# Screening for breast cancer with mammography (Review)

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## ABSTRACT

**Background**
A variety of estimates of the benefits and harms of mammographic screening for breast cancer have been published and national policies vary.

**Objectives**
To assess the effect of screening for breast cancer with mammography on mortality and morbidity.

**Search strategy**
We searched PubMed (June 2005).

**Selection criteria**
Randomised trials comparing mammographic screening with no mammographic screening.

**Data collection and analysis**
Both authors independently extracted data. Study authors were contacted for additional information.

**Main results**
Seven completed and eligible trials involving half a million women were identified. We excluded a biased trial from analysis. Two trials with adequate randomisation did not show a significant reduction in breast cancer mortality, relative risk (RR) 0.93 (95% confidence interval 0.80 to 1.09) at 13 years; four trials with suboptimal randomisation showed a significant reduction in breast cancer mortality, RR 0.75 (0.67 to 0.83) (P = 0.02 for difference between the two estimates). RR for all six trials combined was 0.80 (0.73 to 0.88).

The two trials with adequate randomisation did not find an effect of screening on cancer mortality, including breast cancer, RR 1.02 (0.95 to 1.10) after 10 years, or on all-cause mortality, RR 1.00 (0.96 to 1.04) after 13 years. We found that breast cancer mortality was an unreliable outcome that was biased in favour of screening, mainly because of differential misclassification of cause of death.

Numbers of lumpectomies and mastectomies were significantly larger in the screened groups, RR 1.31 (1.22 to 1.42) for the two adequately randomised trials; the use of radiotherapy was similarly increased.

**Authors' conclusions**
Screening likely reduces breast cancer mortality. Based on all trials, the reduction is 20%, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15% relative risk reduction. Based on the risk level of women in these trials, the absolute risk reduction was 0.05%. Screening also leads to overdiagnosis and overtreatment, with an estimated 30% increase, or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. It is thus not clear whether screening does more good than harm. Women invited to screening should be fully informed of both benefits and harms.

## PLAIN LANGUAGE SUMMARY

Screening for breast cancer with mammography

Screening uses a test to check people who have no symptoms of a particular disease, to identify people who might have that disease and to allow it to be treated at an early stage when a cure is more likely. Mammography uses X-ray to try to find early breast cancers before a lump can be felt. Many countries have introduced mammography screening for women aged 50 to 69. The review includes seven trials involving a total of half a million women. The review found that mammography screening for breast cancer likely reduces breast cancer mortality, but the magnitude of the effect is uncertain and screening will also result in some women getting a cancer diagnosis even though their cancer would not have led to death or sickness. Currently, it is not possible to tell which women these are, and they are therefore likely to have breasts and lumps removed and to receive radiotherapy unnecessarily. Based on all trials, the reduction in breast cancer mortality is 20%, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15% relative risk reduction. Based on the risk level of women in these trials, the absolute risk reduction was 0.05%. Screening also leads to overdiagnosis and overtreatment, with an estimated 30% increase, or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. It is thus not clear whether screening does more good than harm.

## BACKGROUND

Breast cancer is an important cause of death among women. Early detection through mass screening with mammography has the potential to reduce mortality, but it can also lead to overdiagnosis and overtreatment (WHO 2002). Since screening preferentially identifies slow-growing tumours (length bias) (Final reports 1977; Fox 1979), the harms of unnecessary treatment could reduce or even neutralise any potential benefits.

The only way to estimate the effectiveness of screening reliably is with randomised trials. Large trials, involving a total of half a million women, have been carried out in North America and Europe (Canada 1980; Edinburgh 1978; Göteborg 1982; Malmö 1976; New York 1963; Stockholm 1981; Two-County 1977) and others are ongoing (Singapore 1994; UK age trial 1991). Several systematic reviews and meta-analyses have also been published (Blamey 2000; Cox 1997; Elwood 1993; Glasziou 1992; Glasziou 1995; Glasziou 1997; Gøtzsche 2000; Hendrick 1997; Humphrey 2002; Kerlikowske 1995; Kerlikowske 1997; Larsson 1996; Larsson 1997; Nyström 1993; Nyström 1996; Nyström 1997; Nyström 2000; Nyström 2002; Smart 1995; Swed Cancer Soc 1996; Wald 1993; WHO 2002).

The large number of reviews reflects the controversies surrounding mammography screening and the uncertainties of its effect in various age groups. There is wide variation in screening policies between different countries with some countries abstaining from introducing screening, partly because of lack of a documented reduction in all-cause mortality (Isacsson 1985; Skrabanek 1993; Swift 1993). One area of concern is the potential for radiotherapy treatment of low-risk women, such as those who have their cancers identified at screening, to increase all-cause mortality because of adverse cardiovascular effects (Early Breast C 1995; Early Breast C 2000). In addition, there has been concern that cause of death has not been ascribed in an unbiased fashion in the trials. Finally, carcinoma in situ is much more likely to be detected with mammography and it is known that although less than half of the cases will progress to be invasive (Nielsen 1987), these women will nevertheless be treated with surgery, drugs and radiotherapy.

Meta-analyses of screening are often deficient (Walter 1999) and few of the meta-analyses listed above have taken account of the risk of bias in the individual trials and have considered harms as well as benefits. We have identified important weaknesses in the trials (Gøtzsche 2000; Gøtzsche 2000a; Olsen 2001; Olsen 2001a; Olsen 2001b) and have now updated our Cochrane Review with additional data.

## OBJECTIVES

To study the effect of screening for breast cancer with mammography on mortality and morbidity.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Randomised clinical trials. Trials using less reliable randomisation methods were evaluated separately.

### Types of participants

Women without previously diagnosed breast cancer.

### Types of intervention

Experimental: screening with mammography.

Control: no screening with mammography.

**Types of outcome measures**

Mortality from breast cancer.
Mortality from any cancer.
All-cause mortality.
Use of surgical interventions.
Use of adjuvant therapy.
Harms of mammography.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Breast Cancer Group methods used in reviews.

We used a very broad search strategy. We searched PubMed with (breast neoplasms[MeSH] OR "breast cancer" OR mammography[MeSH] OR mammograph*) AND (mass screening[MeSH] OR screen*). This search was supplemented with a search on author names (Alexander F*, Andersson I*, Baines C*, Bjurstam N*, Duffy S*, Fagerberg G*, Frisell J*, Miller AB, Nystrom L*, Shapiro S, Tabar L*). The latest search was done in June 2005; more than 13,500 records were imported into ProCite and searched for author names, cities and eponyms for the trials.

We scanned reference lists and included letters, abstracts, grey literature and unpublished data to retrieve as much relevant information as possible. There were no language restrictions.

## METHODS OF THE REVIEW

Each author, independently, decided which trials to include based on the prestated criteria. Disagreements were resolved by discussion.

We assessed whether the randomisation was adequate and led to comparable groups following standard criteria as closely as possible (Alderson 2004) and divided the trials into those with adequate randomisation and those with suboptimal randomisation.

Both authors independently extracted methodological and outcome data; disagreements were resolved by discussion. Extracted data included: number of women randomised; randomisation and blinding procedures; exclusions after randomisation; type of mammography; number of screenings and interval between screenings; attendance rate; introduction of screening in the control group; co-interventions; number of cancers identified; breast cancer mortality; cancer mortality; all-cause mortality; harms of mammography; and use of surgical interventions; chemotherapy; radiotherapy; tamoxifen and other adjuvant therapy. We contacted the primary investigators to clarify uncertainties.

**Statistical methods**

We performed intention-to-treat analyses when possible, including all randomised women. A fixed effect model was used, and 95% confidence intervals are presented. In case of heterogeneity in the trial results ($P < 0.10$), we explored possible reasons.

IIn the trials with suboptimal randomisation, we could not carry out a proper analysis for all-cause mortality as we did not have access to the necessary data (see 'Methodological quality of included studies'), but present the data in the graphs for the sake of completeness. For breast cancer mortality, our estimates are not formally correct because we were unable to adjust for baseline differences. However, they turned out to be in close agreement with the estimates and confidence intervals published by the trialists. For completeness, we have shown the pooled estimates for the trials with adequate randomisation and those with suboptimal randomisation taken together, although we believe these summary estimates are likely to be unreliable (see below).

We report outcome data at approximately 7 and 13 years, which were the most common follow-up periods in the trial reports, and present age groups under 50 years of age and above, which is the limit that has most often been used by the trialists.

## DESCRIPTION OF STUDIES

We identified 11 trials and from these excluded 2 small studies of several interventions, including mammography (Berglund 2000; Dales 1979), and 2 trials in progress (Singapore 1994; UK age trial 1991).

Some of the seven eligible trials (Canada 1980; Edinburgh 1978; Göteborg 1982; Malmö 1976; New York 1963; Stockholm 1981; Two-County 1977) comprised slightly different subtrials. The Two-County trial had different randomisation ratios in the two counties (Kopparberg 1977; Östergötland 1978); the Edinburgh and Malmö trials continued to include women as they passed the lower age limit for entry to the trial; and the Canadian trial was actually two trials, one covering the age groups 40 to 49 years (Canada 1980a) and the other 50 to 59 years (Canada 1980b). Most trials covered the age range 45 to 64 years. The Canadian trial was the only one in which the women were individually randomised after invitation and giving informed consent; the others used a variety of procedures based on a prespecified segment of the female population that was randomised to invitation for screening or to a control group.

By definition the intervention always included mammographic screening. The number of consecutive screening invitations was in the range four to nine for all trials except the Two-County and Stockholm trials, in which a large fraction was invited for only two or three screenings. In the Two-County trial, the mammographically screened women were encouraged to perform breast

self-examinations once a month on a fixed date (Rapport 1982). This was Swedish policy generally, but we do not know for certain whether this was also true for the Göteborg, Malmö and Stockholm trials. Clinical examinations of screened women were performed in New York and Edinburgh. In Canada, in the 40- to 49-year age group, screened women had an annual clinical breast examination, whereas control women were examined at the first visit and were taught self-examination for use thereafter. In the 50- to 59-year age group, all women had their breasts clinically examined annually.

General screening of the control group did not occur in the trials from Canada and New York. The control women were invited for screening in their tenth year of follow up in the Edinburgh trial, and after more than 12 years in the Malmö trial, whereas systematic screening in the control group was introduced early in the Göteborg, Stockholm and Two-County trials (see 'Methodological quality of included studies').

In all trials, women in the control groups were offered usual care. This included mammography on indication, that is, in case of suspected malignancy, with the probable exceptions of the New York trial and the first five years of the Two-County trial.

According to the information we identified, the technical quality of the mammograms and the observer variation was assessed only in the Canadian trial. There are data on diagnostic rates, however, that show that the sensitivity in the trials that followed the New York trial has not consistently improved (Fletcher 1993; WHO 2002). Various combinations of one- and two-view mammography were used (see 'Characteristics of included studies').

## METHODOLOGICAL QUALITY

The trials have been conducted and reported over a long period of time, during which standards for reporting trials have improved. The New York trial, for example, was first reported in 1966, but crucial details on the randomisation method, exclusions and blinding were not published until 20 years later (Aron 1986; Shapiro 1985; Shapiro 1988), and data on use of radiotherapy and chemotherapy in the Kopparberg trial were published 14 years after the main results (Tabar 1999). Below we discuss the trial methodology in detail, essential reading to understand the controversies surrounding the effect of screening and the often conflicting information presented. The trials are described consecutively by start date.

**The New York trial** (New York 1963)

*Population studied* The New York trial (also called the HIP or Health Insurance Plan trial) invited women who were members of an insurance plan aged 40 to 64 years from December 1963 to June 1966. It reported an individual randomisation within pairs matched by: age, family size and employment group (Shapiro 1985). It is not clear whether the randomisation method was adequate; it was described as "alternation" by researchers who contacted one of the trial investigators (Freedman 2004). The entry date for a woman was the date she was scheduled for the examination (Shapiro 1966); the matched control was assigned the same date (Shapiro 1985). The matched pairs' method should lead to intervention and control groups of exactly the same size. This is supported by the approximate numbers given in several publications, e.g. "The women were carefully chosen as 31,000 matched pairs" (Strax 1973). The largest published exact number of women invited is 31,092 (Fink 1972).

*Comparability of groups* Post-randomisation exclusions of women with previous breast cancer occurred, but this status "was most completely ascertained for screened women", whereas women in the control group "were identified through other sources as having had breast cancer diagnosed before their entry dates" (Shapiro 1988). Using information in the trial reports (Fink 1972; Shapiro 1985; Shapiro 1994), we calculated that 853 (31,092 - 30,239) women were excluded from the screened group because of previous breast cancer, compared with only 336 (31,092 - 30,756) in the control group. Although it was reported that great care was taken to identify these women, the lead investigator noted that more than 20 years after the trial started, some prior breast cancer cases among the controls were unknown to the investigators and should have been excluded (Shapiro 1985a). This creates a bias in favour of screening for all-cause mortality and likely also for breast cancer mortality, though the authors have written, without providing data, that ascertainment of cases of previous breast cancer was "nearly perfect" in those women who died from breast cancer (Shapiro 1988).

It is difficult to evaluate whether there were other baseline differences between the groups. In one paper (Shapiro 1972), the text describes all randomised women and refers to a table that shows baseline differences as percentages but does not provide the numbers upon which the percentages are based. Footnotes explain that some of the data are based on 10% and 20% samples. The table title refers to women entering the trial in 1964, and not all women as claimed in the text. Assuming that the table title is correct, the data presented are a 1964 subgroup of 10% and 20% samples in some cases, and the resulting samples are therefore too small to study other possible baseline differences than those related to differential exclusion of women with previous breast cancer.

*Assignment of cause of death* We found no data on the autopsy rate. Assignment of cause of death was unblinded for 72% of the women with breast cancer (Shapiro 1988). The differential exclusions and unblinded assessments make us question the reliability of the reported breast cancer mortality rates.

*Likelihood of selection bias* We classified the trial as suboptimally randomised.

**The Malmö trial** (Malmö 1976)

*Population studied* This trial recruited women aged 45 to 69 years. Randomisation was carried out by computer within each birth year cohort (Andersson 1981), dividing a randomly arranged list in the middle (Andersson 1999a). The first publications noted that 21,242 women were randomised to the screening group and 21,240 to the control group (Andersson 1980; Andersson 1981a).

*Comparability of groups* A later publication reported four more women in the control group (Andersson 1983), but the main publication (Andersson 1988) reported only 21,088 women in the study group and 21,195 in the control group and did not account for the 199 or 203 missing women. The number of missing women is largest in the 45 to 50 years age group (137 from the intervention group and 26 or 27 from the control group), mainly because the 1929 birth year cohort was recruited by an independent research project which included mammography (Andersson 2001). The trialists recruited less than the planned 50% of this birth year cohort, but this does not explain why 26 or 27 women are missing from the control group. Exclusion of the 1929 birth year cohort from analysis changes the relative risk for death from breast cancer by only 0.01 (Andersson 2001). For 17 of the 25 birth year cohorts, the size of the study and control groups were identical or differed by only one, as expected. The largest difference in the other eight cohorts, apart from the 1929 one, was 25 fewer women than expected in the study group for the 1921 cohort (Nyström 2002). Thus, the authors of a meta-analysis of the Swedish trials did not report on all randomised women in Malmö (Nyström 2002).

The date of entry into the trial was defined differently for the two groups. For the mammography group, it was the date of invitation (Andersson 1988), and the midpoint of these dates for each birth year cohort defined the date of entry for women in the control group (Andersson 2000). Enrolment began in October 1976 (Andersson 2000) and ended in September 1978 (Andersson 1988). It is not clear whether screening of the control group began in December 1990 (Nyström 2000) or in October 1992 (Nyström 2002). Most women in the control group were never screened (Nyström 2002). We calculated the interval between screening started in the study group and the control group (the intervention contrast), to be 19 years (Nyström 2002). In the meta-analyses of the Swedish trials, breast cancer cases diagnosed before randomisation were explicitly excluded, further reducing the screened group by 393 and the control group by 412 (Nyström 1993); in total 86 more women were excluded from the screened group than the control group. Baseline data on age were not significantly different in the screened group and the control group (Gøtzsche 2000a).

*Assignment of cause of death* The autopsy rate for breast cancer cases as presented in the main publication for this trial (Andersson 1988) was high, 76%, but it was halved from 1985 to 1997 (Andersson 2000). Cause-of-death assessments were blinded up to 1988 (Andersson, personal communication, 10 Oct 2000).

*Likelihood of selection bias* We classified the trial as adequately randomised.

**The Malmö II trial** (Malmö II 1978)

*Population studied* This was an extension of the Malmö trial, called MMST II. Women who reached the age of 45 were enrolled between September 1978 and November 1990; screening of the control group began in September 1991 (Nyström 2000). The long enrolment period gives an average estimated intervention contrast of eight years. Although the entry criterion for age was stated to be 45, the trialists included 6780 women aged 40 to 44 (Nyström 2002).

*Comparability of groups* The MMST II trial has been published only in brief (Andersson 1997). We therefore cannot check whether there were differential postrandomisation exclusions. If the same procedure as in the Malmö trial had been followed, the sizes of the study and control group cohorts should not differ by more than one. However, for 7 of the 13 birth year cohorts, groups differed more (Nyström 2002). The reported numbers in the individual cohorts do not add up to the reported totals, but to 28 fewer in the study group and 28 more in the control group. Because of an administrative error, the entire 1934 birth year cohort was invited for screening (Andersson 1999b). If this cohort is excluded, there is still a gross imbalance, with 5724 women in the study group and only 5289 in the control group for those aged 45-49 (P = 0.00004, Poisson analysis). In total, there were 9581 and 8212 women in the analyses (Nyström 2002).

This trial was neither included nor mentioned in the 1993 meta-analysis of the Swedish trials (Nyström 1993). The lead investigator informed us that it was not conducted according to a formal protocol (Andersson 1999b), whereas the most recent meta-analysis reported that the trial was conducted with the same protocol as the older part of the trial (Nyström 2002).

*Assignment of cause of death* An official registry was used for cause-of-death assessments.

*Likelihood of selection bias* We classified the trial as suboptimally randomised.

**The Two-County trial** (Kopparberg 1977; Two-County 1977; Östergötland 1978)

*Population studied* This trial recruited women 40 years of age and over in Kopparberg and Östergötland; the two subtrials were age-matched and cluster randomised (21 and 24 clusters, respectively). The selection of clusters was stratified to ensure an even distribution between the two groups with respect to residency (urban or rural), socioeconomic factors and size (Kopparberg 1977; Tabar 1979; Östergötland 1978). The randomisation process and the definition of the date of entry have been inconsistently described, and some women were only 38 years of age, below the inclusion criterion (Nyström 2002). According to the first publications, random allocations of the women in each community block took place three to four weeks before screening started (Fagerberg 1985); all women from a given block entered the trial at the same time and

this date was the date of randomisation (Tabar 1985). However, it has also been described that a notary public allocated the clusters in Östergötland by tossing a coin (Nyström 2000) while witnesses were present (Fagerberg, personal communication, undated). We have been unable to find any detailed description of the randomisation in Kopparberg, but found a recent description for the whole trial: "Randomisation was by traditional mechanical methods and took place under the supervision of the trial statistician" (Duffy 2003). Thus it is not clear whether the randomisation was carried out on one occasion or whether it took place over several years.

Women were invited to their first screening from October 1977 to January 1980 in Kopparberg (Tabar 1981). The cohorts in Östergötland were defined between May 1978 and March 1981. It is not clear how many women were randomised, and reported numbers vary considerably, both for numbers randomised (see Additional Table 01: 'Examples of varying numbers of women in the Swedish trials') and for numbers of breast cancer deaths, despite similar follow up (Gøtzsche 2004). Documentation of baseline comparability was called for in 1988 (Andersson 1988a), but appears not to have been published. Since the randomisation was stratified after socioeconomic factors (Tabar 1991), baseline data potentially affecting mortality should exist.

*Comparability of groups* The randomisation procedure seemed to have led to non-comparable groups. First, breast cancer mortality in the control group was almost twice as high in Kopparberg compared to Östergötland (0.0021 versus 0.0012, P = 0.02). This is not apparent from the tabulated data (Tabar 1985). The published graphs are also potentially misleading; although adjacent mortality curves look much the same, the two y-axes are differently scaled (Tabar 1995). Second, in Kopparberg, more women were diagnosed with breast cancer before entry to the trial in the control group than in the study group. How the diagnostic information was obtained was not described (Tabar 1989), and the number of women excluded for this reason was not stated, but can be calculated by comparing two tables (Tabar 1985; Tabar 1989). More women were excluded from the control group than from the study group (P = 0.03); most of the imbalance occurred in the age group 60 to 69 (P = 0.007). In Östergötland, numbers of exclusions were very similar, 1.40% versus 1.39%. Third, age-matching was reported (Tabar 1979; Tabar 1981; Tabar 1985a), but study group women were five months older, on average (Nixon 2000), which is a small bias against screening.

We were unable to ascertain when systematic screening of the control group started. The available information is conflicting and the range of the discrepancies amounts to three years for both counties (Arnesson 1995; Duffy 2003; Nyström 1993, ; Nyström 2000; Nyström 2002; Rapport 1982; Tabar 1979; Tabar 1985; Tabar 1992). It seems most likely that screening of the control group in Kopparberg started in 1982, in accordance with the trial protocol (Rapport 1982) and a doctoral thesis (Nyström 2000), in which case the impression conveyed in the main publication for the trial that screening was offered to the control group after publication of the results in April 1985 is incorrect (Tabar 1985; Tabar 1992). In the protocol, a five-year intervention period was planned but with a stopping rule based on statistical significance testing every six months (Rapport 1982). The trial publications did not mention the repeated looks at the data (Tabar 1985). We estimated an intervention contrast of five years for Kopparberg and eight years for Östergötland. A valid comparison of benefits and harms of screening should be confined to the period prior to screening of the control group.

No information is available from the primary author of this trial (Tabar 2000a; Atterstam 1999; Prorok 2000). We have not received information from Nyström either on the missing account of the randomisation process in Kopparberg, or from the Swedish National Board of Health (Socialstyrelsen), which funded the trial.

*Assignment of cause of death* The autopsy rate was 36% (Projektgruppen 1985). According to an investigator involved with the trial (Crewdson 2002), other Swedish trialists (Nyström 2002), and a WHO report (WHO 2002), cause-of-death assessments were not blind, although this has been disputed by the lead investigator of the trial (Tabar 2002). In a meta-analysis of the Swedish trials, a blinded independent endpoint committee reassessed the death classifications (Nyström 1993).

*Likelihood of selection bias* We classified the trial as suboptimally randomised and likely to be biased.

**The Edinburgh trial** (Edinburgh 1978)

*Population studied* This trial used cluster randomisation with about 87 clusters (the number varies in different reports); the age group was 45-64 years. Coded general practices were stratified by size and allocated by manual application of random numbers. In one district, at least three of the 15 practices initially randomised to the screening group later changed allocation status, and at least four others were added (Alexander 1989). Two of these practices were unintentionally told the wrong group, and three changed allocation group because of "statistical considerations" (Roberts 1984). One practice was included in the follow up even though it was a pilot screening practice that did not participate in the randomisation (Roberts 1990). The trialists have conducted replicate analyses with these women removed (Alexander, personal communication, 3 Oct 2000) but as far as we know the data have not been published.

*Comparability of groups* Doubts about the randomisation were raised by the trialists (Alexander 1989), supported by baseline differences: 26% of the women in the control group and 53% in the study group belonged to the highest socioeconomic level (Alexander 1994), and mammographic screening was associated with an unlikely 26% reduction in cardiovascular mortality (Alexander 1989). Entry dates were defined differently. In most practices, the entry date was the date the invitation letter was issued; for women in hospital, it was the date their names appeared on a list sent to

their general practitioner. The entry date for five practices was not defined. In the control group, the entry date was the date the physician's practice was indexed. Before entry, the general practitioners in the screening practices had to decide whether each woman would be suitable for invitation to screening. Physicians in the control practices decided whether each woman would be eligible to receive a leaflet about breast self-examination (Roberts 1984). The eligibility criteria are thus broader for the control group and the entry dates seem to be earlier. Practices were enrolled one at a time over a period of 2.5 years, from 1979 to 1981 (Alexander 1989). Women turning 45 and women moving into the city were enrolled on an ongoing basis (Roberts 1984). Recruitment of the control group began in the 10th year of follow up (Alexander 1994). The exclusion procedures were different in the study and control groups (Chamberlain 1981; Roberts 1984) and 338 versus 177 women were excluded because of prior breast cancer (Alexander 1994).

*Likelihood of selection bias* This trial was not adequately randomised and was so biased that it cannot provide reliable data. We have therefore shown its results in a separate graph, for completeness only.

**The Canadian trial** (Canada 1980; Canada 1980a; Canada 1980b)

*Population studied* Women aged 40 to 59 years were individually randomised after invitation and giving informed consent. Their names were entered successively on allocation lists, where the intervention was prespecified on each line. An independent review of ways in which the randomisation could have been subverted uncovered no evidence of it (Bailar 1997). Enrolment took place from January 1980 to March 1985 (Canada 1980a).

*Comparability of groups* Fifty-nine women in the age group 40 to 49 years and 54 in the age group 50 to 59 years were excluded after randomisation (Miller 2000; Miller 2002); none were excluded because of previous breast cancer. The comparison groups were nearly identical in size (25,214 versus 25,216 aged 40 to 49 years and 19,711 versus 19,694 aged 50 to 59 years), and similar at baseline for age and nine other factors of potential prognostic importance (Baines 1994; Canada 1980; Canada 1980a; Canada 1980b; Miller 2000; Miller 2002). There were more small node-positive cancers at baseline in the screened group than in the control group among women aged 40 to 49, but this is a post-hoc subgroup finding which is probably a result of the intervention (Baines 1995; Baines 1997; Canada 1980). Several women with positive nodes were probably unrecognized in the control group (Miller 1997a). This is supported by the fact that 47% of women with node-negative cancer in the usual care group died of breast cancer compared with 28% in the mammography group (Miller 1997). Exclusion of the deaths caused by these cancers did not change the result (Baines 1995; Baines 1997; Canada 1980).

*Assignment of cause of death* The autopsy rate was low, 6% (Baines 2001). Cause-of-death assessments were blinded for women with diagnosed breast cancer and for other possible breast cancer deaths for follow up after seven years. For follow up after 13 years, death certificates were used in a minority of cases as some hospitals refused to release clinical records (Miller 2000; Miller 2002).

*Likelihood of selection bias* We classified the trial as adequately randomised.

**The Stockholm trial** (Stockholm 1981)

*Population studied* In this trial, women were invited for screening if they were aged 40 to 64 years in 1981 (born 1917 to 1941) and were born on days 1 to10 in a month, or if they were aged 40 to 64 years in 1982 (born 1918 to 1942) and were born on days 21 to 30 in a month (Frisell 1986). Similarly, there were two groups of controls, but since they were all born on days 11 to 20 in a month, most women served as controls twice (those born in 1918 to 1941). Invitations were sent successively by ascending order of birth date (Frisell 1989). The date of entry was the date of invitation (Frisell 1991). Enrolment of the first cohort began in March 1981 and ended in April 1982; enrolment of the second cohort began in April 1982 and ended in May 1983 (Frisell 2000a).

*Comparability of groups* Since the control women born in 1918 to 1941 served as controls for both subtrials (Frisell 1989a; Frisell 2000b), they should have two entry dates, approximately one year apart, but this was not described. According to the matching, there should be a similar number of women in the screened and control groups in each subtrial, but we found an imbalance in the second subtrial (P = 0.01, Poisson analysis), with 508 more women belonging to the screened group than to the control group (Frisell 1991). Furthermore, in the time period where 19,507 women born 1918 to 1942 were invited to screening, only 929 women, all born in 1942, were included in the control group (Nyström 2002).

The reported numbers of women in the various subgroups are inconsistent, as are the numbers reported to us in personal communications (Frisell 2000a; Frisell 2000b). Because of the problems related to timing and the overlap of the two control groups, results from the two subtrials are not independent, and the estimates cannot be pooled without correction for dependence. It is not clear how these difficulties were handled in the trialists' analysis (Frisell 1991) or in the Swedish meta-analyses (Nyström 1993; Nyström 2000; Nyström 2002).

The first trial report did not describe any women excluded after randomisation, but only breast cancer cases identified during the intervention period were followed up to ascertain breast cancer deaths (Frisell 1991). Exclusions occurred in later publications, but no numbers were given (Frisell 1997; Nyström 1993; Nyström 2000), and the numbers we have received in personal communications have been inconsistent (Frisell 2000a; Frisell 2000b).

Of those attending the first screening, 25% had had a mammogram in the two previous years (Frisell 1989a). Information on screening of the control group varies. A meta-analysis noted that a few women were screened after three years and most after four years (Nyström 1993), a doctoral thesis stated that the controls were invited from October 1985 (Nyström 2000), and the trialists that they were invited during 1986 (Frisell 1989a; Frisell 1991). We estimated an intervention contrast of four years. A valid comparison of benefits and harms of screening should be restricted to this period (Frisell 1991).

*Assignment of cause of death* It is not stated whether cause-of-death assessments were blinded for this initial period. The autopsy rate was 22% (Nyström 2000).

*Likelihood of selection bias* We classified the trial as suboptimally randomised.

**The Göteborg trial** (Göteborg 1982)

*Population studied* This trial included women aged 39 to 59 years. Birth year cohorts were randomised by the city municipality's computer department with the ratio between study group and control group adjusted according to the capacity of the screening unit (Bjurstam 2000; Nyström 2002). The randomisation was by cluster, based on date of birth, in the 1923 to 1935 cohorts, and by individual birth date for the 1936 to 1944 cohorts (Bjurstam 1997).

*Comparability of groups* We found baseline data only on age, and only for those aged 39 to 49 years. Since the allocation ratios are irregular, we could not assess the comparability of groups and adequacy of randomisation. The randomisation ratios were most extreme for the oldest and the youngest birth-year cohorts randomised in clusters; for 1923, there were 2.0 times as many women in the control group as in the study group whereas for 1935, there were only 1.1 times as many. Since breast cancer mortality increases with age, this bias favours screening and can be adjusted for only by comparing the results within each birth-year cohort before they are pooled (Bjurstam 2003).

Entry dates are not defined but the birth year cohorts were randomised one at a time, beginning with the 1923 cohort in December 1982 and ending in April 1984 with the 1944 cohort. A similar proportion of women were excluded from the study and control groups, 254 (1.2%) and 357 (1.2%), because of previous breast cancer (Bjurstam 2003). Information on screening of the control group varies, ranging from three to seven years (Bjurstam 1997; Bjurstam 2003; Nyström 1993, figure; Nyström 2000). We estimated an intervention contrast of five years. A valid comparison of benefits and harms of screening should be confined to this period.

*Assignment of cause of death* The autopsy rate was 31% (Nyström 2000).

*Likelihood of selection bias* We classified the trial as suboptimally randomised.

**Sources of data used for the meta-analyses**

Deaths ascribed to breast cancer: Alexander 1999; Andersson 1988; Bjurstam 1997; Bjurstam 2003; Frisell 1997; Habbema 1986; Miller 1992a; Miller 1992b; Miller 2000; Miller 2002; Nyström 1993; Nyström 1993a; Nyström 2002; Roberts 1990; Shapiro 1977; Shapiro 1982; Tabar 1988; Tabar 1995. Mortality among breast cancer patients: Tabar 1988. Deaths ascribed to cancer, all patients: Andersson 1988; Aron 1986; Miller 2000; Miller 2002; Shapiro 1988; Tabar 1988. All-cause mortality: Andersson 1988; Aron 1986; Bjurstam 1997; Miller 1992a; Miller 1992b; Miller 2000; Miller 2002; Nyström 2000; Nyström 2002; Projektgruppen 1985; Roberts 1990; Shapiro 1977; Tabar 1989. Mastectomies and lumpectomies: Andersson 1988; Frisell 1986; Frisell 1989a; Miller 1993; Shapiro 1972; Tabar 1999. Radiotherapy: Andersson 1988; Benjamin 1996; Shapiro 1972; Tabar 1999. Chemotherapy and hormone therapy: Andersson 1988; Tabar 1999. Number of cancers: Andersson 1988; Bjurstam 1997; Frisell 1989a; Miller 1993; Tabar 1991.

## RESULTS

Seven trials provided data. We classified two trials as adequately randomised (Canada and Malmö) and four as suboptimally randomised (Göteborg, New York, Stockholm, Two-County) as was also the extension of the Malmö trial, MMST II. One trial (Edinburgh) was not adequately randomised and cannot provide reliable data; we have therefore only shown its results for completeness, in a separate graph.

**Deaths ascribed to breast cancer**

We judged assignment of breast cancer mortality to be unreliable and biased in favour of screening (see above and 'Discussion'), but included this outcome because it was the main focus in all trials.

The two adequately randomised trials did not find an effect of screening on deaths ascribed to breast cancer, relative risk (RR) 1.05 (95% confidence interval 0.83 to 1.33) after 7 years and RR 0.93 (0.80 to 1.09) after 13 years. The four suboptimally randomised trials found a beneficial effect, RR 0.71 (0.61 to 0.83) after 7 years and RR 0.75 (0.67 to 0.83) after 13 years. The difference between the effect estimates for the two groups of trials is significant, both after 7 years (P = 0.005) and after 13 years (P = 0.02). For all six trials taken together, RR 0.80 (0.70 to 0.91) after 7 years and RR 0.80 (0.73 to 0.88) after 13 years.

The adequately randomised trials did not find a beneficial effect of screening on deaths ascribed to breast cancer in the youngest age group (under 50 years of age at randomisation except for 7 years data from Malmö for which the limit was 55 years), RR 1.33, 0.92 to 1.92, after 7 years and RR 0.91, 0.71 to 1.18, after 13 years. The suboptimally randomised trials found RR 0.81, 0.63 to 1.05, after 7 years and RR 0.80, 0.64 to 0.98, after 13 years. For the oldest age group, the estimates for the adequately randomised trials were

RR 0.88, 0.64 to 1.20 and RR 0.94, 0.77 to 1.15, respectively, and for suboptimally randomised trials they were RR 0.67, 0.56 to 0.81 and RR 0.70, 0.62 to 0.80, respectively.

**Deaths ascribed to any cancer**

The two adequately randomised trials did not find an effect of screening on deaths ascribed to any cancer, including breast cancer, RR 1.02 (0.95 to 1.10); the follow up was 10.5 years for Canada and 9 years for Malmö. The suboptimally randomised trials do not provide reliable estimates of cancer mortality (see above); the estimate for two suboptimally randomised trial that provided data (New York and Two-County trials) was RR 0.99 (0.93 to 1.06).

**All-cause mortality**

All-cause mortality was not significantly reduced, RR 0.99 (0.94 to 1.05) after 7 years and RR 1.00 (0.96 to 1.04) after 13 years for the two adequately randomised trials. The suboptimally randomised trials do not provide reliable estimates of the effects on all-cause mortality (see Methodological quality and Discussion), and the reported effects were heterogeneous (P = 0.03 after 7 years and P = 0.001 after 13 years), but for completeness, the mortality estimates are shown in the graphs.

**Surgery**

Significantly more breast operations (mastectomies plus lumpectomies) were performed in the study group than in the control group, RR 1.31 (1.22 to 1.42) for the two adequately randomised trials, and RR 1.42 (1.26 to 1.61) for the suboptimally randomised trials before systematic screening in the control group started (data were available only for Kopparberg and Stockholm). The increased surgery rate could not be explained by the excess of detected tumours at the first screen, but seemed to persist, as the mean follow up was seven years for Canada and nine years for Malmö. For Stockholm, the reported data after five years had been transformed according to the smaller size of the control group (Frisell 1989a). We recorrected and found that also for this trial, the excess of surgery persisted (RR 1.37 after first round and RR 1.48 after five years).

The number of mastectomies (excluding partial mastectomies, quadrantectomies and lumpectomies) was also significantly increased, RR 1.20 (1.08 to 1.32) for the adequately randomised trials, and RR 1.21 (1.06 to 1.38) for the suboptimally randomised trials.

**Radiotherapy**

Significantly more women received radiotherapy in the study groups, RR 1.24 (1.04 to 1.49) for Malmö after nine years, and RR 1.40 (1.17 to 1.69) for Kopparberg before the control group screen.

**Other adjuvant therapy**

We found little information on other adjuvant therapy (see graphs); it differed substantially for two of the Swedish trials despite being carried out at the same time. Chemotherapy was given to only 7% of the breast cancer patients in Malmö but to 31% in Kopparberg before the control group was screened. Conversely, hormone therapy was given to 17% in Malmö, and to 2% in Kopparberg. Information exists from Kopparberg on therapeutic adjuvant therapy given over the years but has not been published (Tabar 1999).

**Harms**

We found no comparative data on psychological morbidity. Duration of sick leave and mobility of the shoulder were registered in the Two-County trial (Rapport 1982) but have not been reported.

## DISCUSSION

**Breast cancer mortality**

The main focus in the screening trials was breast cancer mortality as very large trials are needed to assess the effect of screening on all-cause mortality. We cannot assume, however, that a beneficial effect on breast cancer mortality can be translated into improved overall survival. First, screening may increase mortality because of the increased use of radiotherapy. A meta-analysis predicted that overall, radiotherapy is beneficial for women at high risk of local recurrence. However, it is harmful for women at particularly low risk such as those who have their cancers found by screening, primarily because of damage to the vessels and development of heart failure resulting from at least some types of radiotherapy (Early Breast C 2000). It has been suggested by comparison of left- with right-sided irradiation that radiotherapy may double not only the mortality from heart disease but also from lung cancer (Darby 2005). This excess mortality is likely to be small, however, compared with the reduction in breast cancer mortality.

Second, assessment of cause of death is susceptible to bias. The authors of the Two-County trial assessed cause of death openly and reported a 24% reduction in breast cancer mortality for the Östergötland part (Tabar 2000), whereas a meta-analysis of the Swedish trials based on an official cause of death register reported only a 10% reduction for Östergötland (Nyström 2002). The trial authors reported 10 fewer deaths from breast cancer in the study group despite slightly longer follow up, and 23 more deaths in the control group, and have not provided a plausible explanation of this large discrepancy (Duffy 2002; Tabar 2002).

This bias also seems to favour screening when cause of death is determined blindly. In the New York trial, differential misclassification might be responsible for about half of the reported breast cancer mortality benefit, since a similar number of dubious cases were selected for blinded review from each group, but a much smaller proportion of the screened group were finally classified as having died from breast cancer (Gøtzsche 2004). Furthermore, although the mammographic equipment was standard at the time, its performance was poor. Only 15% of 299 cancers in the study group were detected solely by mammography and mammography did not identify a single case of minimal breast cancer (< 1 cm)

(Thomas 1977). The New York trial reported a 35% reduction in breast cancer mortality after seven years, but we consider it unlikely that it found a true effect.

In conjunction with the first meta-analysis of the Swedish trials, causes of death were reclassified blindly in some patients (Nyström 1993). Breast cancer was considered the underlying cause of death in 419 of the screened group and 409 of the control group according to Statistics Sweden and in 418 and 425 cases, respectively, according to the committee (Nyström 1993). The fact that all 17 reclassifications favoured the screened group suggests differential misclassification. This bias is difficult to avoid (Gøtzsche 2001). Early cancers are treated by lumpectomy and radiotherapy and radiotherapy reduces the rates of local recurrence by about two-thirds (Early Breast C 2000). This might increase the likelihood that deaths among screen-detected breast cancer cases will be misclassified as deaths from other causes (Early Breast C 1995) and that too many deaths in the control group will be misclassified as breast cancer deaths. In fact, for the Swedish trials it was stated that "most patients with locally advanced disease will die due to cancer" and that breast cancer as the underlying cause of death includes women with locally advanced breast cancer, whereas women who have been treated successfully should not be classified as having breast cancer deaths if another specified disease could be the cause of death (Nyström 2000). The use of an official cause of death register as in more recent meta-analyses (Nyström 2002) cannot solve these problems.

Post-randomisation exclusion of women who already had breast cancer at the time of entry to the trial is another possible source of bias. The exclusions were sometimes made many years after the trial started, or even after it had ended. In the Two-County trial, only women who were considered to have died from breast cancer were excluded (Nixon 2000), a highly bias-prone process because those assessing cause of death were not blinded for screening status. Furthermore, the process seems not to have been adequately monitored as it was not possible to identify prior breast cancers in Östergötland by cluster (Nixon 2000). It should therefore not be possible to do analyses that respect the clustering with those women excluded, although such analyses have been reported (Tabar 1989; Tabar 1990; Tabar 1991; Tabar 1995).

The largest effects on breast cancer mortality were reported in trials that had long intervals between screenings (Two-County trial), that invited a large fraction of the women to only two or three screenings (Two-County and Stockholm trials), that started systematic screening of the control group after three to five years (Two-County, Göteborg and Stockholm trials) and that had poor equipment for mammography (New York trial), and the cancers found with mammography were considerably smaller in the Canadian trial than in the Two-County trial (Narod 1997). This suggests that differences in reported effects are related to the methodological quality of the trials rather than to the quality of the mammograms or the screening programs. The sensitivity of mammographic readings in the trials that followed the New York trial has not consistently improved (Fletcher 1993; WHO 2002), and meta-analyses have failed to find an association between mammographic quality and breast cancer mortality (Glasziou 1995; Kerlikowske 1995).

Several of the trials had clinical examination or self-examination of the breasts as part of their design (see Description of studies), but this is not likely to have had a major influence on the effect estimates. The effect of clinical examination is uncertain, and large randomised trials did not find an effect of self-examination (Kösters 2003).

**Cancer mortality**

The major difficulty in assessing cause of death in the trials might have occurred when the patients had been diagnosed with more than one malignant disease (Miller 2001). The importance of autopsy is illustrated by the fact that 21% of the women with breast cancer who died in the Malmö trial had two or three types of different cancers (Andersson 1988a; Janzon 1991). Patients with cachexia and no signs of recurrence of breast cancer would likely be assigned to another type of cancer.

Since cancer mortality is likely to be less subject to bias than breast cancer mortality, we calculated what the expected cancer mortality (including breast cancer mortality) would be if the reported reduction in breast cancer mortality of 29% after seven years for the suboptimally randomised trials were true. Weighting the four trials that provided data (graph 7) after number of cancer deaths, the expected relative risk was 0.95. However, all-cancer mortality in these trials was not reduced, RR 1.00 (0.96 to 1.05), and this estimate was significantly higher than what was expected (P = 0.02). This provides further evidence that assessment of cause of death was biased in favour of screening.

Data from the Two-County trial (Tabar 1988) illustrate the misclassification directly (graph 19) (Gøtzsche 2004). Among women with a diagnosis of breast cancer, mortality for other cancers was significantly higher in the screened group and mortality from all other causes also tended to be higher. The increase in mortality for causes other than breast cancer amounts to 38% of the reported decrease in breast cancer mortality in the Kopparberg part of the trial and 56% in the Östergötland part.

It has been shown that belief in the effectiveness of an intervention may influence the decision on which type of cancer caused the patient's death (Newschaffer 2000). Also, lethal complications of cancer treatments are often ascribed to other causes. The size of this misclassification is 37% for cancer generally and 9% for breast cancer (Brown 1993).

**All-cause mortality**

The trials were not powered to detect an effect on all-cause mortality, but it is an important outcome since breast cancer mortality is biased. The complex designs and insufficient reporting precluded us from providing reliable estimates for all-cause mor-

tality in the trials with suboptimal randomisation; furthermore these trials had introduced early screening of the control group or had differentially excluded women after randomisation. All-cause mortality can be evaluated most reliably for the trials from Canada and Malmö; relative risk after 13 years was 1.00 (0.96 to 1.05).

A similar estimate was reported for the four Swedish trials, RR 1.00 (0.98 to 1.02), after adjustment for imbalances in age (Nyström 2000). In 2002, the authors reported a 2% (non-significant) reduction in all-cause mortality, RR 0.98 (0.96 to 1.00) and stated that they would have expected a 2.3% reduction (Nyström 2002). However, the calculation was incorrect; the expected reduction is only 0.9% (Gøtzsche 2002a). The error has been acknowledged (Erratum 2002; Nyström 2002a), but the published response to our criticism was also incorrect (Nyström 2002b). The reported decrease of 2% in total mortality corresponds to a 10% decrease in all-cancer mortality, which is not plausible (see 'Cancer mortality' above).

The Östergötland part of the Two-County trial contributed about half of the deaths in the 2002 report and had a relative risk for all-cause mortality of 0.98. The women were randomised to only 24 clusters. In the Edinburgh trial there were 87 clusters, but double as many in the invited group belonged to the highest socioeconomic level, compared to the control group (Alexander 1994). Socioeconomic factors are strong mortality predictors and could easily explain a 2% reduction in all-cause mortality, but such data remain unpublished, and are also unavailable for the other Swedish trials. It has been reported that pretrial breast cancer incidence and breast cancer mortality were similar in the invited and control groups in Östergötland (Nyström 2002), but the power of the test was very low (Gøtzsche 2002a). In contrast, another report found that breast cancer mortality was 15% lower in the invited groups in the Two-Country trial and that correction for this difference changed the estimate of the effect from a 31% reduction to a 27% reduction in breast cancer mortality (Duffy 2003).

It is not clear why the unadjusted and age-adjusted estimates for all-cause mortality were the same, RR 0.98, in the 2002 Swedish meta-analysis, that comprised 43,343 deaths, wheras in the 2000 meta-analysis of 27,582 deaths, these estimates were 1.06 (95% CI 1.04 to 1.08) (Gøtzsche 2000) and 1.00 (0.98 to 1.02) (Nyström 2000), with non-overlapping confidence intervals. The Kopparberg part of the Two-County trial was not available for the 2002 meta-analysis, but this should not make any difference since relative risk for Kopparberg was 1.00 (0.96 to 1.04) (Nyström 2000). The only other difference is that the extended data for the Malmö trial (MSST II) were included, but this trial contributed only 702 deaths (1.6%).

All-cause mortality has been reported to be lowered in the Two-County trial when the analysis was confined to women with breast cancer (Tabar 2002a). Such subgroup analyses are very unreliable, as are similar analyses in historically controlled studies (Tabar 2001; Tabar 2003a), since many breast cancer cases in the screened groups will have an excellent prognosis because of overdiagnosis and length bias (Berry 2002).

**Overdiagnosis and overtreatment**

Overdiagnosis is an inevitable consequence of screening and an obvious source of harm (WHO 2002). Screening primarily identifies slow-growing cancers and cell changes which are biologically benign (Doll 1981; Fox 1979). Survival of women with screen-detected cancers is therefore very high, for example, 97% in Malmö after 10 years (Janzon 1991). Even within the same stage, it is higher than for cancers detected clinically (Moody-Ayers 2000). Many more ductal carcinoma in situ lesions are detected in the screened groups, 123 versus 20 before the control screen in the Two-County trial (Tabar 1992a), and these lesions are particularly benign (Ernster 1996). The Canadian trial found that overdiagnosis of nonpalpable invasive cancer also occurs (Miller 2002).

The two adequately randomised trials, from Canada and Malmö, did not introduce early screening in the control group, and in these trials there were 30% more cancers in the screened groups than in the control groups and 31% more mastectomies and lumpectomies (Andersson 1988; Miller 1993). There were similar increases in the suboptimally randomised trials before the control group screen (graphs 14 and 21). In the New York trial, there was little difference between the groups, as expected, since far more breast cancer cases were excluded from the screened group than from the control group (Shapiro 1977; Shapiro 1982; Shapiro 1989). Tumour data from this trial are therefore unreliable.

Large observational studies support these findings. Incidence increases of 40 to 60% have been reported for Australia, Finland, Norway, Sweden, UK and USA (Barratt 2005; Douek 2003; Fletcher 2003; Gøtzsche 2004; Jonsson 2005; Ries 2002; WHO 2002; Zahl 2004), without a corresponding decline in incidence after the age of 69 years when the women are no longer screened (Jonsson 2005; Zahl 2004). A small study from Copenhagen has claimed that it is possible to screen without overdiagnosis, but it showed the expected prevalence peak, had very little power , and provided no statistical analyses in support of the claim (Olsen 2003). Another small study from Florence claimed that only 5% of cases were overdiagnosed (Paci 2004).

Screening increased the number of mastectomies by 20%. Since there has been a policy change towards more lumpectomies, this rate could be overestimated. Conversely, opportunistic screening in the control group would lead to an underestimate, and other evidence suggests that this estimate is plausible. The policy change has occurred slowly (Nattinger 2000), and even in 1993 to 1995, 52% of breast surgery in California was mastectomy (Malin 2002). In Stockholm, the increase in mastectomies was actually somewhat larger after five years of screening (25%) than after the first round of screening (16%), and in Southeast Netherlands, where screening was introduced from 1990 to 1998, the rate of breast-conserving surgery increased by 71% while the rate of mastectomy increased by 84% (Gøtzsche 2002), despite the fact that this study did not

include carcinoma in situ. The extent of the lesions is 5 cm or more in half of the women with carcinoma in situ, and they are therefore often treated by mastectomy (BASO audit 2000). In USA, between 1991 and 1998, 25% of all cancers in the first screening round were carcinoma in situ, which increased to 33% in subsequent rounds (May 2000). Although the percentage of cases of carcinoma in situ treated by mastectomy declined from 71% in 1983 to 40% in 1993, the estimated total numbers of mastectomies for this condition increased almost three-fold (Ernster 1997). In the UK, mastectomies increased by 36% for invasive cancer and by 422% for carcinoma in situ from 1990 to 2001 (Douek 2003).

The documented increase in mastectomies contrasts with assertions by trialists (Tabar 1989), policy makers (Statusrapport 1997; Swed Cancer Soc 1996; Westerholm 1988), websites supported by governmental institutions and advocacy groups (Jørgensen 2004), and invitational letters sent to women invited to screening (Jørgensen 2006) that early detection spares patients more aggressive treatments, in particular mastectomy. Publications that base their claims on numbers that include the control group screen (Tabar 2003) are also misleading, as are presentations of relative numbers rather than absolute numbers (Statusrapport 1997), since the proportion of breast preserving operations is said to be increasing, but the trend for the number of mastectomies is not revealed. A small study from Florence without a control group (Paci 2002) was also unreliable (Gøtzsche 2002b).

Quality assurance programs could possibly reduce the surgical activity to some degree, but they could also increase it. In the UK, for example, the surgeons were blamed for not having treated even more women with carcinoma in situ by mastectomy (BASO audit 2000). Not all of the additional operations are necessarily harmful, for example, some cases would represent prophylactic mastectomy in high-risk women.

**False positive diagnoses, psychological distress and pain**

False-positive diagnoses can cause considerable and sustained psychological distress (Bülow 2000). In the Stockholm trial, one-third of women with false-positive findings were not declared cancer-free at six months (Stockholm 1981), and in the UK, women who had been declared cancer free after additional testing or biopsies, were between 1.7 and two times more likely to suffer psychological consequences three years later, before the next screen, than women who received a clear result after their last mammogram (Brett 2001). In USA, three months after they had false-positive results, 47% of women who had highly suspicious readings reported that they had substantial anxiety related to the mammogram, 41% had worries about breast cancer, 26% reported that the worry affected their daily mood, and 17% that it affected their daily function (compared to 3% with a normal mammogram) (Lerman 1991). In Norway, 18 months after screening mammography, 29% of women with false-positive results and 13% of women with negative results reported anxiety about breast cancer (Gram 1990). In USA, the estimated cumulative risk of a false-positive result after 10 mammograms was 49% and 19% would have had a biopsy (Elmore 1998). The percentage of false-positive screening mammograms increased from 4% to 8% in a seven-year period (Elmore 1998), and more recent data have shown a recall rate in women aged 50 to 54 years as high as 13 to 14% after the first mammogram, compared to 8% in UK (Smith-Bindman 2003).

Thus, it seems that screening inflicts important psychological distress for many months on more than a tenth of the healthy population of women who attend a screening program. The women are not being informed about this risk (Jørgensen 2004; Slaytor 1998; Werkö 1995) or the risk of receiving a diagnosis of carcinoma in situ (Jørgensen 2004; Thornton 1997).

Thirty-two per cent of women having their first mammogram experienced pain (Miller 2001a), and a further 23% felt it was very uncomfortable (McNoe 1996). Half of 81 women declined an invitation to the second round of screening noted that the major reason was that their first mammogram was painful (Elwood 1998).

**Other recent reviews of screening**

Previous reviews have generally not heeded the methodological quality of the trials, but when the methods were assessed blindly, the researchers judged the Canadian trial to be of high quality and the Two-County trial to be of poor quality (Glasziou 1995).

Only one of the recent reviews, commissioned by the US Preventive Services Task Force, has been systematic (Humphrey 2002). It excluded the Edinburgh trial and reported a relative risk of 0.84 (0.77 to 0.91) for breast cancer mortality. The authors noted that "although most of these trials were flawed in design or execution, there is insufficient evidence to conclude that most were seriously biased and consequently invalid" and were concerned whether, across all age groups, the magnitude of benefit is sufficient to outweigh the harms. The Task Force gave mammography screening a grade B recommendation (US Task Force 2002).

A recent WHO report (WHO 2002) was not a systematic review and paid little attention to the varying quality of the trials; it even included a non-randomised study in its meta-analysis. A global summit on mammography screening in Milan in 2002 did not involve a systematic review either and had the character of a consensus conference (Boyle 2003).

The meta-analyses of the Swedish trials are not systematic reviews as they do not include all relevant trials. There are many possibilities for bias in cluster randomised trials (Puffer 2003), and numbers of randomised women are inconsistently reported (see table: Examples of varying numbers of women in the Swedish trials). In Stockholm, for example, the number of randomised women decreased by 4.5% in the screening group, but increased by 3.6% in the control group (Gøtzsche 2000) in the Swedish 1993 review (Nyström 1993), compared to the trial report (Frisell 1997). In the 2000 and 2002 reviews (Nyström 2000; Nyström 2002),

numbers have increased by 1.6% in both groups, but should have been the same as in the 1993 report, since all women were identified through their unique identification number (Nyström 2002), which has been used in Sweden for more than three decades; exclusions of women with previous breast cancer was completed with the 1993 review; and all three reviews were based on exact age at randomisation, and the age range is the same. The varying numbers therefore indicate that the randomisation has not been respected. The estimates in the Swedish reviews were adjusted for differences in age. Since the distribution of age would be expected to differ in various socioeconomic strata, such adjustment would be expected to lead to other imbalances (Gøtzsche 2000). Furthermore, simulation studies have shown that adjustments quite often increase bias rather than reduce it (Deeks 2003). The most recent review of the Swedish trials reported two relative risks for breast cancer mortality, RR 0.79 (0.70 to 0.89) with the evaluation model and RR 0.85 (0.77 to 0.94) with the follow-up model (Nyström 2002).

**What is the bottom line on screening?**

The decision to embark on the UK screening program was made mainly because of the positive results in the New York and Two-County trials (UK age trial 1991). Policy makers and many scientists have believed that the benefit of screening was well documented. However, information essential to judging the reliability of the trials was often unpublished or published only in Swedish, in theses, letters, conference reports, reviews, or in journals that are not widely read, and with titles and abstracts that did not indicate that important data were to be found. Furthermore, the harms of screening received very little attention.

The largest reported effect in the Swedish trials is a 29% relative reduction in breast cancer mortality for women aged 50 to 69 years (Nyström 1993). This corresponds to an absolute reduction in breast cancer mortality of 0.1%. Since all-cause mortality is about 10% in the same time period (Nyström 1996), survival after 10 years is 90.3% if women are invited to screening, and 90.2% if they are not invited. This benefit corresponds to a life extension of two days, on average, per woman who is invited (described as two days per woman per screen in the WHO report (WHO 2002), but it is not per screen but per 10 years of screening (Nyström 1993)).

We have given reasons above that make us believe that a realistic estimate of the effect would be a 15% relative reduction in breast cancer mortality. This agrees with the systematic review done for the US Preventive Services Task Force that suggested 16% (Humphrey 2002), and with the most recently updated meta-analysis of the Swedish trials that reported 15% with the follow-up model (Nyström 2002). Since the trials did not find a reduction in all-cancer mortality, this could still be an overestimate but if we assume the effect is 15%, and that the level of overdiagnosis is 30% which appears to be a robust estimate, it means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. In addition, 10 healthy women, who would not have had a breast cancer diagnosis if there had not been screening, will be diagnosed as cancer patients and will be treated unnecessarily (see analysis graph 14). In addition, it is likely that more than 200 women will experience important psychological distress for many months because of false positive findings.

The balance between good and harm from screening is thus not clear. From the estimated benefit of an average life extension of one day, one should subtract the time it takes for the woman to travel and attend the screening sessions and the time used by staff members and other people, e.g. her general practitioner. In addition, the harmful effects of screening need to be considered, and there is loss of income and other costs. The National Health Service in the UK has never invested more in implementing a new type of clinical practice (Gray 1989).

It has been suggested that resources be redirected to interventions with proven benefit in breast cancer (Baum 2000) or used for other purposes (NBCC 2002). For comparison, the benefit is 200 times greater when women with node-positive breast cancer are treated with tamoxifen, since the average life extension is six months, also after 10 years (Early Breast C 1998).

## AUTHORS' CONCLUSIONS

### Implications for practice

Despite the shortcomings of the trials, screening appears to lower breast cancer mortality. However, the chance that a woman will benefit from attending screening is very small, and considerably smaller than the risk that she will experience harm. It is thus not clear whether screening does more good than harm. Women, clinicians and policy makers should consider the trade-offs carefully when they decide whether or not to attend or support screening programs.

Screening advocates and their organisations have generally emphasized the benefits and omitted information on the major harms in information materials (Dixon-Woods 2001; Jørgensen 2004; NHS leaflet 2001; US Task Force 2002) and in invitational letters (Jørgensen 2006). Most women therefore tend to exaggerate substantially the benefits and to be unaware of the major harms of screening (Barratt 1997; Barratt 1999; Domenighetti 2003; Schwartz 2004). This needs to be corrected to ensure that the requirements for informed consent for women contemplating whether or not to attend a screening program can be met.

### Implications for research

Breast cancer mortality is an unreliable outcome measure in screening trials (and therefore also in cohort studies of the effectiveness of national programs) that exaggerates the benefit. Because of the problems with the quality of the screening trials and the reported

analyses, it would be useful if independent researchers performed an individual patient data meta-analysis, where exclusions of randomised women are not allowed. It would also be useful to get data on all-cancer mortality for all the trials since misclassification of cause of death often concerns deaths from other cancers. Finally, to improve the efficiency of screening programs and to reduce overdiagnosis and overtreatment, research is needed to identify means of separating cancers likely to result in death from the many benign cancers identified by screening that do not need treatment.

## POTENTIAL CONFLICT OF INTEREST

None. We had no a priori opinion on the effect of screening for breast cancer when we were asked in 1999 by the Danish Institute for Health Technology Assessment, the National Board of Health, to review the randomised trials.

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* *Indicates the major publication for the study*

# TABLES

## Characteristics of included studies

| **Study** | **Canada 1980** |
|---|---|
| Methods | Individual randomisation in blocks of 2 or 4, stratified by centre and 5-year age group (see also text).<br>Cause of death was assessed blinded and independently by two specialists for women with diagnosed breast cancer and for other possible breast cancer deaths. |
| Participants | Women aged 40-59.<br>Number randomised: see below. |
| Interventions | Two-view mammography cranio-caudal and mediolateral (later medio-lateral oblique except in two centres).<br>4-5 cycles of screening with yearly interval. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Surgical interventions. |
| Notes | Attendance rate: 100% in first round.<br>Mammography in control group: Screening of high risk groups not precluded.<br>(see also Canada 1980a and 1980b) |
| Allocation concealment | D – Not used |

| **Study** | **Canada 1980a** |
|---|---|
| Methods | See Canada 1980. |
| Participants | Women aged 40-49.<br>50,472 randomised.<br>59, distributed equally between the two groups, were excluded from analyses. |
| Interventions | See Canada 1980.<br>Screened women had an annual clinical examination while control women were examined at the first visit and were taught self-examination thereafter. |
| Outcomes | See Canada 1980. |
| Notes | Attendance rate: 100% in first round, 89% in second, decreasing to 86% in fifth round.<br>Mammography in control group: 7% between first and second year, increasing to 18% between fourth and fifth year had a mammogram. |
| Allocation concealment | D – Not used |

**Characteristics of included studies** (*Continued*)

| **Study** | **Canada 1980b** |
|---|---|
| Methods | See Canada 1980. |
| Participants | Women aged 50-59.<br>39,459 randomised.<br>54, distributed equally between the two groups, were excluded from analyses. |
| Interventions | See Canada 1980.<br>All women had their breasts examined annually. |
| Outcomes | See Canada 1980. |
| Notes | Attendance rate: 100% in first round, 90% in second, decreasing to 87% in fifth round.<br>Mammography in control group: 5% between first and second year, increasing to 8% between fourth and fifth year had a mammogram. |
| Allocation concealment | D – Not used |

| **Study** | **Edinburgh 1978** |
|---|---|
| Methods | Stratified cluster randomisation; general practices were clusters; stratification was by size of practice. About 87 clusters (numbers vary in different reports, see also text).<br>Blinding of outcome assessment not stated. |
| Participants | Women aged 45-64.<br>Number of women and practices randomised inconsistently reported (see text).<br>Very biased exclusions occurred: exclusion procedures different in study and control group, 177 previous breast cancer cases excluded from control group and 338 from study group. |
| Interventions | Two-view mammography at first screen: cranio-caudal and oblique (except in one practice); only oblique in later rounds.<br>Screened group: mammography and physical examination year 1, 3, 5 and 7; physical examination year 2, 4 and 6.<br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Radiotherapy. |
| Notes | Attendance rate: Ca. 60 % in first round; 44% in seventh round.<br>Mammography in control group: unknown. |
| Allocation concealment | D – Not used |

| **Study** | **Göteborg 1982** |
|---|---|
| Methods | See Göteborg 1982a and 1982b |
| Participants | Women aged 39-59.<br>Number of women randomised: 21,904 to screening, 30,318 to control (see also text).<br>254 women (1.2%) excluded from the screening group and 357 (1.2%) from the control group due to a history of breast carcinoma prior to randomisation. |
| Interventions | See Göteborg 1982a and 1982b |
| Outcomes | Total mortality. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | Breast cancer mortality. |
| Notes | Mammography in control group: 18% during last two years. |
| Allocation concealment | D – Not used |

| **Study** | **Göteborg 1982a** |
|---|---|
| Methods | Individual randomisation within year of birth cohort - by day of birth in the cohorts 1923-35 and by computer software for the cohorts 1936-44 - randomisation ratio varied by cohort, on average approximately 1:1.2 (see also text).<br><br>Blinding of outcome assessment. |
| Participants | Women aged 39-49.<br><br>Number of women randomised: 11,792 to screening, 14,321 to control (see also text).<br><br>68 women (0.6%) excluded from the screening group and 104 (0.7%) from the control group due to a history of breast carcinoma prior to randomisation. |
| Interventions | Two-view mammography at first screen, single at later rounds - single read at first three rounds; double read thereafter.<br><br>5 cycles with an interval of 18 months.<br><br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality. |
| Notes | Attendance rate: 85%, 78%, 79%, 77%, 75% in rounds 1-5.<br>66% at first screen in control group.<br>Mammography in control group: 19% during last two years; 51% ever.<br>Early systematic screening of control group. |
| Allocation concealment | D – Not used |

| **Study** | **Göteborg 1982b** |
|---|---|
| Methods | Individual randomisation by computer software - randomisation ratio varied by cohort, on average approximately 1:1.6.<br><br>Blinding of outcome assessment. |
| Participants | Women aged 50-59.<br><br>Number of women randomised not stated explicitly, but can be calculated by comparing two trial reports (see Göteborg 1992 above for total numbers). |
| Interventions | Two-view mammography at first screen, single at later rounds - single read at first three rounds; double read thereafter.<br><br>4 cycles with an interval of 18 months.<br><br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality. |
| Notes | Attendance rate: 83% at first screen.<br>78% at first screen in control group.<br>Early systematic screening of control group. |
| Allocation concealment | D – Not used |

**Characteristics of included studies** (*Continued*)

| **Study** | **Kopparberg 1977** |
|---|---|
| Methods | Stratified cluster randomisation; seven blocks each contained 3 units (in three blocks the units were parishes and in four municipalities); randomisation ratio 2:1 (see also text).<br><br>Blinding of outcome assessment not stated. |
| Participants | Women aged 40 and above.<br><br>21 units randomised: 47,389 women in screening areas and 22,658 in control areas (33,641 vs. 16,359 in age group 40-69; 39,051 vs. 18,846 in age group 40-74).<br><br>No parishes or municipalities excluded. Exclusion criteria for patients unclear but probably biased (see text). |
| Interventions | One-view mammography, mediolateral oblique; additional views on suspicion.<br><br>Number of screenings: two cycles pre-stated, but more may have occured (see text).<br>Interval between screens were 2 years for women aged 40-49;<br>3 years for women aged 50 and above. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Surgical interventions.<br>Chemotherapy.<br>Radiotherapy. |
| Notes | Attendance rate: 91-94% for women younger than 60 years; 50-80% for women above 60 years.<br><br>Unclear when screening started in control group (see text).<br><br>Early systematic screening of control group. |
| Allocation concealment | D – Not used |

| **Study** | **Malmö 1976** |
|---|---|
| Methods | Individual randomisation; within each birth cohort a computer list was randomised and the first half invited for screening.<br><br>Blinding of outcome assessment: deaths among breast cancer cases assessed blinded and independently by a pathologist and an oncologist; discrepancies resolved by an internist. |
| Participants | Women aged 45-69.<br><br>21,242 randomised into screened group; 21,240 or 21,244 into control group (see text).<br><br>Biased exclusions seem to have occurred: 154 women excluded from control group<br>49 from study group (see text). |
| Interventions | One-view or two-view mammography; two-view in 1st and 2nd round; one-view or two-view in later rounds depending on parenchymal pattern.<br><br>5-6 cycles according to protocol; 8 cycles in 1988; more during 1988-1992.<br><br>Interval between screens: 18-24 months.<br><br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Surgical interventions.<br>Chemotherapy.<br>Radiotherapy. |
| Notes | Attendance rate: Circa 70%; 74% in first round ranging from 64% in oldest age group to 79% in youngest. |

| | |
|---|---|
| | Mammography in control group: screening offered to age group 50-69 in 1991; invited in 1992 and completed in 1993.<br><br>6% had more than 3 mammograms during study ; 24% had one or more; 35% among women aged 45-49 at entry. |
| Allocation concealment | D – Not used |

| **Study** | **Malmö II 1978** |
|---|---|
| Methods | See text of the review; extension of Malmö 1976. |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |
| Allocation concealment | D – Not used |

| **Study** | **New York 1963** |
|---|---|
| Methods | Individual randomisation within matched pairs; pairs derived from a computer list sorted by age, family size and employment group.<br><br>A blinded review was carried out in a subsample of death certificates where cause of death was breast cancer. The panel much more often stated breast cancer as cause of death in the control group. |
| Participants | Women aged 40-64.<br><br>Probably 31,092 pairs of women were randomised into screening and control group.<br><br>Very biased exclusions occurred: probably 336 previous breast cancer cases were excluded from the control group and 853 from study group (see text). |
| Interventions | Two view mammography: cephalocaudal and lateral.<br>4 cycles (three were planned according to the first publications).<br><br>Screened group: annual physical examinations.<br><br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Surgical interventions.<br>Radiotherapy. |
| Notes | Attendance rate: 65% in total population, ca. 58%, 50% and 40% participated in 2, 3 and 4 screens, respectively.<br><br>Mammography in control group: not described. |
| Allocation concealment | D – Not used |

| **Study** | **Stockholm 1981** |
|---|---|
| Methods | Individual randomisation by day of birth; 1-10 and 21-31 in study group and 11-20 in control group (see also text).<br><br>Blinding of outcome assessment:<br>not stated. |
| Participants | Women aged 40-64.<br><br>Number of women randomised inconsistently reported (see text). |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | Exclusions after randomisation unclear (see text). |
| Interventions | Single oblique mammography; recalled for conventional three-view if malignancies suspected.<br>2 cycles (number not predetermined - screening introduced in control group because of results from Kopparberg).<br>Ca. 2 years; 2.5 years to complete first round and 2.1 to complete second round.<br>Control group: usual care. |
| Outcomes | Total mortality.<br>Breast cancer mortality.<br>Surgical interventions. |
| Notes | Attendance rate: ca. 80%.<br>Mammography in control group: 8% during one year; 25% in study group during three years previous to screening.<br>Early systematic screening of control group. |
| Allocation concealment | D – Not used |

| **Study** | **Two-County 1977** |
|---|---|
| Methods | Stratified cluster randomisation (see Kopparberg 1977 and Östergötland 1978 for details).<br>Blinding of cause of death assessments in some later updates. |
| Participants | Women aged 40-74.<br>(See Kopparberg 1977 and Östergötland 1978 for details). |
| Interventions | See Kopparberg 1977 and Östergötland 1978.<br>Screened women were encouraged to perform self-examination of the breasts every month.<br>Control women: usual care. |
| Outcomes | See Kopparberg 1977 and Östergötland 1978. |
| Notes | See Kopparberg 1977 and Östergötland 1978. |
| Allocation concealment | D – Not used |

| **Study** | **Östergötland 1978** |
|---|---|
| Methods | Stratified cluster randomisation; 12 blocks (consisting of 164 parishes in total) were each split into 2 units of roughly equal size and socio-economic composition; randomisation ratio 1:1 (see also text).<br>Blinding of outcome assessment not stated. |
| Participants | Women aged 40 and above.<br>24 units with 92934<br>women randomised into 47001 in screening parishes and 45933 in control parishes (39034 vs. 37936 in age group 40-74).<br>No parishes or municipalities excluded.<br>Women with a previous history of breast cancer were excluded after randomisation; exclusions seem unbiased (see text). |
| Interventions | One-view mammography, mediolateral oblique; women who reported a lump were examined clinically and by complete mammography.<br>2 screens for women above 70 years, 3 for women originally in age group 40-69. |

| | |
|---|---|
| | Interval between screens: 2-2.5 years. |
| Outcomes | Total mortality.<br>Breast cancer mortality. |
| Notes | Attendance rate: ca. 90% in first round,<br>80% in second, very age dependent.<br>Mammography in control group: no data.<br>Early systematic screening of control group. |
| Allocation concealment | D – Not used |

## Characteristics of excluded studies

| Study | Reason for exclusion |
|---|---|
| Berglund 2000 | Multiple risk factor intervention study, with several interventions, incl. mammography, not a randomised trial but alternating allocation of birth year cohorts with resulting age differences at baseline between the two groups; 50 women died from cancer of 8,712 participants, no data on breast cancer. |
| Dales 1979 | Multiple risk factor intervention trial, with several interventions, regular mammography was only one of the interventions and only about 1000 women were invited for mammography. |

## Characteristics of ongoing studies

| Study | Singapore 1994 |
|---|---|
| Trial name or title | Singapore Breast Screening Project |
| Participants | Women aged 50-64.<br>Number of randomised women 166,600.<br>Exclusions after randomisation only occurred in the screening group. More than 1500 women were excluded, 468 because they were dead; previous cancer at any site was an exclusion criterion. |
| Interventions | Two-view mammography.<br>Only one prevalence screen. |
| Outcomes | No data on mortality yet. |
| Starting date | 1994 |
| Contact information | See reference |
| Notes | |

| Study | UK age trial 1991 |
|---|---|
| Trial name or title | UK Age Trial |
| Participants | Women aged 40-41.<br>The aim is to randomise 195,000 women.<br>Deaths in women with breast cancer diagnosed before entry to the trial will be excluded. |
| Interventions | Two-view with grid in 1st round and one-view in later rounds unless otherwise indicated.<br>Annual screens according to protocol. |
| Outcomes | Total mortality. |

**Characteristics of ongoing studies** (*Continued*)

| | |
|---|---|
| | Breast cancer mortality.<br>Benign biopsies. |
| Starting date | 1991 |
| Contact information | See reference |
| Notes | |

## ADDITIONAL TABLES

**Table 01. Examples of varying numbers of women in the Swedish trials**

| Study | Age range | Study group | Control group | Reference |
|---|---|---|---|---|
| Malmö | 40-74 | 21242 | 21240 | Andersson 1980 |
| | 40-74 | 21242 | 21244 | Andersson 1983 |
| | 40-74 | 21088 | 21195 | Andersson 1988 |
| Kopparberg | total | 47389 | 22658 | Socialstyrelsen 1985 |
| | 40-74 | 39051 | 18846 | Tabar 1985 |
| | 40-74 | 38589 | 18582 | Tabar 1989 |
| | 40-74 | 38562 | 18478 | Nyström 1993 |
| | 40-74 | 38589 | 18582 | Tabar 1995 |
| | 40-74 | 38568 | 18479 | Nyström 2000 |
| | 40-74 | 38588 | 18582 | Nixon 2000 |
| | 40-74 | data not available | data not available | Nyström 2002 |
| | 40-49 | 9625 | 5053 | Tabar 1988 |
| | 40-49 | data not available | data not available | Nyström 1993a |
| | 40-49 | 9582 | 5031 | Tabar 1995 |
| | 40-49 | 9650 | 5009 | Nyström 1997 |
| Östergötland | total | 47001 | 45933 | Socialstyrelsen 1985 |
| | 40-74 | 39034 | 37936 | Tabar 1985 |
| | 40-74 | 38491 | 37403 | Tabar 1989 |
| | 40-74 | 38405 | 37145 | Nyström 1993 |
| | 40-74 | 38491 | 37403 | Tabar 1995 |
| | 40-74 | 38942 | 37675 | Nyström 2000 |
| | 40-74 | 39105 | 37858 | Nixon 2000 |
| | 40-74 | 38942 | 37675 | Nyström 2002 |
| | 40-49 | 10312 | 10625 | Tabar 1988 |
| | 40-49 | data not available | data not available | Nyström 1993a |

**Table 01. Examples of varying numbers of women in the Swedish trials** (*Continued*)

| Study | Age range | Study group | Control group | Reference |
|---|---|---|---|---|
| | 40-49 | 10262 | 10573 | Tabar 1995 |
| | 40-49 | 10240 | 10411 | Nyström 1997 |
| Stockholm | 40-64 | 40318 | 19943 | Frisell 1989a |
| | 40-65 (sic) | 38525 | 20651 | Nyström 1993 |
| | 40-64 | 40318 | 19943 | Frisell 1997 |
| | 40-69 | 39139 | 20978 | Nyström 2000 |
| | 40-49 | data not available | data not available | Nyström 1993a |
| | 40-49 | 14842 | 7103 | Frisell 1997 |
| | 40-49 | 14185 | 7985 | Nyström 1997 |
| | 40-49 | 14303 | 8021 | Nyström 2002 |
| Göteborg | 40-59 | 20724 | 28809 | Nyström 1993 |
| | 39-59 | 21650 | 29961 | Bjurstam 1997a |
| | 40-59 | 21000 | 29200 | Nyström 2000 |
| | 40-49 | 10821 | 13101 | Nyström 1993a |
| | 39-49 | 11724 | 14217 | Bjurstam 1997 |
| | 40-49 | 10888 | 13203 | Nyström 2002 |

## ANALYSES

### Comparison 01. Screening with mammography versus no screening

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Deaths ascribed to breast cancer, 7 years follow up | 10 | 455487 | Relative Risk (Fixed) 95% CI | 0.80 [0.70, 0.91] |
| 02 Deaths ascribed to breast cancer, 13 years follow up | 8 | 438250 | Relative Risk (Fixed) 95% CI | 0.80 [0.73, 0.88] |
| 03 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malmö 55) | 8 | 195528 | Relative Risk (Fixed) 95% CI | 0.96 [0.78, 1.18] |
| 04 Deaths ascribed to breast cancer, 7 years follow up, women at least 50 years of age (Malmö 55) | 7 | 261044 | Relative Risk (Fixed) 95% CI | 0.72 [0.62, 0.85] |
| 05 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age | 7 | 168671 | Relative Risk (Fixed) 95% CI | 0.84 [0.72, 0.99] |
| 06 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age | 7 | 268874 | Relative Risk (Fixed) 95% CI | 0.77 [0.69, 0.86] |

| | | | | |
|---|---|---|---|---|
| 07 Deaths ascribed to any cancer, all women | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 08 Overall mortality, 7 years follow up | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 09 Overall mortality, 13 years follow up | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 10 Overall mortality, 7 years follow up, women below 50 years of age | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 11 Overall mortality, 7 years follow up, women at least 50 years of age | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 12 Overall mortality, 13 years follow up, women below 50 years of age | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 13 Overall mortality, 13 years follow up, women at least 50 years of age | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 14 Number of mastectomies and lumpectomies | 5 | 250479 | Relative Risk (Fixed) 95% CI | 1.35 [1.26, 1.44] |
| 15 Number of mastectomies | 5 | 250479 | Relative Risk (Fixed) 95% CI | 1.20 [1.11, 1.30] |
| 16 Number treated with radiotherapy | 2 | 100383 | Relative Risk (Fixed) 95% CI | 1.32 [1.16, 1.50] |
| 17 Number treated with chemotherapy | 2 | 100383 | Relative Risk (Fixed) 95% CI | 0.96 [0.78, 1.19] |
| 18 Number treated with hormone therapy | 2 | 100383 | Relative Risk (Fixed) 95% CI | 0.73 [0.55, 0.96] |
| 19 Mortality among breast cancer patients in the Two-County study, 7 years follow up | | | Relative Risk (Fixed) 95% CI | Subtotals only |
| 20 Results for biased trial | | | Relative Risk (Fixed) 95% CI | Totals not selected |
| 21 Number of cancers | | | Relative Risk (Fixed) 95% CI | Subtotals only |

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Breast Neoplasms [mortality; *radiography]; Cause of Death; *Mammography; Mass Screening [adverse effects]; Randomized Controlled Trials

**MeSH check words**

Female; Humans

## COVER SHEET

| | |
|---|---|
| **Title** | Screening for breast cancer with mammography |
| **Authors** | Gøtzsche PC, Nielsen M |
| **Contribution of author(s)** | PCG wrote the draft protocol and did the searches. Both authors extracted the main data independently for this update and contributed to the review. PCG is guarantor. |
| **Issue protocol first published** | 2000/1 |

| | |
|---|---|
| **Review first published** | 2001/4 |
| **Date of most recent amendment** | 07 November 2006 |
| **Date of most recent SUBSTANTIVE amendment** | 12 July 2006 |
| **What's New** | Data on treatment (surgery, radiotherapy and other adjuvant therapy), data after extended follow-up from the trials, and data on numbers of cancers identified have been added. |
| **Date new studies sought but none found** | Information not supplied by author |
| **Date new studies found but not yet included/excluded** | Information not supplied by author |
| **Date new studies found and included/excluded** | 01 June 2005 |
| **Date authors' conclusions section amended** | Information not supplied by author |
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## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Screening with mammography versus no screening, Outcome 01 Deaths ascribed to breast cancer, 7 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 01 Deaths ascribed to breast cancer, 7 years follow up

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 38/25214 | 28/25216 | | 5.4 | 1.36 [ 0.83, 2.21 ] |
| Canada 1980b | 38/19711 | 39/19694 | | 7.5 | 0.97 [ 0.62, 1.52 ] |
| Malmö 1976 | 63/21088 | 66/21195 | | 12.7 | 0.96 [ 0.68, 1.35 ] |
| Subtotal (95% CI) | 66013 | 66105 | | 25.5 | 1.05 [ 0.83, 1.33 ] |
| Total events: 139 (Screening), 133 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.44 df=2 p=0.49 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.38 p=0.7 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982a | 6/10821 | 10/13101 | | 1.7 | 0.73 [ 0.26, 2.00 ] |
| Göteborg 1982b | 21/9903 | 37/15708 | | 5.5 | 0.90 [ 0.53, 1.54 ] |
| Kopparberg 1977 | 71/39051 | 52/18846 | | 13.5 | 0.66 [ 0.46, 0.94 ] |
| Malmö II 1978 | 29/9581 | 33/8212 | | 6.8 | 0.75 [ 0.46, 1.24 ] |
| New York 1963 | 81/31000 | 124/31000 | | 23.8 | 0.65 [ 0.49, 0.86 ] |
| Stockholm 1981 | 53/38525 | 40/20651 | | 10.0 | 0.71 [ 0.47, 1.07 ] |
| Östergötland 1978 | 53/39034 | 67/37936 | | 13.1 | 0.77 [ 0.54, 1.10 ] |
| Subtotal (95% CI) | 177915 | 145454 | | 74.5 | 0.71 [ 0.61, 0.83 ] |
| Total events: 314 (Screening), 363 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.51 df=6 p=0.96 $I^2$ =0.0% | | | | | |
| Test for overall effect z=4.37 p=0.00001 | | | | | |
| Total (95% CI) | 243928 | 211559 | | 100.0 | 0.80 [ 0.70, 0.91 ] |
| Total events: 453 (Screening), 496 (No screening) | | | | | |
| Test for heterogeneity chi-square=10.12 df=9 p=0.34 $I^2$ =11.0% | | | | | |
| Test for overall effect z=3.47 p=0.0005 | | | | | |

## Analysis 01.02. Comparison 01 Screening with mammography versus no screening, Outcome 02 Deaths ascribed to breast cancer, 13 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 02 Deaths ascribed to breast cancer, 13 years follow up

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 105/25214 | 108/25216 | | 9.9 | 0.97 [ 0.74, 1.27 ] |
| Canada 1980b | 107/19711 | 105/19694 | | 9.6 | 1.02 [ 0.78, 1.33 ] |
| Malmö 1976 | 87/20695 | 108/20783 | | 9.8 | 0.81 [ 0.61, 1.07 ] |
| Subtotal (95% CI) | 65620 | 65693 | | 29.3 | 0.93 [ 0.80, 1.09 ] |
| Total events: 299 (Screening), 321 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.48 df=2 p=0.48 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.87 p=0.4 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982 | 88/21650 | 162/29961 | | 12.4 | 0.75 [ 0.58, 0.97 ] |
| Kopparberg 1977 | 126/38589 | 104/18582 | | 12.8 | 0.58 [ 0.45, 0.76 ] |
| New York 1963 | 218/31000 | 262/31000 | | 23.9 | 0.83 [ 0.70, 1.00 ] |
| Stockholm 1981 | 66/40318 | 45/19943 | | 5.5 | 0.73 [ 0.50, 1.06 ] |
| Östergötland 1978 | 135/38491 | 173/37403 | | 16.0 | 0.76 [ 0.61, 0.95 ] |
| Subtotal (95% CI) | 170048 | 136889 | | 70.7 | 0.75 [ 0.67, 0.83 ] |
| Total events: 633 (Screening), 746 (No screening) | | | | | |
| Test for heterogeneity chi-square=4.94 df=4 p=0.29 $I^2$ =19.0% | | | | | |
| Test for overall effect z=5.34 p<0.00001 | | | | | |
| Total (95% CI) | 235668 | 202582 | | 100.0 | 0.80 [ 0.73, 0.88 ] |
| Total events: 932 (Screening), 1067 (No screening) | | | | | |
| Test for heterogeneity chi-square=11.73 df=7 p=0.11 $I^2$ =40.3% | | | | | |
| Test for overall effect z=4.91 p<0.00001 | | | | | |

## Analysis 01.03. Comparison 01 Screening with mammography versus no screening, Outcome 03 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malmö 55)

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 03 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malmö 55)

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 38/25214 | 28/25216 | | 15.6 | 1.36 [ 0.83, 2.21 ] |
| Malmö 1976 | 28/7981 | 22/8082 | | 12.2 | 1.29 [ 0.74, 2.25 ] |
| Subtotal (95% CI) | 33195 | 33298 | | 27.9 | 1.33 [ 0.92, 1.92 ] |
| Total events: 66 (Screening), 50 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.02 df=1 p=0.89 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.51 p=0.1 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982a | 6/10821 | 10/13101 | | 5.1 | 0.73 [ 0.26, 2.00 ] |
| Kopparberg 1977 | 12/9625 | 8/5053 | | 5.9 | 0.79 [ 0.32, 1.93 ] |
| Malmö II 1978 | 29/9581 | 33/8212 | | 19.9 | 0.75 [ 0.46, 1.24 ] |
| New York 1963 | 39/14849 | 48/14911 | | 26.8 | 0.82 [ 0.54, 1.24 ] |
| Stockholm 1981 | 20/14842 | 12/7103 | | 9.1 | 0.80 [ 0.39, 1.63 ] |
| Östergötland 1978 | 11/10312 | 10/10625 | | 5.5 | 1.13 [ 0.48, 2.67 ] |
| Subtotal (95% CI) | 70030 | 59005 | | 72.1 | 0.81 [ 0.63, 1.05 ] |
| Total events: 117 (Screening), 121 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.72 df=5 p=0.98 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.59 p=0.1 | | | | | |
| Total (95% CI) | 103225 | 92303 | | 100.0 | 0.96 [ 0.78, 1.18 ] |
| Total events: 183 (Screening), 171 (No screening) | | | | | |
| Test for heterogeneity chi-square=5.37 df=7 p=0.61 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.43 p=0.7 | | | | | |

## Analysis 01.04. Comparison 01 Screening with mammography versus no screening, Outcome 04 Deaths ascribed to breast cancer, 7 years follow up, women at least 50 years of age (Malmö 55)

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 04 Deaths ascribed to breast cancer, 7 years follow up, women at least 50 years of age (Malmö 55)

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980b | 38/19711 | 39/19694 | | 11.2 | 0.97 [ 0.62, 1.52 ] |
| Malmö 1976 | 35/13107 | 44/13113 | | 12.7 | 0.80 [ 0.51, 1.24 ] |
| Subtotal (95% CI) | 32818 | 32807 | | 23.9 | 0.88 [ 0.64, 1.20 ] |
| Total events: 73 (Screening), 83 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.39 df=1 p=0.53 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.80 p=0.4 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982b | 21/9903 | 37/15708 | | 8.2 | 0.90 [ 0.53, 1.54 ] |
| Kopparberg 1977 | 59/29426 | 44/13793 | | 17.2 | 0.63 [ 0.43, 0.93 ] |
| New York 1963 | 52/16151 | 80/16089 | | 23.1 | 0.65 [ 0.46, 0.92 ] |
| Stockholm 1981 | 33/25476 | 28/12840 | | 10.7 | 0.59 [ 0.36, 0.98 ] |
| Östergötland 1978 | 42/28722 | 57/27311 | | 16.8 | 0.70 [ 0.47, 1.04 ] |
| Subtotal (95% CI) | 109678 | 85741 | | 76.1 | 0.67 [ 0.56, 0.81 ] |
| Total events: 207 (Screening), 246 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.58 df=4 p=0.81 $I^2$ =0.0% | | | | | |
| Test for overall effect z=4.13 p=0.00004 | | | | | |
| Total (95% CI) | 142496 | 118548 | | 100.0 | 0.72 [ 0.62, 0.85 ] |
| Total events: 280 (Screening), 329 (No screening) | | | | | |
| Test for heterogeneity chi-square=4.02 df=6 p=0.67 $I^2$ =0.0% | | | | | |
| Test for overall effect z=3.95 p=0.00008 | | | | | |

## Analysis 01.05. Comparison 01 Screening with mammography versus no screening, Outcome 05 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 05 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 105/25214 | 108/25216 | | 33.9 | 0.97 [ 0.74, 1.27 ] |
| Malmö 1976 | 8/3658 | 16/3769 | | 4.9 | 0.52 [ 0.22, 1.20 ] |
| Subtotal (95% CI) | 28872 | 28985 | | 38.8 | 0.91 [ 0.71, 1.18 ] |
| Total events: 113 (Screening), 124 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.96 df=1 p=0.16 $I^2$ =49.0% | | | | | |
| Test for overall effect z=0.69 p=0.5 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982a | 34/11724 | 59/14217 | | 16.7 | 0.70 [ 0.46, 1.06 ] |
| Kopparberg 1977 | 22/9582 | 16/5031 | | 6.6 | 0.72 [ 0.38, 1.37 ] |
| New York 1963 | 64/13740 | 82/13740 | | 25.7 | 0.78 [ 0.56, 1.08 ] |
| Stockholm 1981 | 24/14842 | 12/7103 | | 5.1 | 0.96 [ 0.48, 1.91 ] |
| Östergötland 1978 | 23/10262 | 23/10573 | | 7.1 | 1.03 [ 0.58, 1.84 ] |
| Subtotal (95% CI) | 60150 | 50664 | | 61.2 | 0.80 [ 0.64, 0.98 ] |
| Total events: 167 (Screening), 192 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.51 df=4 p=0.83 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.13 p=0.03 | | | | | |
| Total (95% CI) | 89022 | 79649 | | 100.0 | 0.84 [ 0.72, 0.99 ] |
| Total events: 280 (Screening), 316 (No screening) | | | | | |
| Test for heterogeneity chi-square=4.18 df=6 p=0.65 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.09 p=0.04 | | | | | |

## Analysis 01.06. Comparison 01 Screening with mammography versus no screening, Outcome 06 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 06 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980b | 107/19711 | 105/19694 | | 14.5 | 1.02 [ 0.78, 1.33 ] |
| Malmö 1976 | 79/17430 | 92/17426 | | 12.7 | 0.86 [ 0.64, 1.16 ] |
| Subtotal (95% CI) | 37141 | 37120 | | 27.2 | 0.94 [ 0.77, 1.15 ] |
| Total events: 186 (Screening), 197 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.69 df=1 p=0.41 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.57 p=0.6 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Göteborg 1982b | 54/9926 | 103/15744 | | 11.0 | 0.83 [ 0.60, 1.15 ] |
| Kopparberg 1977 | 104/29007 | 88/13551 | | 16.6 | 0.55 [ 0.42, 0.73 ] |
| New York 1963 | 101/16505 | 130/16505 | | 17.9 | 0.78 [ 0.60, 1.01 ] |
| Stockholm 1981 | 42/25476 | 33/12840 | | 6.1 | 0.64 [ 0.41, 1.01 ] |
| Östergötland 1978 | 112/28229 | 150/26830 | | 21.2 | 0.71 [ 0.56, 0.91 ] |
| Subtotal (95% CI) | 109143 | 85470 | | 72.8 | 0.70 [ 0.62, 0.80 ] |
| Total events: 413 (Screening), 504 (No screening) | | | | | |
| Test for heterogeneity chi-square=4.54 df=4 p=0.34 $I^2$ =11.8% | | | | | |
| Test for overall effect z=5.28 p<0.00001 | | | | | |
| Total (95% CI) | 146284 | 122590 | | 100.0 | 0.77 [ 0.69, 0.86 ] |
| Total events: 599 (Screening), 701 (No screening) | | | | | |
| Test for heterogeneity chi-square=11.22 df=6 p=0.08 $I^2$ =46.5% | | | | | |
| Test for overall effect z=4.73 p<0.00001 | | | | | |

## Analysis 01.07. Comparison 01 Screening with mammography versus no screening, Outcome 07 Deaths ascribed to any cancer, all women

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 07 Deaths ascribed to any cancer, all women

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 280/25214 | 285/25216 | | 20.0 | 0.98 [ 0.83, 1.16 ] |
| Canada 1980b | 464/19711 | 403/19694 | | 28.3 | 1.15 [ 1.01, 1.31 ] |
| Malmö 1976 | 707/21088 | 739/21195 | | 51.7 | 0.96 [ 0.87, 1.06 ] |
| Subtotal (95% CI) | 66013 | 66105 | | 100.0 | 1.02 [ 0.95, 1.10 ] |
| Total events: 1451 (Screening), 1427 (No screening) | | | | | |
| Test for heterogeneity chi-square=4.69 df=2 p=0.10 $I^2$ =57.4% | | | | | |
| Test for overall effect z=0.52 p=0.6 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Kopparberg 1977 | 666/39051 | 319/18846 | | 24.6 | 1.01 [ 0.88, 1.15 ] |
| New York 1963 | 791/30239 | 823/30765 | | 46.6 | 0.98 [ 0.89, 1.08 ] |
| Östergötland 1978 | 510/39034 | 498/37936 | | 28.8 | 1.00 [ 0.88, 1.13 ] |
| Subtotal (95% CI) | 108324 | 87547 | | 100.0 | 0.99 [ 0.93, 1.06 ] |
| Total events: 1967 (Screening), 1640 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.14 df=2 p=0.93 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.29 p=0.8 | | | | | |

## Analysis 01.08. Comparison 01 Screening with mammography versus no screening, Outcome 08 Overall mortality, 7 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 08 Overall mortality, 7 years follow up

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 159/25214 | 156/25216 | | 7.1 | 1.02 [ 0.82, 1.27 ] |
| Canada 1980b | 253/19711 | 250/19694 | | 11.3 | 1.01 [ 0.85, 1.20 ] |
| Malmö 1976 | 1777/21088 | 1809/21195 | | 81.6 | 0.99 [ 0.93, 1.05 ] |
| Subtotal (95% CI) | 66013 | 66105 | | 100.0 | 0.99 [ 0.94, 1.05 ] |
| Total events: 2189 (Screening), 2215 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.13 df=2 p=0.94 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.27 p=0.8 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Göteborg 1982a | 178/10888 | 185/13203 | | 2.4 | 1.17 [ 0.95, 1.43 ] |
| Göteborg 1982b | 349/10112 | 591/15997 | | 6.4 | 0.93 [ 0.82, 1.06 ] |
| Kopparberg 1977 | 2593/39051 | 1216/18846 | | 23.1 | 1.03 [ 0.96, 1.10 ] |
| Malmö II 1978 | 402/9581 | 300/8212 | | 4.5 | 1.15 [ 0.99, 1.33 ] |
| New York 1963 | 890/31000 | 940/31000 | | 13.2 | 0.95 [ 0.87, 1.04 ] |
| Stockholm 1981 | 1768/39139 | 1036/20978 | | 19.0 | 0.91 [ 0.85, 0.99 ] |
| Östergötland 1978 | 2253/39034 | 2204/37936 | | 31.4 | 0.99 [ 0.94, 1.05 ] |
| Subtotal (95% CI) | 178805 | 146172 | | 100.0 | 0.99 [ 0.96, 1.02 ] |
| Total events: 8433 (Screening), 6472 (No screening) | | | | | |
| Test for heterogeneity chi-square=13.75 df=6 p=0.03 $I^2$ =56.4% | | | | | |
| Test for overall effect z=0.74 p=0.5 | | | | | |

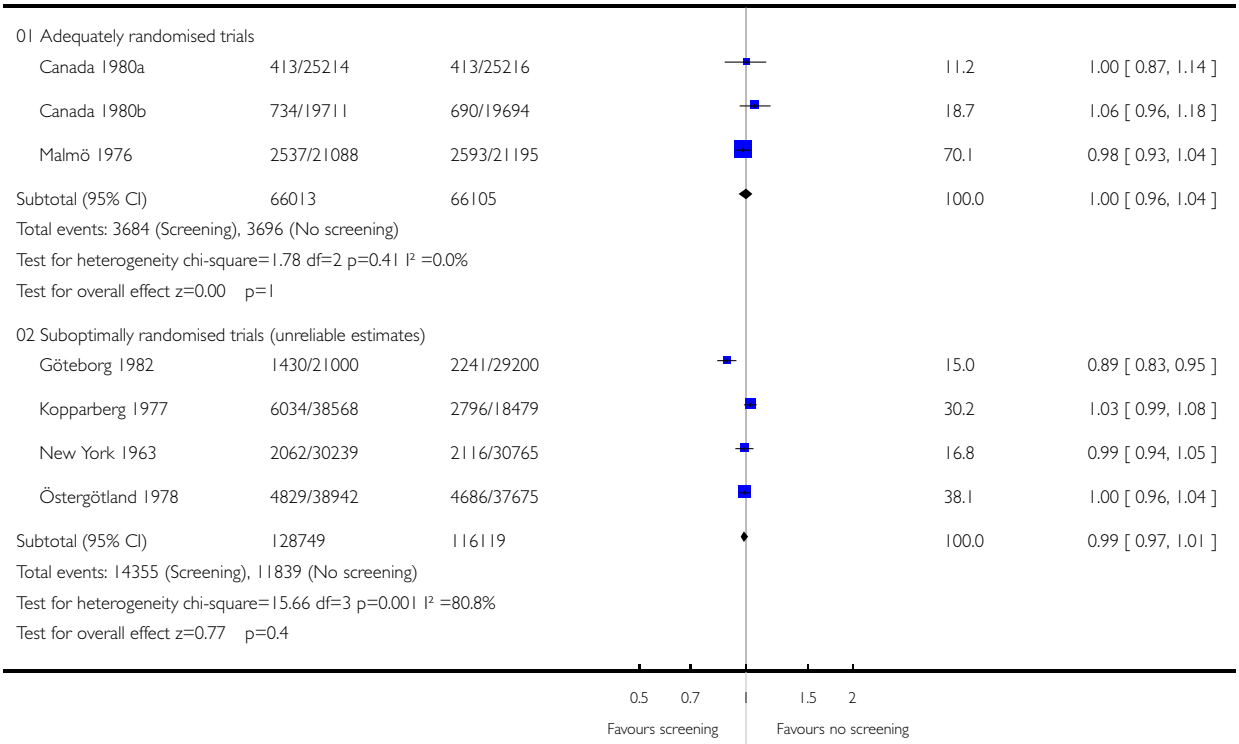
## Analysis 01.09. Comparison 01 Screening with mammography versus no screening, Outcome 09 Overall mortality, 13 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 09 Overall mortality, 13 years follow up

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 413/25214 | 413/25216 | | 11.2 | 1.00 [ 0.87, 1.14 ] |
| Canada 1980b | 734/19711 | 690/19694 | | 18.7 | 1.06 [ 0.96, 1.18 ] |
| Malmö 1976 | 2537/21088 | 2593/21195 | | 70.1 | 0.98 [ 0.93, 1.04 ] |
| Subtotal (95% CI) | 66013 | 66105 | | 100.0 | 1.00 [ 0.96, 1.04 ] |
| Total events: 3684 (Screening), 3696 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.78 df=2 p=0.41 I² =0.0% | | | | | |
| Test for overall effect z=0.00 p=1 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Göteborg 1982 | 1430/21000 | 2241/29200 | | 15.0 | 0.89 [ 0.83, 0.95 ] |
| Kopparberg 1977 | 6034/38568 | 2796/18479 | | 30.2 | 1.03 [ 0.99, 1.08 ] |
| New York 1963 | 2062/30239 | 2116/30765 | | 16.8 | 0.99 [ 0.94, 1.05 ] |
| Östergötland 1978 | 4829/38942 | 4686/37675 | | 38.1 | 1.00 [ 0.96, 1.04 ] |
| Subtotal (95% CI) | 128749 | 116119 | | 100.0 | 0.99 [ 0.97, 1.01 ] |
| Total events: 14355 (Screening), 11839 (No screening) | | | | | |
| Test for heterogeneity chi-square=15.66 df=3 p=0.001 I² =80.8% | | | | | |
| Test for overall effect z=0.77 p=0.4 | | | | | |



## Analysis 01.10. Comparison 01 Screening with mammography versus no screening, Outcome 10 Overall mortality, 7 years follow up, women below 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 10 Overall mortality, 7 years follow up, women below 50 years of age

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 159/25214 | 156/25216 | | 100.0 | 1.02 [ 0.82, 1.27 ] |
| Subtotal (95% CI) | 25214 | 25216 | | 100.0 | 1.02 [ 0.82, 1.27 ] |
| Total events: 159 (Screening), 156 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.17 p=0.9 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Göteborg 1982a | 178/10888 | 185/13203 | | 16.2 | 1.17 [ 0.95, 1.43 ] |
| Kopparberg 1977 | 188/9582 | 74/5031 | | 9.4 | 1.33 [ 1.02, 1.74 ] |
| Malmö II 1978 | 402/9581 | 300/8212 | | 31.3 | 1.15 [ 0.99, 1.33 ] |
| Stockholm 1981 | 274/14303 | 172/8021 | | 21.4 | 0.89 [ 0.74, 1.08 ] |
| Östergötland 1978 | 204/10262 | 227/10573 | | 21.7 | 0.93 [ 0.77, 1.12 ] |
| Subtotal (95% CI) | 54616 | 45040 | | 100.0 | 1.07 [ 0.98, 1.16 ] |
| Total events: 1246 (Screening), 958 (No screening) | | | | | |
| Test for heterogeneity chi-square=10.00 df=4 p=0.04 $I^2$ =60.0% | | | | | |
| Test for overall effect z=1.49 p=0.1 | | | | | |

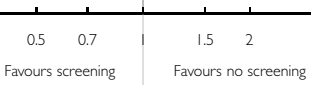
## Analysis 01.11. Comparison 01 Screening with mammography versus no screening, Outcome 11 Overall mortality, 7 years follow up, women at least 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 11 Overall mortality, 7 years follow up, women at least 50 years of age

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980b | 253/19711 | 250/19694 | | 100.0 | 1.01 [ 0.85, 1.20 ] |
| Subtotal (95% CI) | 19711 | 19694 | | 100.0 | 1.01 [ 0.85, 1.20 ] |
| Total events: 253 (Screening), 250 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.12 p=0.9 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Göteborg 1982b | 349/10112 | 591/15997 | | 6.3 | 0.93 [ 0.82, 1.06 ] |
| Kopparberg 1977 | 3485/29007 | 1619/13551 | | 30.6 | 1.01 [ 0.95, 1.06 ] |
| Stockholm 1981 | 1494/24836 | 864/12957 | | 15.7 | 0.90 [ 0.83, 0.98 ] |
| Östergötland 1978 | 3385/28229 | 3332/26830 | | 47.3 | 0.97 [ 0.92, 1.01 ] |
| Subtotal (95% CI) | 92184 | 69335 | | 100.0 | 0.97 [ 0.94, 1.00 ] |
| Total events: 8713 (Screening), 6406 (No screening) | | | | | |
| Test for heterogeneity chi-square=5.02 df=3 p=0.17 $I^2$ =40.3% | | | | | |
| Test for overall effect z=2.19 p=0.03 | | | | | |



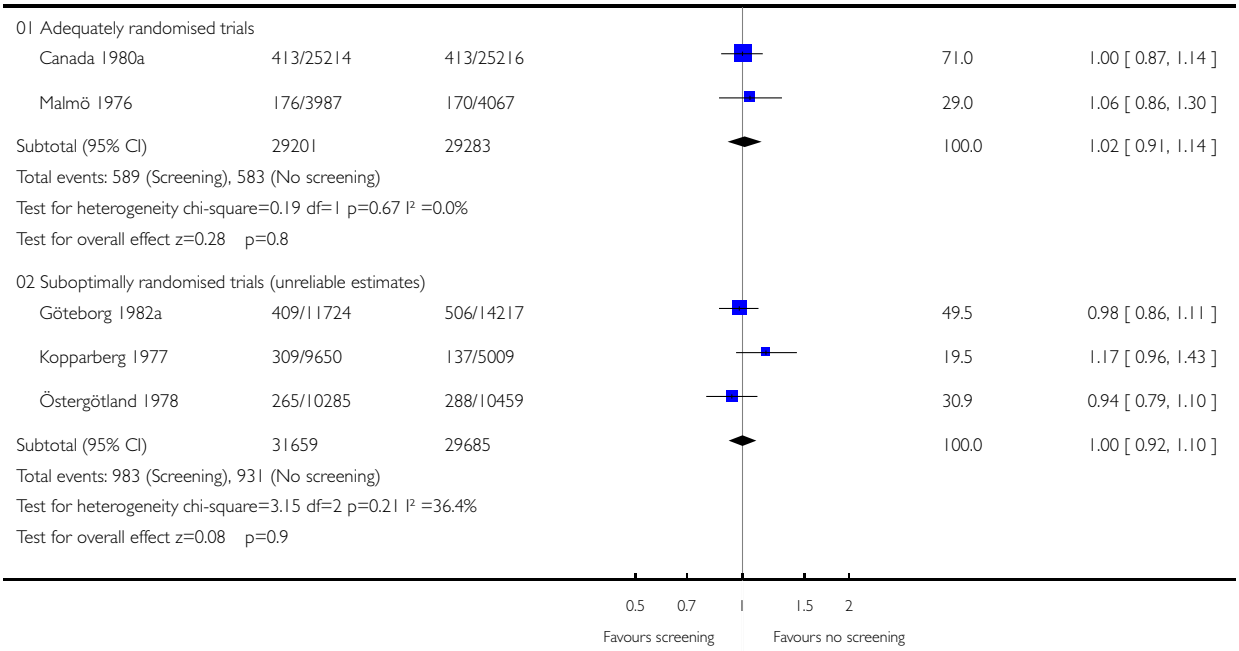
## Analysis 01.12. Comparison 01 Screening with mammography versus no screening, Outcome 12 Overall mortality, 13 years follow up, women below 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 12 Overall mortality, 13 years follow up, women below 50 years of age

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 413/25214 | 413/25216 | | 71.0 | 1.00 [ 0.87, 1.14 ] |
| Malmö 1976 | 176/3987 | 170/4067 | | 29.0 | 1.06 [ 0.86, 1.30 ] |
| Subtotal (95% CI) | 29201 | 29283 | | 100.0 | 1.02 [ 0.91, 1.14 ] |
| Total events: 589 (Screening), 583 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.19 df=1 p=0.67 $I^2$ =0.0% | | | | | |
| Test for overall effect z=0.28 p=0.8 | | | | | |
| 02 Suboptimally randomised trials (unreliable estimates) | | | | | |
| Göteborg 1982a | 409/11724 | 506/14217 | | 49.5 | 0.98 [ 0.86, 1.11 ] |
| Kopparberg 1977 | 309/9650 | 137/5009 | | 19.5 | 1.17 [ 0.96, 1.43 ] |
| Östergötland 1978 | 265/10285 | 288/10459 | | 30.9 | 0.94 [ 0.79, 1.10 ] |
| Subtotal (95% CI) | 31659 | 29685 | | 100.0 | 1.00 [ 0.92, 1.10 ] |
| Total events: 983 (Screening), 931 (No screening) | | | | | |
| Test for heterogeneity chi-square=3.15 df=2 p=0.21 $I^2$ =36.4% | | | | | |
| Test for overall effect z=0.08 p=0.9 | | | | | |

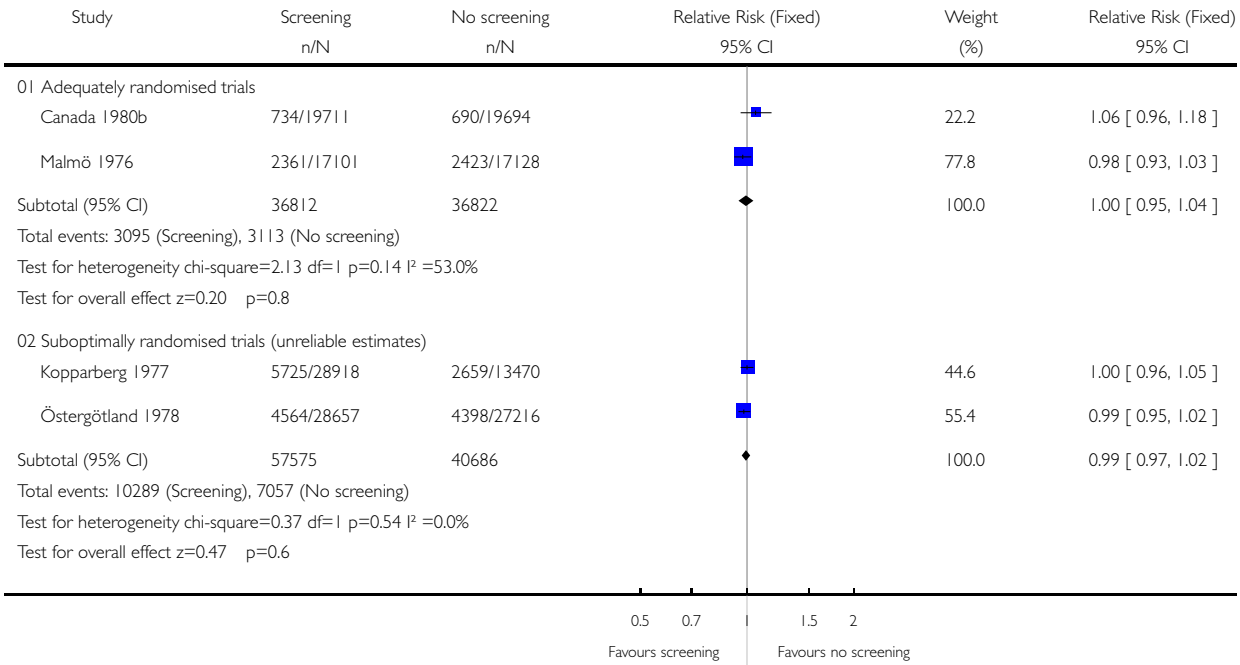


## Analysis 01.13. Comparison 01 Screening with mammography versus no screening, Outcome 13 Overall mortality, 13 years follow up, women at least 50 years of age

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 13 Overall mortality, 13 years follow up, women at least 50 years of age



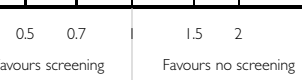
## Analysis 01.14. Comparison 01 Screening with mammography versus no screening, Outcome 14 Number of mastectomies and lumpectomies

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 14 Number of mastectomies and lumpectomies

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 415/25214 | 313/25216 | | 20.4 | 1.33 [ 1.15, 1.53 ] |
| Canada 1980b | 448/19711 | 351/19694 | | 22.9 | 1.28 [ 1.11, 1.46 ] |
| Malmö 1976 | 561/21242 | 419/21244 | | 27.3 | 1.34 [ 1.18, 1.52 ] |
| Subtotal (95% CI) | 66167 | 66154 | | 70.6 | 1.31 [ 1.22, 1.42 ] |
| Total events: 1424 (Screening), 1083 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.28 df=2 p=0.87 $I^2$ =0.0% | | | | | |
| Test for overall effect z=6.85 p<0.00001 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Kopparberg 1977 | 621/39051 | 216/18846 | | 19.0 | 1.39 [ 1.19, 1.62 ] |
| Stockholm 1981 | 360/40318 | 120/19943 | | 10.5 | 1.48 [ 1.21, 1.82 ] |
| Subtotal (95% CI) | 79369 | 38789 | | 29.4 | 1.42 [ 1.26, 1.61 ] |
| Total events: 981 (Screening), 336 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.26 df=1 p=0.61 $I^2$ =0.0% | | | | | |
| Test for overall effect z=5.60 p<0.00001 | | | | | |
| Total (95% CI) | 145536 | 104943 | | 100.0 | 1.35 [ 1.26, 1.44 ] |
| Total events: 2405 (Screening), 1419 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.64 df=4 p=0.80 $I^2$ =0.0% | | | | | |
| Test for overall effect z=8.81 p<0.00001 | | | | | |



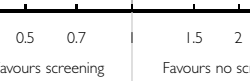
## Analysis 01.15. Comparison 01 Screening with mammography versus no screening, Outcome 15 Number of mastectomies

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 15 Number of mastectomies

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Canada 1980a | 183/25214 | 157/25216 | | 14.7 | 1.17 [ 0.94, 1.44 ] |
| Canada 1980b | 197/19711 | 176/19694 | | 16.4 | 1.12 [ 0.91, 1.37 ] |
| Malmö 1976 | 424/21242 | 339/21244 | | 31.6 | 1.25 [ 1.09, 1.44 ] |
| Subtotal (95% CI) | 66167 | 66154 | | 62.7 | 1.20 [ 1.08, 1.32 ] |
| Total events: 804 (Screening), 672 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.86 df=2 p=0.65 $I^2$ =0.0% | | | | | |
| Test for overall effect z=3.45 p=0.0006 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Kopparberg 1977 | 475/39051 | 196/18846 | | 24.7 | 1.17 [ 0.99, 1.38 ] |
| Stockholm 1981 | 263/40318 | 101/19943 | | 12.6 | 1.29 [ 1.02, 1.62 ] |
| Subtotal (95% CI) | 79369 | 38789 | | 37.3 | 1.21 [ 1.06, 1.38 ] |
| Total events: 738 (Screening), 297 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.45 df=1 p=0.50 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.78 p=0.005 | | | | | |
| Total (95% CI) | 145536 | 104943 | | 100.0 | 1.20 [ 1.11, 1.30 ] |
| Total events: 1542 (Screening), 969 (No screening) | | | | | |
| Test for heterogeneity chi-square=1.33 df=4 p=0.86 $I^2$ =0.0% | | | | | |
| Test for overall effect z=4.43 p<0.00001 | | | | | |



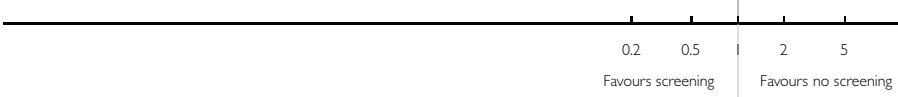
## Analysis 01.16. Comparison 01 Screening with mammography versus no screening, Outcome 16 Number treated with radiotherapy

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 16 Number treated with radiotherapy

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Malmö 1976 | 260/21242 | 209/21244 | | 51.0 | 1.24 [ 1.04, 1.49 ] |
| Subtotal (95% CI) | 21242 | 21244 | | 51.0 | 1.24 [ 1.04, 1.49 ] |
| Total events: 260 (Screening), 209 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=2.36 p=0.02 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Kopparberg 1977 | 433/39051 | 149/18846 | | 49.0 | 1.40 [ 1.17, 1.69 ] |
| Subtotal (95% CI) | 39051 | 18846 | | 49.0 | 1.40 [ 1.17, 1.69 ] |
| Total events: 433 (Screening), 149 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=3.58 p=0.0003 | | | | | |
| Total (95% CI) | 60293 | 40090 | | 100.0 | 1.32 [ 1.16, 1.50 ] |
| Total events: 693 (Screening), 358 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.82 df=1 p=0.36 $I^2$ =0.0% | | | | | |
| Test for overall effect z=4.22 p=0.00002 | | | | | |



## Analysis 01.17. Comparison 01 Screening with mammography versus no screening, Outcome 17 Number treated with chemotherapy

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 17 Number treated with chemotherapy

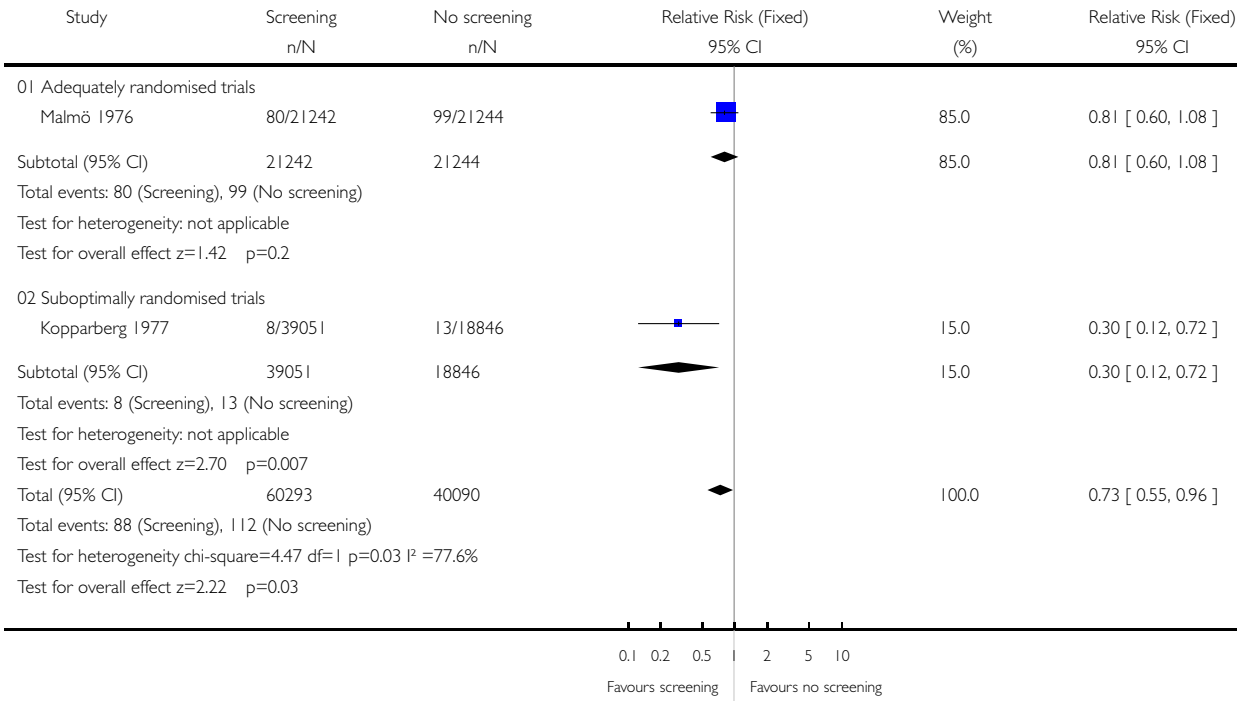
| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials | | | | | |
| Malmö 1976 | 26/21242 | 41/21244 | | 22.8 | 0.63 [ 0.39, 1.04 ] |
| Subtotal (95% CI) | 21242 | 21244 | | 22.8 | 0.63 [ 0.39, 1.04 ] |
| Total events: 26 (Screening), 41 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.82 p=0.07 | | | | | |
| 02 Suboptimally randomised trials | | | | | |
| Kopparberg 1977 | 226/39051 | 103/18846 | | 77.2 | 1.06 [ 0.84, 1.34 ] |
| Subtotal (95% CI) | 39051 | 18846 | | 77.2 | 1.06 [ 0.84, 1.34 ] |
| Total events: 226 (Screening), 103 (No screening) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.48 p=0.6 | | | | | |
| Total (95% CI) | 60293 | 40090 | | 100.0 | 0.96 [ 0.78, 1.19 ] |
| Total events: 252 (Screening), 144 (No screening) | | | | | |
| Test for heterogeneity chi-square=3.42 df=1 p=0.06 $I^2$ =70.8% | | | | | |
| Test for overall effect z=0.36 p=0.7 | | | | | |

## Analysis 01.18. Comparison 01 Screening with mammography versus no screening, Outcome 18 Number treated with hormone therapy

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 18 Number treated with hormone therapy



## Analysis 01.19. Comparison 01 Screening with mammography versus no screening, Outcome 19 Mortality among breast cancer patients in the Two-County study, 7 years follow up

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 19 Mortality among breast cancer patients in the Two-County study, 7 years follow up

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Mortality from cancers other than breast cancer | | | | | |
| Kopparberg 1977 | 13/674 | 3/304 | | 54.6 | 1.95 [ 0.56, 6.81 ] |
| Östergötland 1978 | 12/621 | 3/464 | | 45.4 | 2.99 [ 0.85, 10.53 ] |
| Subtotal (95% CI) | 1295 | 768 | | 100.0 | 2.42 [ 1.00, 5.85 ] |
| Total events: 25 (Treatment), 6 (Control) | | | | | |
| Test for heterogeneity chi-square=0.22 df=1 p=0.64 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.97 p=0.05 | | | | | |
| 02 Mortality from causes other than breast cancer | | | | | |
| Kopparberg 1977 | 47/674 | 15/304 | | 48.7 | 1.41 [ 0.80, 2.49 ] |
| Östergötland 1978 | 34/621 | 19/464 | | 51.3 | 1.34 [ 0.77, 2.31 ] |
| Subtotal (95% CI) | 1295 | 768 | | 100.0 | 1.37 [ 0.93, 2.04 ] |
| Total events: 81 (Treatment), 34 (Control) | | | | | |
| Test for heterogeneity chi-square=0.02 df=1 p=0.89 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.58 p=0.1 | | | | | |

## Analysis 01.20. Comparison 01 Screening with mammography versus no screening, Outcome 20 Results for biased trial

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 20 Results for biased trial

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|
| 01 Deaths ascribed to breast cancer, 7 years follow up | | | | |
| Edinburgh 1978 | 68/23226 | 76/21904 | | 0.84 [ 0.61, 1.17 ] |
| 02 Deaths ascribed to breast cancer, 13 years follow up | | | | |
| Edinburgh 1978 | 176/28628 | 187/26015 | | 0.86 [ 0.70, 1.05 ] |
| 03 Deaths ascribed to breast cancer, 7 years follow up, younger women (below 50 years of age) | | | | |
| Edinburgh 1978 | 13/5913 | 13/5810 | | 0.98 [ 0.46, 2.12 ] |
| 04 Deaths ascribed to breast cancer, 7 years follow up, elderly women (at least 50 years of age) | | | | |
| Edinburgh 1978 | 55/17313 | 63/16094 | | 0.81 [ 0.57, 1.16 ] |
| 05 Deaths ascribed to breast cancer, 13 years follow up, younger women (below 50 years of age) | | | | |
| Edinburgh 1978 | 47/11479 | 53/10267 | | 0.79 [ 0.54, 1.17 ] |
| 06 Deaths ascribed to breast cancer, 13 years follow up, elderly women (at least 50 years of age) | | | | |
| Edinburgh 1978 | 129/17149 | 134/15748 | | 0.88 [ 0.69, 1.12 ] |
| 07 Overall mortality, 7 years follow up | | | | |
| Edinburgh 1978 | 1274/23226 | 1490/21904 | | 0.81 [ 0.75, 0.87 ] |
| 08 Number treated with radiotherapy | | | | |
| Edinburgh 1978 | 75/23226 | 63/21904 | | 1.12 [ 0.80, 1.57 ] |

## Analysis 01.21. Comparison 01 Screening with mammography versus no screening, Outcome 21 Number of cancers

Review: Screening for breast cancer with mammography

Comparison: 01 Screening with mammography versus no screening

Outcome: 21 Number of cancers

| Study | Screening n/N | No screening n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Adequately randomised trials (after 7-9 years) | | | | | |
| Canada 1980a | 426/25214 | 327/25216 | | 28.7 | 1.30 [ 1.13, 1.50 ] |
| Canada 1980b | 460/19711 | 365/19694 | | 32.1 | 1.26 [ 1.10, 1.44 ] |
| Malmö 1976 | 588/21088 | 447/21195 | | 39.2 | 1.32 [ 1.17, 1.49 ] |
| Subtotal (95% CI) | 66013 | 66105 | | 100.0 | 1.30 [ 1.20, 1.40 ] |
| Total events: 1474 (Screening), 1139 (No screening) | | | | | |
| Test for heterogeneity chi-square=0.28 df=2 p=0.87 $I^2$ =0.0% | | | | | |
| Test for overall effect z=6.65 p<0.00001 | | | | | |
| 02 Suboptimally randomised trials (before control group screen) | | | | | |
| Göteborg 1982a | 144/11724 | 155/14217 | | 11.7 | 1.13 [ 0.90, 1.41 ] |
| Stockholm 1981 | 428/40318 | 142/19943 | | 15.8 | 1.49 [ 1.23, 1.80 ] |
| Two-County 1977 | 1378/77080 | 752/55985 | | 72.5 | 1.33 [ 1.22, 1.45 ] |
| Subtotal (95% CI) | 129122 | 90145 | | 100.0 | 1.33 [ 1.24, 1.44 ] |
| Total events: 1950 (Screening), 1049 (No screening) | | | | | |
| Test for heterogeneity chi-square=3.48 df=2 p=0.18 $I^2$ =42.6% | | | | | |
| Test for overall effect z=7.47 p<0.00001 | | | | | |