Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study.

Zackrisson, Sophia; Andersson, Ingvar; Janzon, Lars; Manjer, Jonas; Garne, Jens Peter

Published in:
BMJ (Clinical Research Edition)

DOI:
10.1136/bmj.38764.572569.7C

2006

Link to publication

Citation for published version (APA):
Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study

Sophia Zackrisson, Ingvar Andersson, Lars Janzon, Jonas Manjer and Jens Peter Garne

*BMJ* 2006;332:689-692; originally published online 3 Mar 2006; doi:10.1136/bmj.38764.572569.7C

Updated information and services can be found at: [http://bmj.com/cgi/content/full/332/7543/689](http://bmj.com/cgi/content/full/332/7543/689)

**These include:**

**Data supplement**

"Description of time period"

[http://bmj.com/cgi/content/full/bmj.38764.572569.7C/DC1](http://bmj.com/cgi/content/full/bmj.38764.572569.7C/DC1)

**References**

This article cites 23 articles, 5 of which can be accessed free at: [http://bmj.com/cgi/content/full/332/7543/689#BIBL](http://bmj.com/cgi/content/full/332/7543/689#BIBL)

7 online articles that cite this article can be accessed at: [http://bmj.com/cgi/content/full/332/7543/689#otherarticles](http://bmj.com/cgi/content/full/332/7543/689#otherarticles)

**Rapid responses**

5 rapid responses have been posted to this article, which you can access for free at: [http://bmj.com/cgi/content/full/332/7543/689#responses](http://bmj.com/cgi/content/full/332/7543/689#responses)

You can respond to this article at: [http://bmj.com/cgi/eletter-submit/332/7543/689](http://bmj.com/cgi/eletter-submit/332/7543/689)

**Email alerting service**

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

**Topic collections**

Articles on similar topics can be found in the following collections

- Randomized Controlled Trials: examples (458 articles)
- Radiological diagnosis (538 articles)
- Cancer: breast (638 articles)

**Notes**

To order reprints of this article go to: [http://www.bmjjournals.com/cgi/reprintform](http://www.bmjjournals.com/cgi/reprintform)

To subscribe to *BMJ* go to: [http://bmj.bmjjournals.com/subscriptions/subscribe.shtml](http://bmj.bmjjournals.com/subscriptions/subscribe.shtml)
Research

Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study

Sophia Zackrisson, Ingvar Andersson, Lars Janzon, Jonas Manjer, Jens Peter Garne

Abstract

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

Design Follow-up study.

Setting Malmö, Sweden.

Subjects 42 283 women aged 45-69 years at randomisation.

Interventions Screening for breast cancer with mammography or not (controls). Screening was offered at the end of the randomisation design to both groups aged 45-54 at randomisation but not to groups aged 55-69 at randomisation.

Main outcome measures Rate of over-diagnosis of breast cancer (in situ and invasive), calculated as incidence in the invited groups and unscreened control groups. We also evaluated the rate of over-diagnosis of breast cancer during follow-up. A total of 2525 cases of breast cancer were registered during the study period, 1320 in the invited group over time.

Results The rate of over-diagnosis of breast cancer was 10% in this age group.

Conclusion Conclusions on over-diagnosis of breast cancer in the Malmö mammographic screening trial can be drawn mainly for women aged 55-69 years at randomisation whose control groups were never screened. Fifteen years after the trial ended the rate of over-diagnosis of breast cancer was 10% in this age group.

Introduction

Over-diagnosis of breast cancer at screening may be defined as the detection of cases that would never have come to clinical attention without screening. The rate of this negative side effect of screening has been estimated at 5-50%. The most feasible means of assessing over-diagnosis would be to study the cumulative incidence of breast cancer over time in women invited to screening compared with unscreened controls. The Malmö mammographic screening trial can provide such data. This trial was unique in being a population based trial, with randomisation by individual. The trial period ended after 10 years and at that time 141 more cases of breast cancer were detected in the invited group than in the control group. Each birth year cohort was randomised separately from the start of the trial to 1978, and the first screening round was completed by the end of 1978. The screening interval was 18 to 24 months. The trial ended in December 1986 and was reported in 1988.

We followed the cohorts from the date of randomisation until 31 December 2001, 15 years after the trial ended. Survival and detection of breast cancer for each woman was obtained by record linkage with the Swedish Cancer Registry and the Swedish Causes of Death Registry. We only included a first time diagnosis of breast cancer during follow-up. A total of 2525 cases of breast cancer were registered during the study period, 1320 in invited women and 1205 in controls. Invasive breast cancer constituted 91% (n = 1200) of the cases in the invited group and 93% (n = 1116) in the control group.

The evaluation of the incidence of breast cancer in both groups is based on two time periods. Figure 1 gives a schematic overview of the periods and the screening status for the birth cohorts (see bmj.com for detailed description of periods). Period changes in the excess number of cases of breast cancer in the invited group over time.

When screening of the invited group stops the incidence of breast cancer should decrease over time, the duration of which depends on the distribution of lead times (time from actual detection to the supposed clinical appearance in the absence of screening) of the tumours detected at screening. When the control group is invited, the excess number of cases in the invited group would over time be balanced by an equal number of cases in the control group. The validity of this assumption can be evaluated within the context of the Malmö trial.

We evaluated the rate of over-diagnosis of breast cancer in the Malmö mammographic screening trial 15 years after the trial ended by comparing the incidence of in situ and invasive cancers in the invited groups and unscreened control groups. We also show the changes in incidence when control groups were invited for screening after randomisation.

Methods

In the Malmö mammographic screening trial all women born during 1908-32 and living in Malmö were randomly allocated to invitation to screening with mammography or no screening (controls). The study started in October 1976 and women were invited by letter. The cohort comprised 42 283 women: 21 088 were allocated to the invited group and 21 195 to the control group. Each birth year cohort was randomised separately from the start of the trial to 1978, and the first screening round was completed by the end of 1978. The screening interval was 18 to 24 months. The trial ended in December 1986 and was reported in 1988.

We followed the cohorts from the date of randomisation until 31 December 2001, 15 years after the trial ended. Survival and detection of breast cancer for each woman was obtained by record linkage with the Swedish Cancer Registry and the Swedish Causes of Death Registry. We only included a first time diagnosis of breast cancer during follow-up. A total of 2525 cases of breast cancer were registered during the study period, 1320 in invited women and 1205 in controls. Invasive breast cancer constituted 91% (n = 1200) of the cases in the invited group and 93% (n = 1116) in the control group.

The evaluation of the incidence of breast cancer in both groups is based on two time periods. Figure 1 gives a schematic overview of the periods and the screening status for the birth cohorts (see bmj.com for detailed description of periods). Period
Research

1 comprises the phase when the randomised design was maintained, which for women born during 1908-17 equalled the trial time, for women born during 1918-22 the trial time and the years after the trial up to age 70, and for women born during 1923-32 the trial time and the years after until invitation of the control groups began in 1990. Period 2 refers to the phase after the randomised design ended until the end of follow-up in 2001. In older women (born 1908-22) period 2 implied the end of screening in the invited group and no invitation of the control group. Only the youngest age groups (born 1923-32) were offered screening, in both the invited and the control groups. The timing of invitation of the control groups ranged from September 1990 until February 1993. The screening interval was 18-24 months from 1990 onwards, depending on age and parenchymal pattern of breast tissue. The incidence refers to the total incidence—that is, cancers detected at screening, in the intervals between screenings, among non-attenders, and in the control group.

Statistical analysis

We calculated the incidence of breast cancer, invasive and in situ, in the total study cohort (women born 1908-32) for the invited group and the control group for the total period of follow-up (periods 1 and 2) and separately for periods 1 and 2. This was repeated for two subgroups on the basis of exposure to screening in period 2: women born during 1908-22 (aged 55-69 at randomisation) and those born during 1923-32 (aged 45-54 at randomisation). We used Cox's proportional hazards analysis to estimate relative rates with 95% confidence intervals of breast cancer in the invited groups compared with the control groups. The analysis was repeated for the total follow-up, including only invasive breast cancer.

To compare incidence rates without a majority of prevalent cases, we compared the incidence in period 1 after the exclusion of breast cancer cases in the time period corresponding to the first two screening rounds. The first two rounds were excluded to be able to include non-attenders in the first round who attended the second round and had a cancer detected. SPSS 11.0 for Windows was used for all calculations.

Results

Over-diagnosis can be illustrated in the Malmö mammographic screening trial as the cumulative number of breast cancers in the group invited for screening and the control group for the total follow-up. A clear difference in the cumulative number of all cancers, invasive and in situ, is seen in the invited and control groups in women born 1908-22, when screening of the control group never occurred (fig 2). The curves separate immediately and continue to widen for several years. A difference remains during the whole of follow-up. The curves converged when screening stopped. In women born during 1923-32, the curves separate immediately but converge when the control groups were invited from 1990 onwards, reflecting the prevalence screening. A small difference re-emerges between the groups at the end of follow-up.

When over-diagnosis was expressed as a rate, the following was noted. Fifteen years after the trial ended the invited group showed a 10% significantly higher incidence of breast cancer (table 1). When cancer in situ was excluded, the incidence was 7% higher. Despite differences in exposure to screening, the older and the younger women had similar relative rates of over-diagnosis (10% and 8%).

Incidence during periods 1 and 2

During period 1 the incidence of breast cancer was 24% higher in the invited group than in the control group (table 2). During period 2, the incidence was 5% lower in the invited group than in the control group.

Women in the invited group who were aged 45-54 at randomisation had a 16% higher rate of breast cancer than the control group (table 2). Incidence did not differ during period 2, when both the invited and the control groups were screened. In
women aged 55-69 at randomisation, whose control groups were never invited for screening, a 32% higher incidence was seen in period 1 followed by an 8% lower rate in the invited than in the control group in period 2.

After exclusion of the first two screening rounds in period 1, the excess incidence of all breast cancers was reduced. Relative rates were 1.12 (0.99 to 1.27) in the total cohort, 1.19 (1.00 to 1.40) in women aged 55-69 at randomisation, and 1.04 (0.86 to 1.25) in women aged 45-54 at randomisation.

Causes of death
During follow-up 9279 deaths occurred in the invited group and 9514 in the control group. Among 584 deaths in women in the invited group with breast cancer 212 (36.3%) were due to breast cancer, which was the case in an Italian study. Some studies did not include ductal cancer in situ in the main analyses, whereas others carried out analyses both with and without this type of cancer. We believe that in situ cancers should be included in analyses.

The main explanation for the excess number of cases in the invited group is the lead time of cases detected by screening. Owing to death due to intercurrent disease some of the cases would never have come to clinical attention. In addition some cases may have been non-progressive and therefore would never become noticeable in the absence of screening. This means that a long follow-up is necessary to estimate the magnitude of over-diagnosis and that analysis after only a few screening rounds is insensitive. In our study about 60% of the women aged 55-69 years at randomisation had died by the end of follow-up.

Age at randomisation
55-69 years
When screening ends a reduction in breast cancer incidence is expected in the former invited groups. Among women aged 55-69 at randomisation, however, we found only a modest reduction during period 2. The lead time has been shown to be longer in older women than in younger women. This fact together with an age dependent increasing general death rate

Table 1 Incidence and relative rates for breast cancer according to age and trial group in Malmö mammographic screening trial from randomisation until end of follow-up (31 December 2001)

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Age at randomisation</th>
<th>No of cases of breast cancer (No invasive)</th>
<th>Person years</th>
<th>Incidence per 1000 person years*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invited group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1908-32</td>
<td>45 to 69 (all)</td>
<td>1320 (1200)</td>
<td>426 812</td>
<td>3.09</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1908-32</td>
<td>45 to 69</td>
<td>790 (719)</td>
<td>231 376</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk (95% CI) invited v controls

Table 2 Incidence and relative rates of all breast cancers by age at randomisation and trial group in periods 1 and 2

<table>
<thead>
<tr>
<th>Period and birth cohort</th>
<th>Age at randomisation</th>
<th>Invited group</th>
<th>Control group</th>
<th>Relative rate (95% CI) invited v controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No of breast cancer cases</td>
<td>Person years</td>
<td>Incidence &amp;10/1000 person years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only invited group was screened in period 1. In period 2 women born during 1908-22 were not screened but screening took place of former invited and control groups in women born 1923-32.
could explain the remaining substantial over-diagnosis at the end of the period of observation. Moller et al recently showed a 32% reduction in breast cancer incidence in Swedish women past the upper age limit of their screening programme.19 The women in our study were older when screening stopped, which may explain the difference.

45-54 years

No definite conclusions can be drawn for over-diagnosis in the younger cohorts as the control groups were later screened. This resulted in an equalisation of the cumulative rate at first but at the end a not statistically significant 8% higher incidence in the former invited group. In other trials almost no excess incidence was shown when the control group was invited, which is to be interpreted as similar rates of over-diagnosis in both groups.6

Exclusion of prevalent cases

We analysed the extent of excess incidence after exclusion of prevalent cases (the first two screening rounds) and found a remaining, but reduced, excess incidence. This shows that the excess incidence is not just related to prevalent cases in a population exposed to screening. Two screening rounds correspond to four years, and the average lead time has been estimated to be two to four years depending on age.11 12 Most of the prevalent cases in the invited group and their corresponding cases in the control group should therefore have been accounted for. An increasing incidence at incident screens could be due to higher sensitivity of the screening procedure, which in turn may be due to improvements in mammography, increased knowledge among radiologists, or changes in the criteria for recall.

Factors influencing over-diagnosis

Attendance rates for screening decrease with age, as shown in both the Malmö mammographic screening trial and in the subsequent service screening programme.9 10 On the other hand, women who had been screened in the Malmö trial were more likely to attend the service screening programme9 and probably also to undergo mammography after screening had ended. Furthermore, mammography of asymptomatic women outside the trial in the control groups may lead to underestimation of over-diagnosis. It is widely agreed that screening using mammography can reduce mortality from breast cancer.16-20 The rate of over-diagnosis is another issue to be considered in the ongoing discussion about clinical and public health implications of breast cancer screening.

What is already known on this topic

Rates of over-diagnosis in screening for breast cancer have been estimated at 5% to 50%

Evidence from randomised controlled trials is lacking

What this study adds

Over-diagnosis of breast cancer was 10% in women randomised to screening at age 55-69 years compared with an unscreened control group

Calculations are based on direct observations of follow-up 15 years after the end of a randomised controlled trial

Contributors: SZ, IA, LJ, JM, and JPG designed and planned the study. SZ did the statistical analyses and wrote the paper. All authors contributed to the drafting of the paper and the final version. SZ is guarantor.

Funding: None.

Competing interests: None declared.

Ethical approval: Ethical committee of Lund University.

1 Baines CJ. Are there downsides to mammography screening? Breast 2005;11:87-10.
25 (Accepted 27 January 2006) doi 10.1136/bmj.38764.572569.7C

Department of Clinical Sciences in Malmö, Epidemiological Research Group, Lund University, Malmö University Hospital, SE-205 02, Malmö, Sweden
Sophia Zackrisson doctor
Lars Jansson professor
Jonas Manjer associate professor
Medical Radiology, Malmö University Hospital
Ingvar Andersson associate professor
Department of Surgery, Aarhus University Hospital, DK 8000 Århus C, Denmark
Jens Peter Garne associate professor
Correspondence to: S Zackrisson sophia.zackrisson@med.lu.se

BMJ Online First bmj.com