Screening for breast cancer with mammography (Review)

Gøtzsche PC, Nielsen M

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Screening for breast cancer with mammography

Peter C Gøtzsche[1], Margrethe Nielsen[1]

[1]The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark

Contact address: Peter C Gøtzsche, The Nordic Cochrane Centre, Rigshospitalet, Blegdamsvej 9, 3343, Copenhagen, DK-2100, Denmark. pcg@cochrane.dk.

Editorial group: Cochrane Breast Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2011.
Review content assessed as up-to-date: 20 November 2008.

Citation: Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD001877. DOI: 10.1002/14651858.CD001877.pub4.

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 methods

We searched PubMed (November 2008).

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

Eight eligible trials were identified. We excluded a biased trial and included 600,000 women in the analyses. Three trials with adequate randomisation did not show a significant reduction in breast cancer mortality at 13 years (relative risk (RR) 0.90, 95% confidence interval (CI) 0.79 to 1.02); four trials with suboptimal randomisation showed a significant reduction in breast cancer mortality with an RR of 0.75 (95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI 0.74 to 0.87).

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. The trials with adequate randomisation did not find an effect of screening on cancer mortality, including breast cancer, after 10 years (RR 1.02, 95% CI 0.95 to 1.10) or on all-cause mortality after 13 years (RR 0.99, 95% CI 0.95 to 1.03).

Numbers of lumpectomies and mastectomies were significantly larger in the screened groups (RR 1.31, 95% CI 1.22 to 1.42) for the two adequately randomised trials that measured this outcome; the use of radiotherapy was similarly increased.

Authors' conclusions

Screening is likely to reduce breast cancer mortality. As the effect was lowest in the adequately randomised trials, a reasonable estimate is a 15% reduction corresponding to an absolute risk reduction of 0.05%. Screening led to 30% overdiagnosis and overtreatment, 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 and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false positive findings. It is thus not clear whether screening does more good than harm. To help ensure that the women are fully informed of both benefits and harms before they decide whether or not to attend screening, we have written an evidence-based leaflet for lay people that is available in several languages on www.cochrane.dk.

PLAIN LANGUAGE SUMMARY

Screening for breast cancer with mammography

Screening with mammography uses X-ray to try to find breast cancer before a lump can be felt. The goal is to treat cancer early, when a cure is more likely. The review includes seven trials that involved 600,000 women who were randomly assigned to receive screening mammograms or not. The review found that screening for breast cancer likely reduces breast cancer mortality, but the magnitude of the effect is uncertain. 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 or lumps removed and to receive radiotherapy unnecessarily. The review estimated that screening leads to a reduction in breast cancer mortality of 15% and to 30% overdiagnosis and overtreatment. 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. Furthermore, more than 200 women will experience important psychological distress for many months because of false positive findings.

It is thus not clear whether screening does more good than harm. Women invited to screening should be fully informed of both the benefits and harms. To help ensure that the requirements for informed consent for women contemplating whether or not to attend a screening program can be met, we have written an evidence-based leaflet for lay people that is available in several languages on www.cochrane.dk.

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 also leads 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 reliably estimate the effectiveness of screening is with randomised trials. Large trials, involving 650,000 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; UK age trial 1991), and several systematic reviews and meta-analyses have been published (Berry 1998; Blamey 2000; Cox 1997; Demissie 1998; 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 effects in women of various ages. There is wide variation in screening policies between different countries, with some countries abstaining from introducing screening partly because of the 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 is 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 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 or considered harms as well as benefits. We have identified important weaknesses in the trials (Gøtzsche 2000; Gøtzsche 2000a; Gøtzsche 2004; 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.

METHODS

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 interventions

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

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 in the author field (Alexander F*, Andersson I*, Baines C*, Bjurstam N*, Duffy S*, Fagerberg G*, Frisell J*, Miller AB, Moss S*, Nystrom L*, Shapiro S, Tabar L*). The latest search was done on 22 November 2008; more than 24,000 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.

Data collection and analysis

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 (Higgins 2008). We 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, by including all randomised women. A fixed-effect model with the Mantel-Haenszel method was used, and 95% confidence intervals (CI) are presented. In case of heterogeneity in the trial results ($P < 0.10$), we explored possible reasons. We present the analyses in the graphs as risk ratios, for convenience, but also discuss the absolute risk reductions (or increases) and risk differences as these are more important than relative risks for trials in low-risk populations with few events, such as in the trials we reviewed.
In 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 'Risk of bias in 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 CIs published by the trialists. For completeness, we have shown the pooled estimates for the trials with adequate randomisation and those with suboptimal randomisation 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 age limit that has most often been used by the trialists.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 11 trials. From these we excluded two small trials of several interventions including mammography (Berglund 2000; Dales 1979) and a trial involving 166,600 women where the only intervention was a prevalence screen and where exclusions after randomisation occurred only in the screened group; previous cancer at any site was an exclusion criterion and more than 1500 women were excluded from the screened group, 468 because they had already died (Singapore 1994).

Some of the eight eligible trials (Canada 1980; Edinburgh 1978; Göteborg 1982; Malmö 1976; New York 1963; Stockholm 1981; Two-County 1977; UK age trial 1991) 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 group 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, but the UK age trial invited women aged 39 to 41 years to participate. The Canadian trial was the only one in which the women were individually randomised after invitation and gave 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 of four to nine for all trials except the Two-County and Stockholm trials, in which a large fraction were 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.

The women in the control group were not invited to screening at any point in time in the New York trial, whereas they were invited for screening after 10 to 13 years of follow up in the Edinburgh, Malmö and UK age trials. In the Canadian trial, most of the women in the control group were invited when the trial ended (Baines 2005). Some women were invited for screening while the trial was still ongoing in the Göteborg, Stockholm and Two-County trials (see 'Risk of bias in included studies').

In all trials, women in the control groups were offered usual care. This included mammography on indication, that is for 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').

Risk of bias in included studies

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). 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, which is essential reading to understand the controversies surrounding the effects 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 Health Insurance Plan (HIP) trial) invited women who were members of an insurance plan and 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, for example "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

Postrandomisation 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 minus 30,239) women were excluded from the screened group because of previous breast cancer compared with only 336 (31,092 minus 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 those women 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 described all randomised women and referred to a table that showed baseline differences as percentages but did not provide the numbers upon which the percentages were based. Footnotes explained that some of the data were based on 10% and 20% samples. The table title referred 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 in some cases were a 1964 subgroup of 10% and 20% samples. These 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. It did not account for the 199 or 203 missing women. The number of missing women was 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 that 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 were 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 in 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 at 76%, but it was halved from 1985 to 1997 (Andersson 2000). Cause-of-death

assessments were blinded up to 1988 (Andersson 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 years 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 years, 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, the group size differed more for seven of the 13 birth year cohorts (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 to 49 years (P = 0.00004, Poisson analysis). In total, there were 9581 and 8212 women in the analyses, respectively (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). When the breast cancer mortality rate in the screening group is plotted against the control group rate for eight trials, with data from younger women, the Malmö II trial is a clear outlier (Berry 1998).

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 allocation 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 public notary allocated the clusters in Östergötland by tossing a coin (Nyström 2000) while witnesses were present (Fagerberg, personal communication, 1999). 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 (Table 1) 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 it 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 seems 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 was 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 in the control group were diagnosed with breast cancer before entry to the trial 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 years (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 on average five months older (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 this 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 (Atterstam 1999; Prorok 2000; Tabar 2000a). 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. 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 to 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 2000) but as far as we know the data have not been published.

Comparability of groups

Doubts about the randomisation process 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 were 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 years of age 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 (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 were 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 years, 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 unrecognised 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 have been 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 from 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 were 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; 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 varied. 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 for screening from October 1985 (Nyström 2000), and the trialists noted 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 were 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 favoured screening and can be adjusted for only by comparing the results within each birth-year cohort before they are pooled (Bjurstam 2003).

Entry dates were 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 varied, ranging from three to seven years after randomisation (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.
The UK age trial (UK age trial 1991)
Population studied
This trial included women aged 39 to 41 years who were randomised individually between 1991 and 1997 to an intervention group or a control group, in a ratio of 1:2. Women in the control group received no information about the trial. The trial was undertaken in 23 breast-screening units in England, Wales, and Scotland. Women were identified from lists of patients from general practitioners held on local Health Authority databases and randomisation was carried out stratified by practice. Prior to this, the general practitioners could remove women with previous breast cancer and others deemed inappropriate to invite for screening. From 1992 onwards the allocations were carried out on the Health Authority computer system with specifically written software. Before this, for women in three early centres, random numbers generated from the coordinating centre computer were applied to the lists.
Comparability of groups
We found baseline data only on age; the mean age was 40.38 and 40.39 years, respectively.
Thirty and 51 persons (0.05%) were excluded from analysis for similar reasons in the two groups. The intervention contrast was 10 years. A valid comparison of benefits and harms of screening should be confined to this period.
Assignment of cause of death
There was no information on autopsy rate; information on cause of death was obtained from the central register of the National Health Service.
Likelihood of selection bias
We classified the trial as adequately 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; Moss 2006; 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; Moss 2006; 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; Moss 2005; Tabar 1991.

Effects of interventions

Eight trials provided data. We classified three trials as adequately randomised (Canada, Malmö and UK age trial) 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. As the results from the UK age trial were obtained after a mean follow up of 10.7 years, we included them in the results both after 7 and after 13 years. The adequately randomised trials provided 40% of the breast cancer deaths after 13 years (Analysis 1.2).

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 three adequately randomised trials did not find a statistically significant effect of screening on deaths ascribed to breast cancer, relative risk (RR) 0.93 (95% CI 0.79 to 1.09) after 7 years and RR 0.90 (95% CI 0.79 to 1.02) after 13 years. The four suboptimally randomised trials found a beneficial effect: RR 0.71 (95% CI 0.61 to 0.83) after 7 years and RR 0.75 (95% CI 0.67 to 0.83) after 13 years. For all seven trials taken together the RR was 0.81 (95% CI 0.72 to 0.90) after 7 years and RR 0.81 (95% CI 0.74 to 0.87) after 13 years.
The adequately randomised trials did not find a statistically significant effect of screening on deaths ascribed to breast cancer in the youngest age group (under 50 years of age at randomisation except for 7 year data from Malmö for which the limit was 55 years): RR 0.94 (95% CI 0.78 to 1.14) after 7 years and RR 0.87 (95% CI 0.73 to 1.03) after 13 years. The suboptimally randomised trials found an RR of 0.81 (95% CI 0.63 to 1.05) after 7 years and RR of 0.80 (95% CI 0.64 to 0.98) after 13 years. For the oldest age group, the estimates for the adequately randomised trials were RR 0.88 (95% CI 0.64 to 1.20) and RR 0.94 (95% CI 0.77 to 1.15), respectively; for suboptimally randomised trials they were RR 0.67 (95% CI 0.56 to 0.81) and RR 0.70 (95% CI 0.62 to 0.80), respectively.
Deaths ascribed to any cancer
The adequately randomised trials did not find an effect of screening on deaths ascribed to any cancer, including breast cancer (RR 1.02, 95% CI 0.95 to 1.10); the follow up was 10.5 years for Canada and 9 years for Malmö (data were not available for the UK age trial). The suboptimally randomised trials did 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 (95% CI 0.93 to 1.06).

All-cause mortality

All-cause mortality was not significantly reduced (RR 0.98, 95% CI 0.94 to 1.03 after 7 years; and RR 0.99, 95% CI 0.95 to 1.03 after 13 years) for the three adequately randomised trials. The suboptimally randomised trials did not provide reliable estimates of the effects on all-cause mortality (see 'Risk of bias in included studies' and 'Discussion') and the reported effects were heterogeneous (P = 0.03 after 7 years; P = 0.001 after 13 years). For completeness, the mortality estimates are shown in the graphs.

Surgery

Significantly more breast operations (mastectomies plus lumpectomies) were performed in the study groups than in the control groups: RR 1.31 (95% CI 1.22 to 1.42) for the two adequately randomised trials; RR 1.42 (95% CI 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; RR 1.48 after five years).

The number of mastectomies (excluding partial mastectomies, quadrantectomies and lumpectomies) was also significantly increased: RR 1.20 (95% CI 1.08 to 1.32) for the adequately randomised trials; RR 1.21 (95% CI 1.06 to 1.38) for the suboptimally randomised trials.

Radiotherapy

Significantly more women received radiotherapy in the study groups: RR 1.24 (95% CI 1.04 to 1.49) for Malmö after nine years; and RR 1.40 (95% CI 1.17 to 1.69) for Kopparberg before the control group screen.

Other adjuvant therapy

We found little information on other adjuvant therapy. It differed substantially for two of the Swedish trials even though they were 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 (Analysis 1.17). Conversely, hormone therapy was given to 17% in Malmö, and to 2% in Kopparberg (Analysis 1.18). 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 recorded 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. This is 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 Östergötland (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. They 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. 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 was 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 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.

Postrandomisation 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 seemed 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). A study that used the same registers as those used by the trialists found that a large number of breast cancer cases and deaths seemed to be missing in reports on the Two-County trial (Zahl 2006). Another study found that the large reduction in breast cancer mortality agreed poorly with the cancer stages that were reported for the trial (Zahl 2001).

The largest effects on breast cancer mortality were reported in trials that had long intervals between screenings (Two-County trial), invited a large fraction of the women to only two or three screenings (Two-County and Stockholm trials), 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 risk of bias in 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 were 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 (Analysis 1.1) were true. Weighting the four trials that provided data on number of cancer deaths (Analysis 1.7), the expected relative risk was 0.95. However, all-cancer mortality in these trials was not reduced (RR 1.00, 95% CI 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) illustrates the misclassification directly (Analysis 1.19) (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 mortality in the trials with suboptimal randomisation. Furthermore, these trials had introduced early screening of the control group or had differentially excluded women after randomisation. Incidentally, however, all-cause mortality after 13 years was the same in adequately randomised trials and in suboptimally randomised trials

(RR 0.99, 95% CI 0.95 to 1.03; and RR 0.99, 95% CI 0.97 to 1.01, respectively).

In 2000, the estimate reported for the four Swedish trials was RR 1.00 (95% CI 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, 95% CI 0.96 to 1.00) and stated that they would have expected a 2.3% reduction (Nyström 2002). However, the calculation was incorrect and the expected reduction, given their results, was only 0.9% (Gøtzsche 2002a). The error has been acknowledged (The Lancet 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 for screening 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 with an RR of 0.98. The 2002 Swedish meta-analysis comprised 43,343 deaths whereas in the 2000 meta-analysis of 27,582 deaths the estimates were RR 1.06 (95% CI 1.04 to 1.08) (Gøtzsche 2000) and RR of 1.00 (95% CI 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 have made any difference since the RR for Kopparberg was 1.00 (95% CI 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 lower 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 cancer screening and an obvious source of harm (WHO 2002). Screening primarily identifies slow-growing cancers and cell changes that are biologically benign (Doll 1981; Ernster 1996; 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).

The level of overdiagnosis and overtreatment was about 30% in the trials that did not introduce early screening in the control group, and somewhat larger in the suboptimally randomised trials before the control group screen. This is apart from the New York trial, which is unreliable since far more breast cancer cases were excluded from the screened group than from the control group (Shapiro 1977; Shapiro 1982; Shapiro 1989).

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). A small study from Copenhagen 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).

A recent systematic review that adjusted for decreases in incidence, if any, in older age groups no longer screened found an overdiagnosis of 35% for invasive cancer and 52% when carcinoma in situ was included, in countries with organised screening programmes (Jørgensen 2009).

Screening increased the number of mastectomies by 20%. Since screening advances the time of diagnosis, a policy change towards more lumpectomies could have led to an overestimate. However, the policy change has occurred slowly (Nattinger 2000) and even in the period 1993 to 1995, 52% of breast surgery in California was mastectomy (Malin 2002). In Stockholm, the increase in mastectomies was larger after five years of screening (25%) than after the first round (16%), and when screening was introduced in Southeast Netherlands, 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 percentage of cases of carcinoma in situ treated by mastectomy declined from 71% in 1983 to 40% in 1993 in USA, but 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).

Conversely, opportunistic screening in the control group would lead to an underestimate of overdiagnosis. In the trials from Malmö and Canada about 25% of the women in the control group reported having received a mammogram during the trial (Baines 1994; Andersson 1988).

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; Gøtzsche 2009) 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). 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).

False- positive diagnoses, psychological distress and pain

False-positive diagnoses can cause considerable and sustained psychological distress (Brewer 2007; Bülow 2000), not only until it is known whether or not there is a cancer (Brodersen 2006) but sometimes continuing after the women are declared free from cancer (Brodersen 2007). Many women experience anxiety, worry, despondency, sleeping problems, negative impact on sexuality and behaviour, and changes in their relationships with family, friends, and acquaintances as well as in existential values (Brodersen 2006; Brodersen 2007). This can go on for months, and some women will feel more vulnerable about disease and see a doctor more often (Barton 2001).

In the Stockholm trial, one-third of women with false-positive findings were not declared cancer-free at six months (Lidbrink 1996). In the UK, women who had been declared cancer-free after additional testing or biopsies were twice as likely to suffer psychological consequences three years later than women who received a clear result after their last mammogram (Brett 2001). In the 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 the 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 recently the recall rate in women aged 50 to 54 years was as high as 13% to 14% after the first mammogram, compared to 8% in the UK (Smith-Bindman 2003). In Norway, 21% will have experienced a false alarm after 10 mammograms (Hofvind 2004). However, such percentages are often too low because recalls due to poor technical quality of the mammogram were not included (Hofvind 2004). As the women are just as affected by such recalls as by a real suspicion of cancer (Brodersen 2006) they should be counted as false alarms.

Thus, it seems that screening inflicts important psychological distress for many months on more than a 10th of the healthy population of women who attend a screening program. The women are not being informed about this risk (Gøtzsche 2009; Jørgensen 2004; Slaytor 1998; Werkö 1995) or the risk of receiving a diagnosis of carcinoma in situ (Gøtzsche 2009; Jørgensen 2004; Thornton 1997).

About half of the women report that it is painful to have a mammogram taken (Armstrong 2007; Miller 2002a; McNoe 1996), and half of the women who decline an invitation to the second round of screening note 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 an RR of 0.84 (95% CI 0.77 to 0.91) for breast cancer mortality. The authors noted that "the mortality benefit of mammography screening is small enough that biases in the trials could erase or create it" 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 comprehensive 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 were inconsistently reported (Table 1). 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 the exact age at randomisation, and the age range was the same. The varying numbers therefore indicate that the randomisation was not respected. The estimates in the Swedish reviews were adjusted for differences in age, but since the distribution of age would be expected to differ over 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 an RR of 0.85 (95% CI 0.77 to 0.94) with the follow-up model (Nyström 2002); another estimate giving an RR of 0.79 (95% CI 0.70 to 0.89) was based on an 'evaluation model', which was flawed (Berry 1998).

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 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 described. 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, which corresponds to an absolute reduction in breast cancer mortality of 0.1% after 10 years (Nyström 1993). This benefit corresponds to a life extension of two days, on average, per woman who is invited for screening. This is 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 that make us believe that a realistic estimate of the effect is 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 all-cause mortality was about 10% during 10 years (Nyström 1996), survival after 10 years is 90.30% if women are invited to screening and 90.25% if they are not invited.

The trials did not find a reduction in all-cancer mortality. Our estimate could therefore be an overestimate but, if we assume the effect is 15%, it means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged. This number can be deduced from the first meta-analysis of the Swedish trials, taking into account that the effect is only half as large as indicated in that paper (Nyström 1993, page 976). It can also be deduced from our review, for example after seven years (Analysis 1.1) there were 384 deaths from breast cancer in the adequately randomised trials out of 173,061 women in the control group; a 15% effect corresponds to 326.4 deaths in a study group of the same size, which gives 0.7 women per 2000. Similarly, if we assume that the level of overdiagnosis is 30%, which might be an underestimate, it means that for every 2000 women invited for screening throughout 10 years 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 1.14; there were 1083 cancers in the control group in the adequately randomised trials out of 66,154 women, which gives 325 overdiagnosed cancers, or 9.8 per 2000). 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, for example 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 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 may 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 emphasised the benefits and omitted information on the major harms in their information materials (Dixon-Woods 2001; Jørgensen 2004; NHS leaflet 2001; US Task Force 2002) and in invitational letters (Jørgensen 2006; Gøtzsche 2009). Most women therefore tend to substantially exaggerate the benefits and to be unaware of the major harms of screening (Barratt 1997; Barratt 1999; Domenighetti 2003; Schwartz 2004). To help ensure that the requirements for informed consent for women contemplating whether or not to attend a screening program can be met, we have written an evidence-based leaflet for lay people (Gøtzsche 2009). The leaflet has been carefully tested among general practitioners and lay people. It is available on the BMJ website in English (Gøtzsche 2009) and in several languages, including English, on the website of The Nordic Cochrane Centre at www.cochrane.dk.

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) and 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 were not allowed. It would also be useful to obtain 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.

ACKNOWLEDGEMENTS

We thank Freda Alexander, Ingvar Andersson, Cornelia Baines, Niels Bjurstam, Gunnar Fagerberg, Jan Frisell, Anthony B Miller and Sam Shapiro for comments on their trials, Friederike M Perl for pointing out an inconsistency in one of the trials, Mike Clarke for advice, Ole Olsen who was an author on the 2001 version of this review and wrote the draft section on methodological quality of the trials for that version, and Kay Dickersin for comments on the 2006 update of the review.

REFERENCES

References to studies included in this review

Canada 1980 ***{published and unpublished data}***

Bailar JC 3rd, MacMahon B. Randomization in the Canadian National Breast Screening Study: a review for evidence of subversion. *Canadian Medical Association Journal* 1997;**156**(2):193–9.

Baines CJ. Personal communication 18 Jan 2001.

Baines CJ. A different view on what is known about breast screening and the Canadian National Breast Screening Study. *Cancer* 1994;**74**(4):1207–11.

Baines CJ. Impediments to recruitment in the Canadian National Breast Screening Study: response and resolution. *Controlled Clinical Trials* 1984;**5**(2):129–40.

Baines CJ. NBSS: changes were made, suspicious changes were not [letter]. *CMAJ* 1997;**157**(3):248–50.

Baines CJ. The Canadian National Breast Screening Study: a perspective on criticisms. *Annals of Internal Medicine* 1994;**120**(4):326–34.

Baines CJ. The Canadian National Breast Screening Study: responses to controversy. *Womens Health Issues* 1992;**2**(4): 206–11.

Baines CJ. The Canadian National Breast Screening Study. Why? What next? And so what?. *Cancer* 1995;**76 Suppl** (10):2107–12.

Baines CJ, Christen A, Simard A, Wall C, Dean D, Duncan L, et al.The National Breast Screening Study: pre-recruitment sources of awareness in participants. *Canadian Journal of Public Health* 1989;**80**(3):221–5.

Baines CJ, McFarlane DV, Miller AB. Sensitivity and specificity of first screen mammography in 15 NBSS centres. *Canadian Association of Radiologists Journal* 1988;**39**(4): 273–6.

Baines CJ, McFarlane DV, Miller AB. The role of the reference radiologist. Estimates of inter-observer agreement and potential delay in cancer detection in the national breast screening study. *Investigative Radiology* 1990;**25**(9):971–6.

Baines CJ, McFarlane DV, Wall C. Audit procedures in the National Breast Screening Study: mammography interpretation. *Canadian Association of Radiologists Journal* 1986;**37**(4):256–60.

Baines CJ, Miller AB. Mammography versus clinical examination of the breasts. *Journal of the National Cancer*

Institute. Monographs 1997;**22**:125–9.
Baines CJ, Miller AB, Bassett AA. Physical examination. Its role as a single screening modality in the Canadian National Breast Screening Study. *Cancer* 1989;**63**(9):1816–22.
Baines CJ, Miller AB, Kopans DB, Moskowitz M, Sanders DE, Sickles EA, et al.Canadian National Breast Screening Study: assessment of technical quality by external review. *AJR. American Journal of Roentgenology* 1990;**155**(4):743–7.
Baines CJ, Miller AB, Wall C, McFarlane DV, Simor IS, Jong R, et al.Sensitivity and specificity of first screen mammography in the Canadian National Breast Screening Study: a preliminary report from five centers. *Radiology* 1986;**160**(2):295–8.
Baines CJ, To T. Changes in breast self-examination behavior achieved by 89,835 participants in the Canadian National Breast Screening Study. *Cancer* 1990;**66**(3): 570–6.
Baines CJ, To T, Wall C. Women's attitudes to screening after participation in the National Breast Screening Study. A questionnaire survey. *Cancer* 1990;**65**(7):1663–9.
Baines CJ, Vidmar M, McKeown Eyssen G, Tibshirani R. Impact of menstrual phase on false-negative mammograms in the Canadian National Breast Screening Study. *Cancer* 1997;**80**(4):720–4.
Baines CJ, Wall C, Risch HA, Kuin JK, Fan IJ. Changes in breast self-examination behavior in a cohort of 8214 women in the Canadian National Breast Screening Study. *Cancer* 1986;**57**(6):1209–16.
Basinski AS. The Canadian National Breast Screening Study: opportunity for a rethink. *CMAJ* 1992;**147**(10): 1431–4.
Boyd NF. The review of randomization in the Canadian National Breast Screening Study. Is the debate over?. *CMAJ* 1997;**156**(2):207–9.
Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, et al.Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *Journal of the National Cancer Institute* 1995;**87**(9):670–5.
Boyd NF, Jensen HM, Cooke G, Han HL. Relationship between mammographic and histological risk factors for breast cancer. *Journal of the National Cancer Institute* 1992; **84**(15):1170–9.
Boyd NF, Jong RA, Yaffe MJ, Tritchler D, Lockwood G, Zylak CJ. A critical appraisal of the Canadian National Breast Cancer Screening Study. *Radiology* 1993;**189**(3): 661–3.
Boyd NF, Lockwood GA, Martin LJ, Knight JA, Jong RA, Fishell E, et al.Mammographic densities and risk of breast cancer among subjects with a family history of this disease. *Journal of the National Cancer Institute* 1999;**91** (16):1404–8.
Boyd NF, Wolfson C, Moskowitz M, Carlile T, Petitclerc M, Ferri HA, et al.Observer variation in the interpretation of xeromammograms. *Journal of the National Cancer Institute* 1982;**68**(3):357–63.
Bryant H. The review of randomization in the Canadian National Breast Screening Study. What does the verdict mean for clinicians?. *CMAJ* 1997;**156**(2):213–5.
Burhenne LJ, Burhenne HJ. The Canadian National Breast Screening Study: a Canadian critique. *American Journal of Roentgenology* 1993;**161**(4):761–3.
Busetti MC, Miller AB, To T, Rohan TE. Risk factors for breast cancer mortality among the National Breast Screening Study of Canada participants. *Cancer Detection and Prevention* 1996;**20**(2):122–9.
Cohen MM, Kaufert PA, MacWilliam L, Tate RB. Using an alternative data source to examine randomization in the Canadian National Breast Screening Study. *Journal of Clinical Epidemiology* 1996;**49**(9):1039–44.
Goel V, Cohen MM, Kaufert P, MacWilliam L. Assessing the extent of contamination in the Canadian National Breast Screening Study. *American Journal of Preventive Medicine* 1998;**15**(3):206–11.
Goldman B. When considering attacks against the National Breast Screening Study, consider the sources. *CMAJ* 1993; **148**(3):427–8.
Gray C. US resistance to Canadian mammogram study not only about data. *CMAJ* 1993;**148**(4):622–3.
Haiart DC, Henderson J. A comparison of interpretation of screening mammograms by a radiographer, a doctor and a radiologist: results and implications. *The British Journal of Clinical Practice* 1991;**45**(1):43–5.
Harvey BJ, Miller AB, Baines CJ, Corey PN. Effect of breast self-examination techniques on the risk of death from breast cancer. *CMAJ* 1997;**157**(9):1205–12.
Holowaty PH, Miller AB, Baines CJ, Risch H. Canadian National Breast Screening Study: first screen results as predictors of future breast cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 1993;**2**(1):11–9.
Howe GR, Sherman GJ, Semenciw RM, Miller AB. Estimated benefits and risks of screening for breast cancer. *Canadian Medical Association Journal* 1981;**124**(4): 399–403.
Jain MG, Miller AB, Rohan TE, Rehm JT, Bondy SJ, Ashley MJ, et al.Body mass index and mortality in women: follow-up of the Canadian National Breast Screening Study cohort. *International Journal of Obesity and Related Metabolic Disorders* 2005;**29**(7):792–7.
Kopans DB, Feig SA. The Canadian National Breast Screening Study: a critical review. *American Journal of Roentgenology* 1993;**161**(4):755–60.
Kopans DB, Halpern E, Hulka CA. Mammography screening for breast cancer. Reply to the commentaries. *Cancer* 1994;**74**(4):1212–6.
Kopans DB, Halpern E, Hulka CA. Statistical power in breast cancer screening trials and mortality reduction among women 40-49 years of age with particular emphasis on the National Breast Screening Study of Canada. *Cancer* 1994;

74(4):1196–203.
Miller AB. Canadian National Breast Screening Study: response [letter]. *CMAJ* 1993;**149**(10):1374–5.
Miller AB. Mammography in mass screening [letter]. *European Journal of Cancer* 1980;**16**(5):737–9.
Miller AB. More on breast cancer screening. *Cancer Forum* 1988;**12**:1–3.
Miller AB. Re: "Author of Canadian breast cancer study retracts warnings" [letter]. *Journal of the National Cancer Institute* 1992;**84**(17):1365–70.
Miller AB. Re: May we agree to disagree, or how do we develop guidelines for breast cancer screening in women? [letter]. *Journal of the National Cancer Institute* 1994;**86**(22):1729–31.
Miller AB. Routine mammography and the National Breast Screening Study. *CMAJ* 1984;**130**(3):259-60, 273.
Miller AB. The Canadian national breast screening study. In: Day NE, Miller AB editor(s). *Screening for Breast Cancer*. Toronto: Hans Huber, 1988:51–8.
Miller AB. The Canadian National Breast Screening Study: update on breast cancer mortality. *NIH Consensus Development Conference on Breast Cancer Screening for Women ages 40-49*. National Institutes of Health, 1997: 51–3.
Miller AB. The costs and benefits of breast cancer screening. *American Journal of Preventive Medicine* 1993;**9**(3):175–80.
Miller AB, Baines CJ, Sickles EA. Canadian National Breast Screening Study. *American Journal of Roentgenology* 1990; **155**:1133–4.
Miller AB, Baines CJ, To T, Wall C. Canadian national breast screening study [correction]. *CMAJ* 1993;**148**:718.
Miller AB, Baines CJ, To T, Wall C. Screening mammography re-evaluated. *The Lancet* 2000;**355**:747.
Miller AB, Baines CJ, To T, et al.The Canadian national breast screening study. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer Screening*. Cambridge: Cambridge University Press, 1991:45–55.
Miller AB, Baines CJ, Turnbull C. The role of the nurse-examiner in the National Breast Screening Study. *Canadian Journal of Public Health* 1991;**82**(3):162–7.
Miller AB, Howe GR, Wall C. The National Study of Breast Cancer Screening Protocol for a Canadian Randomized Controlled trial of screening for breast cancer in women. *Clinical and Investigative Medicine* 1981;**4**(3-4):227–58.
Narod SA. On being the right size: A reappraisal of mammography trials in Canada and Sweden. *The Lancet* 1997;**349**:1849.
Simard A, Paquette L, Baillargeon J, Falardeau M. Perception of cancer detection and early treatment in a population participating in the National Breast Screening Study in Canada. *Canadian Journal of Public Health* 1989; **80**(3):226–7.

Canada 1980a ***{published and unpublished data}***
Kopans DB. Canadian National Breast Screening Study [letter]. *The Lancet* 1997;**350**(9080):810.
Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *Canadian Medical Association Journal* 1992;**147**(10):1459–76.
Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study: update on breast cancer mortality. *Journal of the National Cancer Institute. Monographs* 1997; **NA**(22):37–41.
Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Annals of Internal Medicine* 2002;**137**(5 Part 1):305–12.

Canada 1980b ***{published and unpublished data}***
Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *Canadian Medical Association Journal* 1992;**147**(10):1477–88.
Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *Journal of the National Cancer Institute* 2000;**92**:1490–9.

Edinburgh 1978 ***{published data only}***
Alexander F, Roberts MM, Lutz W, Hepburn W. Randomisation by cluster and the problem of social class bias. *Journal of Epidemiology and Community Health* 1989; **43**(1):29–36.
Alexander FE. The Edinburgh Randomized Trial of Breast Cancer Screening. *Journal of the National Cancer Institute. Monographs* 1997;**22**:31–5.
Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, et al.14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *The Lancet* 1999;**353**(9168):1903–8.
Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, et al.The Edinburgh randomised trial of breast cancer screening: results after 10 years of follow-up. *British Journal of Cancer* 1994;**70**(3): 542–8.
Alexander FE, Anderson TJ, Donnan PT, Prescott RJ. Edinburgh trial of screening for breast cancer [letter]. *The Lancet* 1990;**335**(8695):969–70.
Alexander FE, Anderson TJ, Donnan PT, Prescott RJ. Edinburgh trial of screening for breast cancer [letter]. *The Lancet* 1990;**335**:1290–1.
Alexander FE, Anderson TJ, Hubbard AL. Screening status in relation to biological and chronological characteristics of breast cancers: a cross sectional survey. *Journal of Medical Screening* 1997;**4**(3):152–7.
Alexander FE, Brown HK, Prescott RJ. Improved classification of socio-economic status explains differences in all-cause mortality in the randomised trial of breast cancer screening. *Journal of Epidemiology and Biostatistics* 1998;**3**(2):219–24.
Alexander FE, O'Brien F, Hepburn W, Miller M. Association between mortality among women and socioeconomic factors in general practices in Edinburgh: an application of small area statistics. *BMJ* 1987;**295**(6601):754–6.
Alexander FE, Roberts MM, Huggins A, Muir BB. Use of

risk factors to allocate schedules for breast cancer screening. *Journal of Epidemiology and Community Health* 1988;**42**(2): 193–9.

Anderson TJ, Lamb J, Alexander F, Lutz W, Chetty U, Forrest AP, et al.Comparative pathology of prevalent and incident cancers detected by breast screening. Edinburgh Breast Screening Project. *The Lancet* 1986;**1**(8480):519–23.

Anderson TJ, Lamb J, Donnan P, Alexander FE, Huggins A, Muir BB, et al.Comparative pathology of breast cancer in a randomised trial of screening. *British Journal of Cancer* 1991;**64**(1):108–13.

Benjamin DJ. The efficacy of surgical treatment of breast cancer. *Medical Hypotheses* 1996;**47**(5):389–97.

Chamberlain J, Atkinson AB, Cochrane AL. Trial of early detection of breast cancer: Description of method. *British Journal of Cancer* 1981;**44**:618–27.

Chamberlain J, Coleman D, Ellamn R, Moss S. Progress report of the UK trial of early detection of breast cancer. In: Day NE, Miller AB editor(s). *Progress report of the UK trial of early detection of breast cancer*. Toronto: Hans Huber, 1988:45–9.

Chamberlain J, Coleman D, Ellman R, Moss S, Thomas B, Price J. Sensitivity and specifity of screening in the UK trial of early detection of breast cancer. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer Screening*. Cambridge: Cambridge University Press, 1991:3–17.

Chetty U, Wang CC, Forrest AP, Roberts MM. Benign breast disease and cancer. *The British Journal of Surgery* 1980;**67**(11):789–90.

Dean C, Roberts MM, French K, Robinson S. Psychiatric morbidity after screening for breast cancer. *Journal of Epidemiology and Community Health* 1986;**40**(1):71–5.

French K, Porter AM, Robinson SE, McCallum FM, Howie JG, Roberts MM. Attendance at a breast screening clinic: a problem of administration or attitudes. *BMJ* 1982;**285** (6342):617–20.

Milne L. Mammography in the Edinburgh breast screening project. *Radiography* 1979;**45**(536):176–8.

Nicholson S, Farndon JR. Edinburgh trial of screening for breast cancer [letter]. *The Lancet* 1990;**335**(8700):1290–1.

Owen AW, Forrest AP, Anderson TJ, Samuel E, Young GB, Scott AM. Breast screening and surgical problems. *The British Journal of Surgery* 1977;**64**(10):725–8.

Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest P, et al.Edinburgh trial of screening for breast cancer: mortality at seven years. *The Lancet* 1990; **335**(8684):241–6.

Roberts MM, Alexander FE, Anderson TJ, Forrest AP, Hepburn W, Huggins A, et al.The Edinburgh randomised trial of screening for breast cancer: description of method. *British Journal of Cancer* 1984;**50**(1):1–6.

Screening for breast cancer. Report from Edinburgh Breast Screening Clinic. *BMJ* 1978;**2**(6131):175–8.

UK Trial of Early Detection of Breast Cancer Group. 16-year mortality from breast cancer in the UK Trial of Early Detection of Breast Cancer. *The Lancet* 1999;**353**(9168): 1909–14.

UK Trial of Early Detection of Breast Cancer Group. First results on mortality reduction in the UK Trial of Early Detection of Breast Cancer. *The Lancet* 1988;**2**(8608): 411–6.

Wald NJ, Murphy P, Major P, Parkes C, Townsend J, Frost C. UKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening. *BMJ* 1995;**311**(7014):1189–93.

Göteborg 1982 ***{published data only}***

Bjurstam N, Björneld L, Warwick J, Sala E, Duffy SW, Nyström L. The Gothenburg Breast Screening Trial. *Cancer* 2003;**97**:2387–96.

* Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *The Lancet* 2002;**359**(9310):909–19.

Göteborg 1982a ***{published data only}***

Bjurstam N, Björneld L, Duffy SW. The Gothenborg breast screening trial: results from 11 years followup. NIH Consensus Development Conference on Breast Cancer Screening for Women Ages 40-49. National Institutes of Health. 1997:63–4.

Bjurstam N, Björneld L, Duffy SW, Prevost TC. Author Reply. *Cancer* 1998;**83**(1):188–90.

Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Erikson O, et al.The Gothenburg Breast Cancer Screening Trial: preliminary results on breast cancer mortality for women aged 39-49. *Journal of the National Cancer Institute. Monographs* 1997;**22**:53–5.

Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O, et al.The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization. *Cancer* 1997; **80**(11):2091–9.

Miller AB, Baines CJ, To T. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization [letter]. *Cancer* 1998;**83**(1):186–90.

Göteborg 1982b ***{published data only}***

* Nyström L, Rutqvist LE, Wall S, Lindgren A, Lindqvist M, Ryden S, et al.Breast cancer screening with mammography: overview of Swedish randomised trials. *The Lancet* 1993; **341**(8851):973–8.

Kopparberg 1977 ***{published data only}***

Bergkvist L, Tabar L, Bergstrom R, Adami HO. Epidemiologic determinants of the mammographic parenchymal pattern. A population-based study within a mammographic screening program. *American Journal of Epidemiology* 1987;**126**(6):1075–81.

Tabar L, Chen HH, Duffy SW, Krusemo UB. Primary and adjuvant therapy, prognostic factors and survival in 1053 breast cancers diagnosed in a trial of mammography screening. *Japanese Journal of Clinical Oncology* 1999;**29** (12):608–16.

Tabar L, Duffy SW, Krusemo UB. Detection method, tumour size and node metastases in breast cancers diagnosed

during a trial of breast cancer screening. *European Journal of Cancer & Clinical Oncology* 1987;**23**(7):959–62.
Tabar L, Gad A. Screening for breast cancer: the Swedish trial. *Radiology* 1981;**138**(1):219–22.
Tabar L, Gad A, Holmberg L, Ljungquist U. Significant reduction in advanced breast cancer. Results of the first seven years of mammography screening in Kopparberg, Sweden. *Diagnostic Imaging in Clinical Medicine* 1985;**54** (3-4):158–64.

Malmö 1976 ***{published data only}***

Andersson I. *Mammographic screening for breast carcinoma [thesis]*. University of Lund, 1980.
Andersson I. Personal communication 10 Oct 2000.
Andersson I. Personal communication 12 Feb 2001.
Andersson I. Personal communication 15 June 2001.
Andersson I. Personal communication 21 June 1999.
Andersson I. Breast cancer screening in Malmo. *Recent Results in Cancer Research* 1984;**90**:114–6.
Andersson I. Detection bias in mammographic screening for breast carcinoma. *Recent Results in Cancer Research* 1984; **90**:164–5.
Andersson I. Överskattning av besparingar genom screening med mammografi [letter]. *Läkartidningen* 1996;**93**(32-33): 2725.
Andersson I. Radiographic screening for breast carcinoma. I. Program and primary findings in 45-69 year old women. *Acta Radiologica: Diagnosis* 1981;**22**(2):185–94.
Andersson I. Radiographic screening for breast carcinoma. II. Prognostic considerations on the basis of a short-term follow-up. *Acta Radiologica: Diagnosis* 1981;**22**(3A): 227–33.
Andersson I. Radiographic screening for breast carcinoma. III. Appearance of carcinoma and number of projections to be used at screening. *Acta Radiologica: Diagnosis* 1981;**22** (4):407–20.
Andersson I, Andren L, Hildell J, Linell F, Ljungqvist U, Pettersson H. Breast cancer screening with mammography: a population-based, randomized trial with mammography as the only screening mode. *Radiology* 1979;**132**(2):273–6.
Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, et al.Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988;**297**(6654):943–8.
Andersson I, Hellstrom L, Bjurstam N, Lundgren B, Fagerberg G, Tabar L. Bröstcancerscreening med mammografi i Sverige. *Läkartidningen* 1983;**80**(25): 2559–62.
Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmo Mammographic Screening Program. *Journal of the National Cancer Institute. Monographs* 1997;**22**:63–7.
Andersson I, Janzon L. Screening with mammography - a critical attitude is supported by new findings. *Läkartidningen* 1988;**85**(44):3666–9.
Andersson I, Janzon L, Pettersson H. Radiographic patterns of the mammary parenchyma: variation with age at examination and age at first birth. *Radiology* 1981;**138**(1): 59–62.
Andersson I, Janzon L, Sigfusson BF. Mammographic breast cancer screening - a randomized trial in Malmo, Sweden. *Maturitas* 1985;**7**(1):21–9.
Andersson I, Nystrom L. Mammography screening [letter]. *Journal of the National Cancer Institute. Monographs* 1995; **87**(16):1263–4.
Andersson I, Sigfusson BF. Screening for breast cancer in Malmo: a randomized trial. *Recent Results in Cancer Research* 1987;**105**:62–6.
Garne JP, Aspegren K, Balldin G, Ranstam J. Increasing incidence of and declining mortality from breast carcinoma. Trends in Malmo, Sweden, 1961-1992. *Cancer* 1997;**79**(1): 69–74.
Gullberg B, Andersson I, Janzon L, Ranstam J. Screening mammography [letter]. *The Lancet* 1991;**337**(8735):244.
Ikeda DM, Andersson I, Wattsgard C, Janzon L, Linell F. Interval carcinomas in the Malmo Mammographic Screening Trial: radiographic appearance and prognostic considerations. *AJR. American Journal of Roentgenology* 1992;**159**(2):287–94.
Janzon L, Andersson I. The Malmö mammographic screening trial. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer Screening*. Cambridge: Cambridge University Press, 1991:37–44.
Ringberg A, Andersson I, Aspegren K, Linell F. Breast carcinoma in situ in 167 women-incidence, mode of presentation, therapy and follow-up. *European Journal of Surgical Oncology* 1991;**17**(5):466–76.

Malmö II 1978 ***{published data only}***

* Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmo Mammographic Screening Program. *Journal of the National Cancer Institute. Monographs* 1997;**22**:63–7.

New York 1963 ***{published data only}***

Aron JL, Prorok PC. An analysis of the mortality effect in a breast cancer screening study. *Journal of the National Cancer Institute. Monographs* 1986;**15**:36–43.
Chu KC, Connor RJ. Analysis of the temporal patterns of benefits in the Health Insurance Plan of Greater New York trial by stage and age. *American Journal of Epidemiology* 1991;**133**(10):1039–49.
Chu KC, Smart CR, Tarone RE. Analysis of breast cancer mortality and stage distribution by age for the Health Insurance Plan clinical trial. *Journal of the National Cancer Institute* 1988;**80**(14):1125–32.
Connor RJ, Prorok PC, Weed DL. The case-control design and the assessment of the efficacy of cancer screening. *Journal of Clinical Epidemiology* 1991;**44**(11):1215–21.
Final reports of National Cancer Institute ad hoc working groups on mammography screening for breast cancer and a summary report of their joint findings and recommendations. *DHEW Publication No. (NIH) 77 1400*. US Department of Health, Education and Welfare, 1977.
Fink R, Shapiro S. Significance of increased efforts to gain participation in screening for breast cancer. *American*

Journal of Preventive Medicine 1990;**6**(1):34–41.
Fink R, Shapiro S, Lewison J. The reluctant participant in a breast cancer screening program. *Public Health Reports* 1968;**83**(6):479–90.
Fink R, Shapiro S, Roester R. Impact of efforts to increase participation in repetitive screenings for early breast cancer detection. *American Journal of Public Health* 1972;**62**(3): 328–36.
Friedman DR, Dubin N. Case-control evaluation of breast cancer screening efficacy. *American Journal of Epidemiology* 1991;**133**(10):974–84.
Habbema JD, van Oortmarssen GJ, van Putten DJ. An analysis of survival differences between clinically and screen-detected cancer patients. *Statistics in Medicine* 1983;**2**(2): 279–85.
Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. *American Journal of Epidemiology* 1986;**77**(2):317–20.
Shapiro S. Determining the efficacy of breast cancer screening. *Cancer* 1989;**63**(10):1873–80.
Shapiro S. Evaluation of two contrasting types of screening programs. *Preventive Medicine* 1973;**2**(2):266–77.
Shapiro S. Evidence on screening for breast cancer from a randomized trial. *Cancer* 1977;**39**(6 Suppl):2772–82.
Shapiro S. Periodic screening for breast cancer: the HIP Randomized Controlled Trial. Health Insurance Plan. *Journal of the National Cancer Institute. Monographs* 1997; **22**:27–30.
Shapiro S. Screening: assessment of current studies. *Cancer* 1994;**74 Suppl**(1):231–8.
Shapiro S. The status of breast cancer screening: a quarter of a century of research. *World Journal of Surgery* 1989;**13** (1):9–18.
Shapiro S, Goldberg JD, Hutchison GB. Lead time in breast cancer detection and implications for periodicity of screening. *American Journal of Epidemiology* 1974;**100**(5): 357–66.
Shapiro S, Strax P, Venet L. Evaluation of periodic breast cancer screening with mammography: methodology and early observations. 1966 [classical article]. *CA: A Cancer Journal for Clinicians* 1990;**40**(2):111–25.
Shapiro S, Strax P, Venet L. Evaluation of periodic breast cancer screening with mammography. Methodology and early observations. *JAMA* 1966;**195**(9):731–8.
Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA* 1971;**215** (11):1777–85.
Shapiro S, Strax P, Venet L, Fink R. The search for risk factors in breast cancer. *American Journal of Public Health and the Nation's Health* 1968;**58**(5):820–35.
Shapiro S, Strax P, Venet L, Venet W. Changes in 5-year breast cancer mortality in a breast cancer screening program. *Proceedings. National Cancer Conference* 1972;**7**:663–78.
Shapiro S, Venet W, Strax P, Venet L. *Periodic screening for breast cancer: The health insurance plan project and its sequelae, 1963-1986*. Baltimore: Johns Hopkins University Press, 1988:The health insurance plan project and its sequelae.
Shapiro S, Venet W, Strax P, Venet L. Current results of the breast cancer screening randomized trial: The health insurance plan (HIP) of greater New York study. In: Day NE, Miller AB editor(s). *Screening for breast cancer*. Toronto: Hans Huber, 1988:3–15.
Shapiro S, Venet W, Strax P, Venet L, Roeser R. Prospects for eliminating racial differences in breast cancer survival rates. *American Journal of Public Health* 1982;**72**(10):1142–5.
Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Journal of the National Cancer Institute. Monographs* 1985;**67**:65–74.
Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten- to fourteen-year effect of screening on breast cancer mortality. *Journal of the National Cancer Institute* 1982;**69**(2):349–55.
Smart CR. Highlights of the evidence of benefit for women aged 40-49 years from the 14-year follow-up of the Breast Cancer Detection Demonstration Project. *Cancer* 1994;**74** (1 Suppl):296–300.
Strax P. Advances in detection of early breast cancer. *Cancer Detection and Prevention* 1983;**6**(4-5):409–14.
Strax P. Benefit of breast cancer screening on morbidity and mortality. In: Bostrom H, et al. editor(s). *Health control in detection of cancer*. Stockholm: Almqvist and Wiksell, 1976: 133–45.
Strax P. Mass screening for control of breast cancer. *Cancer* 1984;**53**(3 Suppl):665–70.
Strax P. Physical methods in breast cancer diagnosis. *Israel Journal of Medical Sciences* 1981;**17**(9-10):847–53.
Strax P, Venet L, Shapiro S. Mass screening in mammary cancer. *Cancer* 1969;**23**(4):875–8.
Strax P, Venet L, Shapiro S. Value of mammography in reduction of mortality from breast cancer in mass screening. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1973;**117**(3):686–9.
Strax P, Venet L, Shapiro S, Gross S. Mammography and clinical examination in mass screening for cancer of the breast. *Cancer* 1967;**20**(12):2184–8.
Strax P, Venet L, Shapiro S, Gross S, Venet W. Breast cancer found on repetitive examination in mass screening. *Archives of Environmental Health* 1970;**20**(6):758–63.
Thomas LB, Ackerman LV, McDivitt RW, Hanson TAS, Hankey BF, Prorok PC. Report of NCI ad hoc pathology working group to review the gross and microscopic findings of breast cancer cases in the HIP study. *Journal of the National Cancer Institute* 1977;**59**(2):496–541.

Stockholm 1981 ***{published data only}***

Frisell J. *Mammographic screening for breast cancer [thesis]*. Stockholm: Södersjukhuset, 1989. [: ISBN: 91–7900–659–0]
Frisell J. Personal communication 13 Nov 2000.
Frisell J. Personal communication 16 Nov 2000.
Frisell J, Eklund G, Hellstrom L, Glas U, Somell A. The Stockholm breast cancer screening trial - 5-year results and

stage at discovery. *Breast Cancer Research and Treatment* 1989;**13**(1):79–87.

Frisell J, Eklund G, Hellstrom L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening - preliminary report on mortality in the Stockholm trial. *Breast Cancer Research and Treatment* 1991;**18**(1):49–56.

Frisell J, Eklund G, Hellstrom L, Somell A. Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. *Breast Cancer Research and Treatment* 1987;**9**(3):219–25.

Frisell J, Eklund G, Nilsson R, Hellstrom L, Somell A. Additional value of fine-needle aspiration biopsy in a mammographic screening trial. *The British Journal of Surgery* 1989;**76**(8):840–3.

Frisell J, Glas U, Hellstrom L, Somell A. Randomized mammographic screening for breast cancer in Stockholm. Design, first round results and comparisons. *Breast Cancer Research and Treatment* 1986;**8**(1):45–54.

Frisell J, Lidbrink E. The Stockholm Mammographic Screening Trial: Risks and benefits in age group 40-49 years. *Journal of the National Cancer Institute. Monographs* 1997;**22**:49–51.

Frisell J, Lidbrink E, Hellstrom L, Rutqvist LE. Followup after 11 years - update of mortality results in the Stockholm mammographic screening trial. *Breast Cancer Research and Treatment* 1997;**45**(3):263–70.

Frisell J, von Rosen A, Wiege M, Nilsson B, Goldman S. Interval cancer and survival in a randomized breast cancer screening trial in Stockholm. *Breast Cancer Research and Treatment* 1992;**24**(1):11–6.

Lidbrink E, Elfving J, Frisell J, Jonsson E. Neglected aspects of false positive findings of mammography in breast cancer screening: analysis of false positive cases from the Stockholm trial. *BMJ* 1996;**312**(7026):273–6.

Lidbrink E, Frisell J, Brandberg Y, Rosendahl I, Rutqvist LE. Nonattendance in the Stockholm mammography screening trial: relative mortality and reasons for nonattendance. *Breast Cancer Research and Treatment* 1995;**35**(3):267–75.

von Rosen A, Frisell J, Glas U, Hellstrom L, Nilsson R, Skoog L, et al.Non-palpable invasive breast carcinomas from the Stockholm screening project. *Acta Oncologica (Stockholm, Sweden)* 1989;**28**(1):23–7.

von Rosen A, Frisell J, Nilsson R, Wiege M, Auer G. Histopathologic and cytochemical characteristics of interval breast carcinomas from the Stockholm Mammography Screening Project. *Acta Oncologica (Stockholm, Sweden)* 1992;**31**(4):399–402.

Two-County 1977 ***{published data only}***

Summary of the discussion on breast cancer screening. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer screening*. Cambridge: Cambridge University Press, 1991: 78–80.

Chen HH, Tabar L, Fagerberg G, Duffy SW. Effect of breast cancer screening after age 65. *Journal of Medical Screening* 1995;**2**(1):10–4.

Day NE. Surrogate measures in the design of breast screening trials. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer Screening*. Cambridge: Cambridge University Press, 1991:391–403.

Day NE, Williams DR, Khaw KT. Breast cancer screening programmes: the development of a monitoring and evaluation system. *British Journal of Cancer* 1989;**59**(6): 954–8.

Duffy S, Tabar L, Krusemo UB, Day N. Randomization by cluster in the Swedish two-county trial: recent results from Kopparberg and implications for interpretation [abstract]. Nordic Cancer Union 1989, Symposium in Stockholm 17-19 Aug 1989.

Duffy SW, Chen HH, Tabar L, Fagerberg G, Paci E. Sojourn time, sensitivity and positive predictive value of mammography screening for breast cancer in women aged 40-49. *International Journal of Epidemiology* 1996;**25**(6): 1139–45.

Duffy SW, Day NE, Tabar L, Chen HH, Smith TC. Markov models of breast tumor progression: some age-specific results. *Journal of the National Cancer Institute. Monographs* 1997;**22**:93–7.

Duffy SW, South MC, Day NE. Cluster randomization in large public health trials: the importance of antecedent data. *Statistics in Medicine* 1992;**11**(3):307–16.

Duffy SW, Tabar L. Screening for breast cancer [letter]. *The Lancet* 1995;**346**(8978):852.

Duffy SW, Tabar L, Fagerberg G, Gad A, Grontoft O, South MC, et al.Breast screening, prognostic factors and survival - results from the Swedish two county study. *British Journal of Cancer* 1991;**64**(6):1133–8.

Duffy SW, Tabar L, Vitak B, et al.The Swedish Two-County Trial of mammographic screening: cluster randomisation and end point evaluation. *Annals of Oncology* 2003;**14**(8): 1196–8.

Duffy SW, Tabar L, Vitak B, Yen MF, Warwick J, Smith RA, et al.The Swedish Two-County Trial of mammographic screening: cluster randomisation and end point evaluation. *Annals of Oncology* 2003;**14**(8):1196–8.

Fagerberg CJG, Tabar L. The results of periodic one-view mammography screening in a randomized, controlled trial in Sweden. In: Day NE, Miller AB editor(s). *Screening for breast cancer*. Toronto: Hans Huber, 1988:33–8.

Holmberg L, Adami HO, Lundstrom T, Persson I, Tabar L. [Mass screening mammography results in an increased need for surgical wards]. *Läkartidningen* 1986;**83**(22):2047–9.

Holmberg L, Adami HO, Persson I, Lundstrom T, Tabar L. Demands on surgical inpatient services after mass mammographic screening. *BMJ* 1986;**293**(6550):779–82.

Holmberg LH, Tabar L, Adami HO, Bergstrom R. Survival in breast cancer diagnosed between mammographic screening examinations. *The Lancet* 1986;**2**(8497):27–30.

Nixon R, Prevost TC, Duffy SW, Tabar L, Vitak B, Chen HH. Some random-effects models for the analysis of matched-cluster randomised trials: application to the Swedish two-county trial of breast-cancer screening. *Journal of Epidemiology and Biostatistics* 2000;**5**(6):349–58.

Nixon RM, Pharoah P, Tabar L, et al.Mammographic screening in women with a family history of breast cancer:

some results from the Swedish two-county trial. *Revue D'épidémiologie et de Santé Publique* 2000;**48**(4):325–31.
Projektgruppen för WE-studien i Kopparbergs och Östergötlands län samt socialstyrelsens bearbetningsgrupp för WE-projektet. Reply on mammography [Replik om mammografi]. *Läkartidningen* 1985;**82**:2674.
Prorok PC. Personal communication 2 Feb 2000.
Rapport över mammografiscreening i Kopparbergs och Östergötlands läns landsting (WE-projektet) - Resultat efter första screeningsomgången. *Unknown*. Stockholm: Socialstyrelsen, 1982.
Socialstyrelsens beredningsgrupp för WE-projektet. Minskad mortalitet i bröstcancer genom hälskontroll med mammografi. *Nordisk Medicin* 1985;**100**:175–8.
Tabar L. Personal communication 17 Jan 2000.
Tabar L. Mammografins förmåga finna högriskfallen ar nyckelfrågan [letter]. *Läkartidningen* 1996;**93**(38):3221.
Tabar L. SBUs aktuella statistik inaktuell [letter]. *Läkartidningen* 1995;**92**(48):4540–1.
Tabar L, Akerlund E, Gad A. Five-year experience with single-view mammography randomized controlled screening in Sweden. *Recent Results in Cancer Research* 1984;**90**: 105–13.
Tabar L, Chen HH, Fagerberg G, Duffy SW, Smith TC. Recent results from the Swedish Two-County Trial: the effects of age, histologic type, and mode of detection on the efficacy of breast cancer screening. *Journal of the National Cancer Institute. Monographs* 1997;**22**:43–7.
Tabar L, Duffy SW. Criticisms of Swedish mammography trials were wrong [letter]. *BMJ* 1999;**319**:1367.
Tabar L, Duffy SW, Burhenne LW. New Swedish breast cancer detection results for women aged 40-49. *Cancer* 1993;**72 Suppl**(4):1437–48.
Tabar L, Duffy SW, Chen HH. Quantitative interpretation of age-specific mortality reductions from the Swedish Breast Cancer-Screening Trials [letter]. *Journal of the National Cancer Institute* 1996;**88**(1):52–5.
Tabar L, Duffy SW, Day NE. Screening with mammography [letter]. *International Journal of Technology Assessment in Health Care* 1990;**6**(3):498–500.
Tabar L, Duffy SW, Yen MF, et al.All-cause mortality among breast cancer patients in a screening trial: support for breast cancer mortality as an end point. *Journal of Medical Screening* 2002;**9**(4):159–62.
Tabar L, Duffy SW, Yen MF, Warwick J, Vitak B, Chen HH, et al.All-cause mortality among breast cancer patients in a screening trial: support for breast cancer mortality as an end point. *Journal of Medical Screening* 2002;**9**(4):159–62.
Tabar L, Faberberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. *British Journal of Cancer* 1987;**55**(5):547–51.
Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al.Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *The Lancet* 1985;**1**(8433):829–32.
Tabar L, Fagerberg CJG, Day NE. The results of periodic one-view mammographic screening in Sweden. Part 2: Evaluation of the results. In: Day NE, Miller AB editor(s). *Screening for breast cancer*. Toronto: Hans Huber, 1988: 39–44.
Tabar L, Fagerberg CJG, South MC, Day NE, Duffy SW. The Swedish Two-county Trial of mammographic screening for breast cancer: recent results on mortality and tumour characteristics. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer screening*. Cambridge University Press: Cambridge University Press, 1991:23–36.
Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A. Screening for breast cancer in women aged under 50: mode of detection, incidence, fatality, and histology. *Journal of Medical Screening* 1995;**2**(2):94–8.
Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A. Tumour development, histology and grade of breast cancers: prognosis and progression. *International Journal of Cancer* 1996;**66**(4):413–9.
Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al.Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* 1995; **75**(10):2507–17.
Tabar L, Fagerberg G, Day NE, Duffy SW. The Swedish two-county trial of mammographic screening for breast cancer: recent results on mortality and tumor characteristics. *Pathologie-Biologie* 1992;**39**(9):846.
Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM. Breast cancer treatment and natural history: new insights from results of screening. *The Lancet* 1992;**339**(8790): 412–4.
Tabar L, Fagerberg G, Duffy SW, Day NE. Mammografi minskar dödligheten i bröstcancer signifikant. *Läkartidningen* 1990;**87**(1-2):36–9.
Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *Journal of Epidemiology and Community Health* 1989;**43**(2):107–14.
Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiologic Clinics of North America* 1992;**30**(1):187–210.
Tabar L, Gad A, Akerlund E, Fors B, Fagerberg G, Baldetorp L. Screening for breast cancer in Sweden. A randomised controlled trial. In: Logan WW, Muntz EP editor(s). *Reduced dose mammography*. New York: Masson, 1979: 407–14.
Tabar L, Smith RA, Vitak B, et al.Mammographic screening: a key factor in the control of breast cancer. *Cancer Journal (Sudbury, Mass.)* 2003;**9**(1):15–27.
Tabar L, Vitak B, Chen HH, Prevost TC, Duffy SW. Update of the Swedish Two-County Trial of breast cancer screening: histologic grade-specific and age-specific results. *Swiss Surgery* 1999;**5**(5):199–204.
Tabar L, Vitak B, Chen HH, et al.The Swedish Two-

County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. *Radiologic Clinics of North America* 2000;**38**(4):625–51.
Tabar L, Vitak B, Yen MF, Chen HH, Smith RA, Duffy SW. Number needed to screen: lives saved over 20 years of follow-up in mammographic screening. *Journal of Medical Screening* 2004;**11**(3):126–9.
Warwick J, Tabar L, Vitak B, Duffy SW. Time-dependent effects on survival in breast carcinoma: results of 20 years of follow-up from the Swedish Two-County Study. *Cancer* 2004;**100**(7):1331–6.

UK age trial 1991 ***{published data only}***
Moss S. A trial to study the effect on breast cancer mortality of annual mammographic screening in women starting at age 40. Trial Steering Group. *Journal of Medical Screening* 1999;**6**(3):144–8.
Moss S, Thomas I, Evans A, Thomas B, Johns L. Randomised controlled trial of mammographic screening in women from age 40: results of screening in the first 10 years. *British Journal of Cancer* 2005;**92**:949–54.
Moss S, Waller M, Anderson TJ, Cuckle H. Randomised controlled trial of mammographic screening in women from age 40: predicted mortality based on surrogate outcome measures. *British Journal of Cancer* 2005;**92**:955–60.
Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L, for the Trial Management Group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *The Lancet* 2006;**368**:2053–60.

Östergötland 1978 ***{published data only}***
Arnesson LG, Fagerberg G, Grontoft O, Lundstrom B. Surgical biopsy of non-palpable mammary lesions. Technique and results. *Acta Chirurgica Scandinavica* 1986; **152**:97–101.
Arnesson LG, Smeds S, Fagerberg G. Recurrence-free survival in patients with small breast cancer. An analysis of cancers 10 mm or less detected clinically and by screening. *The European Journal of Surgery* 1994;**160**(5):271–6.
Arnesson LG, Smeds S, Fagerberg G, Grontoft O. Follow-up of two treatment modalities for ductal cancer in situ of the breast. *The British Journal of Surgery* 1989;**76**(7):672–5.
Arnesson LG, Smeds S, Hatschek T, Nordenskjold B, Fagerberg G. Hormone receptors, ploidy and proliferation rate in breast cancers up to 10 mm. *European Journal of Surgical Oncology* 1992;**18**(3):235–40.
Arnesson LG, Vitak B, Manson JC, Fagerberg G, Smeds S. Diagnostic outcome of repeated mammography screening. *World Journal of Surgery* 1995;**19**(3):372–7.
Fagerberg G. Experience from randomized controlled breast screening with mammography in Ostergotland county, Sweden: a preliminary report. *Recent Results in Cancer Research* 1984;**90**:117.
Fagerberg G, Baldetorp L, Grontoft O, Lundstrom B, Manson JC, Nordenskjold B. Effects of repeated mammographic screening on breast cancer stage distribution. Results from a randomised study of 92 934 women in a Swedish county. *Acta Chirurgica Scandinavica* 1985;**24**(6):465–73.
Hatschek T, Carstensen J, Fagerberg G, Stal O, Grontoft O, Nordenskjold B. Influence of S-phase fraction on metastatic pattern and post-recurrence survival in a randomized mammography screening trial. *Breast Cancer Research and Treatment* 1989;**14**(3):321–7.
Hatschek T, Fagerberg G, Stal O, Sullivan S, Carstensen J, Grontoft O, et al.Cytometric characterization and clinical course of breast cancer diagnosed in a population-based screening program. *Cancer* 1989;**64**(5):1074–81.
Hatschek T, Grontoft O, Fagerberg G, Stal O, Sullivan S, Carstensen J, et al.Cytometric and histopathologic features of tumors detected in a randomized mammography screening program: correlation and relative prognostic influence. *Breast Cancer Research and Treatment* 1990;**15** (3):149–60.
Lundström B, Fagerberg G. Clinical problems in relation to breast cancer screening with mammography. A preliminary report. *Acta Chirurgica Scandinavica. Supplementum* 1984; **519**:61–3.
Vitak B. Invasive interval cancers in the Ostergotland Mammographic Screening Programme: radiological analysis. *European Radiology* 1998;**8**(4):639–46.

References to studies excluded from this review

Berglund 2000 ***{published data only}***
* Berglund G, Nilsson P, Eriksson K F, Nilsson J A, Hedblad B, Kristenson H, et al.Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. *Journal of Internal Medicine* 2000;**247**:19–29.

Dales 1979 ***{published data only}***
Dales LG, Friedman GD, Collen MF. Evaluating periodic multiphasic health checkups: a controlled trial. *Journal of Chronic Diseases* 1979;**32**:385–404.

Singapore 1994 ***{published data only}***
Ng EH, Ng FC, Tan PH, Low SC, Chiang G, Tan KP, et al.Results of intermediate measures from a population-based, randomized trial of mammographic screening prevalence and detection of breast carcinoma among Asian women: the Singapore Breast Screening Project. *Cancer* 1998;**82**(8):1521–8.

Additional references

Alexander 1989
Alexander F, Roberts MM, Lutz W, Hepburn W. Randomisation by cluster and the problem of social class bias. *Journal of Epidemiology and Community Health* 1989; **43**(1):29–36.

Alexander 1994
Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, et al.The Edinburgh randomised trial of breast cancer screening: results after 10 years of follow-up. *British Journal of Cancer* 1994;**70**(3): 542–8.

Alexander 1999
Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, et al.14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *The Lancet* 1999;**353**(9168):1903–8.

Alexander 2000
Alexander F. Personal communication 3 Oct 2000.

Andersson 1980
Andersson I. *Mammographic screening for breast carcinoma [thesis]*. University of Lund, 1980.

Andersson 1981
Andersson I. Radiographic screening for breast carcinoma. I. Program and primary findings in 45-69 year old women. *Acta Radiologica: Diagnosis* 1981;**22**(2):185–94.

Andersson 1981a
Andersson I. Radiographic screening for breast carcinoma. II. Prognostic considerations on the basis of a short-term follow-up. *Acta Radiologica: Diagnosis* 1981;**22**(3A): 227–33.

Andersson 1983
Andersson I, Hellstrom L, Bjurstam N, Lundgren B, Fagerberg G, Tabar L. Bröstcancerscreening med mammografi i Sverige. *Läkartidningen* 1983;**80**(25): 2559–62.

Andersson 1988
Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, et al.Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988;**297**(6654):943–8.

Andersson 1988a
Andersson I, Janzon L. Mammografi för screening - kritisk inställning stöds av nya fynd [Screening with mammography - a critical attitude is supported by new findings]. *Läkartidningen* 1988;**85**(44):3666–9.

Andersson 1997
Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmo Mammographic Screening Program. *Journal of the National Cancer Institute* 1997;**22**:63–7.

Andersson 1999a
Anderssson I. Personal communication 15 June 1999.

Andersson 1999b
Andersson I. Personal communication 21 June 1999.

Andersson 2000
Andersson I. Personal communication 10 Oct 2000.

Andersson 2001
Andersson I. Personal communication 12 Feb 2001.

Armstrong 2007
Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screeningmammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. *Annals of Internal Medicine* 2007;**146**:516–26.

Arnesson 1995
Arnesson LG, Vitak B, Manson JC, Fagerberg G, Smeds S. Diagnostic outcome of repeated mammography screening. *World Journal of Surgery* 1995;**19**(3):372–7.

Aron 1986
Aron J, Prorok PC. An analysis of the mortality effect in a breast cancer screening study. *International Journal of Epidemiology* 1986;**15**:36–43.

Atterstam 1999
Atterstam I. Nil [Ohederliga arbetsmetoder undergräver mammografiresultat]. Svenska Dagbladet 1999, 21. juli; Vol. sect 1:6.

Bailar 1997
Bailar JC 3rd, MacMahon B. Randomization in the Canadian National Breast Screening Study: a review for evidence of subversion. *Canadian Medical Association Journal* 1997;**156**(2):193–9.

Baines 1994
Baines CJ. The Canadian National Breast Screening Study: a perspective on criticisms. *Annals of Internal Medicine* 1994;**120**(4):326–34.

Baines 1995
Baines CJ. The Canadian National Breast Screening Study. Why? What next? And so what?. *Cancer* 1995;**76 Suppl** (10):2107–12.

Baines 1997
Baines CJ, Miller AB. Mammography versus clinical examination of the breasts. *Journal of the National Cancer Institute. Monographs* 1997;**22**:125–9.

Baines 2001
Baines CJ. Personal communication 18 Jan 2001.

Baines 2005
Baines CJ. Personal communication 30 Nov 2005.

Barratt 1997
Barratt AL, Cockburn J, Redman S, Paul C, Perkins J. Mammographic screening: results from the 1996 National Breast Health Survey. *The Medical Journal of Australia* 1997; **167**:521–4.

Barratt 1999
Barratt A, Cockburn J, Furnival C, McBride A, Mallon L. Perceived sensitivity of mammographic screening: women's views on test accuracy and financial compensation for missed cancers. *Journal of Epidemiology and Community Health* 1999;**53**:716–20.

Barratt 2005
Barratt A, Howard K, Irwig L, Salkeld G, Houssami N. Model of outcomes of screening mammography: information to support informed choices. *BMJ* 2005;**330**: 936–8.

Barton 2001
Barton MB, Moore S, Polk S, Shtatland E, Elmore JG, Fletcher SW. Increased patient concern after false-positive mammograms: clinician documentation and subsequent ambulatory visits. *Journal of General Internal Medicine* 2001;**16**:150–6.

BASO audit 2000
NHS cancer screening programmes. BASO Breast Audit 1999/2000. www.cancerscreening.nhs.uk/breastscreen/publications.html (accessed Dec 12, 2001).

Baum 2000
Baum M, Tobias JS. Investment in treatment would be more effective (letter). *BMJ* 2000;**321**:1528.

Benjamin 1996
Benjamin DJ. The efficacy of surgical treatment of breast cancer. *Medical Hypotheses* 1996;**47**(5):389–97.

Berry 1998
Berry DA. Benefits and risks of screening mammography for women in their forties: a statistical appraisal. *Journal of the National Cancer Institute* 1998;**90**:1431–9.

Berry 2002
Berry DA. The Utility of Mammography for Women 40 to 50 Years of Age (Con). In: DeVita VT, Hellman S, Rosenberg SAe editor(s). *Progress in Oncology*. Sudbury: Jones and Bartlett, 2002:346–72.

Bjurstam 1997
Bjurstam N, Bjorneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O, et al.The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39-49 years at randomization. *Cancer* 1997; **80**(11):2091–9.

Bjurstam 2000
Bjurstam N. Personal communication 10 Oct 2000.

Bjurstam 2003
Bjurstam N, Björneld L, Warwick J, Sala E, Duffy SW, Nyström L. The Gothenburg Breast Screening Trial. *Cancer* 2003;**97**:2387–96.

Blamey 2000
Blamey RW, Wilson ARM, Patnick J. ABC of breast diseases: screening for breast cancer. *BMJ* 2000;**321**: 689–93.

Boyle 2003
Boyle P. Global summit on mammography screening. *Annals of Oncology* 2003;**14**:1159-60.

Brett 2001
Brett J, Austoker J. Women who are recalled for further investigation for breast screening: psychological consequences 3 years after recall and factors affecting re-attendance. *Journal of Public Health Medicine* 2001;**23**(4): 292–300.

Brewer 2007
Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. *Annals of Internal Medicine* 2007;**146**:502–10.

Brodersen 2006
Brodersen J. Measuring psychosocial consequences of false-positive screening results - breast cancer as an example (PhD thesis). Institute of Public Health, Faculty of Health Sciences, Department of General Practice, University of Copenhagen. (http://cms.ku.dk/sund-sites/ifsv-sites/ifsv-inst/ominstituttet/afdelinger/almen_medicin/medarbejdere/publicationdetail/?id=1109837) 2006.

Brodersen 2007
Brodersen J, Thorsen H, Kreiner S. Validation of a condition-specific measure for women having an abnormal screening mammography. *Value in Health* 2007;**10**: 294–304.

Brown 1993
Brown BW, Brauner C, Minnotte MC. Noncancer deaths in white adult cancer patients. *Journal of the National Cancer Institute* 1993;**85**(12):979–87.

Bülow 2000
Bülow B von. Psykologiske følger af screening for brystkræft blandt raske kvinder. *Ugeskrift for Laeger* 2000;**162**:1053–9.

Chamberlain 1981
Chamberlain J, Atkinson AB, Cochrane AL. Trial of early detection of breast cancer: Description of method. *British Journal of Cancer* 1981;**44**:618–27.

Cox 1997
Cox B. Variation in the effectiveness of breast screening by year of follow-up. *Journal of the National Cancer Institute. Monographs* 1997;**22**:69–72.

Crewdson 2002
Crewdson J. Swedes doubt mammography trial: disparities found in landmark study. *Chicago Tribune* 2002; **March 15**:http://www.chicagotribune.com/news/chi-0203150264mar15.story (accessed 15 March, 2002).

Darby 2005
Darby S, McGale P, Taylor C, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries. *Lancet Oncology* 2005;**6**(8):557–65.

Deeks 2003
Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG, International Stroke Trial Collaborative Group, European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technology Assessment (Winchester, England)* 2003;**7**(27):1–173.

Demissie 1998
Demissie K, Mills OF, Rhoads GG. Empirical comparison of the results of randomized controlled trials and case-control studies in evaluating the effectiveness of screening mammography. *Journal of Clinical Epidemiology* 1998;**52**: 81–91.

Dixon-Woods 2001
Dixon-Woods M, Baum M, Kurinczuk JJ. Screening for breast cancer with mammography. *The Lancet* 2001;**358**: 2167–8.

Doll 1981
Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute* 1981;**66**:1191–308.

Domenighetti 2003
Domenighetti G, D'Avanzo B, Egger M, Berrino F, Perneger T, Mosconi P, et al.Women's perception of the benefits of mammography screening: population-based survey in four countries. *International Journal of Epidemiology* 2003;**32**: 816–21.

Douek 2003
Douek M, Baum M. Mass breast screening: is there a hidden cost?. *The British Journal of Surgery* 2003;**90 Suppl 1**:(Abstract Breast 14).

Duffy 2002
Duffy SW, Tabár L, Smith RA. The mammographic screening trials: commentary on the recent work by Olsen and Gøtzsche (authors' reply). *Journal of Surgical Oncology* 2002;**81**:164–6.

Duffy 2003
Duffy SW, Tabar L, Vitak B, Yen MF, Warwick J, Smith RA, et al.The Swedish Two-County Trial of mammographic screening: cluster randomisation and end point evaluation. *Annals of Oncology* 2003;**14**(8):1196–8.

Early Breast C 1995
Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: An overview of the randomized trials. *The New England Journal of Medicine* 1995;**333**:1444–55.

Early Breast C 1998
Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *The Lancet* 1998;**35**:1451–67.

Early Breast C 2000
Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. *The Lancet* 2000;**355**:1757–70.

Elmore 1998
Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *The New England Journal of Medicine* 1998;**338**(16):1089–96.

Elwood 1993
Elwood JM, Cox B, Richardson AK. The effectiveness of breast cancer screening by mammography in younger women. The Online Journal of Current Clinical Trials [electronic resource] 1993; Vol. Doc No 32.

Elwood 1998
Elwood M, McNoe B, Smith T, Bandaranayake M. Once is enough - why some women do not continue to participate in a breast screening programme. *The New Zealand Medical Journal* 1998;**111**:180–3.

Ernster 1996
Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson C. Incidence of and treatment for ductal carcinoma in situ of the breast. *JAMA* 1996;**275**(12):913–8.

Ernster 1997
Ernster VL, Barclay J. Increases in ductal carcinoma in situ (DCIS) of the breast in relation to mammography: a dilemma. *Journal of the National Cancer Institute. Monographs* 1997;**NA**(22):151–6.

Fagerberg 1985
Fagerberg G, Baldetorp L, Grontoft O, Lundstrom B, Manson JC, Nordenskjold B. Effects of repeated mammographic screening on breast cancer stage distribution. Results from a randomised study of 92 934 women in a Swedish county. *Acta Radiologica. Oncology* 1985;**24**(6):465–73.

Final reports 1977
Final reports of National Cancer Institute ad hoc working groups on mammography screening for breast cancer and a summary report of their joint findings and recommendations. *DHEW Publication No. (NIH) 77 1400*. US Department of Health, Education and Welfare, 1977.

Fink 1972
Fink R, Shapiro S, Roester R. Impact of efforts to increase participation in repetitive screenings for early breast cancer detection. *American Journal of Public Health* 1972;**62**(3): 328–36.

Fletcher 1993
Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the International Workshop on Screening for Breast Cancer. *Journal of the National Cancer Institute* 1993; **85**(20):1644–56.

Fletcher 2003
Fletcher SW, Elmore JG. Clinical practice. Mammographic screening for breast cancer. *The New England Journal of Medicine* 2003;**348**:1672–80.

Fox 1979
Fox MS. On the diagnosis and treatment of breast cancer. *JAMA* 1979;**241**(5):489–94.

Freedman 2004
Freedman DA, Petitti DB, Robins JM. On the efficacy of screening for breast cancer. *International Journal of Epidemiology* 2004;**33**:43–55.

Frisell 1986
Frisell J, Glas U, Hellstrom L, Somell A. Randomized mammographic screening for breast cancer in Stockholm. Design, first round results and comparisons. *Breast Cancer Research and Treatment* 1986;**8**(1):45–54.

Frisell 1989
Frisell J, Eklund G, Hellstrom L, Glas U, Somell A. The Stockholm breast cancer screening trial - 5-year results and stage at discovery. *Breast Cancer Research and Treatment* 1989;**13**(1):79–87.

Frisell 1989a
Frisell J. *Mammographic screening for breast cancer [thesis]*. Stockholm: Södersjukhuset, 1989. [: ISBN: 91–7900–659–0]

Frisell 1991
Frisell J, Eklund G, Hellstrom L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening - preliminary report on mortality in the Stockholm trial. *Breast Cancer Research and Treatment* 1991;**18**(1):49–56.

Frisell 1997
Frisell J, Lidbrink E, Hellstrom L, Rutqvist LE. Followup after 11 years - update of mortality results in the Stockholm mammographic screening trial. *Breast Cancer Research and Treatment* 1997;**45**(3):263–70.

Frisell 2000a
Frisell J. Personal communication 13 Nov 2000.

Frisell 2000b
Frisell J. Personal communication 16 Nov 2000.

Glasziou 1992
Glasziou PP. Meta-analysis adjusting for compliance: the example of screening for breast cancer. *Journal of Clinical Epidemiology* 1992;**45**(11):1251–6.

Glasziou 1995
Glasziou PP, Woodward AJ, Mahon CM. Mammographic screening trials for women aged under 50. A quality assessment and meta-analysis. *The Medical Journal of Australia* 1995;**162**(12):625–9.

Glasziou 1997
Glasziou P, Irwig L. The quality and interpretation of mammographic screening trials for women ages 40-49. *Journal of the National Cancer Institute. Monographs* 1997; **22**:73–7.

Gram 1990
Gram IT, Lund E, Slenker SE. Quality of life following a false positive mammogram. *Brithis Journal of Cancer* 1990; **62**(6):1018–22.

Gray 1989
Gray JAM. Breast screening programme. *BMJ* 1989;**298**: 48.

Gøtzsche 2000
Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable?. *The Lancet* 2000;**355**(9198): 129–34.

Gøtzsche 2000a
Gøtzsche PC, Olsen O. Screening mammography re-evaluated [reply]. *The Lancet* 2000;**355**:752.

Gøtzsche 2001
Gøtzsche PC. Screening for breast cancer with mammography. *The Lancet* 2001;**358**:2167–8.

Gøtzsche 2002
Gøtzsche PC. Trends in breast-conserving surgery in the Southeast Netherlands: Comment on article by Ernst and colleagues Eur J Cancer 2001, 37, 2435-2440. *European Journal of Cancer* 2002;**38**:1288.

Gøtzsche 2002a
Gøtzsche PC. Update on effects of screening mammography. *Lancet* 2002;**360**:338.

Gøtzsche 2002b
Gøtzsche PC. Misleading paper on mastectomy rates in a screening programme. BMJ. http://bmj.com/cgi/eletters/ 325/7361/418#24972, 26 Aug 2002.

Gøtzsche 2004
Gøtzsche PC. On the benefits and harms of screening for breast cancer. *International Journal of Epidemiology* 2004; **33**:56–64.

Gøtzsche 2009
Gøtzsche P, Hartling OJ, Nielsen M, Brodersen J, Jørgensen KJ. Breast screening: the facts - or maybe not. *BMJ* 2009; **338**:446–8.

Habbema 1986
Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. *Journal of the National Cancer Institute* 1986;**77**(2):317–20.

Hendrick 1997
Hendrick RE, Smith RA, Rutledge JH 3rd, Smart CR. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. *Journal of the National Cancer Institute. Monographs* 1997; **22**:87–92.

Higgins 2008
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. Available from www.cochrane-handbook.org*. The Cochrane Collaboration, 2008.

Hofvind 2004
Hofvind S, Thoresen S, Tretli S. The cumulative risk of a false-positive recall in the Norwegian Breast Cancer Screening Program. *Cancer* 2004;**101**:1501–7.

Humphrey 2002
Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2002;**137**(5 Part 1):347–60.

Isacsson 1985
Isacsson S-O, Larsson L-G, Janzon L. Är dokumentationen verkligen tillräcklig? Forcera inte fram screening utan debatt. *Läkartidningen* 1985;**82**(32-33):2672–3.

Janzon 1991
Janzon L, Andersson I. The Malmö mammographic screening trial. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer Screening*. Cambridge: Cambridge University Press, 1991:37–44.

Jonsson 2005
Jonsson H, Johansson R, Lenner P. Increased incidence of incasive breast cancer after the introduction of service screening with mammography in Sweden. *International Journal of Cancer* 2005;**117**(5):842–7.

Jørgensen 2004
Jørgensen KJ, Gøtzsche PC. Presentation on websites of possible benefits and harms from screening for breast cancer: cross sectional study. *BMJ* 2004;**328**:148–51.

Jørgensen 2006
Jørgensen KJ, Gøtzsche PC. Content of invitations for publicly funded screening mammography. *BMJ* 2006;**332**: 538–41.

Jørgensen 2009
Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ* 2009;**339**:b2587.

Kerlikowske 1995
Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. *JAMA* 1995;**273**(2):149–54.

Kerlikowske 1997
Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 69 years: comparison of relative and absolute benefit. *Journal of the National Cancer Institute. Monographs* 1997;**22**:79–86.

Kösters 2003
Kösters JP, Gøtzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. *The Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD003373]

Larsson 1996
Larsson LG, Nystrom L, Wall S, Rutqvist L, Andersson I, Bjurstam N, et al.The Swedish randomised mammography screening trials: analysis of their effect on the breast cancer related excess mortality. *Journal of Medical Screening* 1996;**3** (3):129–32.

Larsson 1997
Larsson LG, Andersson I, Bjurstam N, Fagerberg G, Frisell J, Tabar L, et al.Updated overview of the Swedish Randomized Trials on Breast Cancer Screening with Mammography: age group 40-49 at randomization. *Journal of the National Cancer Institute. Monographs* 1997;**22**:57–61.

Lerman 1991
Lerman C, Trock B, Rimer BK, Boyce A, Jepson C, Engstrom PF. Psychological and behavioral implications of abnormal mammograms. *Annals of Internal Medicine* 1991; **114**(8):657–61.

Lidbrink 1996
Lidbrink E, Elfving J, Frisell J, Jonsson E. Neglected aspects of false positive findings of mammography in breast cancer screening: analysis of false positive cases from the Stockholm trial. *BMJ* 1996;**312**(7026):273–6.

Malin 2002
Malin JL, Kahn KL, Adams J, Kwan L, Laouri M, Ganz PA. Validity of cancer registry data for measuring the quality of breast cancer care. *Journal of the National Cancer Institute* 2002;**94**(11):835–44.

McNoe 1996
McNoe B, Miller D, Elwood M. Women's experience of the Otago-Southland breast screening programme - a compilation of five studies. Hugh Adam Cancer Epidemiology Unit for the Ministry of Health, New Zealand 1996.

Miller 1992a
Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *Canadian Medical Association Journal* 1992;**147**(10):1459–76.

Miller 1992b
Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992;**147**(10):1477–88.

Miller 1993
Miller AB. The costs and benefits of breast cancer screening. *American Journal of Preventive Medicine* 1993;**9**(3):175–80.

Miller 1997
Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study: update on breast cancer mortality. *Journal of the National Cancer Institute. Monographs* 1997; **NA**(22):37–41.

Miller 1997a
Miller AB. The Canadian National Breast Screening Study: update on breast cancer mortality. NIH Consensus Development Conference on Breast cancer screening for women ages 40-49. 1997:51–3.

Miller 2000
Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *Journal of the National Cancer Institute* 2000;**92**:1490–9.

Miller 2001
Miller AB. Screening for breast cancer with mammography. *The Lancet* 2001;**358**:2164.

Miller 2002
Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Annals of Internal Medicine* 2002;**137**(5 Part 1):305–12.

Miller 2002a
Miller D, Martin I, Herbison P. Interventions for relieving the pain and discomfort of screening mammography. *The Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD002942]

Moody-Ayers 2000
Moody-Ayers SY, Wells CK, Feinstein AR. "Benign" tumors and "early detection" in mammography-screened patients of a natural cohort with breast cancer. *Archives of Internal Medicine* 2000;**160**:1109–15.

Moss 2005
Moss S, Thomas I, Evans A, Thomas B, Johns L. Randomised controlled trial of mammographic screening in women from age 40: results of screening in the first 10 years. *British Journal of Cancer* 2005;**92**:949–54.

Moss 2006
Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L, for the Trial Management Group. Effect of

mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *The Lancet* 2006;**368**:2053–60.

Narod 1997

Narod SA. On being the right size: A reappraisal of mammography trials in Canada and Sweden. *The Lancet* 1997;**349**:1849.

Nattinger 2000

Nattinger AB, Hoffmann RG, Kneusel RT, Schapira MM. Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. *The Lancet* 2000;**356**(9236):1148–53.

NBCC 2002

National Breast Cancer Coalition. Positions, Facts and Analyses. http://www.stopbreastcancer.org/bin/index.htm (accessed 7 July 2002).

Newschaffer 2000

Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison nonprostate cancer cohort. *Journal of the National Cancer Institute* 2000;**92**(8):613–21.

NHS leaflet 2001

Breast screening: an informed choice. www.cancerscreening.nhs.uk/breastscreen/publications/ia-02.html (accessed 2 Oct, 2002).

Nielsen 1987

Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *British Journal of Cancer* 1987;**56**(6):814–9.

Nixon 2000

Nixon R, Prevost TC, Duffy SW, Tabar L, Vitak B, Chen HH. Some random-effects models for the analysis of matched-cluster randomised trials: application to the Swedish two-county trial of breast-cancer screening. *Journal of Epidemiology and Biostatistics* 2000;**5**(6):349–58.

Nyström 1993

Nyström L, Rutqvist LE, Wall S, Lindgren A, Lindqvist M, Ryden S, et al.Breast cancer screening with mammography: overview of Swedish randomised trials. *The Lancet* 1993; **341**(8851):973–8.

Nyström 1993a

Nyström L, Larsson L-G. Breast cancer screening with mammography [reply]. *The Lancet* 1993;**341**:1531–2.

Nyström 1996

Nyström L, Larsson LG, Wall S, Rutqvist LE, Andersson I, Bjurstam N, et al.An overview of the Swedish randomised mammography trials: total mortality pattern and the representivity of the study cohorts. *Journal of Medical Screening* 1996;**3**(2):85–7.

Nyström 1997

Nyström L, Wall S, Rutqvist LE, Andersson I, Bjurstam N, Fagerberg G, et al.Update of the overview of the Swedish randomized trials on breast cancer screening with mammography. NIH Consensus Development Conference on Breast Cancer Screening for Women Ages 40-49. National Institutes of Health. 1997:65–9.

Nyström 2000

Nyström L. *Assessment of population screening: the case of mammography [thesis]*. Umeå: Umeå University Medical Dissertations, 2000.

Nyström 2002

Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *The Lancet* 2002;**359**(9310):909–19.

Nyström 2002a

Nyström L. Personal communication 31 July 2002.

Nyström 2002b

Nyström L, Andersson I, Bjurstam N, Frisell J, Rutqvist LE. Update on effects of screening mammography. *The Lancet* 2002;**360**:339–40.

Olsen 2003

Olsen AH, Jensen A, Njor SH, Villadsen E, Schwartz W, Vejborg I, et al.Breast cancer incidence after the start of mammography screening in Denmark. *British Journal of Cancer* 2003;**88**:362–5.

Paci 2002

Paci E, Duffy SW, Giorgi D, Zappa M, Crocetti E, Vezzosi V, et al.Are breast cancer screening programmes increasing rates of mastectomy? Observational study. *BMJ* 2002;**325**: 418.

Paci 2004

Paci E, Warwick J, Falini P, Duffy SW. Overdiagnosis in screening: is the increase in breast cancer incidence rates a cause for concern?. *Journal of Medical Screening* 2004;**11** (1):23–7.

Projektgruppen 1985

Projektgruppen för WE-studien i Kopparbergs och Östergötlands län samt socialstyrelsens bearbetningsgrupp för WE-projektet. Reply on mammography [Replik om mammografi]. *Läkartidningen* 1985;**82**:2674.

Prorok 2000

Prorok PC. Personal communication 2 Febr 2000.

Puffer 2003

Puffer S, Torgerson D, Watson J. Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ* 2003;**327**:785–9.

Rapport 1982

Rapport över mammografiscreening i Kopparbergs och Östergötlands läns landsting (WE-projektet) - Resultat efter första screeningsomgången. *Unknown*. Stockholm: Socialstyrelsen, 1982.

Ries 2002

Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al.SEER Cancer Statistics Review, 1973-1999. http://seer.cancer.gov/csr/1973_1999/. Bethesda, Md: National Cancer Institute, 2002 (accessed 26 June, 2003).

Roberts 1984

Roberts MM, Alexander FE, Anderson TJ, Forrest AP, Hepburn W, Huggins A, et al.The Edinburgh randomised

trial of screening for breast cancer: description of method. *British Journal of Cancer* 1984;**50**(1):1–6.

Roberts 1990
Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest P, et al.Edinburgh trial of screening for breast cancer: mortality at seven years. *The Lancet* 1990; **335**(8684):241–6.

Schwartz 2004
Schwartz LM, Woloshin S, Fowler FJ Jr, Welch HG. Enthusiasm for cancer screening in the United States. *JAMA* 2004;**291**:71–8.

Shapiro 1966
Shapiro S, Strax P, Venet L. Evaluation of periodic breast cancer screening with mammography. Methodology and early observations. *JAMA* 1966;**195**(9):731–8.

Shapiro 1972
Shapiro S, Strax P, Venet L, Venet W. Changes in 5-year breast cancer mortality in a breast cancer screening program. *Journal of the National Cancer Institute* 1972;**7**:663–78.

Shapiro 1977
Shapiro S. Evidence on screening for breast cancer from a randomized trial. *Cancer* 1977;**39 Suppl**(6):2772–82.

Shapiro 1982
Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten- to fourteen-year effect of screening on breast cancer mortality. *Journal of the National Cancer Institute* 1982;**69**(2):349–55.

Shapiro 1985
Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Journal of the National Cancer Institute. Monographs* 1985;**67**:65–74.

Shapiro 1985a
Shapiro S. Discussion II. *Journal of the National Cancer Institute. Monographs* 1985;**67**:75.

Shapiro 1988
Shapiro S, Venet W, Strax P, Venet L. *Periodic screening for breast cancer: The health insurance plan project and its sequelae, 1963-1986*. Baltimore: Johns Hopkins University Press, 1988:The health insurance plan project and its sequelae.

Shapiro 1989
Shapiro S. The status of breast cancer screening: a quarter of a century of research. *World Journal of Surgery* 1989;**13** (1):9–18.

Shapiro 1994
Shapiro S. Screening: assessment of current studies. *Cancer* 1994;**74 Suppl**(1):231–8.

Skrabanek 1993
Skrabanek P. Breast cancer screening with mammography [letter]. *The Lancet* 1993;**341**:1531.

Slaytor 1998
Slaytor EK, Ward JE. How risks of breast cancer and benefits of screening are communicated to women: analysis of 58 pamphlets. *BMJ* 1998;**317**(7153):263–4.

Smart 1995
Smart CR, Hendrick RE, Rutledge JH 3rd, Smith RA. Benefit of mammography screening in women ages 40 to 49 years. Current evidence from randomized controlled trials. *Cancer* 1995;**75**(7):1619–26.

Smith-Bindman 2003
Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, et al.Comparison of screening mammography in the United States and the United kingdom. *JAMA* 2003;**290**:2129–37.

Socialstyrelsen 1985
Socialstyrelsens beredningsgrupp för WE-projektet. Minskad mortalitet i bröstcancer genom hälskontroll med mammografi. *Nordisk Medicin* 1985;**100**:175–8.

Statusrapport 1997
Unknown. *Tidlig opsporing og behandling af brystkræft: statusrapport*. København: Sundhedsstyrelsen, 1997.

Strax 1973
Strax P, Venet L, Shapiro S. Value of mammography in reduction of mortality from breast cancer in mass screening. *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1973;**117**(3):686–9.

Swed Cancer Soc 1996
Swedish Cancer Society and the Swedish National Board of Health and Welfare. Breast-cancer screening with mammography in women aged 40-49 years. *International Journal of Cancer* 1996;**68**(6):693–9.

Swift 1993
Swift M. Screening mammography [letter]. *The Lancet* 1993;**342**:549–50.

Tabar 1979
Tabar L, Gad A, Akerlund E, Fors B, Fagerberg G, Baldetorp L. Screening for breast cancer in Sweden. A randomised controlled trial. In: Logan WW, Muntz EP editor(s). *Reduced dose mammography*. New York: Masson, 1979: 407–14.

Tabar 1981
Tabar L, Gad A. Screening for breast cancer: the Swedish trial. *Radiology* 1981;**138**(1):219–22.

Tabar 1985
Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al.Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985;**1**(8433):829–32.

Tabar 1985a
Tabar L, Gad A, Holmberg L, Ljungquist U. Significant reduction in advanced breast cancer. Results of the first seven years of mammography screening in Kopparberg, Sweden. *Diagnostic Imaging in Clinical Medicine* 1985;**54** (3-4):158–64.

Tabar 1988
Tabar L, Fagerberg CJG, Day NE. The results of periodic one-view mammographic screening in Sweden. Part 2:

Evaluation of the results. In: Day NE, Miller AB editor(s). *Screening for breast cancer*. Toronto: Hans Huber, 1988: 39–44.

Tabar 1989
Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *Journal of Epidemiology and Community Health* 1989;**43**(2):107–14.

Tabar 1990
Tabar L, Duffy SW, Day NE. Screening with mammography [letter]. *International Journal of Technology Assessment in Health Care* 1990;**6**(3):498–500.

Tabar 1991
Tabar L, Fagerberg CJG, South MC, Day NE, Duffy SW. The Swedish Two-county Trial of mammographic screening for breast cancer: recent results on mortality and tumour characteristics. In: Miller AB, Chamberlain J, Day NE, et al. editor(s). *Cancer screening*. Cambridge: Cambridge University Press, 1991:23–36.

Tabar 1992
Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiologic Clinics of North America* 1992;**30**(1):187–210.

Tabar 1995
Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al.Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* 1995; **75**(10):2507–17.

Tabar 1999
Tabar L, Chen HH, Duffy SW, Krusemo UB. Primary and adjuvant therapy, prognostic factors and survival in 1053 breast cancers diagnosed in a trial of mammography screening. *Japanese Journal of Clinical Oncology* 1999;**29** (12):608–16.

Tabar 2000
Tabar L, Vitak B, Chen HH, et al.The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. *Radiologic Clinics of North America* 2000;**38**(4):625–51.

Tabar 2000a
Tabar L. Personal communication 17 Jan 2000.

Tabar 2001
Tabar L, Vitak B, Chen HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001;**91**(9):1724–31.

Tabar 2002
Tabár L, Smith RA, Duffy SW. Update on effects of screening mammography. *Lancet* 2002;**360**:337.

Tabar 2002a
Tabar L, Duffy SW, Yen MF, Warwick J, Vitak B, Chen HH, et al.All-cause mortality among breast cancer patients in a screening trial: support for breast cancer mortality as an end point. *Journal of Medical Screening* 2002;**9**(4):159–62.

Tabar 2003
Tabar L, Smith RA, Vitak B, Yen MF, Chen TH, Warwick J, et al.Mammographic screening: a key factor in the control of breast cancer. *Cancer Journal* 2003;**9**(1):15–27.

Tabar 2003a
Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet* 2003;**361**:1405–10.

The Lancet Erratum 2002
The Lancet Erratum. Department of error: update on screening mammography. The Lancet 2002; Vol. 360, issue 9340:1178.

Thomas 1977
Thomas LB, Ackerman LV, McDivitt RW, Hanson TAS, Hankey BF, Prorok PC. Report of NCI ad hoc pathology working group to review the gross and microscopic findings of breast cancer cases in the HIP study. *Journal of the National Cancer Institute* 1977;**59**(2):496–541.

Thornton 1997
Thornton H. The voice of the breast cancer patient - a lonely cry in the wilderness. *European Journal of Cancer* 1997;**33**(6):825–8.

US Task Force 2002
US Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. *Annals of Internal Medicine* 2002;**137**(5 Part 1):344–6.

Wald 1993
Wald NJ, Chamberlain J, Hackshaw A. Report of the European Society for Mastology Breast Cancer Screening Evaluation Committee (1993). *Breast* 1993;**2**:209–16.

Walter 1999
Walter SD, Jadad AR. Meta-analysis of screening data: a survey of the literature. *Statistics in Medicine* 1999;**18**(24): 3409–24.

Werkö 1995
Werkö L. Mammografi, vinst och risk. *Läkartidningen* 1995;**92**:4540.

Westerholm 1988
Westerholm B. Stötande syn på medelålders kvinnors värde. *Läkartidningen* 1988;**85**(47):4056–7.

WHO 2002
Vainio H, Bianchini F, eds. *IARC Handbooks of Cancer Prevention. Volume 7. Breast Cancer Screening*. Lyon: IARC Press, 2002. [: ISBN 92–832–3007–8]

Zahl 2001
Zahl P-H, Kopjar B, Mæhlen J. Norwegian breast cancer mortality rates and validity in Swedish mammography trials. *Tidsskrift for den Norske Lægeforening* 2001;**121**:1928–31.

Zahl 2004
Zahl PH, Strand BH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. *BMJ* 2004;**328**:921–4.

Zahl 2006

Zahl P-H, Gøtzsche PC, Andersen JM, Mæhlen J. Results of the Two-County trial of mammography screening are not compatible with contemporaneous official Swedish breast cancer statistics. *Danish Medical Bulletin* 2006;**53**:438–40.

References to other published versions of this review

Olsen 2001

Olsen O, Gøtzsche PC. Screening for breast cancer with mammography (Cochrane Review). *The Cochrane Library* 2001, Issue 4. [DOI: 10.1002/14651858.CD001877]

Olsen 2001a

Olsen O, Gøtzsche PC. Systematic review of screening for breast cancer with mammography. http://image.thelancet.com/extras/fullreport.pdf 2001.

Olsen 2001b

Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *The Lancet* 2001;**358**: 1340–2.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Canada 1980

Methods	Individual randomisation in blocks of 2 or 4, stratified by centre and 5-year age group (see also text) 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 years. Number randomised: see below.
Interventions	Two-view mammography: cranio-caudal and mediolateral (later medio-lateral oblique except in two centres) 4-5 cycles of screening with yearly interval.
Outcomes	Total mortality. Breast cancer mortality. Surgical interventions.
Notes	Attendance rate: 100% in first round. Mammography in control group: Screening of high risk groups not precluded (see also Canada 1980a and 1980b)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Canada 1980a

Methods	See Canada 1980.
Participants	Women aged 40-49 years. 50,472 randomised. 59, distributed equally between the two groups, were excluded from analyses
Interventions	See Canada 1980. 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 Mammography in control group: 7% between first and second year, increasing to 18% between fourth and fifth year had a mammogram

Canada 1980a (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Canada 1980b

Methods	See Canada 1980.
Participants	Women aged 50-59 years. 39,459 randomised. 54, distributed equally between the two groups, were excluded from analyses
Interventions	See Canada 1980. 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 Mammography in control group: 5% between first and second year, increasing to 8% between fourth and fifth year had a mammogram

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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) Blinding of outcome assessment not stated.
Participants	Women aged 45-64 years. Number of women and practices randomised inconsistently reported (see text) 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 Screened group: mammography and physical examination year 1, 3, 5 and 7; physical examination year 2, 4 and 6 Control group: usual care.

Edinburgh 1978 (*Continued*)

Outcomes	Total mortality. Breast cancer mortality. Radiotherapy.
Notes	Attendance rate: Circa 60% in first round; 44% in seventh round Mammography in control group: unknown.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Göteborg 1982

Methods	See Göteborg 1982a and 1982b.
Participants	Women aged 39-59 years. Number of women randomised: 21,904 to screening, 30,318 to control (see also text) 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. Breast cancer mortality.
Notes	Mammography in control group: 18% during last two years.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Göteborg 1982a

Methods	Individual randomisation within year of birth cohort - by day of birth in the cohorts 1923-1935 and by computer software for the cohorts 1936-1944 - randomisation ratio varied by cohort, on average approximately 1:1.2 (see also text) Blinding of outcome assessment.
Participants	Women aged 39-49 years. Number of women randomised: 11,792 to screening, 14,321 to control (see also text) 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

Göteborg 1982a (*Continued*)

Interventions	Two-view mammography at first screen, single at later rounds - single read at first three rounds; double read thereafter 5 cycles with an interval of 18 months. Control group: usual care.
Outcomes	Total mortality. Breast cancer mortality.
Notes	Attendance rate: 85%, 78%, 79%, 77%, 75% in rounds 1-5. 66% at first screen in control group. Mammography in control group: 19% during last two years; 51% ever. Early systematic screening of control group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Göteborg 1982b

Methods	Individual randomisation by computer software - randomisation ratio varied by cohort, on average approximately 1:1.6 Blinding of outcome assessment.
Participants	Women aged 50-59 years. 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 4 cycles with an interval of 18 months. Control group: usual care.
Outcomes	Total mortality. Breast cancer mortality.
Notes	Attendance rate: 83% at first screen. 78% at first screen in control group. Early systematic screening of control group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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) Blinding of outcome assessment not stated.
Participants	Women aged 40 years and above. 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 years; 39,051 versus 18,846 in age group 40-74 years) 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 Number of screenings: two cycles prestated, but more may have occurred (see text). Interval between screens were 2 years for women aged 40-49 years; 3 years for women aged 50 years and above
Outcomes	Total mortality. Breast cancer mortality. Surgical interventions. Chemotherapy. Radiotherapy.
Notes	Attendance rate: 91-94% for women younger than 60 years; 50-80% for women above 60 years Unclear when screening started in control group (see text). Early systematic screening of control group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Malmö 1976

Methods	Individual randomisation; within each birth cohort a computer list was randomised and the first half invited for screening 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 years. 21,242 randomised into screened group; 21,240 or 21,244 into control group (see text) Biased exclusions seem to have occurred: 154 women excluded from control group, 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 5-6 cycles according to protocol; 8 cycles in 1988; more during 1988-1992 Interval between screens: 18-24 months. Control group: usual care.

Malmö 1976 (*Continued*)

Outcomes	Total mortality. Breast cancer mortality. Surgical interventions. Chemotherapy. 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 years in 1991; invited in 1992 and completed in 1993 6% had more than 3 mammograms during study; 24% had one or more; 35% among women aged 45-49 years at entry

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Malmö II 1978

Methods	See text of the review; extension of Malmö 1976.
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

New York 1963

Methods	Individual randomisation within matched pairs; pairs derived from a computer list sorted by age, family size and employment group 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 years. Probably 31,092 pairs of women were randomised into screening and control group Very biased exclusions occurred: probably 336 previous breast cancer cases were excluded from the control group and 853 from study group (see text)

New York 1963 (*Continued*)

Interventions	Two view mammography: cephalocaudal and lateral. 4 cycles (three were planned according to the first publications) Screened group: annual physical examinations. Control group: usual care.
Outcomes	Total mortality. Breast cancer mortality. Surgical interventions. Radiotherapy.
Notes	Attendance rate: 65% in total population, circa 58%, 50% and 40% participated in 2, 3 and 4 screens, respectively Mammography in control group: not described.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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) Blinding of outcome assessment: not stated.
Participants	Women aged 40-64 years. Number of women randomised inconsistently reported (see text) Exclusions after randomisation unclear (see text).
Interventions	Single oblique mammography; recalled for conventional three-view if malignancies suspected 2 cycles (number not predetermined - screening introduced in control group because of results from Kopparberg) Circa 2 years; 2.5 years to complete first round and 2.1 to complete second round Control group: usual care.
Outcomes	Total mortality. Breast cancer mortality. Surgical interventions.
Notes	Attendance rate: circa 80%. Mammography in control group: 8% during one year; 25% in study group during two years previous to screening Early systematic screening of control group.

Risk of bias

Stockholm 1981 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Two-County 1977

Methods	Stratified cluster randomisation (see Kopparberg 1977 and Östergötland 1978 for details) Blinding of cause of death assessments in some later updates
Participants	Women aged 40-74 years. (See Kopparberg 1977 and Östergötland 1978 for details).
Interventions	See Kopparberg 1977 and Östergötland 1978. Screened women were encouraged to perform self-examination of the breasts every month Control women: usual care.
Outcomes	See Kopparberg 1977 and Östergötland 1978.
Notes	See Kopparberg 1977 and Östergötland 1978.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

UK age trial 1991

Methods	Individual randomisation by computer; randomisation ratio 1:2 Information on cause of death was obtained from the central register of the National Health Service
Participants	Women aged 39-41 years. 53,914 randomised into screened group; 107,007 into control group 30 and 51 excluded after randomisation.
Interventions	Two-view mammography at first screen, and by single mediolateral oblique view thereafter, with recall for full assessment if an abnormality was suspected 7 annual screens planned. Control group: usual care.
Outcomes	Total mortality. Breast cancer mortality.
Notes	Number of cancers in latest report given per 1000 women-years

Risk of bias

UK age trial 1991 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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) Blinding of outcome assessment not stated.
Participants	Women aged 40 years and above. 24 units with 92,934 women randomised into 47,001 in screening parishes and 45,933 in control parishes (39,034 versus 37,936 in age group 40-74 years) No parishes or municipalities excluded. 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 2 screens for women above 70 years, 3 for women originally in age group 40-69 years Interval between screens: 2-2.5 years.
Outcomes	Total mortality. Breast cancer mortality.
Notes	Attendance rate: ca. 90% in first round, 80% in second, very age dependent Mammography in control group: no data. Early systematic screening of control group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Characteristics of excluded studies *[ordered by study ID]*

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

(*Continued*)

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
Singapore 1994	Singapore Breast Screening Project. Randomised 166,600 women aged 50-64 years, but the only intervention was the prevalence screen, and exclusions after randomisation occurred only in the screened group. Previous cancer at any site was an exclusion criterion; more than 1500 women were excluded from the screened group, 468 because they were already dead

DATA AND ANALYSES

Comparison 1. Screening with mammography versus no screening

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths ascribed to breast cancer, 7 years follow up	11	616327	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.90]
1.1 Adequately randomised trials	4	292958	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
1.2 Suboptimally randomised trials	7	323369	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.61, 0.83]
2 Deaths ascribed to breast cancer, 13 years follow up	9	599090	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.74, 0.87]
2.1 Adequately randomised trials	4	292153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.02]
2.2 Suboptimally randomised trials	5	306937	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.67, 0.83]
3 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malmö 55)	9	356368	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.04]
3.1 Adequately randomised trials	3	227333	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.14]
3.2 Suboptimally randomised trials	6	129035	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.05]
4 Deaths ascribed to breast cancer, 7 years follow up, women at least 50 years of age (Malmö 55)	7	261044	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.62, 0.85]
4.1 Adequately randomised trials	2	65625	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.20]
4.2 Suboptimally randomised trials	5	195419	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.56, 0.81]
5 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age	8	329511	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.96]
5.1 Adequately randomised trials	3	218697	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.03]
5.2 Suboptimally randomised trials	5	110814	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.98]
6 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age	7	268874	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.69, 0.86]
6.1 Adequately randomised trials	2	74261	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.77, 1.15]
6.2 Suboptimally randomised trials	5	194613	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.80]

7 Deaths ascribed to any cancer, all women	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Adequately randomised trials	3	132118	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.10]
7.2 Suboptimally randomised trials (unreliable estimates)	3	195871	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.93, 1.06]
8 Overall mortality, 7 years follow up	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Adequately randomised trials	4	292958	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.03]
8.2 Suboptimally randomised trials (unreliable estimates)	7	324977	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.96, 1.02]
9 Overall mortality, 13 years follow up	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Adequately randomised trials	4	292958	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.03]
9.2 Suboptimally randomised trials (unreliable estimates)	4	244868	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.01]
10 Overall mortality, 7 years follow up, women below 50 years of age	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Adequately randomised trials	2	211270	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.04]
10.2 Suboptimally randomised trials (unreliable estimates)	5	99656	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.16]
11 Overall mortality, 7 years follow up, women at least 50 years of age	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Adequately randomised trials	1	39405	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.20]
11.2 Suboptimally randomised trials (unreliable estimates)	4	161519	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.94, 1.00]
12 Overall mortality, 13 years follow up, women below 50 years of age	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Adequately randomised trials	3	219324	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.04]
12.2 Suboptimally randomised trials (unreliable estimates)	3	61344	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.10]
13 Overall mortality, 13 years follow up, women at least 50 years of age	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Adequately randomised trials	2	73634	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.04]
13.2 Suboptimally randomised trials (unreliable estimates)	2	98261	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.02]

14 Number of mastectomies and lumpectomies	5	250479	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.26, 1.44]
14.1 Adequately randomised trials	3	132321	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.22, 1.42]
14.2 Suboptimally randomised trials	2	118158	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.26, 1.61]
15 Number of mastectomies	5	250479	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.11, 1.30]
15.1 Adequately randomised trials	3	132321	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.08, 1.32]
15.2 Suboptimally randomised trials	2	118158	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.06, 1.38]
16 Number treated with radiotherapy	2	100383	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.16, 1.50]
16.1 Adequately randomised trials	1	42486	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.04, 1.49]
16.2 Suboptimally randomised trials	1	57897	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.17, 1.69]
17 Number treated with chemotherapy	2	100383	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.19]
17.1 Adequately randomised trials	1	42486	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.39, 1.04]
17.2 Suboptimally randomised trials	1	57897	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.34]
18 Number treated with hormone therapy	2	100383	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.96]
18.1 Adequately randomised trials	1	42486	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.60, 1.08]
18.2 Suboptimally randomised trials	1	57897	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.12, 0.72]
19 Mortality among breast cancer patients in the Two-County study, 7 years follow up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Mortality from cancers other than breast cancer	2	2063	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [1.00, 5.85]
19.2 Mortality from causes other than breast cancer	2	2063	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.93, 2.04]
20 Results for biased trial	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 Deaths ascribed to breast cancer, 7 years follow up	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.2 Deaths ascribed to breast cancer, 13 years follow up	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.3 Deaths ascribed to breast cancer, 7 years follow up, younger women (below 50 years of age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.4 Deaths ascribed to breast cancer, 7 years follow up, elderly women (at least 50 years of age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

20.5 Deaths ascribed to breast cancer, 13 years follow up, younger women (below 50 years of age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.6 Deaths ascribed to breast cancer, 13 years follow up, elderly women (at least 50 years of age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.7 Overall mortality, 7 years follow up	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.8 Number treated with radiotherapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21 Number of cancers	7	512246	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.23, 1.35]
21.1 Adequately randomised trials (after 7-9 years)	4	292979	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.18, 1.34]
21.2 Suboptimally randomised trials (before control group screen)	3	219267	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.24, 1.44]

Analysis 1.1. Comparison 1 Screening with mammography versus no screening, Outcome 1 Deaths ascribed to breast cancer, 7 years follow up.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 1 Deaths ascribed to breast cancer, 7 years follow up

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980a	38/25214	28/25216		4.1 %	1.36 [0.83, 2.21]
Canada 1980b	38/19711	39/19694		5.7 %	0.97 [0.62, 1.52]
Malm 1976	63/21088	66/21195		9.6 %	0.96 [0.68, 1.35]
UK age trial 1991	105/53884	251/106956		24.4 %	0.83 [0.66, 1.04]
Subtotal (95% CI)	**119897**	**173061**		**43.7 %**	**0.93 [0.79, 1.09]**
Total events: 244 (Screening), 384 (No screening)					
Heterogeneity: Chi^2 = 3.33, df = 3 (P = 0.34); I^2 =10%					
Test for overall effect: Z = 0.92 (P = 0.36)					
2 Suboptimally randomised trials					
Gteborg 1982a	6/10821	10/13101		1.3 %	0.73 [0.26, 2.00]
Gteborg 1982b	21/9903	37/15708		4.2 %	0.90 [0.53, 1.54]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kopparberg 1977	71/39051	52/18846		10.2 %	0.66 [0.46, 0.94]
Malm II 1978	29/9581	33/8212		5.2 %	0.75 [0.46, 1.24]
New York 1963	81/31000	124/31000		18.0 %	0.65 [0.49, 0.86]
Stockholm 1981	53/38525	40/20651		7.6 %	0.71 [0.47, 1.07]
stergtland 1978	53/39034	67/37936		9.9 %	0.77 [0.54, 1.10]
Subtotal (95% CI)	**177915**	**145454**		**56.3 %**	**0.71 [0.61, 0.83]**
Total events: 314 (Screening), 363 (No screening)					
Heterogeneity: Chi^2 = 1.51, df = 6 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 4.37 (P = 0.000012)					
Total (95% CI)	**297812**	**318515**		**100.0 %**	**0.81 [0.72, 0.90]**
Total events: 558 (Screening), 747 (No screening)					
Heterogeneity: Chi^2 = 10.22, df = 10 (P = 0.42); I^2 =2%					
Test for overall effect: Z = 3.81 (P = 0.00014)					

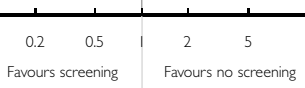
Analysis 1.2. Comparison 1 Screening with mammography versus no screening, Outcome 2 Deaths ascribed to breast cancer, 13 years follow up.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 2 Deaths ascribed to breast cancer, 13 years follow up

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980a	105/25214	108/25216		8.6 %	0.97 [0.74, 1.27]
Canada 1980b	107/19711	105/19694		8.3 %	1.02 [0.78, 1.33]
Malm 1976	87/20695	108/20783		8.5 %	0.81 [0.61, 1.07]
UK age trial 1991	105/53884	251/106956		13.3 %	0.83 [0.66, 1.04]
Subtotal (95% CI)	**119504**	**172649**		**38.7 %**	**0.90 [0.79, 1.02]**
Total events: 404 (Screening), 572 (No screening)					
Heterogeneity: Chi^2 = 2.16, df = 3 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 Suboptimally randomised trials					
Gteborg 1982	88/21650	162/29961		10.8 %	0.75 [0.58, 0.97]
Kopparberg 1977	126/38589	104/18582		11.1 %	0.58 [0.45, 0.76]
New York 1963	218/31000	262/31000		20.7 %	0.83 [0.70, 1.00]
Stockholm 1981	66/40318	45/19943		4.8 %	0.73 [0.50, 1.06]
stergtland 1978	135/38491	173/37403		13.9 %	0.76 [0.61, 0.95]
Subtotal (95% CI)	**170048**	**136889**		**61.3 %**	**0.75 [0.67, 0.83]**
Total events: 633 (Screening), 746 (No screening)					
Heterogeneity: Chi^2 = 4.94, df = 4 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 5.34 (P < 0.00001)					
Total (95% CI)	**289552**	**309538**		**100.0 %**	**0.81 [0.74, 0.87]**
Total events: 1037 (Screening), 1318 (No screening)					
Heterogeneity: Chi^2 = 11.82, df = 8 (P = 0.16); I^2 =32%					
Test for overall effect: Z = 5.15 (P < 0.00001)					



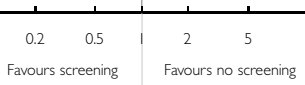
Analysis 1.3. Comparison 1 Screening with mammography versus no screening, Outcome 3 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malmö 55).

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 3 Deaths ascribed to breast cancer, 7 years follow up, women below 50 years of age (Malm 55)

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980a	38/25214	28/25216		8.1 %	1.36 [0.83, 2.21]
Malm 1976	28/7981	22/8082		6.3 %	1.29 [0.74, 2.25]
UK age trial 1991	105/53884	251/106956		48.5 %	0.83 [0.66, 1.04]
Subtotal (95% CI)	**87079**	**140254**		**62.8 %**	**0.94 [0.78, 1.14]**
Total events: 171 (Screening), 301 (No screening)					
Heterogeneity: Chi² = 4.55, df = 2 (P = 0.10); I² =56%					
Test for overall effect: Z = 0.59 (P = 0.56)					
2 Suboptimally randomised trials					
Gteborg 1982a	6/10821	10/13101		2.6 %	0.73 [0.26, 2.00]
Kopparberg 1977	12/9625	8/5053		3.0 %	0.79 [0.32, 1.93]
Malm II 1978	29/9581	33/8212		10.2 %	0.75 [0.46, 1.24]
New York 1963	39/14849	48/14911		13.8 %	0.82 [0.54, 1.24]
Stockholm 1981	20/14842	12/7103		4.7 %	0.80 [0.39, 1.63]
stergtland 1978	11/10312	10/10625		2.8 %	1.13 [0.48, 2.67]
Subtotal (95% CI)	**70030**	**59005**		**37.2 %**	**0.81 [0.63, 1.05]**
Total events: 117 (Screening), 121 (No screening)					
Heterogeneity: Chi² = 0.72, df = 5 (P = 0.98); I² =0.0%					
Test for overall effect: Z = 1.59 (P = 0.11)					
Total (95% CI)	**157109**	**199259**		**100.0 %**	**0.89 [0.77, 1.04]**
Total events: 288 (Screening), 422 (No screening)					
Heterogeneity: Chi² = 6.14, df = 8 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 1.42 (P = 0.16)					



Analysis 1.4. Comparison 1 Screening with mammography versus no screening, Outcome 4 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: 1 Screening with mammography versus no screening

Outcome: 4 Deaths ascribed to breast cancer, 7 years follow up, women at least 50 years of age (Malm 55)

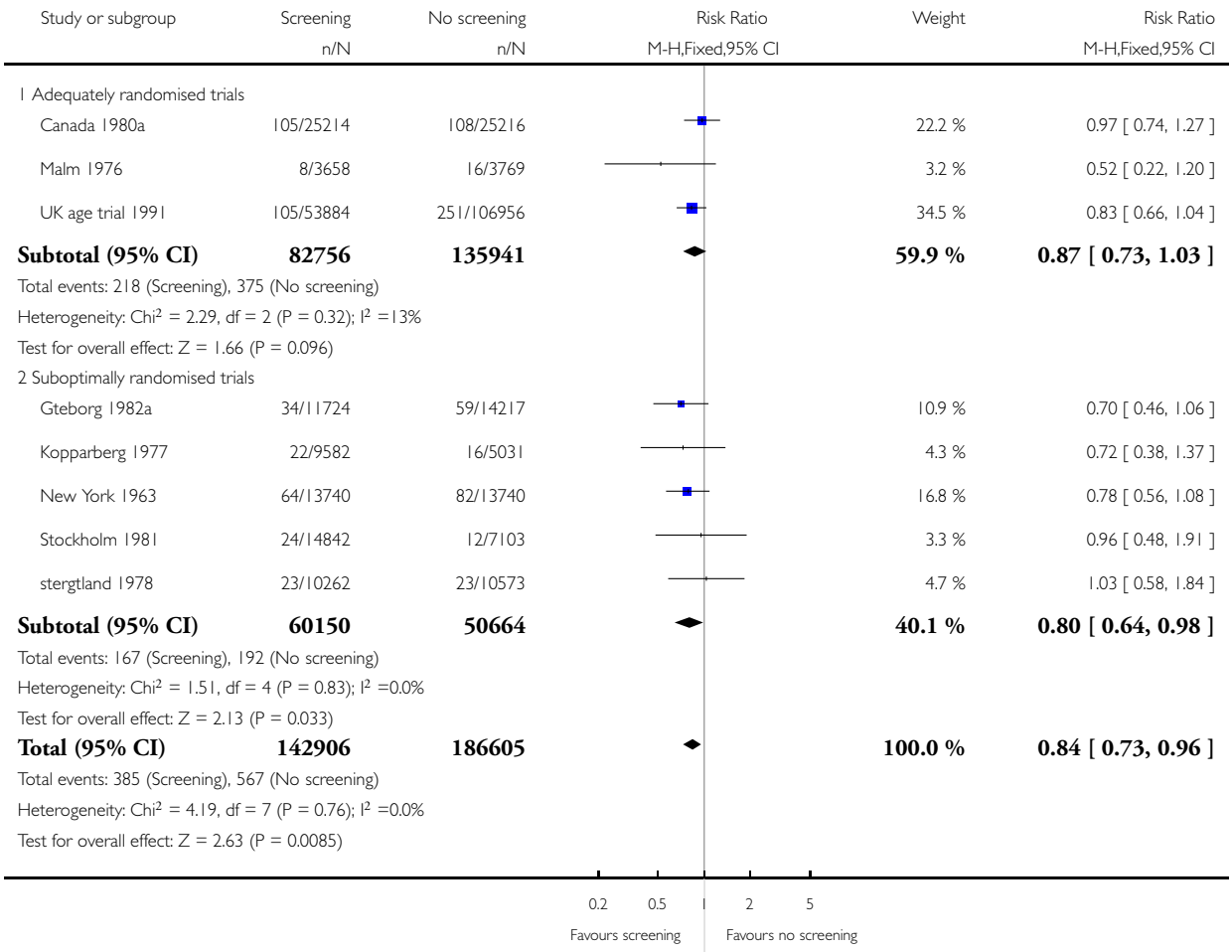
Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980b	38/19711	39/19694		11.2 %	0.97 [0.62, 1.52]
Malm 1976	35/13107	44/13113		12.7 %	0.80 [0.51, 1.24]
Subtotal (95% CI)	**32818**	**32807**		**23.9 %**	**0.88 [0.64, 1.20]**
Total events: 73 (Screening), 83 (No screening)					
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Suboptimally randomised trials					
Gteborg 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]
stergtland 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)					
Heterogeneity: Chi^2 = 1.58, df = 4 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 4.13 (P = 0.000037)					
Total (95% CI)	**142496**	**118548**		**100.0 %**	**0.72 [0.62, 0.85]**
Total events: 280 (Screening), 329 (No screening)					
Heterogeneity: Chi^2 = 4.02, df = 6 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 3.95 (P = 0.000077)					

Analysis 1.5. Comparison 1 Screening with mammography versus no screening, Outcome 5 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 5 Deaths ascribed to breast cancer, 13 years follow up, women below 50 years of age



Analysis 1.6. Comparison 1 Screening with mammography versus no screening, Outcome 6 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 6 Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980b	107/19711	105/19694		14.5 %	1.02 [0.78, 1.33]
Malm 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)					
Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Suboptimally randomised trials					
Gteborg 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]
stergtland 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)					
Heterogeneity: Chi^2 = 4.54, df = 4 (P = 0.34); I^2 =12%					
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)					
Heterogeneity: Chi^2 = 11.22, df = 6 (P = 0.08); I^2 =47%					
Test for overall effect: Z = 4.73 (P < 0.00001)					

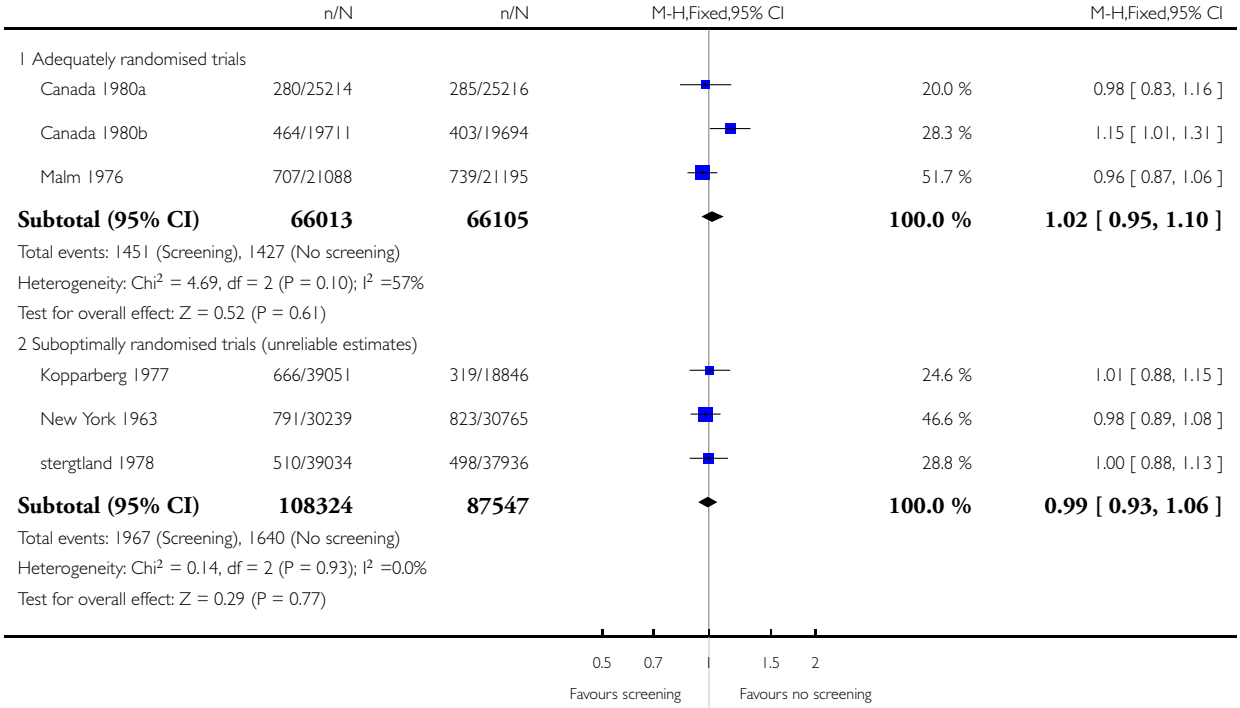
Analysis 1.7. Comparison 1 Screening with mammography versus no screening, Outcome 7 Deaths ascribed to any cancer, all women.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 7 Deaths ascribed to any cancer, all women

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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]
Malm 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)					
Heterogeneity: Chi^2 = 4.69, df = 2 (P = 0.10); I^2 =57%					
Test for overall effect: Z = 0.52 (P = 0.61)					
2 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]
stergtland 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)					
Heterogeneity: Chi^2 = 0.14, df = 2 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					

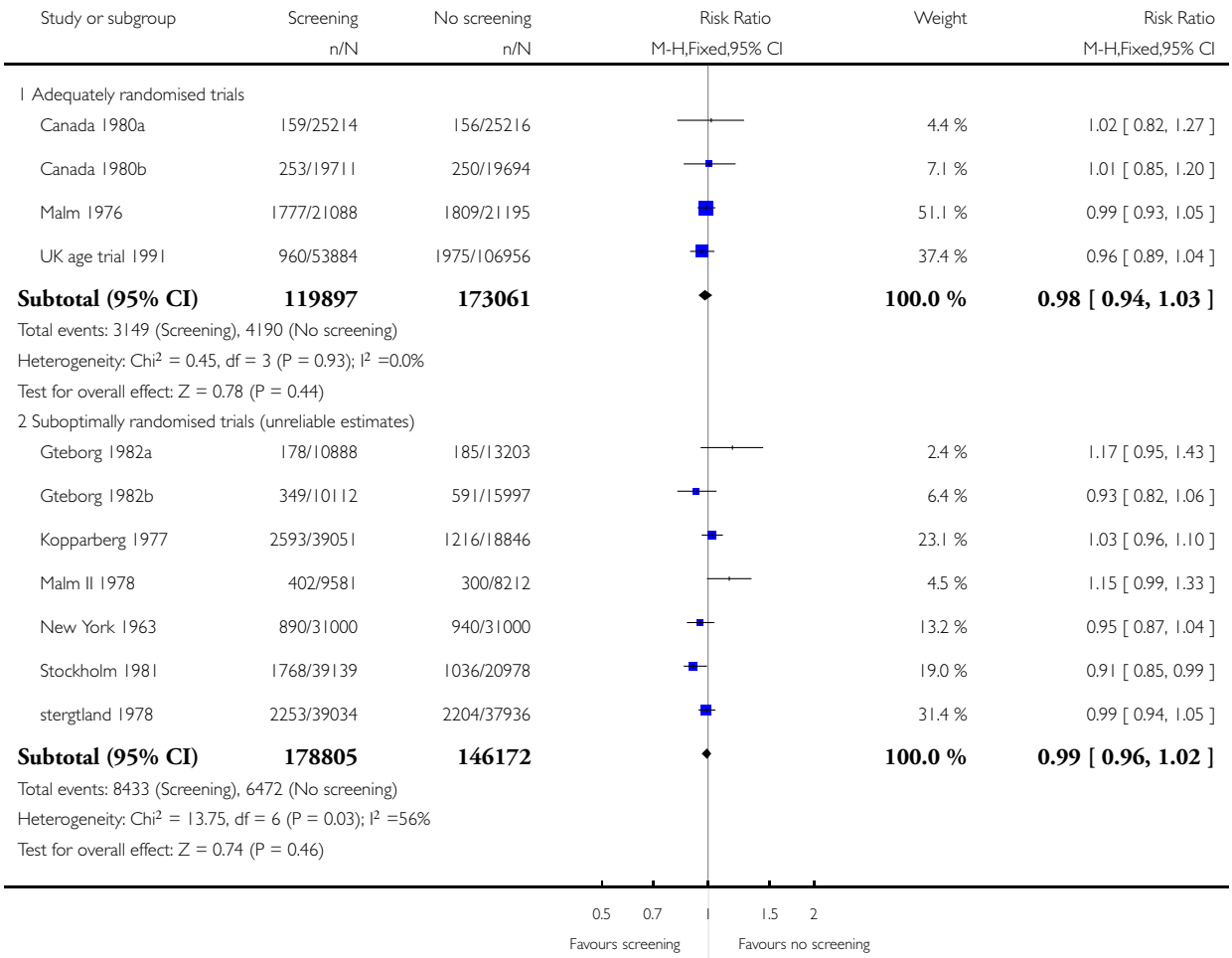


Analysis 1.8. Comparison 1 Screening with mammography versus no screening, Outcome 8 Overall mortality, 7 years follow up.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 8 Overall mortality, 7 years follow up



Analysis 1.9. Comparison 1 Screening with mammography versus no screening, Outcome 9 Overall mortality, 13 years follow up.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 9 Overall mortality, 13 years follow up

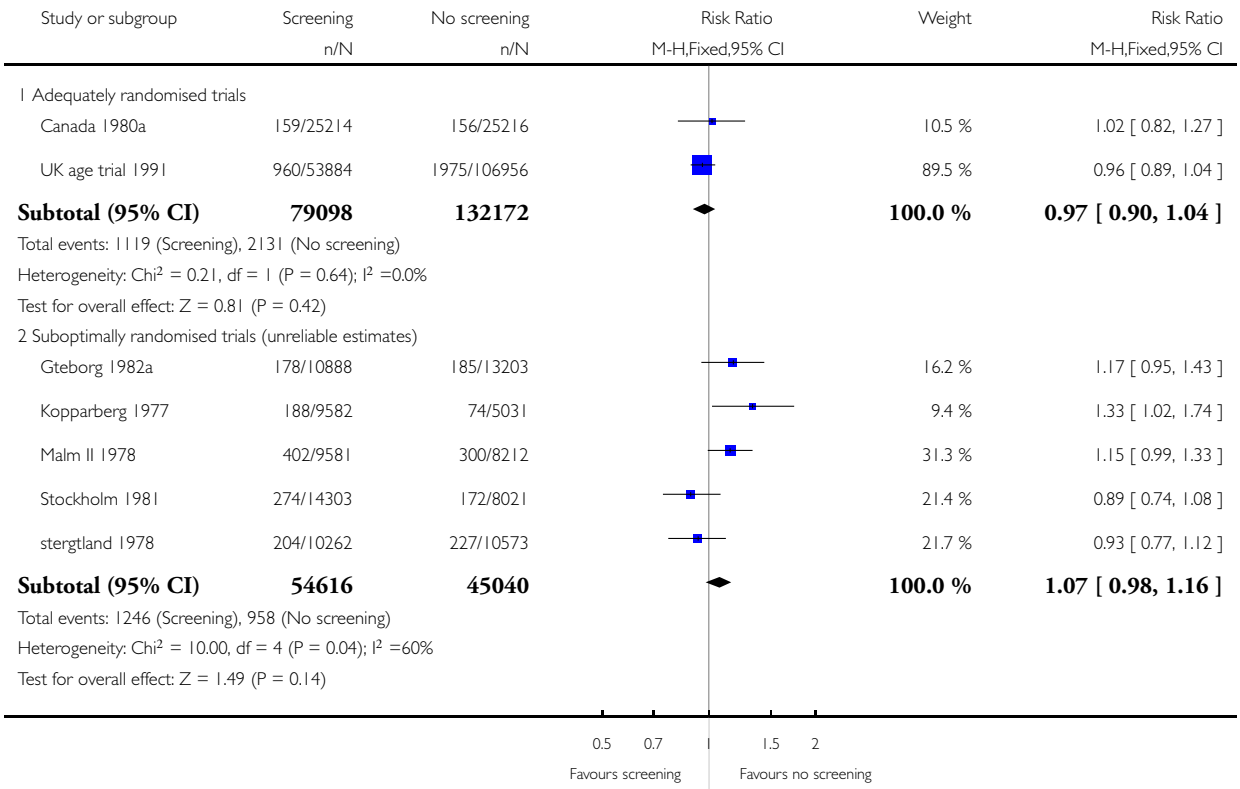
Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980a	413/25214	413/25216		8.2 %	1.00 [0.87, 1.14]
Canada 1980b	734/19711	690/19694		13.8 %	1.06 [0.96, 1.18]
Malm 1976	2537/21088	2593/21195		51.6 %	0.98 [0.93, 1.04]
UK age trial 1991	960/53884	1975/106956		26.4 %	0.96 [0.89, 1.04]
Subtotal (95% CI)	**119897**	**173061**		**100.0 %**	**0.99 [0.95, 1.03]**
Total events: 4644 (Screening), 5671 (No screening)					
Heterogeneity: Chi^2 = 2.38, df = 3 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 Suboptimally randomised trials (unreliable estimates)					
Gteborg 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]
stergtland 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)					
Heterogeneity: Chi^2 = 15.66, df = 3 (P = 0.001); I^2 =81%					
Test for overall effect: Z = 0.77 (P = 0.44)					

Analysis 1.10. Comparison 1 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: 1 Screening with mammography versus no screening

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



Analysis 1.11. Comparison 1 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: 1 Screening with mammography versus no screening

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

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					
2 Suboptimally randomised trials (unreliable estimates)					
Gteborg 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]
stergtland 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)					
Heterogeneity: Chi^2 = 5.02, df = 3 (P = 0.17); I^2 =40%					
Test for overall effect: Z = 2.19 (P = 0.028)					

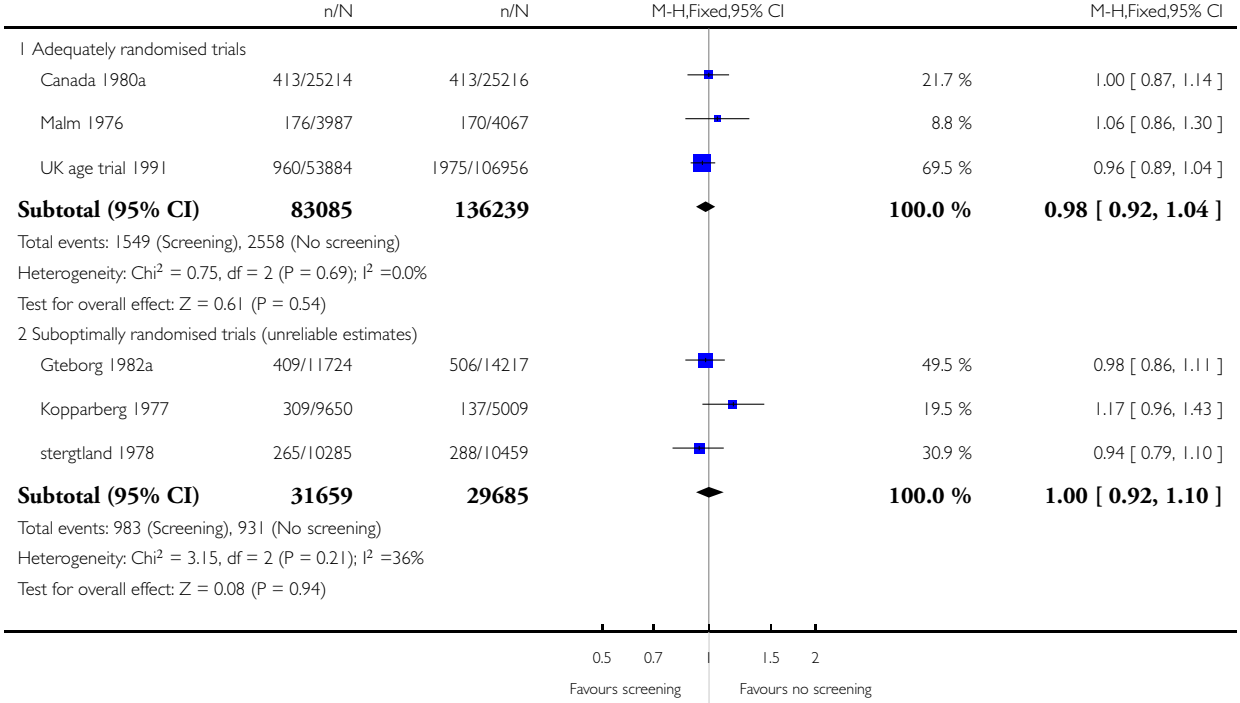
Analysis 1.12. Comparison 1 Screening with mammography versus no screening, Outcome 12 Overall mortality, 13 years follow up, women below 50 years of age.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

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

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980a	413/25214	413/25216		21.7 %	1.00 [0.87, 1.14]
Malm 1976	176/3987	170/4067		8.8 %	1.06 [0.86, 1.30]
UK age trial 1991	960/53884	1975/106956		69.5 %	0.96 [0.89, 1.04]
Subtotal (95% CI)	**83085**	**136239**		**100.0 %**	**0.98 [0.92, 1.04]**
Total events: 1549 (Screening), 2558 (No screening)					
Heterogeneity: Chi^2 = 0.75, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Suboptimally randomised trials (unreliable estimates)					
Gteborg 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]
stergtland 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)					
Heterogeneity: Chi^2 = 3.15, df = 2 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 0.08 (P = 0.94)					



Analysis 1.13. Comparison 1 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: 1 Screening with mammography versus no screening

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

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Canada 1980b	734/19711	690/19694		22.2 %	1.06 [0.96, 1.18]
Malm 1976	2361/17101	2423/17128		77.8 %	0.98 [0.93, 1.03]
Subtotal (95% CI)	**36812**	**36822**		**100.0 %**	**1.00 [0.95, 1.04]**
Total events: 3095 (Screening), 3113 (No screening)					
Heterogeneity: Chi^2 = 2.13, df = 1 (P = 0.14); I^2 =53%					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Suboptimally randomised trials (unreliable estimates)					
Kopparberg 1977	5725/28918	2659/13470		44.6 %	1.00 [0.96, 1.05]
stergtland 1978	4564/28657	4398/27216		55.4 %	0.99 [0.95, 1.02]
Subtotal (95% CI)	**57575**	**40686**		**100.0 %**	**0.99 [0.97, 1.02]**
Total events: 10289 (Screening), 7057 (No screening)					
Heterogeneity: Chi^2 = 0.37, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.47 (P = 0.64)					

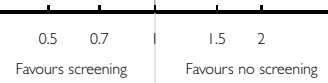
Analysis 1.14. Comparison 1 Screening with mammography versus no screening, Outcome 14 Number of mastectomies and lumpectomies.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 14 Number of mastectomies and lumpectomies

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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]
Malm 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)					
Heterogeneity: Chi^2 = 0.28, df = 2 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 6.85 (P < 0.00001)					
2 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)					
Heterogeneity: Chi^2 = 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)					
Heterogeneity: Chi^2 = 1.64, df = 4 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 8.81 (P < 0.00001)					



Analysis 1.15. Comparison 1 Screening with mammography versus no screening, Outcome 15 Number of mastectomies.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 15 Number of mastectomies

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 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]
Malm 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)					
Heterogeneity: Chi^2 = 0.86, df = 2 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 3.45 (P = 0.00056)					
2 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)					
Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 2.78 (P = 0.0054)					
Total (95% CI)	**145536**	**104943**		**100.0 %**	**1.20 [1.11, 1.30]**
Total events: 1542 (Screening), 969 (No screening)					
Heterogeneity: Chi^2 = 1.33, df = 4 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 4.43 (P < 0.00001)					

Analysis 1.16. Comparison 1 Screening with mammography versus no screening, Outcome 16 Number treated with radiotherapy.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 16 Number treated with radiotherapy

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Malm 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
2 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.58 (P = 0.00035)					
Total (95% CI)	**60293**	**40090**		**100.0 %**	**1.32 [1.16, 1.50]**
Total events: 693 (Screening), 358 (No screening)					
Heterogeneity: Chi^2 = 0.82, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 4.22 (P = 0.000024)					

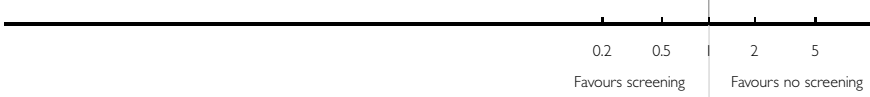
Analysis 1.17. Comparison 1 Screening with mammography versus no screening, Outcome 17 Number treated with chemotherapy.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 17 Number treated with chemotherapy

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Malm 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.82 (P = 0.069)					
2 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)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	**60293**	**40090**		**100.0 %**	**0.96 [0.78, 1.19]**
Total events: 252 (Screening), 144 (No screening)					
Heterogeneity: Chi^2 = 3.42, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 0.36 (P = 0.72)					



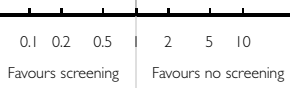
Analysis 1.18. Comparison 1 Screening with mammography versus no screening, Outcome 18 Number treated with hormone therapy.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 18 Number treated with hormone therapy

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequately randomised trials					
Malm 1976	80/21242	99/21244		85.0 %	0.81 [0.60, 1.08]
Subtotal (95% CI)	**21242**	**21244**		**85.0 %**	**0.81 [0.60, 1.08]**
Total events: 80 (Screening), 99 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 Suboptimally randomised trials					
Kopparberg 1977	8/39051	13/18846		15.0 %	0.30 [0.12, 0.72]
Subtotal (95% CI)	**39051**	**18846**		**15.0 %**	**0.30 [0.12, 0.72]**
Total events: 8 (Screening), 13 (No screening)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.70 (P = 0.0069)					
Total (95% CI)	**60293**	**40090**		**100.0 %**	**0.73 [0.55, 0.96]**
Total events: 88 (Screening), 112 (No screening)					
Heterogeneity: Chi^2 = 4.47, df = 1 (P = 0.03); I^2 =78%					
Test for overall effect: Z = 2.22 (P = 0.026)					



Analysis 1.19. Comparison 1 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: 1 Screening with mammography versus no screening

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

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Mortality from cancers other than breast cancer					
Kopparberg 1977	13/674	3/304		54.6 %	1.95 [0.56, 6.81]
stergtland 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)					
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.97 (P = 0.049)					
2 Mortality from causes other than breast cancer					
Kopparberg 1977	47/674	15/304		48.7 %	1.41 [0.80, 2.49]
stergtland 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)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 1.58 (P = 0.11)					

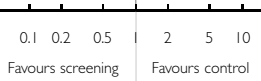
Analysis 1.20. Comparison 1 Screening with mammography versus no screening, Outcome 20 Results for biased trial.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 20 Results for biased trial

Study or subgroup	Screening n/N	No screening n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Deaths ascribed to breast cancer, 7 years follow up				
Edinburgh 1978	68/23226	76/21904		0.84 [0.61, 1.17]
2 Deaths ascribed to breast cancer, 13 years follow up				
Edinburgh 1978	176/28628	187/26015		0.86 [0.70, 1.05]
3 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]
4 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]
5 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]
6 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]
7 Overall mortality, 7 years follow up				
Edinburgh 1978	1274/23226	1490/21904		0.81 [0.75, 0.87]
8 Number treated with radiotherapy				
Edinburgh 1978	75/23226	63/21904		1.12 [0.80, 1.57]

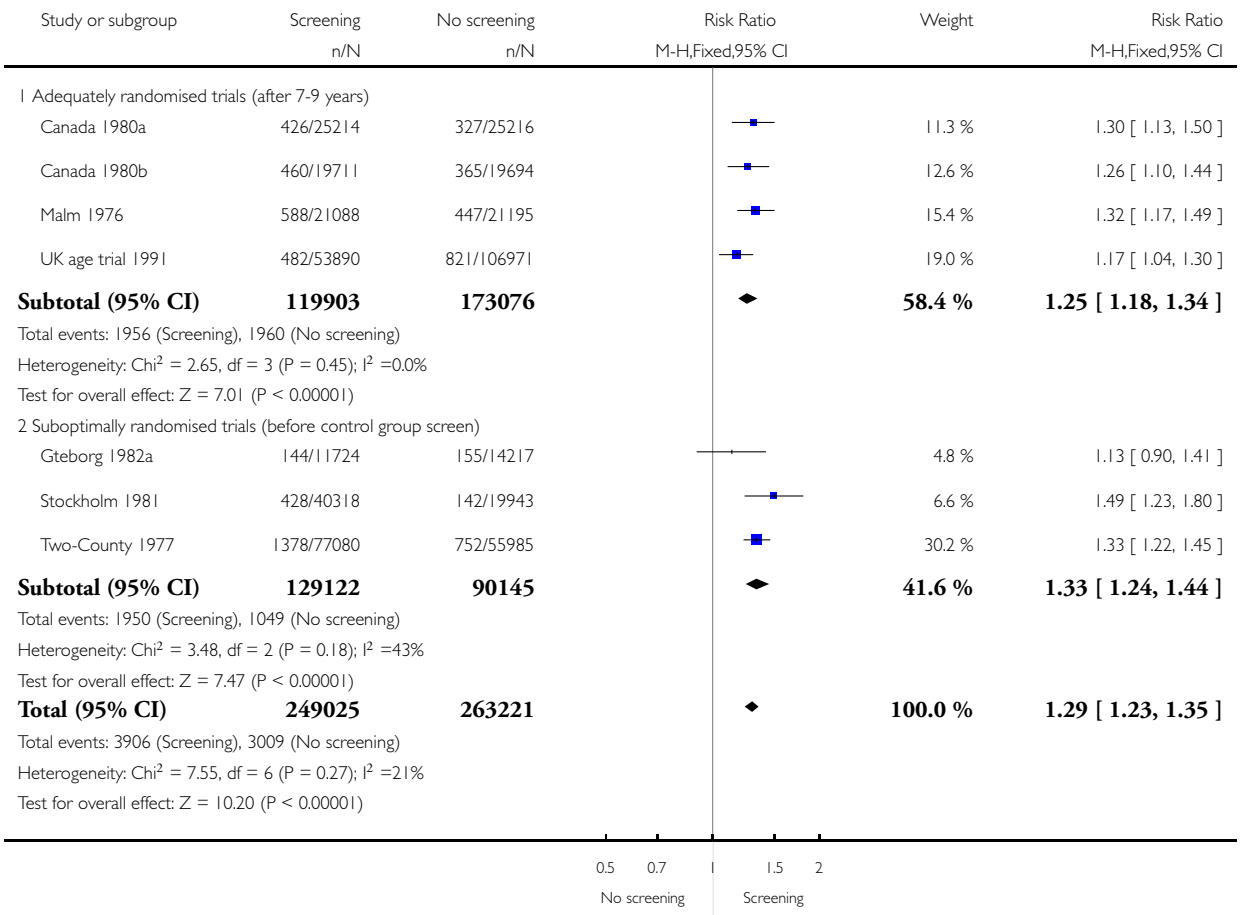


Analysis 1.21. Comparison 1 Screening with mammography versus no screening, Outcome 21 Number of cancers.

Review: Screening for breast cancer with mammography

Comparison: 1 Screening with mammography versus no screening

Outcome: 21 Number of cancers



ADDITIONAL TABLES

Table 1. 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

Table 1. Examples of varying numbers of women in the Swedish trials (*Continued*)

	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
	40-49	10262	10573	Tabar 1995

Table 1. Examples of varying numbers of women in the Swedish trials (*Continued*)

	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

WHAT'S NEW

Last assessed as up-to-date: 20 November 2008.

Date	Event	Description
17 November 2010	Amended	Corrected labels for Figure 1.21.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2001

Date	Event	Description
5 August 2009	New citation required but conclusions have not changed	new citation = no change to conclusions
3 March 2009	New search has been performed	Data from a new trial, UK age trial, added.
12 July 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

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.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- Rigshospitalet, Denmark.

External sources

- Danish Institute for Health Technology Assessment, Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A new outcome was added when we discovered that breast cancer mortality is an unreliable outcome. This was mortality from any cancer.

NOTES

A new trial, the UK age trial, has been added since the 2006 update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mammography [adverse effects; psychology]; *Mass Screening; Breast Neoplasms [*mortality; *radiography]; Cause of Death; Diagnostic Errors; Randomized Controlled Trials as Topic; Risk

MeSH check words

Adult; Female; Humans; Middle Aged