Breast cancer screening in an urban, Swedish population Aspects of non-attendance, interval cancers and over-diagnosis

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List of original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Matson S, Andersson I, Berglund G, Janzon L, Manjer J.
Nonattendance in mammographic screening: a study of intraurban differences in Malmö, Sweden, 1990-1994.
Cancer Detect Prev. 2001;25(2):132-7.

II Zackrisson S, Andersson I, Manjer J, Janzon L.
Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma.
Int J Cancer. 2004:108(5):754-60.

III Zackrisson S, Janzon L, Manjer J, Andersson I.
Improved survival rate for women with interval breast cancer. Results from the Malmö Mammographic Service Screening Program.
In manuscript

IV Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP
Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study.
BMJ, doi.1136/bmj.38764.572569.7C (published 3 March 2006)

Abbreviations

CI	confidence interval
DCIS	ductal cancer in situ
HIP	Health Insurance Plan
HRT	hormone replacement therapy
ICD	International Classification of Diseases
LCIS	lobular cancer in situ
MMSSP	Malmö Mammographic Service Screening Programme
MMST	Malmö Mammographic Screening Trial
NBSS	National Breast Screening Study
OR	odds ratio
p	p-value
r	correlation coefficient
RR	relative risk/relative rate
SD	standard deviation
SES	socio-economic score
TNM	tumour, nodes, metastases

Introduction

Breast cancer is the leading cancer cause of death in women world-wide.[1] Although several risk factors are associated with the occurrence of the disease there is at present no apparent primary prevention strategy. The alternative option in order to reduce the number of deaths from breast cancer is to improve the rate of survival by early detection and treatment.

Several trials have been carried out during the last three decades, four of which were in Sweden, in order to investigate whether it is possible to lower the mortality in breast cancer by inviting women to screening with mammography.[2-10] One of these trials was the Malmö Mammographic Screening Trial, MMST, which was published in 1988.[2] The results showed that women in the study group aged 55 years or older at entry had a not statistically significant 20% reduction in mortality from breast cancer. For the total study cohort, 45-69 years at entry, there was no difference in mortality. To increase the statistical power meta-analyses of the Swedish trials have been carried out.[11;12] A 29% reduction of breast cancer mortality in women aged 50-69 at randomisation was shown in the first one published in 1993. Based on some of the initial trial results, the National Board of Health and Welfare issued guidelines for general screening of women 40-69 years of age in Sweden.[13;14] Initially, no reduction in breast cancer mortality in women aged 40-49 years was shown in the trials, but there is now evidence supporting screening in this age group as well.[15] The randomised trials and their results have been questioned[16;17] but the criticism has been refuted by several authors.[18-21] The benefits of screening include early detection and treatment and better survival from breast cancer. The side-effects are false positive and false negative tests and detection of clinically insignificant cancers to mention some. It is now widely accepted that the advantages outweigh the

disadvantages. In later years evidence of decreased breast cancer mortality related to the introduction of service screening has also been reported.[22-26]

A high rate of attendance, a high diagnostic accuracy and treatment in accordance with established guidelines are key circumstances for an effective screening programme. It is not evident that an effect shown in a meta-analysis is present in all settings or that it persists. Thus attendance and radiographic quality is crucial and has to be continuously monitored. There is no national system for efficacy and quality control of mammographic screening in Sweden. Evaluation is left to the local health authorities responsible for screening.

After the termination of the MMST, the Malmö Mammographic Service Screening Programme, MMSSP, was implemented in 1990. The transition from trial to service screening programme provides a natural, experimental setting for epidemiological studies of factors of significance for the effectiveness of screening in different time periods and under different screening premises. The aim of the present thesis was to focus on three issues of relevance for the effectiveness of mammographic screening: non-attendance, interval cancers and over-diagnosis.

Patterns of attendance

Not all women choose to come to examination. Is this a random phenomenon or can a pattern be discerned? In epidemiology, defined as the study of the distribution and determinants of disease and health related states or events in a population, the main objective is to search for the potential for prevention. Similarly, the identification of factors and circumstances associated with non-attendance at screening can be used to improve the adherence by allocating resources to appropriate groups and areas. The Commission of the European Communities has recommended the level of the attendance to be over 70% in

order to be acceptable.[27] It is known that attendance rate decreases with age and that it is lower in urban than in rural areas. Attendance rates ranged between counties in Sweden from about 60% to 89% in the mid 90's.[28] The attendance rate in MMST was 74%, which was lower than in the other Swedish trials.[2;11]

Patterns of attendance in relation to mode of invitation

What happened to the attendance rate in Malmö when the service screening programme was implemented? The method of invitation and the prerequisites for mammographic screening differed in the MMST and the MMSSP. At the start of the MMST the benefits of mammographic screening were not known. In the MMST women were asked to participate in a trial which aimed to assess the efficacy of screening in reducing breast cancer mortality. They got a scheduled appointment at the same time. When the MMSSP started the efficacy had been demonstrated and there were national guidelines regarding mammographic screening. Furthermore, women in the eligible ages first got an inquiry whether they would be interested in attending screening. Only after having given a positive answer, in some cases after a reminder, they got a scheduled appointment. The change in mode of invitation had not been evaluated and there was hence need to see whether any change had occurred in the rate of non-attendance.

Patterns of morbidity and screening participation in relation to the socio-economic environment

Malmö is a city with about 260 000 inhabitants in southern Sweden and is the country's third largest city. Breast cancer is more common in urban than in rural areas. The incidence of breast cancer was $115.2/10^5$ for the whole of Sweden in 1997 and in Malmö $136.9/10^5$.[29] The breast cancer mortality rate in Malmö was similarly higher than the national average, $40.5/10^5$ vs. $34.5/10^5$ in 1996.[30]

Within the city of Malmö, there are large intra-urban differences in morbidity and mortality of many diseases which covariate with patterns of risk factors and socio-economic circumstances.[31-35] This also applies to breast cancer.[34] A comprehensive socio-economic score for the 18 residential areas in Malmö has been developed to describe the socio-economic circumstances in each area.[36;37] Following the intra-urban differences demonstrated for various conditions in Malmö, there was reason to believe that a similar pattern was present for non-attendance in mammographic screening.

Socio-economic characterisation of attenders and non-attenders

Characterisation of the women who attend and not attend screening has been done in several studies, mainly in not population based service screening settings.[38-51] Factors that have been shown to affect attendance and non-attendance vary according to type of screening programme and country. Various psychosocial circumstances have been shown to be connected with non-attendance in interview studies in the county of Uppsala.[52-54] Furthermore, a register study from the same area showed that non-attendance in service screening was associated with living alone, being not employed and being immigrant from non-Nordic countries to mention some factors.[55] No similar study had been carried out in the city of Malmö and there was hence a need to investigate whether the rate of attendance varied between groups defined in terms of their socio-economic circumstances.

Prognosis for non-attenders with breast cancer

It is well known that there is a self-selection bias in screening programmes which tend to attract preferably the well off, health conscious individuals in a population while those with various risk-factors and socio-economic problems

tend not to attend. This has been demonstrated in other research projects in Malmö[56;57] and in the MMST.[2] It was further documented in a case-control study of the invited group in the MMST.[58] Lidbrink et al showed that women who actively avoided mammography in the Stockholm trial had a significantly higher mortality from breast cancer than had the control group.[59] We wanted to investigate whether non-attendance in mammographic screening in the city of Malmö still was associated with a less favourable prognosis of breast cancer.

Factors related to early detection of breast cancer

There are many factors that may have an impact on the accuracy, i.e. the precision with which individuals with and without disease are identified in a mammographic screening programme; technical equipment, image quality and the staff's experience to mention some. The probability of detection of breast cancer at screening is also related to factors such as the growth rate and the radiographic morphology of breast cancer and the tissue composition of the breast. Mammographic screening will not detect all breast cancers in a population due to non-attendance and *interval cancers*, i.e. cancers appearing between two screening examinations. On the other hand, there is a risk of detecting slow-growing cancers that in absence of screening never would have surfaced clinically in a woman's lifetime, i.e. *over-diagnosis*. Moreover, there are disadvantages with screening represented by false-positive screening results, and the, albeit very small, risk of radiation induced cancer. In addition to non-attendance, the present studies focus on two of the mentioned aspects: interval cancers and over-diagnosis. Some concepts in tumour characteristics and screening related to the occurrence of interval cancer and over-diagnosis need to be considered:

Breast cancer - a heterogeneous disease

Breast cancer is a heterogeneous disease comprising different types of tumours in terms of histology, growth rate and aggressiveness and radiographic presentation. There are several classification systems based on histology, stage, grade etc. From a microscopic point of view a pre-invasive stage (carcinoma in situ) can be identified, implying that the cancer does not infiltrate beyond the basal membrane of the milk ducts and does hence not have the ability to metastasise. Carcinoma in situ can be subdivided into lobular and ductal carcinoma in situ (LCIS and DCIS). DCIS can often be identified radiographically on the basis of characteristic calcifications. The proportion of in situ carcinoma that progresses to invasive disease, if left untreated, is not known but has been estimated to 50-80%.[60;61] An increased risk for subsequent invasive cancer after diagnosis and treatment of carcinoma in situ has also been shown.[62-64]

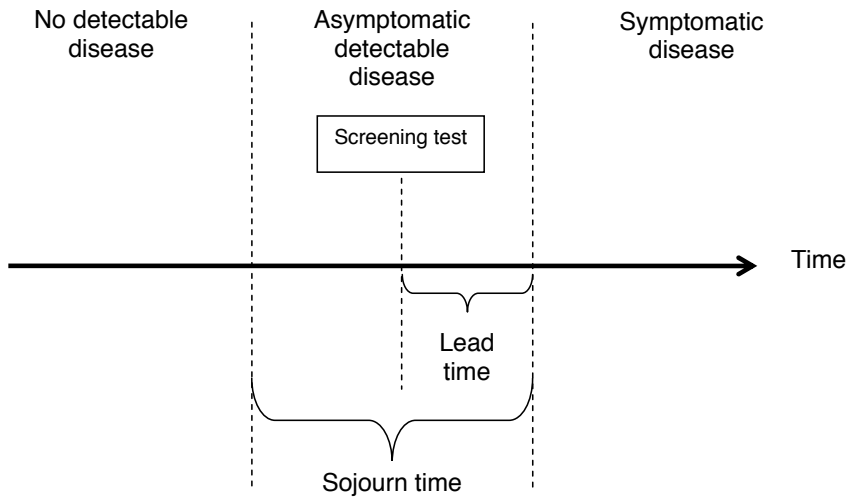

Figure 1: Schematic overview of the progression of a disease and the intervention of a screening test.

Screening detection in relation to tumour growth rate

Breast cancer also represents a wide spectrum of growth rates. One of the prerequisites for screening is that the tumour is relatively slow-growing and has a radiographical appearance that is identifiable. The period of time during which the tumour is detectable is often called *sojourn time*, figure 1.[65] *Lead time* is the period of time from actual detection at screening to the supposed clinical appearance in the absence of screening.[66] Lead time has, depending on age, been estimated to 2-4 years on the average.[67] The probability of detection by screening depends on the length of time the lesion is detectable preclinically, i.e. the sojourn time: the longer the sojourn time the greater the chance of detection. On the contrary, the fast growing tumours are more likely to present as interval cancers, figure 2.

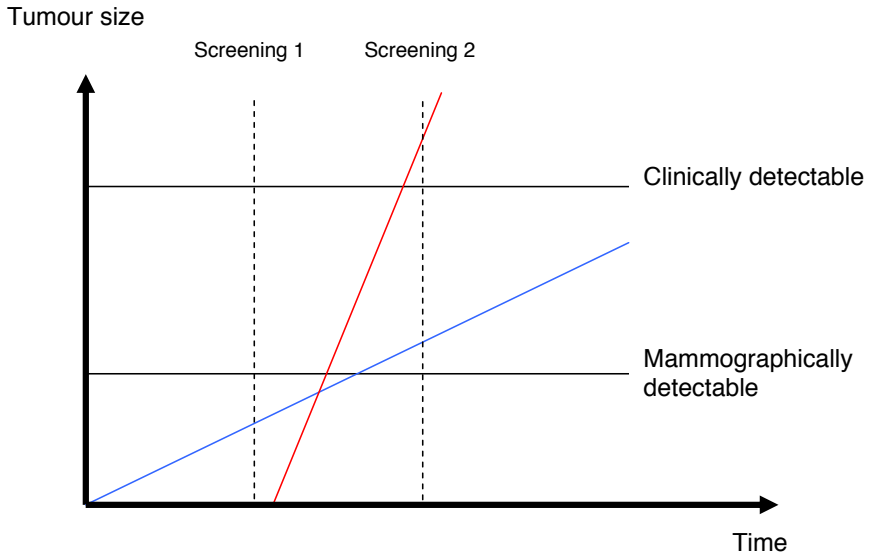

Figure 2. Tumour growth rates in relation to screening.
The blue line represents a slow growing tumour with long sojourn time and high probability of mammographic detection before it presents clinically with symptoms. The red line represents a fast growing tumour more likely to present as an interval cancer.

Probability of detection in relation to radiographic patterns

The radiographic appearance of breast cancer ranges from hardly detectable minimal signs to obvious signs of cancer. Some radiographic patterns of breast cancer are more easily detected at an early stage such as spiculated tumours and calcifications, figure 3, others more difficult such as tumours presenting as non-specific densities and areas with subtle architectural distortion, figure 4. There is some evidence that, from a radiological point of view, tumours easily seen with mammography represent tumours with low histological grade.[68] Pre-invasive cancer is often detected on the basis of calcifications. Therefore, due to lead time and radiographic pattern the sample of breast cancer detected at screening are more than average slow-growing with a more benign course than an average sample of breast cancer cases (*length biased sampling).* [69-71]

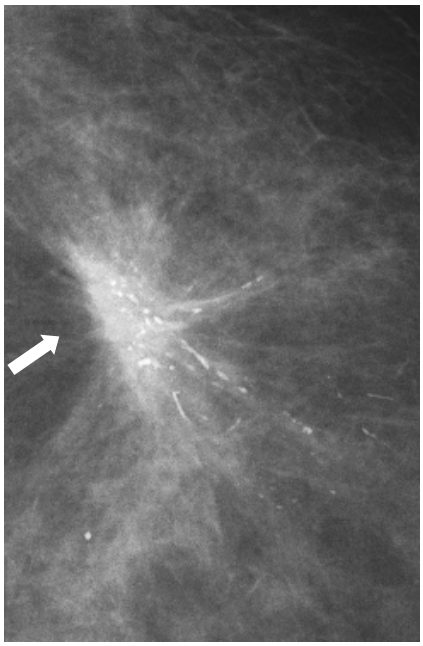

Figure 3. A tumour with typical appearance on the mammogram. A spiculated mass with retraction of the surrounding tissue (arrow). Multiple, linear calcifications. At pathological examination an invasive ductal cancer grade III was found and in addition multifocal DCIS.

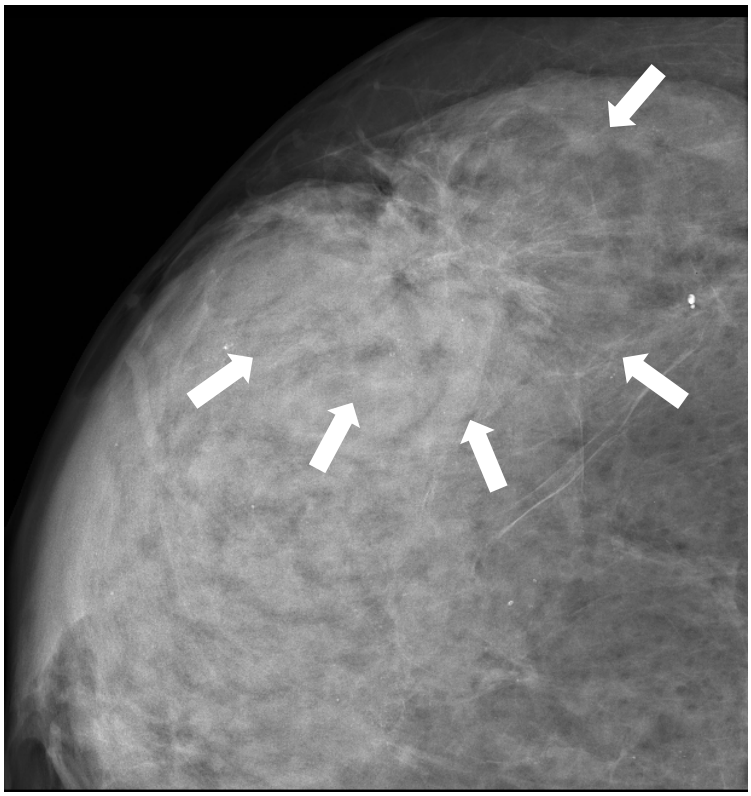

Figure 4. Screening mammogram. An area of architectural distortion (arrows) without evident tumour mass. At pathological examination a 3,0 cm invasive ductal carcinoma grade II was found.

Another factor of importance for detection at screening is the density of the breast parenchyma on the mammogram which is a reflection of the amount of fibro-glandular tissue in relation to fat tissue. The denser the breast appears on the mammogram, the lower the sensitivity of mammography to detect breast cancer.[72-76] Younger age is associated with dense breast and is one of the reasons why lead time is shorter in younger women than in older.[67] The use of hormone replacement therapy, HRT is also known to be associated with dense breasts,[72;77;78] As a consequence HRT-users might have a higher risk for interval cancer, probably due to masking of the tumours and maybe of a more rapid growth rate.[79;80]

Prognosis associated with interval cancer

Interval cancer is usually defined as breast cancer diagnosed between two screening examinations where the preceding screening mammogram was considered normal, figure 5a and b. As inferred from above, one explanation may be fast growth rate[81;82] or atypical presentation on the mammogram.[82] Also, overlooking early signs of breast cancer on the preceding screening mammogram is another explanation. The proportion of missed diagnoses has been shown to vary depending on the review method[83] but is usually rather small, 10-20% of all interval cancers.

It is possible to hypothesise that interval cancers on the average are relatively fast growing and therefore more than average malignant. Thus, a high rate of interval cancers in a screening programme would reduce the effect in terms of mortality reduction. However, data on the survival of interval cancers are conflicting. Interval cancers have been associated with more malignant characteristics than other groups of breast cancer.[80-82] Survival rates among women with interval cancer have in other studies been shown to be similar or even higher than the survival rates in breast cancers from a non-screened population.[3;84;85] The contrary was seen in the MMST where women with interval cancer had a 2.3 times higher risk of dying from breast cancer compared to women with cancer in the control group.[2] The MMST ended 20 years ago and there have been improvements in therapy and technical equipment since then. The subset of cases in a screened population that emerge as interval cancers might have changed and the use of HRT has also increased. There was hence reason to believe that the outcome for women with interval cancer in the MMSSP might differ from that in the MMST.

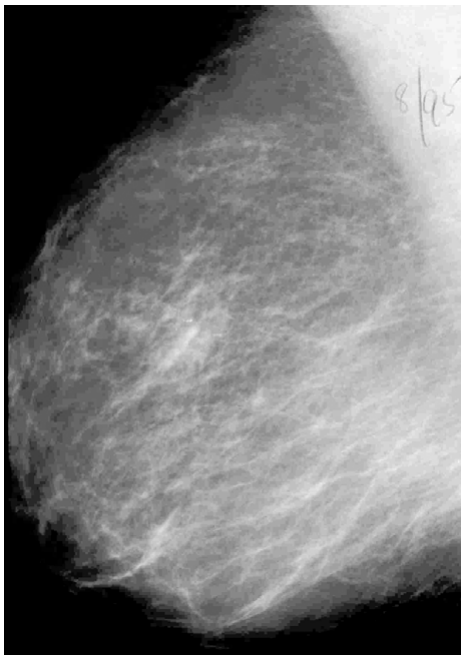

Figure 5a

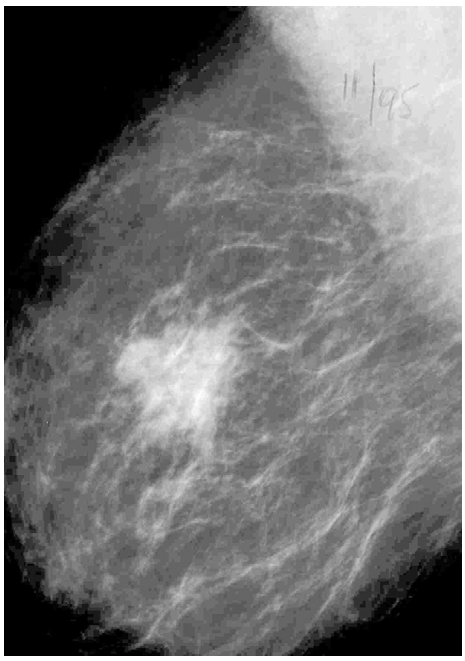

Figure 5b

Figure 5a and b. Example of an interval cancer.
Fig 5a shows a normal screening mammogram. 3 months later the woman presented a 2,5 cm large, irregular tumour which was an invasive ductal carcinoma grade III, fig 5b.

The magnitude of over-diagnosis in breast cancer screening

Due to the lead-time of screen-detected tumours and length bias sampling some breast cancers will be detected at screening which would otherwise not have come to clinical attention due to the women's death in inter-current disease. These tumours are considered as being over-diagnosed at screening and lead eventually also to over-treatment, a potentially harmful effect of screening. False-positive diagnosis at screening is not to be confused with over-diagnosis. Even some invasive cancers are slow-growing and we have observed such cases with virtually no progression over several years. Furthermore it is reasonable to believe that a certain proportion of ductal cancer in situ (DCIS) will not progress to invasive disease. Yen et al estimated the proportion of non-progressive DCIS to be 37% at prevalence screen and 4% at incidence screen, based on statistical modelling.[60]

Two recent studies have shown that up to 50% of the breast cancers diagnosed at screening could be over-diagnosed,[86;87] while some studies have claimed little or no over-diagnosis.[88-90] The above results have been based on estimates rather than actual observations. The cumulative incidence in the randomised controlled trials in the invited groups in relation to in the control groups would be the best way to evaluate over-diagnosis. Over-diagnosis can only be estimated after a time equivalent to the lead-time of the screen-detected tumours has elapsed after the final screening and provided the control groups are not invited to screening.[91] The control groups have eventually been offered screening in the majority of the Swedish trials.[3-6] One of the first trials, the Health Insurance Plan Project (HIP) and also the Edinburgh trial have not been considered suitable for evaluation of over-diagnosis for various reasons.[91] The Canadian studies National Breast Screening Studies I and II (NBSS) were not population based and offered mammography and physical examination and breast self-

examination in different combinations. As a result these studies are not fully comparable with the other trials with mammography alone.[92;93] They showed though, that the excess incidence generated by screening in the invited group persisted at follow-up. However, the way the MMST was conducted and terminated provided a possibility to investigate the rate of over-diagnosis in the 15 oldest birth-year cohorts, whose control groups were never screened.

General aim

- To study aspects of significance for the effectiveness of mammographic screening in an urban, Swedish population.

Specific aims

- To explore whether the pattern of non-attendance among urban women offered breast cancer service screening is different from the pattern of non-attendance in a trial designed to assess the efficacy of screening

- To explore if and how the rate of non-attendance among urban women offered breast cancer screening with mammography varies across residential areas defined in terms of their socio-economic circumstances

- To characterise the non-attenders and attenders in terms of their socio-economic circumstances

- To explore whether non-attendance in an urban breast cancer screening programme is associated with an over-representation of cases with less favourable prognosis

- To explore whether during the last 20 years of breast cancer screening there has been any change in the incidence of and prognosis associated with interval cancer

- To assess the rate of over-diagnosis in a breast cancer screening programme with mammography

Material, methods and results

Subjects in the Malmö Mammographic Screening Trial, MMST

In the MMST I all women born 1908 through 1932 (45-69 years at randomisation) and living in Malmö were randomly allocated to either invitation to screening with mammography or to a control group. The study started in October 1976 and the cohort comprised 42 283 women of which 21 088 were invited and 21 195 controls. Each birth year cohort was randomised separately from the start of the trial to 1978, the first screening round was completed by the end of 1978. Women were invited by personal letter with a scheduled appointment. The screening interval was 18 to 24 months. The trial ended in December 1986 and was reported in 1988.[2]

The MMST II study started in 1978. The cohort comprised 17 786 women born 1933 to 1945, living in Malmö and who were randomly allocated to receive invitation to screening or to a control group. The plan was to invite these women when they turned 45. Due to limited resources, this could not be strictly adhered to. As a consequence, some years no women could be invited, while other years several birth-year cohorts were invited. [94]

After termination of the MMST, the randomised design was maintained for women up to age 70. Women in these ages, belonging to the former invited groups, continued to be invited during the years 1987-90, until they reached the age of 70.

Subjects in the Malmö Mammographic Service Screening Programme, MMSSP

Following recommendations from the National Board of Health and Welfare[13] a service screening programme was established in the city of Malmö in 1990, the Malmö Mammographic Service Screening Programme, MMSSP. Women who are 50-69 years of age are invited every 18-24 months to mammographic screening. Women, who earlier belonged to the MMST trial cohorts and who were younger than 50 years at the start of the MMSSP were also invited. The method for invitation was changed in the first years of the MMSSP compared to the MMST: A two-step procedure was used. First a letter was sent out to women in the eligible age groups asking whether they would be interested in attending the screening programme. Those who answered "yes" eventually got an invitation within about two months, while those answering "no" or who did not answer after having received a reminder were regarded as not interested and were hence not invited. Despite having expressed an interest, some women did eventually not come to examination.

For the current studies databases containing information on attendance and selected technical data of the MMST and the MMSSP were used.

Mammography

Mainly two-view mammography was used during the MMST and MMSSP and always at the first screen. One view (medio-lateral oblique) was used for women whose breasts were predominantly fatty on mammography in subsequent screens. The equipment used was state-of the art mammography. During the MMST and MMSSP double-reading was practised, but not consistently.

Breast cancer cases and causes of death

Status with regard to breast cancer diagnosis and death was obtained by linking screening databases with the Swedish Cancer Registry and the Swedish Cause of Death Registry. This was possible through the 10-digit personal identification number.

The Swedish Cancer Registry was established in 1958. Reporting new cases of breast cancers to the registry is mandatory and completeness and validity is high.[95] Cancers are coded according to the International Classification of Diseases, ICD. The validity of diagnosis and completeness of registration in Malmö has been evaluated by Garne, covering the time period 1961-91. Ninety-nine percent of all women with invasive breast cancer in Malmö were found in the register. The completeness of carcinoma in situ was somewhat lower but improved along the years. The breast cancer diagnosis could be confirmed for 93% of the cases reported to the registry.[96]

The Cause of Death Register contains information on the death of all persons registered as residents in the country irrespective of where the death occurred. Information on age and date of death, cause of death and contributing cause of death is included in the register based on medical death certificates. Causes of death are coded according to the International Classification of Diseases, Injuries and Causes of Death, ICD. Completeness of the register is almost 100%. [97] Medical death certificates are based on either clinical examination by an attending physician or by the coroner at autopsy. Garne has similarly assessed the validity by reviewing clinical and autopsy records of breast cancer cases in Malmö 1964-92. The rate of disagreement was 3.6%.[98] The autopsy frequency in Malmö was higher than the average in Sweden during many years, around 80%,[99] but has declined during the 1990's to below 20%.

Treatment

Malmö University Hospital is the only hospital for somatic diseases in the city. Virtually all women with breast cancer in the city are treated by a team specialised in breast diseases. Women with breast cancer are treated according to stage at diagnosis irrespective of screening status. Guidelines for treatment of patients with breast cancer have been issued by The South Swedish Breast Cancer Group and have been adopted by Malmö University Hospital.[100] Each patient with breast cancer is discussed at a weekly breast cancer conference where specialists in radiology, surgery, pathology, oncology and plastic surgery are represented. Diagnosis of breast cancer, stage, hormone receptor status and treatment is continuously entered into a register run by the South Swedish Breast Cancer Group. Information on stage at diagnosis, according to TNM,[101] taking into account the size (T), the prevalence of positive lymph nodes (N) and distant metastases (M), for the women included in two of the studies (paper II and III) has been obtained from this register.

Socio-demographic factors

Malmö can be divided into 18 residential areas known to differ with regard to socio-economic factors. The socio-economic profile of the areas is based on official statistics from Malmö City Council and data from Statistics Sweden.[31] A comprehensive socio-economic score (SES) was calculated from four variables: migration rate, percentage of residents with foreign citizenship as a proportion of all citizens with a foreign background, dependency on social welfare support (with negative signs) and employment rate (with a positive sign). The variables were standardised by subtraction with the mean level for all areas in Malmö and divided with the standard deviation for all areas before they were added up to a score.[37] (Paper I)

To obtain an individual socio-economic profile for women in the screening programme, linkage was done through Statistics Sweden with the 1990 Swedish Population Census and the Income Register. (Paper II) This is the latest census available in Sweden and it is based on a mandatory inquiry sent to all households. In our study cohort, less than 1% did not adhere to the census.

Studies

Non-attendance in mammographic screening: a study of intra-urban differences in Malmö, Sweden, 1990-1994. **(Paper I)**

Aim:
To describe the geographic and age patterns of non-attendance among women invited to mammographic screening in Malmö and to identify socio-economic circumstances related to non-attendance.

Material and methods:
32 605 women, 45-68 years of age, who were invited to screening between 1990 and 1994 were identified. 11 376 women did not attend. Age-specific and age-adjusted non-attendance rates were calculated for 17 residential areas (the harbour area was excluded due to too few inhabitants). A socio-economic score was calculated for each area, SES, as described above.

Differences in rate of non-attendance among areas were tested with the Chi-square test. Comparisons were done separately for women in 5-year age groups. Association between rate of non-attendance and the socio-economic score was assessed in a least-square regression model adjusted for differences among areas with regard to the number of 45-68 year old women living in the areas. The

association was expressed in terms of a correlation coefficient (r). Two-tailed p-values <0.05 were regarded as statistically significant.

Results:

The rate of non-attendance ranged from 31% in the youngest age group (45-49 years at invitation) to 35%, in the oldest age group (65-68 years). Small, but statistically significant differences in non-attendance was seen between the different 5-year age groups, $p<0.01$. Statistically significant differences in rate of non-attendance were also noted within each age group between residential areas. Between residential areas the rate of non-attendance ranged from 23% to 43%. Marked differences were also seen in the SES between the areas. The rate of non-attendance was higher in areas with a low SES than it was in areas with a high SES. The corresponding weighted correlation coefficient between the SES and the rate of non-attendance was -0.78 ($p<0.01$).

Conclusion:

The rate of non-attendance among urban women offered breast cancer screening with mammography varied substantially across residential areas. Women living in areas with less favourable socio-economic circumstances seemed less willing to participate.

Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma. **(Paper II)**

Aim:

To assess changes in non-attendance, proportion of advanced breast cancer and survival among non-attenders in the MMSSP compared to in the MMST. To

describe non-attenders in MMSSP in socio-economic terms and risk for advanced breast cancer compared to attenders.

Material and methods:

Attenders and non-attenders at first screening among 33800 women invited to screening in the MMSSP 1990-93 were identified. Non-attenders at first screening round in the MMST and the women in the former control group were used for comparison. Attendance rates at first screening, the proportion of advanced breast cancers (stage II-IV) and survival among non-attenders with breast cancer in MMSSP were compared to the non-attenders and with the former control group in MMST. Various socio-economic factors were assessed as potential predictors of non-attendance in the MMSSP, yielding odds ratios (OR) with 95% confidence intervals (CI). Incidence of breast cancer and advanced breast cancer (stage II-IV) during a 10 year period, relative risks (RR) and 95% CI among non-attenders compared to attenders in the MMSSP were assessed.

Results:

Attendance rates were significantly lower in the present service screening programme MMSSP than in the MMST. A lower proportion of advanced breast cancers and a somewhat better survival among women with breast cancer were seen in MMSSP non-attenders compared to MMST non-attenders. In MMSSP non-attendance was associated with being unmarried, being born abroad, being not currently employed, crowded housing conditions and low income. Incidence of advanced breast cancer was higher among non-attenders than among attenders.

Conclusion:

Although attendance rates have declined over time, the distribution of breast cancer among non-attenders seems to have shifted towards less advanced and survival has improved. Furthermore, we could identify several socio-economic groups that were more likely to be non-attenders. The risk for advanced carcinoma at diagnosis was higher among non-attenders.

Improved survival rate for women with interval breast cancer. Results from the Malmö Mammographic Service Screening Programme **(Paper III)**

Aim:

The objective of this study of the MMSSP was to assess changes compared to the former Malmö Mammographic Screening Trial, MMST in terms of stage distribution and rate of survival for women with interval cancer.

Material and methods:

Women with interval cancers in the MMSSP 1991-99 (n=131) were compared with other breast cancer cases within the MMSSP (screen-detected and cancers in non-attenders) and with interval cancer cases and cancers cases among controls in the MMST. Differences in stage distribution were tested with the Chi-square test. Mortality differences between groups were assessed using Cox's proportional hazards analysis, yielding relative risks (RR) for death and breast cancer death, with 95% confidence intervals (CI) before and after adjustment for age and stage.

Results:

The rate of interval cancer was 1.5/1000 women screened 1991-99. The MMSSP interval cancer cases did not differ in stage distribution or survival compared to cancer cases among non-attenders, RR for overall mortality 0.96 (0.57-1.61). Screen-detected cancer cases had a more favourable stage distribution and rate of survival, RR 0.42 (0.23-0.78) than had MMSSP interval cancer cases. MMST interval cancer cases had a higher overall mortality, 1.78 (1.00-3.20) and breast cancer mortality, 2.05 (1.05-4.00) compared to MMSSP interval cancer cases. No significant difference in survival was seen in the MMSSP interval cancer cases compared to cancers cases detected among MMST controls.

Conclusion:

The prognosis for women with interval breast cancer in this urban population has improved during the last 20 years and might therefore be less of a problem in the current screening situation.

Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study **(Paper IV)**

Aim:

To evaluate the rate of over-diagnosis 15 years after the end of the Malmö mammographic screening trial.

Material and methods:

Women were allocated to either invitation to screening or to a control group at the start of MMST. After termination of the randomised design neither the

former invited, nor the control groups aged 55-69 years at randomisation were invited, while both groups aged 45-54 years at randomisation were offered screening. Rate of over-diagnosis was assessed as the relative rate, RR with 95% CI, of breast cancer (in situ and invasive) in the invited compared to the control groups during the period of randomised design (period 1), during the period the randomised design was terminated (period 2) and by the end of follow-up 2001.

Results:

Conclusions on over-diagnosis can be drawn mainly in women aged 55-69 years at randomisation in which the control groups were never screened. The RR was 1.32 (1.14 to 1.53) in period 1 and 0.92 (0.79 to 1.06) in period 2. At the end of follow-up it was 1.10 (0.99 to 1.22). Among younger women there was a 16% higher rate of breast cancer in the invited group compared to the control group during period 1. When both groups were invited in period 2, no difference was seen. This gave a RR of 1.08 (0.96-1.22) at the end of follow-up.

Conclusion:

Conclusions on over-diagnosis can mainly be drawn in women aged 55-69 years at randomisation, whose control groups were never offered screening. In this age group there exists over-diagnosis as a consequence of screening, which amounted to 10% 15 years after the end of the trial. If the control groups are invited no conclusions on over-diagnosis can be drawn.

General discussion

Attendance rates in relation to screening premises and mode of invitation

European guidelines recommend a participation rate of more than 70% to be acceptable, while more than 75% is a desirable level.[27] In an urban population one might expect the rates to be lower than in rural areas. The average attendance rate in the MMST was 74% and in the MMSSP 65% (paper II). There may be multiple possible explanations why the attendance rate has decreased along the years. One may be the mode of invitation. The inquiry in the MMSSP whether or not one would be interested in participating in the screening programme may have had a negative effect in some cases. The rationale behind this procedure was to give women the opportunity to make an informed decision. A consequence may have been a postponement of the decision and non-attendance in higher proportions compared with a straight forward invitation including an appointment. It has been demonstrated that attendance rate is related to the mode of invitation and especially that attendance rates increase when there is a pre-assigned date of appointment in the letter of invitation.[102;103] There is need for more research on what strategy is the optimal.

While women participated for free in the MMST, a fee of about 120 SEK (about 15 USD) was introduced at the start of the MMSSP. This was the case for the majority of the service screening programmes nationwide. The cost for screening has in some studies been shown to be a barrier[104;105] and of no importance in another.[106] It remains to be evaluated to what extent the cost may discourage women from attending.

Idealistic motives may also partly explain the higher attendance in the MMST: women asked to participate in a trial may feel that they do something for the research and for future patients. Some of the first preventive projects in Malmö conducted during the 1970's had generally high attendance rates.[107;108] while a later project had considerably lower attendance.[56] This probably illustrates changes in the attitude within the population to attend health care projects. Ever since the introduction of service screening in Sweden there has been an intense debate in the press whether screening was effective or not and whether the radiation might even induce breast cancer. This might have discouraged some women from attending.

Patterns of non-attendance in relation to socio-economic circumstances

There seem to be patterns of non-attendance in a population; it is not a random phenomenon. We could define high and low rate areas in terms of non-attendance that could be described in socio-economic terms. Women living in less affluent areas participated to a lower degree. (Paper I) There was a strong correlation between socio-economic circumstances and rate of non-attendance. About 60% of the variance in non-attendance between areas could be accounted for by socio-economic circumstances, (r^2=0.61). Using an epidemiological approach it may hence be possible to reach further in how to encourage attendance.

The pattern was confirmed on an individual basis in paper II where it was shown that several individual socio-economic circumstances predicted non-attendance. Women who were not born in Sweden were less prone to participate, which has been shown in another Swedish study as well.[55] This may illustrate language barriers in understanding the information in the invitation letter, at least in some of these women. It may also reflect cultural differences. Furthermore,

immigrants from non-Nordic countries often come from areas with lower breast cancer incidence and these women may be less aware of the risk for breast cancer. Women living alone were less likely to participate than married or co-habiting women, which is in line with previous reports.[38;40;44;47;48;52;55;109] Marital status can be considered as a proxy for social support which may be important for the woman when deciding whether to participate or not. Women who were not currently employed were less likely to attend than employed women, which may reflect the level of education.

Epidemiological studies can thus be used to monitor factors related to attendance in terms of time, place and person. Even though the individual socio-economic circumstances in many cases only are indicators of psycho-social circumstances or health behaviour, identifying socio-economic predictors for non-attendance may be used in order to modify the invitation to screening. Efforts to improve attendance among the identified groups may include more individualised information, probably in several languages and taking into consideration ethnic characteristics. Identification of areas with high rates of non-attendance may lead to allocation of resources towards such areas or groups.

The non-attenders in MMSSP are not a homogeneous group: some women used options for mammography outside the screening programme. Some studies have found that this solution mainly was used by women who were socio-economically well off and with an interest in their own health.[46;48] We believe that this probably applies to our studies as well. If there were no options for mammography outside the screening programme, it would strengthen our results *(paper I and II)*.

A representative sample in a register study can only be achieved by using high quality registries. To our knowledge, there are not any systematic errors in the screening register at Malmö University Hospital. The screening register is regularly updated with the population register to keep track of the women in the age groups eligible for screening. By using the 1990 Swedish Population Census, it was possible to obtain information of the individual socio-economic circumstances for both the attenders and the non-attenders in the MMSSP. *(paper II)*. This reduced the risk for selection bias since non-attenders at screening probably would not answer inquiries or participate in interviews to the same extent as attenders.

Breast cancer in non-attenders

If healthy women with low risk for breast cancer were the non-attenders, non-attendance would be less of a problem. The monitoring of attendance rates must not only be concentrated upon socio-economic factors related to non-attendance, but also on whether there are any differences in cancer incidence and characteristics of the tumours in different groups. In the MMST there was an over-representation of advanced cancers among non-attenders. Both in the MMST and MMSSP attendance decreased with age, when the risk for breast cancer actually is increased. The present results showed, however, that the proportions of advanced stage breast cancer at diagnosis were lower among non-attenders in the MMSSP than in non-attenders in the MMST (paper II). It may partly be explained by increased use of mammography outside the screening programme. The results of the trials, the national guidelines together with increased information on breast cancer in the society may have resulted in an increased awareness of breast cancer over time which in turn might influence women to seek advice earlier nowadays. Cohort and period effects could not be accounted for in this study. In addition to a more favourable staging, improvements in therapy over time could account for the better survival seen

among non-attenders in the MMSSP compared to the MMST. Still, both non-attenders in the MMSSP and the MMST had a slightly worse survival than the unscreened control group, although not statistically significant, which may be a question of power.

Socio-economic circumstances have been shown to affect survival in several studies in that women with worse socio-economic situation had a worse prognosis independent of stage at diagnosis and other prognostic factors.[110-113] Since all women have equal access to health care in Sweden, economic barriers is probably not the explanation. The explanation might be sought for in cancer host-interactions where smoking, alcohol use, nutritional status etc. might have an impact on the capability to fight tumours. Better coping mechanisms and social support might be other factors that explain why socio-economically well-off women may have a better survival. This has so far received little scientific attention.

Is interval cancer an issue?

Our results indicate that the prognosis for women with interval cancer has improved since the previous publication in 1988.[2] There are several possible explanations. Improvements in therapy and increased awareness of breast cancer are some. However, various cohort effects such as HRT-use among women with interval cancers in the current screening programme may be different from in the MMST. Due to HRT-use the increased density of the parenchyma may conceal tumours. Tumours may also be stimulated by the hormone therapy. Higher frequency of HRT-use among women who get an interval cancer compared to women with screen-detected cancers have been found, supporting this theory.[79;80;114] Moreover, HRT has in several studies been associated with better differentiated tumours, i.e. lower tumour grade, which would mean better

prognosis for HRT-related interval cancers compared to other interval cancers. [80;115-118]

We did not find any worse 5-year survival for women with interval cancer in the MMSSP compared to a pre-screening group of breast cancers not exposed to screening. This is in line with results from other trials.[84;85] The pre-screening group of breast cancer was chosen to have been diagnosed and treated as close in time as possible to the MMSSP interval cancers, why potential differences with regard to these factors should have had a small impact on the result.

The cancer cases and information on survival has been obtained from the Swedish Cancer Registry and the Swedish Causes of Death Registry *(paper II-IV)*. Both registries are of high quality and have been evaluated for diagnoses and death from breast cancer in the city of Malmö especially.[95-98] The small discrepancies seen in causes of death in Malmö reviewed by Garne et al,[98] could in large part be explained by the fact that prior to 1980, breast cancer and other malignancies recorded as "contributing cause of death" were automatically, independent of time since diagnosis and clinical course, recorded as the "underlying cause of death". Furthermore, the autopsy rate in Malmö has radically declined during the 90's, which contribute to further uncertainty in the assessment of cause of death.[99] This should be taken into account when comparing breast cancer mortality in different time periods, this problem can be eliminated by using all cause mortality *(paper II-III)*.

The prognosis for women with interval cancer in the current service screening programme is not worse than for women with clinically detected tumours and has also improved compared to in the MMST. Interval cancers therefore seem to be less of a problem in the current screening situation. The interval cancer group is a heterogeneous group including both slow growing cancers that were

overlooked at screening and fast growing tumours. Regarding them as one entity probably dilutes the differences that would appear if only the fast-growing tumours were considered in a survival analysis. The subset of very fast growing tumours, which actually are identified only through the fact that they appear between screenings, would be an interesting group to study more. What are the biological characteristics of these tumours? This could add to the knowledge about cancer treatment and maybe these tumours should be treated differently from other breast cancers?

Estimating the magnitude of over-diagnosis in breast cancer screening

The risk for women being diagnosed with clinically insignificant breast cancer when participating in a screening programme has always been considered when balancing the pros and cons of screening.[66] Nevertheless, the main topic during the years has been whether mammographic screening has an effect on breast cancer mortality or not. In later years there has been a call for reliable estimates of the magnitude of over-diagnosis. Earlier studies have shown diverging results and different statistical approaches have been used why comparisons must be carefully made.[86-90] The MMST is the only randomised, controlled trial in which a large part of the control group was never invited to screening. This provided the possibility to study the excess cancer incidence generated by screening in the invited group compared to the incidence in the control group over a long period of time. The end of follow-up in our study was at least 10 years after termination of screening of the former invited group, which means that the effect of lead time should have been accounted for. The magnitude of over-diagnosis cannot in full be estimated until the end of lifetime. Among the women aged 55-69 years at randomisation, 60% had died at the end of follow-up.

The number of women using screening options outside the trial and service screening programme may have had an influence on the results, with different effects depending on in which group of women it took place: among non-attenders in the screened group, in former attenders when they were no longer invited to screening and among women in the control groups. This may both raise and lower the level of over-diagnosis. Furthermore, there has been a technical development along the years of this follow-up and will also be in the future which may result in an increase in the rate of over-diagnosis. Hopefully it will also provide better diagnostic accuracy which may decrease the influence of other negative side-effects of screening such as false-positive tests and false negative tests.

The study with the highest rates of over-diagnosis by Zahl et al[86] may not have had a sufficient follow-up time to account for lead time. Their conclusions were also based on an expected decrease in the breast cancer incidence after women had passed their upper age limit for invitation to screening, which did not occur. However, women previously attending a screening programme are likely to continue to seek mammography and secondly, screening actually continued after age 70 in many areas in Sweden. The paper by Jonsson et al[87], studying whether there has been an increase in the incidence of invasive breast cancer after introduction of service screening, found an excess incidence of about 20-50% depending on age. The calculations were based on historical incidence before the introduction of screening which was extrapolated as being the underlying incidence during and after screening. However, there is a risk, which the authors point out, that the real underlying incidence in the absence of screening could have increased due to use of HRT and changes in parity-patterns. This would mean that the excess incidence could have been overestimated.

It is still not known what role DCIS play in over-diagnosis. In many countries the report to the cancer registries on DCIS is scarce, which prevent large register studies from being carried out. It has been shown that the proportion of progressive DCIS detected at screening is relatively small.[60] In our study, cancer in situ accounted for a small, but not negligible part of the over-diagnosis. There is hence need for more studies on the natural course of DCIS.

Recently, it has been argued that a large part of invasive breast cancers would have regressed spontaneously if left untreated.[119-121] There is no reliable research supporting this view. It may be true for a few cancers but most of the excess incidence is explained by long lead time and death in inter-current disease. It does, however, lead to the discussion about tumour-host interactions. We certainly need to know more about the biological characteristics of different tumours, but also more about tumour-host interactions. Are certain individuals more prone to fight cancer?

Concluding remarks

Screening must be seen in the light of a national goal - that is decreasing death from breast cancer in a population. As indicated earlier, an effect shown in a meta-analysis may not be applicable for all times and places. It requires that women come to screening, that the diagnostic test is sensitive and that the important tumours are detected. Accordingly, it is crucial for each local authority responsible for screening to follow non-attendance and interval cancer rates. Assessing changes in mortality from breast cancer should however, due to statistical reasons, be done on a national level. Achieving the national goal relies on the basis of quality control at the local level.

The balance between the society's aim of reducing death from breast cancer and to give women a chance to make an informed decision is delicate. Women have

the right to be informed about the risk of being diagnosed with a biologically insignificant cancer and that screening does not have the ability to detect 100% of the breast cancers. This may result in lower attendance rates, but with a maintained respect for the individual woman. Women have the right to make an informed decision whether to participate or not,[122] but few screening programmes in Sweden and abroad provide balanced information when inviting women.[123]

Service screening has by now been operating for almost 20 years in Sweden. In addition to the earlier trials, this could provide a large amount of data which could be an invaluable tool in further understanding the complicated patterns that are generated when a large population is screened for disease. Who should then initiate the discussion whether mammographic screening gives the results that we expect? In addition to monitoring national mortality rates, those responsible for screening programmes should use the data generated in the programme for research on diagnosis and treatment strategies to continuously improve the outcome. Also the individual woman should ask questions about the benefits and risk of screening: “Can I trust a positive or a negative screening test and what would be the consequences in each case?” We can give answers to many, but not all of these questions and we should start using the accumulated knowledge more efficiently.

Conclusions

- In this urban population the attendance rate was lower in the service screening programme than it was in a former breast cancer screening trial. In both settings, attendance decreased with age.

- The rate of non-attendance among urban women offered breast cancer screening with mammography varied substantially across residential areas. Women living in areas with less favourable socio-economic circumstances participated to a lower extent.

- In the service screening programme, MMSSP, several socio-economic groups were identified that were more likely to be non-attenders.

- Although attendance rates have declined over time, the distribution of breast cancer among non-attenders seems to have shifted towards less advanced and survival has improved.

- The prognosis for women with interval breast cancer in this urban population has improved during the last 20 years and might therefore be less of a problem in the current screening situation.

- Conclusions on over-diagnosis in the MMST can mainly be drawn in women aged 55-69 years at randomisation, whose control groups were never offered screening. In this age group one in ten breast cancers may be over-diagnosed.

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Summary in Swedish
Sammanfattning på svenska

Bakgrund

Ett flertal studier har genomförts, varav fyra i Sverige, för att undersöka om man genom att bjuda in kvinnor till mammografi regelbundet, kan minska dödligheten i bröstcancer. I en sammanslagen studie kunde man visa att dödligheten till följd av bröstcancer kunde minskas med upp till 30%. Allmän screening med mammografi rekommenderas i Sverige av Socialstyrelsen sedan sent 1980-tal. Samtliga landsting erbjuder också detta, men i lite olika åldersgrupper. Under flera år på 1990-talet pågick en debatt rörande om studierna hade genomförts på rätt sätt och man ifrågasatte nyttan av screening. Med tiden har ytterligare studier bekräftat att mammografiscreening är effektivt, vilket nu är den allmänna uppfattningen.

I Malmö genomfördes en av de grundläggande mammografistudierna mellan 1976 och 1986, ”The Malmö Mammographic Screening Trial, MMST”. Denna följdes av allmän mammografiscreening av alla kvinnor mellan 50 och 69 år från 1990.

För att mammografiscreening skall vara effektivt är det av vikt att kvinnor verkligen kommer till undersökning, att tumörer upptäcks och behandlas. Det är därför viktigt att kontinuerligt följa upp verksamheten. Malmö erbjuder goda möjligheter att studera faktorer som har betydelse för screeningens effektivitet under olika tidsperioder och förutsättningar. Denna avhandling har som mål att studera tre faktorer som har relevans för screening: icke-deltagande, intervallcancrar och överdiagnostik.

Deltagarmönster i Malmö

En hög deltagarfrekvens är nödvändig för att uppnå goda resultat med screening, det vill säga för att sänka dödligheten i bröstcancer. Om man kan identifiera ett mönster bland kvinnor som väljer att utebli från screening kan man rikta information och insatser till grupper som har lågt deltagande. Malmö kan delas in i 18 områden med olika socioekonomisk karaktär. Det är känt att det finns stora skillnader i förekomsten av olika sjukdomar och hälsorelaterade tillstånd mellan dessa områden. I det första arbetet, baserat på 32000 kvinnor inbjudna till screening mellan 1990 och 1994, undersökte vi om det fanns skillnader mellan områdena i hur många kvinnor som deltog i screening. Andelen kvinnor som uteblev från screening varierade mellan 23 och 43%, s.k. icke-deltagare. Områdenas socioekonomiska förhållande kartlades med hjälp av ett mått baserat på bland annat andel socialbidragstagare, andel med utländsk bakgrund, andel förvärvsarbetande m fl. faktorer. Vi undersökte om det fanns en koppling mellan andelen icke-deltagare i de olika områdena och områdenas socioekonomiska omständigheter. Det visade sig att områden med lågt deltagande hade sämre socioekonomiska förhållanden.

Kvinnans individuella situation och kopplingen till icke-deltagande

I arbete II ville vi undersöka om kopplingen mellan socioekonomi och icke-deltagande också gällde för den enskilda kvinnan. Genom samkörning av screeningregistret i Malmö och Folk-och bostadsräkningen 1990 (Statistiska Centralbyrån) kunde vi se om vissa faktorer hängde samman med att inte delta i screeningprogrammet 1990-93. Kvinnor som var ensamstående, skilda eller änkor hade större sannolikhet att inte komma än de som var gifta/samboende. Kvinnor med utländsk bakgrund var oftare icke-deltagare än svenska kvinnor. Att inte ha ett arbete, trångboddhet och låg inkomst var också kopplat till icke-

deltagande. Resultaten stämde väl överens med tidigare både svenska och utländska studier.

Prognosen för icke-deltagare med bröstcancer

Hälsoundersökningar och screeningprogram har en tendens att locka företrädelsevis hälsomedvetna, friska individer medan individer med förhöjd risk inte kommer. I arbete II ville vi undersöka om detta också gällde mammografiscreening i Malmö. I en tidigare studie (MMST) hade kvinnor som inbjöds till screening men inte deltog och som fick bröstcancer betydligt sämre överlevnad än kvinnor med bröstcancer i en oscreenad kontrollgrupp. Det visade sig att detta mönster inte var lika tydligt i det nuvarande screeningprogrammet. Både andelen avancerade tumörer var lägre och överlevnaden bättre hos icke-deltagare nu än i MMST och det var inte någon skillnad jämfört med bröstcancer hos kvinnor i en oscreenad kontrollgrupp. Detta trots att deltagarfrekvensen i mammografiscreening har sjunkit från 74 % i studien till 65 % i det nuvarande screeningprogrammet. Detta kan bero på att det finns mer information om bröstcancer i samhället och att icke-deltagare numera är mer medvetna om risken för bröstcancer och därmed söker hjälp tidigare. Vidare finns det en andel bland icke-deltagarna i screeningprogrammet som utnyttjar screeningalternativ i privat regi. Olika typer av inbjudningsförfarande användes under de båda tidsperioderna vilket sannolikt hade en viss inverkan.

Bröstcancer som uppträder mellan två screeningomgångar

Bröstcancer innefattar ett brett spektrum av olika typer av tumörer. En del är mycket långsamväxande och andra växer till snabbt. Vidare är det lättare att se vissa typer av tumörer på mammografibilden än andra. Om en kvinna har varit på screening där man inte sett något onormalt själv upptäcker en knuta i bröstet innan hon blir kallad till nästa screening inom 1,5-2 år, har hon råkat ut för en så kallad intervallcancer. Ett screeningprogram kan alltså inte upptäcka alla

tumörer och intervallcancrar brukar utgöra mellan 10-20 % av tumörerna i en screenad befolkning. En del av intervallcancrarna är snabbväxande och hinner därför uppträda mellan två screeningomgångar. En mindre andel är ”missade” cancrar som uppvisat mycket vaga tecken på mammografibilden eller har bildtolkningen försvårats av körtelrika bröst vilket gör det svårare att upptäcka tumören. Eftersom intervallcancrarna uppträder i det relativt korta intervallet mellan screeningomgångarna skulle man kunna tänka sig att de är mer aggressiva och har sämre prognos än andra cancrar. I MMST hade kvinnor med intervallcancer dubbelt så stor risk att dö i bröstcancer som kvinnor med cancer i en oscreenad kontrollgrupp. Ett flertal tidigare studier har dock inte kunnat visa att så är fallet. Därför ville vi i arbete III undersöka om våra tidigare fynd fortfarande gällde för intervallcancerfallen i det nuvarande screeningprogrammet. Det visade sig att överlevnaden för kvinnor med intervallcancer i nuvarande screeningprogrammet var betydligt bättre än i den tidigare studien. De hade inte heller sämre överlevnad än en grupp av kvinnor med kliniskt upptäckta cancrar (dvs. cancrar som inte upptäckts med mammografi) och som inte screenats. Detta tyder framförallt på att behandlingen för bröstcancer har blivit effektivare för mer aggressiva tumörer. Det skulle också delvis kunna bero på att dagens intervallcancrar är av en annan typ än de tidigare, exempelvis beroende på den utbredda användningen av hormonbehandling i och efter klimakteriet.

Överdiagnostik i mammografiscreening

Mammografiscreening har en tendens att lättare fånga upp långsamväxande tumörer beroende på att de är i ett upptäckbart stadium under en längre tidsperiod än mer snabbväxande som tenderar att dyka upp i intervallet mellan undersökningarna. Avsikten med mammografisk hälsokontroll är att tidigarelägga diagnosen och därmed förbättra prognosen. Man vet att man i genomsnitt tidigarelägger diagnosen cirka 3 år, mindre hos yngre och mer hos

äldre. Det finns dock en stor variation kring detta medelvärde baserat på tumörernas tillväxthastighet och andra faktorer. En del tumörer växer mycket långsamt och en viss proportion av så kallade cancer in situ, som är att betrakta som ett förstadium, utvecklas troligen aldrig till invasiv, ”farlig” cancer. Detta betyder att mammografiscreening upptäcker en del tumörer, som annars aldrig skulle ha upptäckts beroende på att kvinnan skulle ha avlidit i någon annan sjukdom. Dessa tumörer kan anses vara överdiagnostiserade och därmed leda till onödig behandling både kirurgiskt samt eventuellt med cellgifter och strålning.

Tidigare studier har visat mycket skilda resultat, allt från att ingen överdiagnostik finns upp till att var tredje tumör skulle vara upptäckt i onödan. De resultaten har varit baserade på statistiska modeller, vilket kan ge en viss osäkerhet. Genom att följa upp Malmöstudien, MMST, 15 år efter dess avslutning avseende antal bröstcancrar som upptäckts i den inbjudna gruppen jämfört med i den oscreenade kontrollgruppen, kan man få en god uppfattning om hur många extra cancrar som upptäckts i den inbjudna gruppen. Detta var genomförbart för de kvinnor som var 55-69 år då studien startade. I den åldersgruppen visade det sig att var tionde tumör i den inbjudna gruppen skulle kunna vara upptäckt i onödan, arbete IV. Överdiagnostik måste sättas i relation till hur många liv som räddas med screening. Man anser allmänt att fördelarna överväger nackdelarna med screening. Tyvärr är det i nuläget inte möjligt att säga vilken kvinna som har nytta av screening och vem som får en tumör upptäckt i onödan. För detta behövs bättre metoder för att klassificera tumörernas biologiska egenskaper.

Konklusion

Denna avhandling har således fokuserat på tre aspekter som kan vara viktiga för screeningens effektivitet: icke-deltagande, intervallcancrar och överdiagnostik. Det visade sig att icke-deltagandet varierade stort inom olika områden i Malmö

och att det fanns en koppling till områdets socioekonomiska omständigheter. Vidare kunde flera socioekonomiska omständigheter hos den enskilda kvinnan förutsäga icke-deltagande. Denna kunskap kan utnyttjas till att individualisera själva inbjudan till screening där hänsyn tas till dessa faktorer. Man kan också tänka sig att rikta resurser för att öka deltagandet i vissa grupper eller områden. Både för icke-deltagare med bröstcancer och kvinnor med intervallcancer har prognosen förbättrats under senare år. Slutligen uppskattades överdiagnostiken till 10% i den inbjudna gruppen i MMST för kvinnor i åldrarna 55-69 år vid studiens start. Det går dock inte att förutsäga vilken kvinna det är som råkar ut för en sådan cancer.

Det nationella målet med mammografiscreening är att sänka dödligheten i bröstcancer. Det målet bygger på att så många kvinnor som möjligt deltar, att rätt tumörer upptäcks och att rätt behandling ges. Balansen mellan att uppnå sänkt dödlighet i bröstcancer och att ge kvinnor möjlighet att, baserat på god information, ta beslut om hon vill delta eller inte är känslig. Kvinnor har rätt att få veta att mammografiscreening inte kan upptäcka alla tumörer och att det finns en risk att med screening upptäcka en tumör, som är så långsamväxande att den aldrig hade gett upphov till några symtom. Sannolikt skulle detta innebära att fler kvinnor än idag avstår screening, men respekten för den enskilda kvinnans integritet skulle vara bibehållen i högre grad. Både i Sverige och utomlands är informationen om screeningens för- och nackdelar i själva inbjudan oftast knapphändig.

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