possible because of missing data at review. *Time to diagnosis* is the time elapsed between the dates of the index screen and that of the histological diagnosis. The mammographic features of breast cancer can be classified into ill-defined densities (asymmetric density, distortion) and well-defined densities (nodular or spiculated masses) and microcalcifications (amorphous, granular, casting type) or a combination of the above. Breast cancer can seldom present clinically with lymph node and/or distant metastases and without direct or indirect x-ray signs on the mammogram.

Informed consensus review design was applied, which means that screening and diagnostic mammograms, radiological, surgical and pathological reports were reviewed independently by the two reviewers (91). The reviewers were aware of the fact that they were reviewing interval cases. Validation of the individual interval cancer cases was done by the reviewers on the basis of available clinical data. Consensus decision was reached whenever there was any difference in the assessment of the two reviewers. The screening films were first reviewed without the diagnostic mammograms to make a provisional classification of interval cancers into true or missed. The screening mammograms were reviewed again, this time together with the diagnostic mammograms for a definitive classification of interval cancers. If mammography was not performed at diagnosis, the case was considered unclassifiable.

Chi-square statistic was used to test for relationship between interval cancer type and mammographic features, breast density, time to diagnosis and age group. P-values less than or equal to 0.05 were regarded as statistically significant. The analyses were performed using SPSS.

Early deaths from breast cancer

In paper III the lethal breast cancer cases among women 40-74 years of age were analysed by mode of detection, histological prognostic factors and age distribution. These lethal cases were diagnosed in Northern Sweden between 1990 and 1994 and died with breast cancer as the underlying cause of death through December 31, 1998. An expert pathologist (SC) reviewed and classified the histological material for histological type and malignancy grade by the Nottingham Grading System (92). Pearson's exact Chi-square test was

used to test the differences in distribution of prognostic factors by detection mode.

Survival from breast cancer

Survival analysis is a method of measuring disease prognosis in a cohort of patients with a certain disease. When measuring survival from breast cancer in a cohort of screened patients in comparison with an unscreened cohort one should consider the lead-time bias (screen-detected cases can give the false impression of a longer survival compared to clinically detected cases) and length bias (the potential selection of slowly growing tumours by screening.

In paper IV the 5-year and 10-year breast cancer-specific survival rates were calculated by detection mode for women aged 40-74 years in Northern Sweden and for the period 1988 and 2001. The breast cancer-specific survival curves by detection mode were presented graphically according to the Kaplan-Meier method. Survival of the different groups was compared by a multivariate survival analysis according to the Cox proportional hazards regression method. Two sets of analyses were carried out. In one set of analyses we estimated the hazard ratios (HR) for detection modes unadjusted and adjusted for county, age and period of diagnosis, respectively. The other set of analyses was used to estimate the determinants of survival for uninvited and interval cancer cases of TNM-stage I and II. In this set of analyses we used a basic model including only stage and detection mode and an expanded model there we also adjusted for histological grade, age and oestrogen receptor (ER)-status. An interaction factor between stage and detection mode was created and included in the analysis. HR estimates were calculated, confidence intervals were given and the p-values for likelihood ratio tests were given. A significance level of 5% was applied.

Breast cancer-deaths were extracted from the official cause-of-death register. Prognostic factors (age, TNM-stage, tumour size, node status, distant metastases, histological grade and ER-status) were stratified for all cases, interval cancer cases and cases among uninvited.

Mortality from breast cancer

Breast cancer mortality is the major endpoint for the evaluation of the effectiveness of screening. However, it takes several years after screening start before a decline in breast cancer mortality can be shown and the cumulative mortality reduction reaches a significant level.

Breast cancer mortality can be calculated based on either breast cancer as the underlying cause of death (UCD) or on excess mortality. These methods of calculation have been developed over time (53, 55, 93-95). The refined breast cancer mortality applied to a population exposed to screening takes into consideration only cases diagnosed during the intervention and above

the lower age limit of the intervention (96). Mortality from breast cancer in a population exposed to mammography screening can be studied comparatively either over time, e.g. before and after exposure, or between geographic areas with or without exposure. Breast cancer mortality decrease alone does not prove the effectiveness of screening unless other risk factors and treatment regimen are similar in the populations that are being compared.

In paper V the effectiveness of service screening in Northern Sweden was studied. We compared refined breast cancer mortality in a cohort of women aged 40-74 years invited to screening with a cohort of the same age group that was not invited at that time, but 5-7 years later. The cohorts were followed-up for 11 years. We used two outcome measures for refined breast cancer mortality, the UCD-based breast cancer mortality and the excess-mortality. There were 108,000 women in the study population and 77,000 in the control population. Cases of and death from invasive breast cancer were identified. Data concerning screening and mode of detection were collected. A study group and a control group were created from the respective populations. Beside a study period also a reference period was defined to be able to adjust for eventual breast cancer mortality differences between the study and the control population. The study period consisted of an accrual period and a follow-up period of 11 years. Rate ratios of breast cancer deaths and person years in both groups were estimated. Adjustments for lead time and for screening attendance were applied. The number needed to screen was calculated as the ratio between the number of saved lives and that of the screened women.

Table 4. Main results of the studies on women of screening ages 40-74 years in Northern Sweden

Study	*Research questions*	*Methods*	*Main results*	
I	Interval cancer incidence	Rates and rate ratios, cumulative and by age and screen	IC rate IC rate ratio	11/10,000 0.38
	Episode sensitivity	By the incidence and detection method.	Sensitivity	62-73%
II	Radiological review of interval cancer	Informed consensus review.	True Occult Missed Minimal signs	48% 10% 14% 28%
			Spiculated mass Circumscribed mass Calcium only	57% 39% 4.0%
III	Early death from breast cancer	Stratification by detection mode.	Death among screened Deaths among non-attendants	57% 43%
IV	Survival from breast cancer	Cox-regression analysis (hazard ratio).	Uninvited Screen-detected Interval cancer Non-participants	1.00 0.30 0.70 1.60
V	Mortality reduction from breast cancer	Geographical and historical comparison.	Invited Screened	26-30% 31-35%

Results

Our main results are shown in Table 4.

Interval cancer incidence and episode sensitivity

For the six screening rounds of the NMSP the mean interval length was 21 months (range 20.3-22.8 months), the mean attendance rate 82% (range 80-86%) and the mean recall rate was 2.0% (range 1.3-2.5%). Between 1989 and 2002 there were diagnosed 1047 invasive breast cancers among which 768 were screen-detected and 279 interval cancers. Out of the interval cancers 47% presented during the first year and 53% thereafter. The median time for the appearance of interval cancers after index screen was 14 months. The overall screen-detected cancer rate was 29/10,000, increasing from 14/10,000 in ages 40-49 to 51/10,000 in ages 70-74 years. The interval cancer rate was 11/10,000. The screen-detected cancer rates increased across age while the interval cancer rates remained constant, but both rates increased with incident rounds. The overall interval cancer rate ratio was 0.38 (95% CI 0.34-0.44). The rate ratios of interval cancer by age group 40-49, 50-59, 60-69 and 70-74 were 0.50 (95% CI 0.40-0.62), 0.52 (95% CI 0.41-0.65), 0.27 (95% CI 0.20-0.35) and 0.23 (95% CI 0.15-0-36), respectively. The early and the late interval cancer rate ratios were 0.18 (95% CI 0.15-0.22) and 0.20 (95% CI 0.17-0.24) and varied by age and screening round.

The overall episode sensitivity was 0.62 (95% CI 0.59-0.65) and 0.73 (95% CI 0.71-0.76) estimated by the incidence and detection methods, respectively and it varied by age at invitation and screening round. The Poisson regression analysis showed that the likelihood for a tumour to be detected at screening increased by age and recall rate and it was higher in the first round than in subsequent rounds. The relative risk for interval cancer was significantly higher in the incidence rounds (RR=1.6; 95% CI 1.1-2.4) due to the elevated risk of the late interval cancers by 2.3 (95% CI 1.3-4.3).

Radiological review of interval cancer

In this study there are included both in-situ and invasive interval cancer cases diagnosed in the index rounds 4-6. The accrual period for cases was from April 1994 through November 2002, the time span necessary for the completion of screening rounds 4-7, that is intervals 4-6.

During the study period there were 130 979 screens performed, 451 breast cancers were screen-detected and 172 cancers were detected in the intervals between screens. The rate of screen-detected cases thus was 34 per 10,000 screened and the rate of interval cases was 13 per 10,000 screened. Dense breasts were present in 71%. The median age of women at diagnosis was 56 years. True interval cancers were present in 48%, occult in 10%, missed in 14% and minimal signs in 28% of the cases. Spiculated masses were found in

57%, nodular masses in 39% and microcalcifications alone in 3.8% of the cases. Most of the interval cancers (61%) were detected during the second year of the interval. Dense breasts were present in 71%. The age distribution of interval cancer cases was 28%, 35%, 25% and 12% for age groups 40-49, 50-59, 60-69 and 70-74, respectively. Interval cancer was found in the right breast in 52% and in the left breast in 48% of the cases.

We found association between dichotomised interval cancer type and time to diagnosis (p=0.04) but not between interval cancer type and mammographic features (p=0.19) and interval cancer type and breast density (p=0.20). True interval cancers presented in greater number in the second year of screening while missed interval cancers were distributed equally between the first and the second year of the screening round.

Early deaths from breast cancer

In Northern Sweden there were identified 1881 breast cancer patients and 342 breast cancer deaths among women aged 40-74 years diagnosed between 1990 and 1994 and who died before December 31, 1998, during the gradual introduction of organised mammography screening. The mean age of women at breast cancer diagnosis was 60 and at death it was 63 years. The mean survival time to deaths was 3.1 (0.1-8.0) years. In 280 (82%) of these fatal cases breast cancer was diagnosed clinically in symptomatic patients. In the counties with screening the distribution of breast cancer cases by detection mode was the following: 62 (36%) screen-detected, 37 (21%) interval cancers, 25 (15%) cancer cases among non-participants and 49 (28%) clinically diagnosed cases among the not yet invited to screening. Advanced stage breast cancer (stage II+) was recorded in 85%, tumour size of ≥ 20 mm in 72% of the cases, 69% presented spreading to the regional lymph nodes and 24% were found to have distant metastases. Local recurrence and distant metastases presented some time after the primary diagnosis that sooner or later lead to a lethal outcome.

Survival from breast cancer

During the study period 5120 women with invasive breast cancer were identified and the survival estimates were given by detection mode and in particular for the interval cancers. Of all breast cancers 59% were diagnosed in women invited to screening and 37% in uninvited women. The proportion of stage I and II cases constituted 90% of this material.

The 5-year and 10-year survival rates for screen-detected, interval cancer, uninvited and non-participants were 0.93, 0.86, 0.82, 0.74 and 0.86, 0.75, 0.66, 0.52, respectively. A significant survival difference was observed (HR=0.68, 95% CI 0.55-0.85) in the favour of women with breast cancer detected in the screening intervals (n=729) compared to those uninvited (n=1879).

When comparing stage I and II interval cancers cases (n=659) with stage I and II cases among uninvited (n=1626) and estimating survival by stage, the 5-year and 10-year survival showed a decreasing trend in the following order: stage I uninvited cases, stage I interval cancer, stage II interval cancer and stage II uninvited cases. The corresponding 5-year and 10-year survival rates were 0.95, 0.92, 0.89, 0.78 and 0.88, 0.83, 0.78, 0.63, respectively (not published in paper IV). The survival risk for stage II vs. stage I was significantly increased (HR=3.7, 95% CI 2.9-4.8) and for the interaction factor significantly decreased already in the basic model and did not change in the expanded model of the analysis. In the expanded model the survival risk significantly increased by histological grade and decreased by positive ER-status.

Mortality from breast cancer

The mean annual breast cancer incidence rate per 100,000 was 227 in the study group and 181 in the control group during the seven-year accrual period. Among the cases 69% were screen-detected, 22% were interval cancers and 9% did not attend screening. The cumulative number of breast cancer deaths after eleven years of follow-up was 393 in the study group and 319 in the control group. The estimates of the effectiveness of service screening with mammography in Northern Sweden expressed as the relative rates (RR) of breast cancer death for women aged 40-74 years invited to screening compared to that of women not invited to screening was 0.74 (95% CI 0.62-0.88) by the underlying-cause-of-death method (UCD) and 0.70 (95% IC 0.56-0.87) by the excess-mortality method. The biggest effect was seen in the age group 40-49 years, where RR was 0.62 and 0.64 by UCD, and excess-mortality methods, respectively. For the exposed, e.g. for women screened the RR was 0.70 (95% CI 0.57-0.86) and 0.65 (95% CI 0.51-0.84), by the UCD, and the excess-mortality methods. The number needed to screen to save one life was 912 (95% IC 570-2278) during the eleven-year follow-up.

Discussion

There are many organised mammography screening programmes running worldwide based on the experience accumulated form the randomised controlled trials and clinical studies. These fall into three main categories (97): (a) national, government-supported highly organised and distinct from the general health care (e.g. Finland, Norway, Sweden); (b) regional, government-supported, locally organised service distinct from the general health care (e.g. Denmark, Italy); and (c) government-supported screening conducted within the general health care (USA, Germany). The implementation of mammography screening in Sweden from pilot study through clinical trials to nationwide service screening took 23 years and was completed by 1997 (98). By that time more than one million women participated in screening, the compliance rate was 81% and the recall rate 2.2%

The evaluation of the effectiveness (the effect of invitation) of the population based organised service screening programmes is important because of medical, public health and scientific proposes. It shows how the individual programme performs, how results of the trials translate into public health care and it generates data for new research. There are a number of performance indicators and surrogate measures that can tell how a screening programme performs and can predict future mortality reduction. The main outcome measure of the effectiveness of an organised screening programme is the mortality reduction from breast cancer. However, this major impact indicator can first yield relevant estimates years or decades after the introduction of screening. These indicators of the organised service screening have to be compared with target or expected values derived from randomised controlled trials. In the comparison of the estimates with target values the programme settings (age range, interval length, background incidence of breast cancer) have to be accounted for.

The papers included in this thesis present aspects of the evaluation of the effectiveness of population-based organised service screening.

Our most important result shows that population-based organised service screening as a public health intervention can be associated with and has produced in Northern Sweden a clinically and statistically significant reduction of breast cancer mortality in the invited population compared to the uninvited. Our results also show that mode of detection is associated with survival. We showed that the clinically diagnosed advanced cases suffered most often from death during the introduction of service screening in the area. We estimated episode sensitivity and studied interval cancer from the epidemiological and radiological point of view in the Norrbotten Mammography Screening Programme, important performance indicators in the quality control of the intervention.

Interval cancer incidence and episode sensitivity

We estimated interval cancer incidence for the NMSP six screening rounds in Norrbotten County that invites women aged 40-74 years to biannual screening (Paper I). Our study showed an overall interval cancer rate at 11/10.000 and a rate ratio at 0.38., Interval cancers comprised 27% of the total number of cancers detected in participants (interval and screen-detected cases). We estimated the interval cancer rates by screening round and not by calendar year because the NMSP screens with a two-year interval at three screening units simultaneously and non-stop. This means that a screening round hasn't come to an end yet at one unit meanwhile the next screening round has already been started at another unit. The estimation of the interval cancer incidence by calendar year in our setting would yield a mixture of interval cancers belonging to different intervals. So, the recommended calculation of annual interval cancer incidence by the literature is not relevant for our programme. This conceptual difference must be considered for in an international comparison of our results. We adjusted for it and got estimates at 33% and 47% for the early and late interval cancer rate ratios that are in line with the acceptable level of the European guideline (11).

The overall interval cancer rates and rate ratios were estimated as well as the rates and rate ratios by screening round and by age. There was a significantly lower interval cancer incidence in the prevalence round compared to the incidence rounds. Screen-detected cancer rates increased while interval cancer rates remained constant across age. The interval cancer rate ratio decreased with age, it dropped by the half over age sixty compared to age below sixty. The risk of early (≤1 year) and late (>1 year) interval cancers were similar to each other. The likelihood for a breast cancer to be detected at screening increased with age and recall rate.

The incidence rate ratio is the measure of choice for between-programme comparisons because it eliminates geographical differences in breast cancer incidence (86). Between-programme comparison of interval cancer incidence is important but it should be done with caution because programmes usually differ from each other in inclusion criteria, coverage, compliance, age limits, interval length and recall rate and because there are no standardised surveillance methods (85).

Episode sensitivity reflects the capability of an intervention to find cases among the participants (88). We estimated the episode sensitivity overall, by screening round and by age according to the detection and incidence methods. The longer the intervention has been running the more relevant estimate for the episode sensitivity is given by the detection method while the estimate given by the incidence method becomes more and more conservative. The overall episode sensitivity was estimated at 62-73% by the incidence method and the detection method, respectively. Episode sensitivity also shifted somewhat between screening rounds and it increased by age.

The Swedish randomised controlled trials and the thereafter started service screening programmes published reviews of interval cancer incidence (87, 89, 99-103). Their results are similar to ours in spite of some differences in screening setting and review design. For comparison, in the Östergötland mammography screening programme for women aged 40-74 the overall interval cancer rate was 14/10,000 (104), in the Malmö mammography service screening programme for women aged 45-69 it was 15/10,000 (99) and in the Stockholm screening programme it was 18/10,000 and the rate ratio ranged between 0.31%-0.37% (105)

In Scandinavia, the Norwegian (NBCSP) and the Finnish (FMP) national organised service screening programmes are comparable with ours. The NBCSP pilot project started 1996 and offered women aged 50-69 to biannual screening. The participation rate was 79%, the recall rate was 3.6%. (106). The interval cancer rate for the first interval was 18/10,000 and the proportionate incidence was 49% (107). The corresponding incidence rate and rate ratio for women aged 50-69 in the NMSP were 11/10,000 and 37% at a participation rate of 77%.

The Finnish programme invited women 50-59 and partly 60-64 to biannual screening (108). The episode sensitivity for women 50-64 years was estimated at 54-65% by the incidence and detection methods, respectively. Our corresponding figures for the same age group were 48-71%. In the FMP the interval cancer incidence rate and rate ratio for women 50-59 were 9/10,000 and 35% while our corresponding figures were 12/10,000 and 52%.

We could locate two meta-analyses about interval cancer. One study was dedicated to interval cancer of ages 40-49 in randomised controlled trials and service screening programmes. The first-year interval cancer proportionate incidence was 0.42 and 0.63 and the second-year incidence was 0.44 and 0.72, respectively (109). Our adjusted figure for ages 40-49 were 0.48 and 0.54. The interval cancer rates by age group were similar in the New South Wales (NSW) programme and ours: 1.05, 1.11, 0.94 and 0.86 per 1000 for ages 40-49, 50-59, 60-69 and 70-79. Another comparison of NSW-data with that of RCTs and service screening programmes combined gave 0.31 and 0.25 proportionate incidences for the first-year interval cancers. Our adjusted estimate was 0.26.

A recent pooled analysis of eight screening programmes within the European Breast Cancer Screening Network (87) resulted in interval cancer rates for the first year at 5.9 (range 2.1-7.3) per 10,000 screened negative and 12.6 (range 6.3-15) per 10,000 for the second year of the interval. The rate ratios of interval cancer were 0.29 for the first year and 0.63 for the second year of the interval. Interval cancers comprised 28% of the interval and screen-detected cancers.

The strength of our study is the completeness and accuracy of interval cancer data, the wide age range and the long study period. However the possibility

of studying the effect of recall rate and interval length on this material is limited because of small variations of these factors.

Radiological review of interval cancer

The *informed consensus review* of the interval cancer cases in three of the NMSP screening intervals resulted in 48% true, 10% occult, 14% missed and 28% minimal signs interval cancers. More than half of the interval cancers in the NMSP (58%) presented because of the intrinsic limitations of the screening process (true and occult) and in less than half of them (42%) human error could have contributed to their generation (missed and minimal signs). In the Östergötland mammography screening programme that also invites women aged 40-74 the corresponding figures are 49% true, 10% occult and 25% missed (overlooked and misinterpreted) (104).

Interval cancers constitute a heterogeneous group from the tumour biology point of view with different sojourn time. The reduction of different interval cancer types can be addressed by taking specific measures aimed at their causation. The frequency of true interval cancers can eventually be reduced by shortening the length of the interval as they tended to appear during the second year of the interval. The occult interval cancers are caused by the intrinsic limitation of the test method to see through dense breast and detect the lesion. New, more sensitive test methods are needed to reduce the frequency of occult cancers. Digital mammography with or without computer aided detection (CAD) is such a promising method that is more sensitive to breast density (110-114). The false negatives are considered more actionable, that is reducible by interventions that can raise the quality of screening, e.g. two-view imaging, double reading and training of the personnel. A higher recall rate, higher biopsy rate can also reduce interval cancer incidence but over a limit it can produce more harm than benefit (104). Therefore, a balance should be kept between the proportions of false negative and false positive cases.

In this material the late interval cancers overweigh the early interval cancers at a proportion of 61% to 39% and therefore a shortening of the interval could reduce their frequency. The most common mammographic feature was a spiculated mass and the dense breast pattern presented more often (71%) than in the general screening population. We merged true and occult interval cancers into one category (true) and missed and minimal signs interval cancers into another category (false negative or iatrogenic) and then tested for association between the dichotomised interval cancer type and time to diagnosis, age group, mammographic features and breast density. We found association between the dichotomised interval cancer type and time to diagnosis ($p=0.04$) but not between the dichotomised interval cancer type and age group ($p=0.15$), neither between interval cancer type and mammographic features ($p=0.19$) nor between interval cancer type and breast density ($p=0.20$).

When comparing the missed and minimal signs interval cancers we found that the most common mammographic feature in the missed category was the mass (65%) while in the minimal signs category it was the ill-defined density (distortion and asymmetric density) (70%). This difference seems reasonable from the radiological point of view, however it was not statistically tested because of small numbers. Our material is quite small and as such does not allow robust results.

Early deaths from breast cancer

It is well known that breast cancer has a substantial impact on the rate of premature death in women. In Sweden 23% of deaths in women of all ages and 12.8% of deaths in women aged 30-64 years were due to cancer as the main underlying cause of death in the year 2008 (56). In women aged 45-64 years lung cancer and breast cancer were the main causes of death (56). In women aged 65-74 years lung cancer took over the lead from breast cancer as the main cause of death (56).

We studied early death among breast cancer cases in Northern Sweden diagnosed during the first five years of the gradual introduction of service screening in women aged 40-74 years and followed until death from breast cancer or through 1998 (Paper III). We described their distribution by age, detection mode, prognostic factors and circumstances of death. The mean survival time to deaths was 3.1 (0.1-8.0) years. The mean survival time for a patient with systemic breast cancer is estimated to two years with wide individual variation (115).

The mean age at breast cancer diagnosis and death were 60 and 63 years, respectively. The age distribution of the interval-detected lethal cases was significantly lower ($p<0.001$), below age 60, than that of the lethal cases among screen-detected and non-participants. This might suggest that women aged 40-59 at death had faster growing, more aggressive tumours. The relationship between tumour growth rate and malignant capacity of breast cancer has been debated by others (116, 117). It is generally accepted that breast cancer grows on average faster in younger women but its relationship to malignant capacity is conflicting (118-120).

The vast majority (82%) of the women who suffered a premature death because of breast cancer during the study period presented with symptomatic advanced stage or high malignancy grade cancer at diagnosis. Advanced stage breast cancer (stage II+) was recorded in 85%, tumour size of ≥20 mm in 72% of the cases, 69% presented spreading to the regional lymph nodes and 24% were found to have distant metastases. The events that preceded the fatal outcome were the following. Local recurrence and/or distant metastases presented some time after the primary diagnosis that sooner or later lead to disabling complications, organ dysfunctions, deteriorated health status and death.

A shift towards lower stages was observed among screen-detected and interval cancer cases with fatal outcome, a phenomenon reflecting the effect of screening. Another study concluded that the most of the mortality reduction following the introduction of screening was due to downward stage shift from advanced stage towards stage I and not from invasive to in situ cancer (121). Screen-detected and interval cancers had more favourable prognostic characteristics than uninvited and non-participants.

A few asymptomatic women with screen-detected low-grade and <10 mm tumours also presented a fatal outcome in spite of the apparently favourable prognostic characteristics at primary diagnosis. Their early deaths were unforeseen and inexplicable and obviously, early detection and state of the art treatment did not help them survive. This fact was contradictory to research that pretended that the prognosis of small, non-disseminated, low-grade cancers is good (100, 122). The behaviour of small, less than 15 mm, node negative breast cancers suggested that this was a heterogeneous group. Tumours with casting type microcalcifications of sizes T1a, T1b and 10-14 mm behaved as if they were larger and they presented a death rate similar to that of advanced, high-grade tumours (123). These cases were scrutinised for possible explanations of the lethal outcome. The low grade tumours with fatal outcome constituted a heterogeneous group at diagnosis. They differed from each other by detection mode, symptoms, mammographic features, grade and stage. The less than 10 mm tumours with fatal outcome constituted a homogeneous group. They were screen-detected, asymptomatic, high grade, stage I cases with both an invasive and an in situ component on histology and with opacity and calcifications on the mammogram. Research has showed that small invasive caners that present with casting type or granular calcifications alone or in combination with masses had worse prognosis than other types (124).

This study was meant to serve a better understanding of the disease biology and mammographic features of the lesion but our material was too small to allow conclusions on the unforeseen and unpredictable cases with fatal outcome. However, the mammographic features at diagnosis, especially opacity in combination with casting type calcifications, can warrant for a poorer prognosis than expected (125, 126). Bigger, well designed studies are needed for that with access to more modern, third generation prognostic-predictive factors. Such studies are heavily dependent on a high quality tumour register and the possibility of record linkage.

Survival from breast cancer

We studied survival from invasive breast cancer by detection mode with focus on interval cancer in the NMSP (Paper IV) during a 13-year follow-up. Survival rates were highest for women with screen-detected breast cancer followed by women with interval cancer, women with breast cancer among the uninvited and women with breast cancer among the non-participants.

The 5-year and 10-year survival rates by detection mode varied between 0.93 and 0.74 and between 0.86 and 0.52, respectively.

When comparing stage I and II interval cancers with stage I and II cases among the uninvited and estimating survival by stage, the 5-year and 10-year survival showed a decreasing trend in the following order: stage I uninvited cases, stage I interval cancer, stage II interval cancer and stage II uninvited cases. The corresponding 5-year and 10-year survival rates varied between 0.95 an 0.78 and between 0.88 an 0.63. (not published in Paper IV).

When comparing survival by detection mode in screen-detected and non-participants one has to be aware of and eventually adjust for lead time bias, length bias and self selection bias (127, 128). As we focused on interval cancer in our study we did not adjust for the above mentioned biases but compared interval cancer cases with cases among the uninvited that do not suffer from the above biases.

The observation that women with stage I interval cancer had a shorter survival and those with stage II interval cancer a longer survival than expected, suggested us that interval cancers might consist of two subgroups. One subgroup made up of fast-growing tumours presenting at screening as stage I cases yet with worse prognosis than expected due to the high growth rate and one subgroup consisting of slow-growing tumours presenting at screening as stage II+ cases yet with better prognosis than expected due to the slow growth rate. Breast density, observer-related causes and technical limitations might also contribute to cancer detection in the screening intervals. However, two major reasons for interval cancer are related to tumour biology and length of interval. Both fast-growing tumours with shorter sojourn time than the screening interval and slow-growing tumour with longer sojourn time than the screening interval are prone to present as interval cases.

The evidence about interval cancer survival in relation to that of an unscreened population is conflicting. There are studies that report an interval cancer survival rate similar to that of an unscreened control population (119, 127, 129). Our results are consistent with reports that show a higher interval cancer survival rate compared to unscreened (100, 118).

Detection mode was found to have an impact on survival by modifying the prognostic effect of stage, and this finding was not modified by age, grade or ER status.

Mortality from breast cancer

Our results confirm previous findings of the literature and indicate a long-term reduction of breast cancer mortality as an effect of invitation to service screening in parity with the results of several RCTs and service screening (130, 131). We studied breast cancer mortality (UCD) and excess mortality

(EM) in the invited population and in screened women aged 40-74 years after 11 years of follow-up (Paper V).

Refined mortality was used in the geographical comparison of the effectiveness of service screening, that is, only breast cancer cases diagnosed after the woman's first invitation to screening were considered. Adjustments for baseline breast cancer incidence, lead time and self selection were applied.

We found a significantly reduced mortality by between 26% and 30% in the invited population by the UCD and EM methods, respectively. A mortality reduction by between 36% and 38% in the invited by the EM and UCD methods was seen in the youngest age group of 40-49 years, respectively. This effect was comparable to the effect in the 50-69 year age group. An extra 5% mortality reduction was observed in the screened exposed population. The two methods (UCD and EM) of measurement showed similar results with some increasing differences by age.

Our present study was based on the same population as a previous study (55), with six more years of follow-up, confirms the previous results of decreased breast cancer mortality among women invited to screening compared to women not invited to screening. The precision of our results became higher with the longer follow-up time and the effect of screening on age group 40-49 was of the same size as that in the age group 50-59.

In comparison, a large evaluation study of the reduction in breast cancer mortality from organised service screening with mammography in Sweden indicated a 39% to 45% mortality reduction in association with screening after a long follow-up period (22-44 years) depending on the method of investigation (132, 133). The Swedish Organised Service Screening Evaluation Group (SOSSEG) concluded that these results were obtained with modest human costs, expressed in number needed to screen to save one life estimated at 472 (132). The SOSSEG also concluded in an other paper that this result was due to the fact that screening substantially reduced the rates of large tumours and lymph node-positive breast cancer in Sweden which magnitude was consistent with the reduction in breast cancer mortality (83)

The number needed to screen (NNS) is an increasingly used comparative measure and patient-shared decision making information source (134). We also estimated the NNS to save one life after eleven years of follow-up at 912 women aged 40-74 years had to be screened during the accrual period (seven years) to save one life. In comparison, the NNS in the Two-county RCT after 20 years of follow-up was 1499 (95% CI 1046-2642) (135).

Summary

The Norrbotten Mammography Screening Programme (NMSP) was used for the estimation of episode sensitivity, interval cancer incidence and radiological review of interval cancers.

Episode sensitivity of the NMSP was on an acceptable level according to the European guidelines and it increased with age. Interval cancer rate ratios were twice as high in ages 40-59 compared to 60-74. Interval cancer rates showed little variation by age relative to the screen-detected cancer rates that showed an obvious increasing trend with age.

The variation in start of the service screening in the four counties of the region made it possible to study early deaths, breast cancer survival and breast cancer mortality in Northern Sweden.

During the first five years of the introduction of service screening in the region the number of early breast cancer deaths was similar in the counties with and without screening. In the screened counties more than half of the deaths occurred among screening attendant and less than half among non-participants and not yet invited. In the counties without screening all lethal cases were clinically detected. In a few cases with favourable prognostic factors at diagnosis the fatal outcome could not be explained and avoided in spite of early detection and state of the art treatment.

Detection mode proved to have a significant effect on the breast cancer survival rates. The survival rates for interval cancer cases were higher than those for cases among the uninvited.

Refined breast cancer mortality as the main outcome measure for the evaluation of the effectiveness of service screening showed a statistically and clinically significant impact of the intervention on women aged 40-74 invited to screening.

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