Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial

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Summary

Background The efficacy of screening by mammography has been shown in randomised controlled trials in women aged 50 years and older, but is less clear in younger women. A meta-analysis of all previous trials showed a 15% mortality reduction in invited women aged 40–49 years at study entry, but this finding could be due in part to screening of women after age 50 years. The Age trial was designed to study the effect on mortality of inviting women for annual mammography from age 40 years.

Methods 160 921 women aged 39–41 years were randomly assigned in the ratio 1:2 to an intervention group of annual mammography to age 48 years or to a control group of usual medical care. The trial was undertaken in 23 NHS breast-screening units in England, Wales, and Scotland. The primary analysis was based on the intention-to-treat principle and compared mortality rates in the two groups at 10 years' follow-up. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN24647151.

Findings At a mean follow-up of 10·7 years there was a reduction in breast-cancer mortality in the intervention group, in relative and absolute terms, which did not reach statistical significance (relative risk 0·83 [95% CI 0·66–1·04], p=0·11; absolute risk reduction 0·40 per 1000 women invited to screening [95% CI −0·07 to 0·87]). Mortality reduction adjusted for non-compliance in women actually screened was estimated as 24% (RR 0·76, 95% CI 0·51–1·01).

Interpretation Although the reduction in breast-cancer mortality observed in this trial is not significant, it is consistent with results of other trials of mammography alone in this age-group. Future decisions on screening policy should be informed by further follow-up from this trial and should take account of possible costs and harms as well as benefits.

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Introduction

Screening women from age 50 years by mammography has been shown in randomised controlled trials to reduce mortality from breast cancer by around 25% in those offered screening.[1] Although efficacy of mammography in women younger than 50 years is less certain, evidence from long-term follow-up of some randomised controlled trials has increasingly suggested a benefit of screening in this age-group. The Malmo Mammographic Screening Trial, which included two cohorts of women aged 45–49 years and 43–49 years at entry, invited for screening by mammography at 18–24 month intervals, showed a significant 36% reduction in breast-cancer mortality in the combined intervention groups at an average follow-up of 15·5 years and 10 years for the two cohorts in this age-group;[2] however, when the cohorts were analysed separately with a different model the results were non-significant.[1] The Gothenburg trial,[3] which invited women aged 39–49 years at entry for mammography at an 18 month interval, showed a significant 44% reduction in the intervention group at 14 years of follow-up. Table 1[1,3–7] shows the details of previous randomised trials. Various meta-analyses of these trials have been undertaken;[8–11] one that included trials of screening by mammography alone estimated a 19% reduction in breast-cancer mortality in women aged 40–49 years at entry (relative risk 0·81, 95% CI 0·65–1·01),[12] similar to the findings of an updated Swedish overview, which did not include the Kopparberg group of the Two County study.[1] A meta-analysis[11] of all trials showed a significant 15% reduction in breast-cancer mortality (0·85, 0·73–0·98) in women aged 40–49 years at entry who were invited to screening. Many countries have now introduced population-based screening, and whereas most programmes include women from age 50 years, several include younger women too.

Most previous trials have not been designed specifically to study the effect of screening in younger women, and where women younger than 50 years at study entry have been included, to what extent any benefit in these women was due to screening after they reached age 50 years is unclear. A trial in Canada, in which women aged 40–49 years were randomly assigned either annual mammography and physical examination or usual care after an initial physical examination, with all women being taught self examination of their breasts, showed no effect of mammography at 13 years of follow-up, although the confidence intervals were wide[7] and concerns have been expressed about the quality of mammography in this trial and the use of a volunteer population.[14]

The Age trial was designed specifically to overcome these issues by studying the effect of annual invitation to mammography starting at age 40 years, compared with

	Screening interval (months)	CBE included	Study recruitment	Length of follow-up (years)	Age range at entry (years)	Relative risk of breast-cancer mortality (95% CI)
HIP[4]	12	Yes	1963–66	18	40–49	0·77 (0·53–1·11)
Ostergotland[5]	24	No	1978–81	17	38–49	1·05 (0·64–1·71)
Kopparberg[5]	24	No	1976–78	17	40–49	0·76 (0·42–1·40)
Malmo I[5]	18–24	No	1976–78	19	45–49	0·74 (0·44–1·25)
Malmo II[5]	18–24	No	1978–90	12·7	43–49	0·65 (0·39,1·08)
Gothenburg[3]	18	No	1982–84	13	39–49	0·56 (0·34–0·91)
Stockholm[3]	28	No	1981–83	15	39–49	1·52 (0·80–2·88)
Edinburgh[6]	24	Yes (annual)	1978–81	14	45–49	0·83 (0·54–1·27)
NBSS[7]	12	Yes	1980–85	12	40–49	0·97 (0·74–1·27)

CBE=clinical breast examination.

Table 1: **Randomised trials of breast screening in women younger than 50 years**

an uninvited control group. The women in the control group will receive their first invitation between the ages of 50 years and 52 years, as is policy in the NHS breast-screening programme. In 2005, we published results on the predicted reduction in breast-cancer mortality in the intervention group based on surrogate outcomes measures[15] using the pathological characteristics of cancers in both groups to calculate three prognostic indices: the Nottingham Prognostic Index (NPI)[16] and indices developed from the Swedish Two County Study[17] and the Edinburgh randomised trial of breast cancer screening.[18] These indices were used to calculate the predicted number of women dying from breast cancer within 10 years of date of entry in each group of the trial. We present here the first results for observed breast-cancer mortality.

Methods

Patients and procedures

The design of the study has been described in detail elsewhere.[19] Briefly, 160 921 women aged 39–41 years were randomly assigned between 1991 and 1997 to either an intervention group or a control group in a ratio of 1:2. The trial was undertaken in 23 NHS breast-screening units in England, Wales, and Scotland. Women were identified from lists of patients of general (family) practitioners (GPs) held on local Health Authority databases, and individual randomisation was carried out stratified by GP practice. A prior notification list was prepared by the Health Authority for each GP who could remove before randomisation women for whom it was inappropriate to invite for screening, such as those under care for breast cancer. From 1992 onwards, randomisation and allocation to trial group were carried out on the Health Authority computer system with specifically written software. Before this, for women in three early centres to join the trial, random numbers generated from the coordinating centre computer were applied to GP lists provided by the Health Authority. The trial-group code was then held on each woman's record at the Health Authority and details were sent in batches to the screening centres where screening invitations were generated for those in the intervention group. In a mammography screening trial, it is not possible to blind the screening centres to intervention status. Stratification by GP practice ensured a similar distribution by geographical area in each group of the trial. The average age of women at randomisation was 40·4 years in both the control and intervention groups.[20]

Women in the intervention group were offered annual screening by mammography up to and including the calendar year of their 48th birthday; those in the control group received usual medical care. Ethics approval was obtained from London (formerly North Thames) Multicentre Research Ethics Committee. Women in the control group received no information about the trial. It was judged acceptable at the time to have an uninvited control group who were unaware of their inclusion in the trial, since such a group is no different to a geographically distinct population who are followed up to monitor cancer incidence and mortality and who are receiving the usual standard of care for the general population. All women in the intervention group were sent an information leaflet

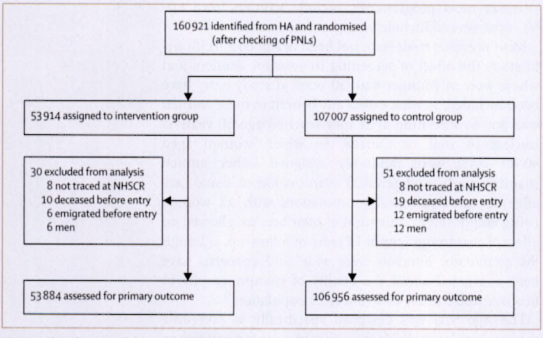

Figure 1: **Flow diagram of the progress through the phases of the trial**
PNL=prior notification list.

about the trial with their letter of invitation and acceptance of the invitation to attend screening was taken as informed consent to participate.

The original intention was to offer women in the intervention group seven annual screens because any additional screens would have little effect on 10-year mortality. The protocol was subsequently revised to reduce the potential 6 year interval before a women received her first invitation in the national programme. All women in the intervention group, including previous non-responders, were re-invited annually unless they requested not to be invited again. In three centres, screening in the trial ceased prematurely (after four, five, and six rounds, respectively) because of insufficient resources to manage the additional workload. These three centres were included in the primary intention-to-treat analysis, although the effect of excluding them was also studied. Screening in the trial was by two-view mammography at first screen, and by single mediolateral oblique view thereafter, with recall for full assessment if an abnormality was suspected. All women in both groups become eligible to join the NHS breast-screening programme and would receive their first invitation between the ages of 50 years and 52 years.

The whole population has been followed up through flagging at the NHS central register (NHSCR) to determine breast-cancer incidence and mortality, mortality from all causes, and emigration.

Statistical analysis

The trial was originally designed to recruit 190 000 women to have 80% power to detect a 20% reduction in breast-cancer mortality after 10 years of follow-up at the 5% significance level. However, financial and workload constraints on NHS breast-screening units hampered recruitment and no new centres entered after 1996. In 1999, the data monitoring committee recommended that, since further accrual would result in only marginal gains in power and would delay achievement of mean follow-up times, recruitment should cease. The revised power, based on the original estimates of breast cancer mortality in the control group of 3·3 per 1000, was 72%.

Information about all deaths was obtained from the NHSCR; cause of death was taken as the underlying cause of death as coded on the death certificate. The analysis included deaths from breast cancer occurring between date of entry to the trial and Dec 31, 2004. Person-years in the intervention and control groups were calculated from date of trial entry to Dec 31, 2004, or to death or loss to follow-up due to emigration, whichever was earliest. All screening in the trial had been completed by this date. Deaths in cases where the date of diagnosis of breast cancer preceded date of entry to the trial were excluded. Date of diagnosis was obtained from pathology laboratory records or from cancer registrations.

Cumulative mortality rates were calculated by dividing the total number of deaths from breast cancer at each year since randomisation by the total number of women in each group. This calculation provides a crude estimate of cumulative breast-cancer mortality. However, the plots of these rates reflect the decreasing completeness of follow-up with increasing time since randomisation. Nelson-Aalen estimates of the cumulative mortality were calculated as the number of breast-cancer deaths in each year since randomisation divided by the number of woman-years observed during that year and by summing these individual rates.[21]

The primary analysis was based on the intention-to-treat principle and compared the mortality rates in the whole of the intervention group with the control group. Additionally, the method described by Cuzick and co-workers[22] was used to estimate breast-cancer mortality and corresponding 95% CIs in those accepting the first screening test relative to the control group, with the assumption that the underlying rate in acceptors is equivalent to that in the control group adjusted for the rate in the non-acceptors. The number needed to screen (NNS)[23] was calculated as the reciprocal of the absolute risk reduction.

This study is registered as an International Standard Randomised Controlled Trial, number 24647151.

Role of the funding source

The funding bodies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 160 921 women were randomised into the trial; more than 99·9% of these have been successfully flagged at NHSCR. The outcomes of screening in the first 10 years of the trial have been described in detail elsewhere.[20] Uptake of screening was 68% at the first (prevalent) screen and 69–70% in those re-invited. Overall, 81% of women attended at least one routine screen; the mean number of screens per woman was 4·5, or 5·6 for those attending at

	Number of women	Women years	All cause deaths		Breast cancer deaths		Rate ratio (95% CI) intervention vs control group
			n	Rate per 1000 women years	n	Rate per 1000 women years	
Intervention	53 884	578 390	960	1·66	105	0·18	0·83 (0·66–1·04)
Control	106 956	1 149 380	1975	1·72	251	0·22	

Table 2: **Mortality from all causes and from breast cancer in the intervention and control groups**

	Number of women	Women years	All cause deaths		Breast cancer deaths		Rate ratio* (95% CI) attenders *vs* control arm
			n	Rate per 1000 women years	n	Rate per 1000 women years	
Attenders	36538	394473	495	1·25	68	0·17	0·76 (0·51–1·01)
Non-attenders	17346	183917	465	2·53	37	0·20	

*Adjusted for rates in non-attenders.

***Table 3*: Mortality in attenders and non-attenders at first screen in intervention group**

least one screen. Detection rates of breast cancer (invasive and in situ) were 1·0 per 1000 at the prevalent screen and 1·0–1·6 per 1000 at subsequent screens; they increased with successive screening rounds (and hence with age) in line with underlying incidence and did not increase greatly until the later screening rounds at ages 46 years or older.

Since this earlier publication, a further six women have been excluded from the analysis in the intervention group (one emigration before randomisation and five mistakenly identified men) and 15 from the control group (seven emigrations and eight mistakenly identified men); 81 have now been excluded in total (figure 1).

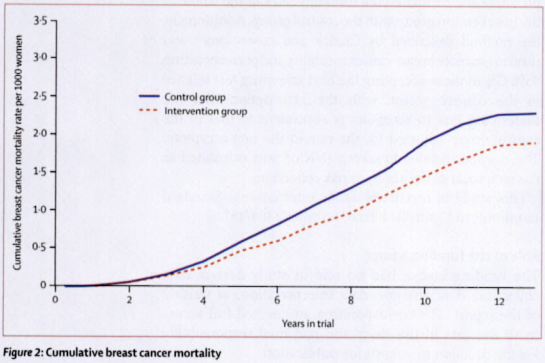

***Figure 2*: Cumulative breast cancer mortality**

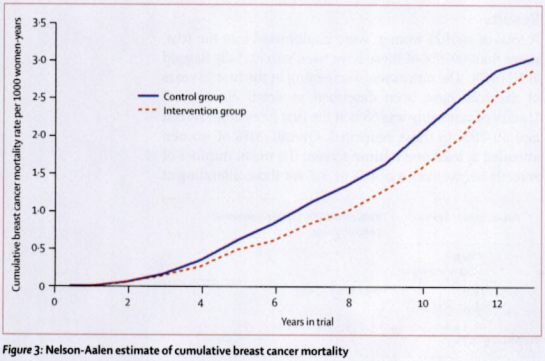

***Figure 3*: Nelson-Aalen estimate of cumulative breast cancer mortality**

The mean follow-up to Dec 31, 2004, was 10·7 years; follow-up ranged from 7 years to 14 years. Table 2 shows mortality in the two groups of the trial from all causes and from breast cancer. The risk of all-cause mortality in the intervention group relative to that in the control group was 0·97 (95% CI 0·89–1·04). The reduction in breast-cancer mortality in the intervention group, relative to the control group, of 17% did not reach statistical significance (RR 0·83, 95% CI 0·66–1·04) The absolute observed reduction in breast cancer mortality was 0·037 per 1000 women-years or 0·40 per 1000 women randomly assigned to the intervention group (95% CI –0·07 to 0·87).

Table 3 shows mortality in women in the intervention group according to whether they attended in response to their first invitation to screening. All-cause mortality in first screen non-attenders was significantly higher than in attenders (2·53 *vs* 1·25 per 1000 women-years; RR 2·01, 95% CI 1·78–2·29; p<0·0001) and in women in the control group (2·53 *vs* 1·72 per 1000 women-years; RR 1·47, 1·33–1·63, p<0·0001; tables 2 and 3). Breast cancer mortality in the non-attenders did not differ from that in the control group (0·20 *vs* 0·22 per 1000 women-years; 0·92, 0·63–1·30). After adjustment for non-attendance at the first screen there was a 24% reduction in breast cancer mortality in women accepting their first invitation (table 3). The absolute reduction was 0·59 per 1000 (95% CI –0·11 to 1·28) women attending (who were at slightly increased risk) or 0·56 per 1000 women attending, adjusted for selection bias.

There was no evidence of heterogeneity between screening units, either when analysed individually (χ^2=11·17, p=0·97) or when grouped into those where the number of screens per woman (including all trial screens) was above or below the mean of 4·87 (χ^2=0·08, p=0·78). Exclusion of the three centres where screening in the trial ceased prematurely[20] gave a similar estimated mortality reduction. Figure 2 shows the crude cumulative breast cancer mortality in the two trial groups by time since entry to the trial. Figure 3 shows the Nelson-Aalen estimate of cumulative breast cancer mortality. The curves begin to diverge after 3 years of follow-up but appear to converge again after around 10 years; however, the

	Women years	Intervention		Women years	Control		Rate ratio (95% CI) intervention *vs* control group
		n	Rate per 1000 women years		n	Rate per 1000 women years	
0–5 years	267 930	26	0·10	532 206	65	0·12	0·79 (0·48–1·27)
5–15 years	310 460	79	0·25	617 173	186	0·30	0·84 (0·64–1·10)

Table 4: **Breast cancer mortality in intervention and control groups by time period**

women-years of follow-up beyond 10 years is small at present.

Table 4 shows the breast cancer mortality in the first 5 years from date of entry and at 5–15 years of follow-up. There was no significant difference between the effect of invitation to screening on breast-cancer mortality in the two periods. Although some of those women with more than 10 years of follow-up (in both groups of the trial) will have been invited for their first screen as part of the NHS breast-screening programme by Dec 31, 2004, such screening would not yet be expected to have an influence on breast cancer mortality. Screening in the intervention group continued for 8–9 years, and after excluding deaths in individuals diagnosed with breast cancer in both groups after 10 years of follow-up, the mortality reduction is 19% (RR 0·81, 95% CI 0·64–1·02).

The analysis based on surrogate outcome measures using the pathological characteristics of cancers in both groups to calculate prognostic indices, indicated a 10–11% reduction in breast cancer mortality at 10 years from date of entry.[15] We have therefore repeated both the surrogate analysis and that of observed mortality restricted to those women with dates of entry before Jan 1, 1995, who have the potential for 10 years of follow-up. The relative risk of observed mortality from breast cancer was 0·79 (95% CI 0·60–1·06) compared with a predicted reduction based on surrogate outcome measures of 10–14%, depending on the prognostic index used. The surrogate analysis was based only on those cases diagnosed up to Dec 31, 1999, and part of the difference between the surrogate and observed results is due to breast cancer deaths in cases diagnosed since Dec 31, 1999. If these are excluded the relative risk of observed mortality from breast cancer was 0·81 (95% CI 0·58–1·11).

The number needed to screen (NNS) to prevent one death over 10 years was 2512 (95% CI 1149 to –13 544) for 7–9 years. In practice, women in the intervention group received an average of seven invitations, so that this figure is equivalent to approximately 17 600 invitations. A negative number needed to screen at the upper end of the confidence interval indicates the non-significance of the rate ratio. This estimate is more favourable when the analysis is restricted to women with the potential for 10 years of follow-up and breast cancer deaths within 10 years (NNS 2315, 95% CI 1059 to –12495).

Discussion

This trial did not find a significant reduction in breast cancer mortality in women offered annual screening between the ages of 40 years and 48 years. The trial was designed specifically to look at the effect on breast-cancer mortality of inviting women to screening from age 40 years compared with invitation from age 50 years as in the current NHS breast-screening programme. This approach was used to avoid the problem present in previous trials in which some women reached age 50 years shortly after entry, and to provide results relevant to decisions on public-health policy.

The power of the trial to show a reduction was diminished both by the smaller than planned sample size and by the lower than anticipated mortality from breast cancer in the control group (2·35 per 1000 *vs* 3·3 per 1000), resulting in a revised power of 60% to detect a 20% mortality reduction, and the CI does not exclude a reduction of 34% or an increase of 4%. The lower than expected mortality in the control group is probably due to improvements in treatment and survival since the initial calculations were made. Around 13% of all deaths in the control group were due to breast cancer and the 3% reduction in all-cause mortality in the intervention group (RR 0·97 95% CI 0·89–1·04) was consistent with a 17% reduction in deaths from breast cancer.

The estimated mortality reduction in women accepting their first invitation was 24%, with those not accepting being at a slightly lower risk than the control arm. A higher mortality from all causes in non-acceptors of screening than in either acceptors or controls has been observed in other screening trials.[24]

The reduction in mortality from breast cancer in the intervention group becomes apparent relatively soon after the start of the trial, consistent with a shorter lead time in this age group than in women aged 50 years and over. Although the effect seems to be reduced slightly with longer follow-up, there is relatively little follow-up beyond 10 years at present. The later screens in the trial took place at 7–8 years from date of entry, and the effect of these screens is unlikely to have emerged yet. Furthermore, the percentage of women who are screened out of the total number randomised to the intervention group (as opposed to the uptake of invitation) falls in later years due to women moving out of the areas included in the trial and therefore no longer being invited for screening. By the fourth screening round the

percentage of all women randomised to the intervention group who were screened had fallen to 58%. In a national screening programme all women would continue to be invited, irrespective of movement around the country, and the effect of intervention would therefore be expected to be greater than reported here.

The observed mortality reduction remains larger than that previously predicted based on surrogate outcome measures, even when the tumour population and follow-up are restricted to make the two analyses as comparable as possible. Morrison[25] has suggested that use of surrogate endpoints could lead to an under estimate of the effect of screening. Improvements in treatment since the time when the prognostic indices were validated might also have increased the potential benefit of earlier diagnosis by screening.

In a number of cancer screening trials, review of case notes is undertaken to improve ascertainment of cause of death. Use of underlying cause of death from the death certificate could potentially cause bias in either direction. Treatment of early cancers by lumpectomy and radiotherapy might increase the likelihood that deaths among screen-detected breast cancers will be misclassified as death from other causes,[26] thus biasing the results in favour of screening. Conversely, because breast cancer is more likely to be diagnosed in the intervention group of a screening trial, deaths in this group are more likely to be attributed to breast cancer, resulting in a bias against screening.[27] However, a previous UK trial of screening for breast cancer, in which verification of cause of death was undertaken, concluded that certified underlying cause of death was an adequate endpoint.[28] That trial found an almost equal number of errors in either direction when verified cause of death was compared with that from the death certificate, with an overall bias of less than 1%. Similar findings have been reported from Sweden.[29]

We have not attempted to adjust for contamination of the control group by private screening, but the evidence we have suggests that the extent of such screening is small.[20] Any such contamination would reduce the observed benefit of screening in the intervention group.

There are a number of possible harmful effects of screening which need to be weighed against any beneficial effects. One potential disadvantage of mammographic screening is the risk of radiation induced breast cancer. In 2001, Law and Faulkner[30] calculated the ratio of detected cancers to those induced, assuming annual two-view mammography before age 50 years. Allowing for the true benefit-to-risk ratio to be lower than the ratio of detected to induced cancers and for some uncertainty in the cancer induction risk factors, they estimated that this ratio would exceed 1, and hence the benefit of screening would probably outweigh the risk for women down to age 40 years for all but 2% of women receiving the higher dose.

In the present trial the use of single-view mammography after the first screen reduced the dose received. The average received dose in the trial based on samples from participating centres was about 7% higher than those for older women in the NHS breast screening programme,[31] probably due to increased breast density; assuming that 5% of screens other than the first are by two views, the number of cancers induced per 1000 women screened between 40 years and 49 years is reduced by a factor of around 0·75, whereas our detection rates are some 30% higher than assumed by Law and Faulkner, thus increasing the benefit-to-risk ratio by a factor of 1·7. The percentage of women for whom the risk might outweigh benefit as estimated by this method will therefore be very small.

Whereas a study has estimated the potential harmful effect of mammographic screening due to radiation exposure to be higher in this age-group than previously estimated,[32] our estimated benefit is higher than that at which their calculations suggested that harm outweighed benefit, which was a mortality reduction of below 10% in women screened annually with two-view mammography.

Other disadvantages include false positive results, which can cause increased anxiety as well as further investigations and could possibly lead to an unnecessary biopsy. In the present trial, the recall rates for assessment varied from 5% at prevalent screen to 3% at later screens. Whereas these figures are lower than those in women aged 50 years and older (and those at subsequent screens would be reduced if two views had been used), the lower cancer detection rate means that the positive predictive value will be substantially reduced. Overall, 5% of first screens and 3% of subsequent screens in the trial resulted in false positive outcomes. 17 030 women in the intervention group accepted all invitations to routine trial screens and have attended at least seven screens. Of these regular attenders, 23% (3913) had at least one false positive result, compared with an estimated 12% of women older than 50 years screened regularly as part of the national programme.[33] Of these 3913, 92% (3616) were not required to undergo cytology or surgical biopsy procedures, 4% (171) required cytology only, 2% (90) required surgical biopsy only, and 1% (36) underwent both cytology and surgical biopsy.

There has been much debate over the extent of overdiagnosis of breast cancer as a result of screening.[34] A report by the Advisory Committee on Breast Screening in England[33] has estimated that one in eight women would not have had their breast cancer diagnosed if they had not gone for screening. The extent of overdiagnosis in the current trial cannot be estimated at this stage because screening in the intervention group has only recently ended and there will still be an excess of breast cancers in this group due to lead time. The cumulative incidence of breast cancer (invasive and in situ) to Dec 31, 2001, was 1·53 and 1·29 per 1000 women years in the intervention and control groups, respectively. Once all women in both groups have been invited for their first screen as part of the national programme, any overdiagnosis due to screening in the trial should be apparent.

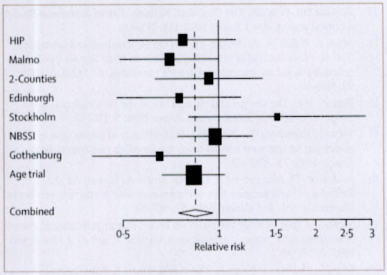

Figure 4: **Breast cancer mortality results of the randomised mammography trials in women younger than 50 years**

The absolute benefit of screening in this age-group in terms of deaths prevented will be lower than that in older women, but the life-years saved per death prevented will tend to be greater. If we assume an average of 35 life-years saved per death prevented and a cost of £37·50 per woman invited, the results of the trial to date suggest a cost per life year saved of £18 838 (95% CI £8620–∞), based on seven invitations per woman. The upper limit of the confidence interval was set to infinity because the absolute observed reduction in breast cancer mortality was not significant at the 5% level. This figure is higher than for other screening interventions, but remains lower than the threshold included in guidance from the National Institute for Health and Clinical Excellence.[35] Additionally, as discussed above, we do not believe that the full effect of screening in the trial has yet emerged, whereas the full costs are included so that this figure may be reduced in the future. The NNS is dependent on follow-up time and will decrease if the size of mortality reduction increases with increased time after the end of fieldwork.

The decision to use only single view mammography after the initial screen was taken partly because of concerns about the effects of radiation in this age-group. We have observed that sensitivity at subsequent screens seems lower than that at initial screens.[20] The NHS breast-screening programme now routinely uses two-view mammography at all screens and this approach has resulted both in improved detection rates and reduced recall rates.[36] Use of two-view mammography in younger women might result in similar benefit, although it would also increase radiation dose. Double reading of films is not policy in the NHS breast-screening programme, but most trial centres used double reading. Use of double reading could be of particular value in women with dense breasts and hence in younger women in whom dense breasts are more common.[37]

Although the reduction in breast cancer mortality observed in this trial is not significant, it is consistent with results of other trials of mammography alone. Table 1 summarises the previous randomised trials and the results for women younger than 50 years. Figure 4 summarises these results and those of a meta-analysis including the current trial. Including all trials, there is an overall 16% reduction in breast cancer mortality (RR 0·84, 95% CI 0·74–0·95). However, all trials except the Age trial have included women up to age 49 years at entry, so that at least some of the benefit is likely to have arisen from screening beyond age 50 years. The overview of the Swedish trials showed a 15% reduction in women aged 40–44 years at entry, the closest age-group to that in our trial, at a median of 14·7 years' follow-up. These are the only published data available we are aware of for this age-group. Combination of this result with that from our study in a meta-analysis also gives an estimated 16% reduction (RR 0·84, 95% CI 0·69–1·01). The greatest reductions in the Swedish trials were observed in Gothenburg, which had an 18 month screening interval, and in Malmo where the interval was 18–24 months. These results together with those of our study therefore lend support to the possibility that mammographic screening with an interval of 12–18 months from age 40 years could reduce breast cancer mortality by 15–17%. The use of two views and re-invitation of all women would probably have increased the efficacy observed in this trial.

For more on **cost of breast cancer screening** see http://www.cancerscreening.nhs.uk/breastscreen/index.html#cost

Further follow-up of this trial will provide more information about the full effect of screening in this age-group. We will analyse mortality at an average of 14 years of follow-up; longer follow-up will be possible but will require censoring of breast cancer diagnoses to exclude the effect of the national screening programme from age 50 years. There is a need for research to identify more accurately, perhaps by modelling, the benefit of commencing screening at different ages below 50 years. Costs, both financial and in terms of false positive examinations, will be higher than with screening after the age of 50 years in view of the fact that the absolute risk reduction will be less in younger women.

The UK national screening programme has only recently completed the extension of invitations to age 70 years. Future decisions on screening policy should consider all possible variables, including screening frequency as well as both ends of the age range. Meanwhile it is important that individual women are provided with full information about both the possible harms and costs of screening.

Contributors

SMM and HC developed the protocol and are principal investigators for the trial and HC chairs the Trial Management Group. AE was responsible for radiological review and is a member of the Trial Management Group. LB is a member of the pathology review panel and represents the panel on the Trial Management Group. MW did the statistical analysis. LJ was responsible for data management and for assistance with the analysis. All authors have participated in planning the analysis and interpretation of the results and have seen and approved the final version.

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Age trial centres
Avon Breast Screening, Aylesbury Breast Screening Service, Breast Test Wales, Cumbria Breast Screening Service, Epping Breast Screening Service, Greater Manchester Breast Screening Service, Hanley Breast Screening, Humberside Breast Screening Service, Newcastle Breast Screening Service, North of London Breast Screening Service, Nottingham Breast Screening, Pennine Breast Screening Programme, Peterborough Breast Imaging, Sheffield Breast Screening, South Derbyshire Breast Screening Service, South East London Breast Screening Service, South East Scotland Breast Screening Programme, Surrey Breast Screening Service, Warrington Breast Screening Service, Welcome Centre Breast Unit, West Sussex Breast Screening Service, Wiltshire Breast Screening Service, Wirral Breast Centre.

Conflict of interest statement
We declare that we have no conflict of interest.

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