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# Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial

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## Summary

**Background** The appropriate age range for breast cancer screening remains a matter of debate. We aimed to estimate the effect of mammographic screening at ages 40–48 years on breast cancer mortality.

**Methods** We did a randomised, controlled trial involving 23 breast screening units across Great Britain. We randomly assigned women aged 39–41 years, using individual randomisation, stratified by general practice, in a 1:2 ratio, to yearly mammographic screening from the year of inclusion in the trial up to and including the calendar year that they reached age 48 years (intervention group), or to standard care of no screening until the invitation to their first National Health Service Breast Screening Programme (NHSBSP) screen at approximately age 50 years (control group). Women in the intervention group were recruited by postal invitation. Women in the control group were unaware of the study. The primary endpoint was mortality from breast cancers (with breast cancer coded as the underlying cause of death) diagnosed during the intervention period, before the participant's first NHSBSP screen. To study the timing of the mortality effect, we analysed the results in different follow-up periods. Women were included in the primary comparison regardless of compliance with randomisation status (intention-to-treat analysis). This Article reports on long-term follow-up analysis. The trial is registered with the ISRCTN registry, ISRCTN24647151.

**Findings** 160 921 women were recruited between Oct 14, 1990, and Sept 24, 1997. 53 883 women (33·5%) were randomly assigned to the intervention group and 106 953 (66·5%) to the control group. Between randomisation and Feb 28, 2017, women were followed up for a median of 22·8 years (IQR 21·8–24·0). We observed a significant reduction in breast cancer mortality at 10 years of follow-up, with 83 breast cancer deaths in the intervention group versus 219 in the control group (relative rate [RR] 0·75 [95% CI 0·58–0·97]; p=0·029). No significant reduction was observed thereafter, with 126 deaths versus 255 deaths occurring after more than 10 years of follow-up (RR 0·98 [0·79–1·22]; p=0·86).

**Interpretation** Yearly mammography before age 50 years, commencing at age 40 or 41 years, was associated with a relative reduction in breast cancer mortality, which was attenuated after 10 years, although the absolute reduction remained constant. Reducing the lower age limit for screening from 50 to 40 years could potentially reduce breast cancer mortality.

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## Introduction

The UK, along with many other countries, has a breast cancer screening programme offering mammography to women aged 50–70 years every 3 years.[1] There remains uncertainty as to the appropriate age at which to start screening, specifically about whether to screen women younger than 50 years.[2] Recommendations from official and charitable bodies vary.[3–5] Mammographic screening in this age group presents a greater challenge than at older ages in both radiological and public health terms. First, the typical composition of the breast is more radiologically dense in younger women, reducing the sensitivity of mammography.[6] Second, breast cancer incidence and mortality are lower in women younger than 50 years than in women aged 50 years and older, so the potential absolute gain from screening is lower.[2] Third, there is evidence that tumours in younger women progress more rapidly, are more likely to be oestrogen receptor negative, and have unfavourable histological grade.[5,7] Thus, there remains interest in the effects, both favourable and unfavourable, of mammography screening in women aged 40–49 years.

Two major UK studies of mammographic screening before 50 years of age are the AgeX trial[8] of extending the screening age range to 47–73 years, and the UK Age trial[9] of yearly screening from the age of 40 years. The AgeX trial is not expected to report results until 2026. The UK Age trial reported 17-year follow-up results in 2015,

## Research in context

### Evidence before this study

We searched PubMed with no date or language restrictions with the search terms "breast" AND "screening" AND "mammography" AND "age" AND "trial". This search yielded eight trials. Results from all the trials (except the UK Age trial) included the effect of screening after participants younger than 50 years at randomisation reached age 50 years. In meta-analyses of these trials, Cochrane and US Preventive Services Task Force reviews found 13–16% reductions in breast cancer mortality with invitation to screening before age 50 years. There is considerable uncertainty about overdiagnosis of breast cancer in this age group, as previous estimates vary widely. Previous publications from the UK Age trial indicated an early relative reduction in breast cancer mortality with the intervention of screening beginning at age 40 or 41 years, and this reduction was attenuated after 10 years. Results on breast cancer incidence indicated little or no overdiagnosis in addition to that which would occur from screening those aged 50 years and older.

### Added value of this study

The results here, with 6 additional years of follow-up since the last publication, confirm the early reduction in breast cancer mortality associated with annual mammographic screening commencing at age 40 or 41 years. The relative rate of breast cancer mortality was not significantly different after 10 years, but the absolute reduction remains roughly constant. Our results confirm the finding of minimal overdiagnosis beyond that which would occur when screening those aged 50 years and older.

### Implications of all the available evidence

Mammographic screening between the ages of 40 and 49 years reduces breast cancer mortality and adds little to the burden of overdiagnosis. There is a need for research to clarify whether substantial progress in both early-detection technology and treatment of breast cancer might modify the reduction in breast cancer mortality observed in randomised controlled trials of screening in the age group of 40–49 years.

showing a reduction in breast cancer mortality with yearly screening from the age of 40 years, which was significant in the first 10 years after randomisation, and was attenuated thereafter.[9] In this paper, we report on breast cancer incidence and mortality results in the UK Age trial after 23 years of follow-up.

## Methods

### Study design and participants

The design of the UK Age trial has been described elsewhere.[10] In brief, women aged 39–41 years were randomly assigned to yearly screening up to and including the calendar year that they reached age 48 years (intervention group), or to usual care, which was no screening until the first National Health Service Breast Screening Programme (NHSBSP) screen at approximately 50 years of age (control group). The trial was conducted in 23 breast screening units in England, Wales, and Scotland. Women were identified from general practitioner (GP) lists, which were then held by Family Health Services Authorities. There were no formal exclusions on the grounds of comorbidities. However, GPs were informed of which of their patients were on the randomisation lists and could remove women whom they considered unsuitable for invitation. Recruitment by centre is shown in the appendix (p 1).

See Online for appendix

Women in the intervention group were invited to participate by post. They received a trial information leaflet with their letter of invitation. Acceptance of the invitation to attend screening was taken to be informed consent to participate in the trial. The women in the uninvited control group were unaware of their inclusion in the trial, which was deemed acceptable because it was analogous to a geographically distinct population that are followed up to monitor cancer and mortality and receive no deviation from the usual care.[9] Ethics approval was obtained from the London Central Research Ethics Committee.

### Randomisation and masking

Women were randomly assigned (1:2) to the intervention group or control group. From April 1, 1992, onwards, randomisation and allocation to trial group were carried out on the Health Authorities computer system using ad hoc software. Randomisation used computerised random number generation and was done by Health Authority personnel independently of the screening centres and without the screening services having previous sight of the randomisation status. Before this, in three centres that started the trial early, when randomisation on the system was not yet available to the trial, random number lists were generated, also from a computerised random number generator, by the trial coordinators and applied to GP practice lists. This randomisation was also done independently of screening services, without their knowledge of randomisation status. It was not feasible to blind the screening services thereafter, because they had to deliver the screening to the intervention group. Individual randomisation was done, stratified by GP practice, so that a third of the women in any practice were allocated to the intervention group, but otherwise randomisation was unrestricted and unblocked. For each general practice, the entire randomisation allocation was performed in a single run.

### Procedures

Screening in the trial was by two-view film (analogue) mammography at the first screen, with single view

thereafter, unless otherwise indicated. Mammograms were double read (both reads done locally). All women in the intervention group were re-invited for screening yearly unless they requested otherwise. Women who moved to areas not covered by the trial were not re-invited for screening as part of the trial, but were able to self-refer to either their previous or their nearest participating screening centre. Screening in three centres ceased prematurely (after four, five, and six rounds of screening) due to the inability of the centres to manage the additional workload.

Women were flagged with the National Health Service (NHS) Central Register, and the trialists have been notified of all breast cancers, breast cancer deaths, and deaths from all other causes, up to Feb 28, 2017. Since 2015, notifications were supplied by NHS Digital. At the age of 50 years, both groups became eligible for invitation to screening every 3 years as part of the NHSBSP, and received their first invitation between age 50 and 52 years. The intervention phase of the trial ceased for each participant when they were invited to their first NHSBSP screen. Cessation in all centres followed this protocol, except for three centres that had to stop screening early because of logistic and capacity issues.

### Outcomes

The primary endpoint was mortality from breast cancers diagnosed in the intervention period of the trial. This was defined as deaths from all breast cancers diagnosed after randomisation, but before first NHSBSP invitation, in both groups. A death was considered to be from breast cancer if it was given as the underlying cause of death on the death certificate. Secondary endpoints were mortality from all breast cancers diagnosed after randomisation until the data cutoff date, all-cause mortality (in the entire trial population and in the subgroup of women with breast cancer), mortality from causes other than breast cancer (in the entire trial population and in the subgroup of women with breast cancer), and incidence of breast cancer.

### Statistical analysis

Originally, the trial had been planned to include 195 000 participants, planning an analysis at 10 years; however, this number was revised in view of slower recruitment and an amended estimate of the likely control group breast cancer mortality rate. Consequently, the trial was designed to have 90% power to detect a 20% reduction in breast cancer mortality in the intervention group at 14 years of follow-up, assuming 30% non-compliance, a control group mortality rate of 0·317 per 1000 person-years of follow-up, and one-sided testing. This trial design would have required 65 000 women in the intervention group and 130 000 in the control group. Because of the capacity issues in the screening units, the Trial Steering and Data Monitoring Committees decided that recruitment should cease at 160 000 participants, which would give 80% power to detect a reduction of 24% in breast cancer mortality in the intervention group at 10 years of follow-up. The Trial Management Group decided that two-sided testing should be used, to reduce the risk of a false-positive trial result. With 160 000 participants (53 000 in the intervention group and 107 000 in the control group) and two-sided testing, there was 88% power to detect a reduction of 26% at 14 years of follow-up with two-sided testing. A p value of less than 0·05 was considered significant.

Mortality data, from breast cancer, other causes, and all causes, were analysed by Poisson regression, for purposes of significance testing between the intervention group and control group, and estimation of relative rates (RR) for the intervention group compared to the control group, and 95% CIs for these rates.[11] Nelson-Aalen estimates of cumulative hazard were also calculated.[12] Incidence data were analysed with the same methods as for mortality data. The primary analysis compared the mortality outcome between the entire intervention group and control group on the principle of intention to treat. We also estimated the per-protocol effect of being screened, adjusted for self-selection bias by the method of Cuzick and colleagues.[13]

In estimating the effect on mortality from cancers diagnosed in the intervention period of the trial, there is a potential bias against the intervention. This bias arises because the intervention group will include mortality from cancers diagnosed at screening that otherwise would have been diagnosed at or after the first NHSBSP screen, and for which the equivalent deaths would therefore not be included in the control group. This bias can be minimised by including cancers diagnosed at a contemporaneous screen at the end of the intervention period in both groups.[14] We therefore did a secondary post-hoc analysis redefining the intervention period cancers as those diagnosed up to and including the first NHSBSP screen in both groups. Thus, this endpoint was mortality from all breast cancers diagnosed after randomisation and either before or at the first NHSBSP screen in both groups. We also analysed mortality from all causes, from causes other than breast cancer, from all cancers (including breast cancer), and from ischaemic heart disease. This included analyses of deaths from all causes, and from all causes except breast cancer, within the women with breast cancer, to determine whether there was bias in cause-of-death ascertainment.

We undertook one further post-hoc analysis, estimating years of life saved from breast cancer in the intervention group, by calculating the years lost to breast cancer up to the final follow-up date of Feb 28, 2017. We then subtracted the average life-years lost in the intervention group from the average life-years lost in the control group. Significance of the difference between groups was calculated by bootstrap methods.[15] We then calculated a test-based 95% CI on the total years of life saved from breast cancer in the intervention group, on the basis of the bootstrap significance test.

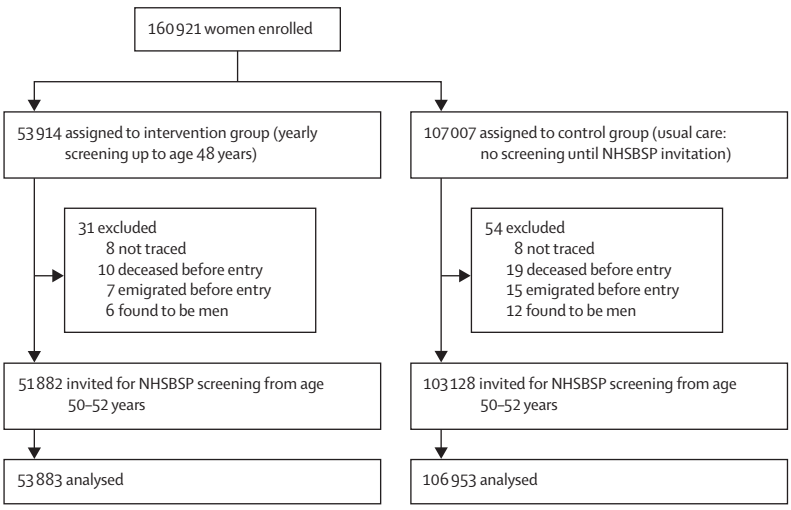


***Figure 1:*** **Trial profile**
NHSBSP=National Health Service Breast Screening Programme. It could not be guaranteed that some of the women diagnosed with breast cancer before age 50 years did not receive an invitation to NHSBSP screening.

| | Intervention group | | Control group | | RR (95% CI) |
|---|---|---|---|---|---|
| | Deaths, n | Follow-up, person-years | Deaths, n | Follow-up, person-years | |
| **Cancers diagnosed in the intervention period, up to immediately before first NHSBSP screen (primary analysis)** | | | | | |
| Total | 209 | 1 201 010 | 474 | 2 385 006 | 0·88 (0·74–1·03) |
| **Observation period** | | | | | |
| <10 years | 83 | 532 729 | 219 | 1 058 236 | 0·75 (0·58–0·97) |
| ≥10 years | 126 | 668 281 | 255 | 1 326 770 | 0·98 (0·79–1·22) |
| **Cancers diagnosed in the period up to and including the first NHSBSP screen (post-hoc analysis)** | | | | | |
| Total | 216 | 1 201 010 | 498 | 2 385 006 | 0·86 (0·73–1·01) |
| **Observation period** | | | | | |
| <10 years | 83 | 532 729 | 219 | 1 058 236 | 0·75 (0·58–0·97) |
| ≥10 years | 133 | 668 281 | 279 | 1 326 770 | 0·95 (0·77–1·17) |

RR=relative rate. NHSBSP=National Health Service Breast Screening Programme.

***Table 1:*** **Mortality from breast cancers by period of cancer diagnosis and follow-up period**

All statistical analyses were done with Stata (version 15.1). The trial protocol is given in the appendix (pp 2–6). This trial is registered with the ISRCTN registry, ISRCTN24647151.

### Role of the funding source

The funders of the trial had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SMM, DV, DP, and SWD had access to raw data. 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

Recruitment took place between Oct 14, 1990, and Sept 24, 1997. 160 921 women were randomly assigned to either the intervention group (n=53 914) or control group (n=107 007; figure 1). After exclusions and losses to tracing, there were 53 883 women (99·9% of those randomly assigned) in the intervention group and 106 953 (99·9%) in the control group included in the analysis. As reported by Johns and colleagues,[16] at first invitation, participation in screening was 36 622 screens (68·1%) following 53 801 invitations in the intervention group and subsequently was 176 746 (69·1%) following 255 618 invitations. There were 2134 (4·9%) false positives of 43 709 results at first intervention screen (not necessarily first invitation) and 7041 (3·2%) of 216 930 at subsequent intervention screens. Of those attending screening during the intervention period, 7893 (18·1%) of 43 709 women had at least one false-positive result.[17] In terms of attrition due to all-cause mortality, emigration, or other loss to follow-up, 150 909 (93·8%) of 160 836 women completed 20-year follow-up, 38 988 (24·2%) completed 24-year follow-up, and 9605 (5·9%) completed 25-year follow-up (with equal relative proportions in the intervention group and control group; data not shown). Participants were followed up for a median of 22·8 years (IQR 21·8–24·0) until the final data cutoff date of Feb 28, 2017.

In the total follow-up period, there were 10 439 deaths, 683 (7%) of which were breast cancer deaths from breast cancers diagnosed during the intervention period. Breast cancer mortality, as of Feb 28, 2017, from breast cancers diagnosed during the intervention period is shown in table 1. The cumulative mortality graphs are given in figure 2A. Mortality by cancer grade is shown in the appendix (p 7). At 10 years of follow-up, breast cancer mortality was significantly lower in the intervention group than in the control group, with 83 deaths in the intervention group versus 219 deaths in the control group (RR 0·75 [95% CI 0·58–0·97]; p=0·029). After more than 10 years of follow-up, no significant difference in breast cancer mortality was observed in the intervention group compared with the control group, with 126 deaths versus 255 deaths occurring in this period (0·98 [0·79–1·22]; p=0·86). Overall, there was no significant reduction in breast cancer mortality in the intervention group compared with the control group, with 209 deaths in the intervention group versus 474 deaths in the control group by the end of follow-up (0·88 [0·74–1·03]; p=0·13).

The per-protocol effect of being screened in the intervention period, adjusted for selection bias, was a significant reduction in breast cancer mortality in the intervention group compared with the control group at 10 years after randomisation (RR 0·66 [95% CI 0·46–0·95]; p=0·025), no significant reduction after more than 10 years of follow-up (0·98 [0·75–1·27]; p=0·89), and no significant reduction overall (0·84 [0·68–1·04]; p=0·11).

Table 1 also shows breast cancer mortality for the secondary post-hoc analysis of cancers diagnosed up to and including the first NHSBSP screen in both groups. At 10 years after randomisation, results were similar to

the primary analysis; there was a significant reduction in mortality in the intervention group, with 83 deaths in the intervention group versus 219 deaths in the control group (RR 0·75 [95% CI 0·58–0·97]; p=0·029). After more than 10 years of follow-up, no significant reduction was observed, with 133 deaths versus 279 deaths (0·95 [0·77–1·17]; p=0·63). Overall, there was no significant difference, with 216 deaths versus 498 deaths (0·86 [0·73–1·01]; p=0·068).

The absolute difference in breast cancer mortality was –0·6 deaths per 1000 women invited for screening (95% CI –1·3 to 0·1). This corresponds to 1667 women needing to be invited and, given the 69% average participation rate, 1150 needing to screen in the age group of 40–49 years to prevent one breast cancer death, or slightly less than one breast cancer death prevented per 1000 screened. This finding was relatively stable over time, as can be seen by the roughly constant distance between the two mortality curves in figure 2A. In a post-hoc analysis, there were 8442·5 (95% CI 7766·2–9118·7) years of life lost to breast cancer in the control group, 78·9 years per thousand women, and 3632·4 (95% CI 3201·1–4063·6) years of life lost to breast cancer in the intervention group, 67·4 years per thousand women. Thus, there were 11·5 (95% CI 1·0–22·0) years saved per thousand women invited (p=0·031), or 620 years of life saved in total.

No significant difference in all-cause mortality was found between the two groups by the end of follow-up, with 3507 deaths in the intervention group versus 6932 deaths in the control group (RR 1·01 [95% CI 0·96–1·05]; p=0·66). Mortality from causes other than breast cancer was also not different between the two groups, with 3169 deaths versus 6189 deaths (1·02 [0·97–1·07]; p=0·43). We also analysed deaths from all cancers (including breast cancer) and from ischaemic heart disease. There was no significant difference between groups in deaths from all cancers, with 1770 deaths versus 3564 deaths (0·99 [0·93–1·05]; p=0·74), or in deaths from ischaemic heart disease, with 230 deaths versus 444 deaths (1·03 [0·87–1·20]; p=0·72).

We also investigated deaths from all causes, and from all causes except breast cancer, within the women with breast cancer, to determine whether treatment of cancers had a differential effect on mortality between the intervention group and control group. There was a significant reduction in death from any cause in women with breast cancer in the intervention group, with 418 deaths in the intervention group versus 928 deaths in the control group (RR 0·87 [95% CI 0·77–0·98]; p=0·024), and no significant reduction in deaths from all causes except breast cancer in the intervention group, with 93 deaths versus 208 deaths (0·86 [95% CI 0·67–1·11]; p=0·24).

The cumulative incidence of breast cancer by trial group is shown in figure 2B, and breast cancer incidence by trial group and by period of follow-up is shown in table 2. For total cancers, up to just before the first NHSBSP screen, there were 953 breast cancers in the intervention group versus 1731 breast cancers in the control group (RR 1·09 [95% CI 1·00–1·19]; p=0·047). Up to and including the first NHSBSP screen, there were 1125 cancers versus 2247 cancers (0·99 [0·93–1·07]; p=0·79). At the end of follow-up, there were 2617 cancers versus 5260 cancers (0·99 [0·94–1·04]; p=0·70). Thus, there was no difference in total breast cancer incidence between the intervention group and the control group, including after NHSBSP screening had commenced. The results show no significant differences between groups with respect to incidence of invasive cancers. More in-situ cancers were reported in the intervention group during the intervention period than in the control group, which

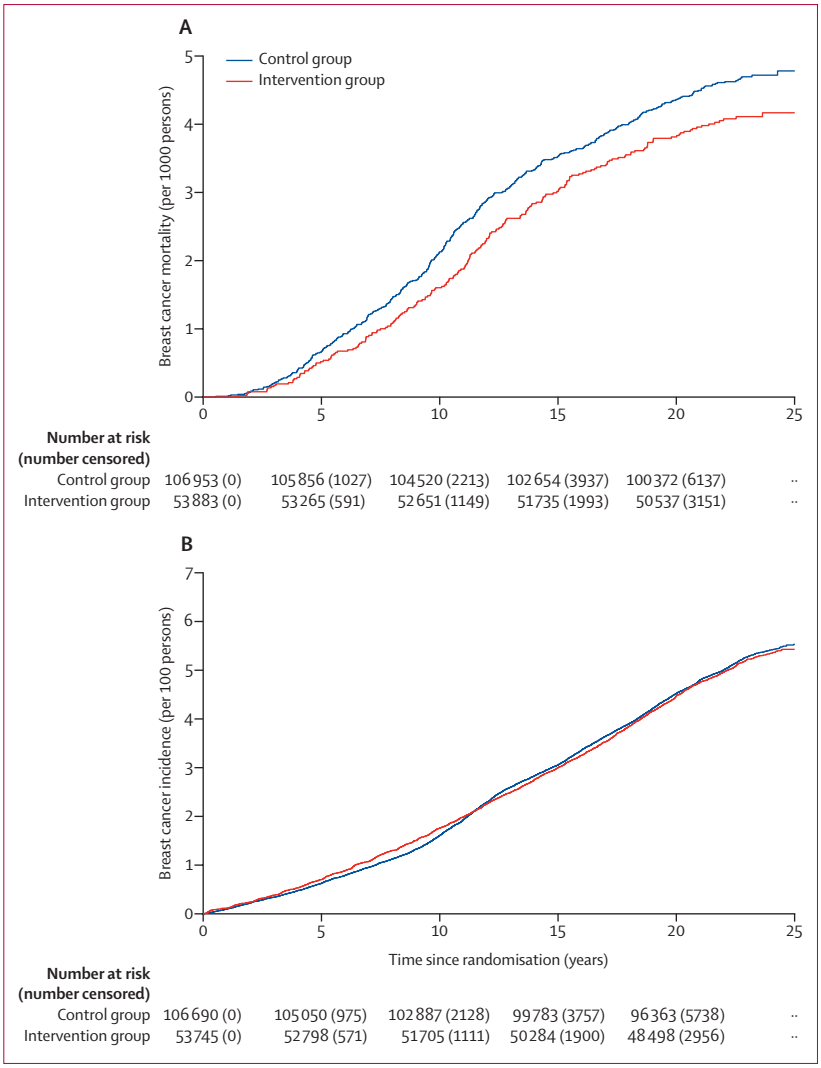


***Figure 2:*** **Breast cancer mortality and incidence**
(A) Cumulative breast cancer mortality from randomisation to end of follow-up, from cancers diagnosed during the intervention period of the trial. (B) Cumulative incidence of breast cancer of any type, from randomisation to end of follow-up. Initial numbers are smaller than the totals analysed for mortality because women with breast cancer before randomisation have been excluded from the analysis of breast cancer incidence.

| | Intervention group | | Control group | | Intervention group *vs* control group, RR (95% CI) |
|---|---|---|---|---|---|
| | Breast cancers, n | Follow-up, person-years | Breast cancers, n | Follow-up, person-years | |
| **Invasive cancers only** | | | | | |
| Intervention period | 835 | 569 632 | 1628 | 1 129 985 | 1·02 (0·94–1·11) |
| Up to and including first NHSBSP screen | 970 | 569 632 | 2021 | 1 129 985 | 0·95 (0·88–1·04) |
| By the end of follow-up | 2288 | 1 177 990 | 4640 | 2 339 852 | 0·98 (0·93–1·03) |
| **In-situ cancers only** | | | | | |
| Intervention period | 118 | 573 221 | 103 | 1 137 432 | 2·27 (1·75–2·95) |
| Up to and including first NHSBSP screen | 155 | 573 221 | 226 | 1 137 432 | 1·36 (1·11–1·67) |
| By the end of follow-up | 329 | 1 195 224 | 620 | 2 375 349 | 1·05 (0·92–1·20) |
| **All cancers** | | | | | |
| Intervention period | 953 | 569 016 | 1731 | 1 129 491 | 1·09 (1·00–1·19) |
| Up to and including first NHSBSP screen | 1125 | 569 016 | 2247 | 1 129 491 | 0·99 (0·93–1·07) |
| By the end of follow-up | 2617 | 1 174 649 | 5260 | 2 334 516 | 0·99 (0·94–1·04) |

Intervention period was defined as the period from randomisation up to immediately before first NHSBSP screen. RRs and 95% CIs are for incidence of breast cancer in intervention group compared with control group. RR=relative rate. NHSBSP=National Health Service Breast Screening Programme.

*Table 2:* **Cumulative incidence of breast cancer by trial group, cancer type, and follow-up period**

was attenuated with no significant difference by the end of follow-up (table 2).

## Discussion

The results of the UK Age trial at 23 years of follow-up mostly confirm those reported after 17 years of follow-up.[9] There was a substantial and significant reduction in breast cancer mortality, of the order of 25%, associated with the invitation to yearly mammography between age 40 and 49 years in the first 10 years. This effect was attenuated thereafter, with little or no effect of the intervention on breast cancer deaths occurring 10 years or more after randomisation. However, the absolute benefit remained roughly constant up to the end of follow-up, with approximately one death prevented per 1000 women screened.

With the 17-year results, we speculated that the absence of an effect after 10 years was due to a lesser effect of the intervention on mortality from grade 3 tumours, whereby some breast cancer deaths were postponed rather than prevented. The updated results here do not confirm this postponement theory, given that the absolute reduction in breast cancer mortality remained approximately constant in the long term. However, the updated data are consistent with the intervention having a lesser effect on mortality from grade 3 cancers. There was a substantial reduction in mortality in the intervention group from grade 1 and 2 breast cancers, but no difference in mortality from grade 3 breast cancers. Similarly, survival with grade 1 and 2 breast cancers in the intervention group was higher than that of the corresponding cancers in the control group, whereas survival from grade 3 breast cancers was the same in both groups.[18] It should be noted that in the Swedish Two-County trial,[19] in women aged 40–74 years (73% of whom were aged 50 years or older), most of the breast cancer mortality reduction was in grade 3 cancers. However, they also found a reduced effect on grade 3 cancers in the age group of 40–49 years.[7]

The significant early effect on breast cancer mortality, which loses significance with long-term follow-up, reflects the fact that the deaths prevented by the intervention were in the first 10 years after randomisation. However, there were no compensatory additional breast cancer deaths after 10 years of follow-up, and so the absolute benefit from the intervention remains the same in the long term. This finding is not unprecedented in cancer screening. The National Lung Screening trial[20] in the USA found that the absolute number of lung cancer deaths prevented by low-dose CT screening remained roughly constant from 6 years to 13 years of follow-up, whereas the relative reduction in lung cancer mortality was attenuated from 20% at 6 years to 14% at 13 years.

Overall, our results are consistent with a meta-analysis of the randomised trials of mammography.[21] However, our trial specifically recruited women at ages 39–41 years, so that all of the trial screening would take place before the age of 50 years. The other trials did not have this design feature.

There was no indication of an effect of the intervention on deaths from causes other than breast cancer, and no effect on all-cause mortality. The latter is to be expected, since the effect on all-cause mortality is overwhelmingly driven by causes of death on which the intervention has no effect.[22] In this trial, breast cancer deaths from cancers diagnosed in the intervention phase comprised only 683 (7%) of all 10 439 deaths. It is also of interest that there was no evidence of an increase in deaths from causes other than breast cancer in women diagnosed with breast cancer in the intervention group. It has been suggested that the observed reduction in breast cancer mortality in this trial and other screening trials could be because of misclassification of cause of death or failure to count

deaths from other causes in women with breast cancer as an indirect effect of the screening (such as heart disease deaths as a result of increased use of radiotherapy).[23] The absence of an increase in risk of death from other causes in women with breast cancer in the intervention group in this study suggests that this concern is unwarranted.

Results with respect to breast cancer incidence suggest at worst modest overdiagnosis in this age group, and that any overdiagnosed cancers would otherwise be diagnosed at NHSBSP screening from age 50 years onwards. Therefore, screening in the age group of 40–49 years does not appear to add to overdiagnosed cases from screening at age 50 years and older. There might have been some overdiagnosis in the intervention group and during the intervention period, which was balanced when the control group received screening in the NHSBSP. However, we cannot directly observe or estimate overdiagnosis in a trial in which the control group also receives screening, albeit later than the intervention group.

There are several limitations to this study, some relating to the period of the intervention. The screening in the intervention period took place throughout the 1990s and early 2000s, during which considerable changes in diagnosis, screening, and therapy took place. The screening method was film screening and was mainly single-view mammography. The average non-participation rate was 31%, and three centres had to cease screening early because of capacity problems.[9,16] These factors suggest that the mortality benefit observed in the trial is conservative. On the one hand, since therapies have changed substantially in recent decades, there might be less scope for screening to reduce mortality in our current era. On the other hand, recent results suggest that even with effective adjuvant systemic therapies, there is still a substantial survival advantage from diagnosis and treatment at an early stage.[24,25]

Our results suggest a reduction in breast cancer mortality with annual mammography in women aged 40–49 years within the first 10 years of follow-up, and no overdiagnosis in addition to that which arises from screening at age 50 years and older. Further evaluation of screening in women younger than 50 years, with modern screening and treatment protocols, is warranted.

#### Contributors

SMM and HC developed the protocol for the trial. HC chaired the trial management group during the conduct of the trial. AE was responsible for radiological review. IOE was responsible for pathology review. DV was responsible for the primary data analyses. SWD, SS, OB, LJ, and JM contributed to statistical analysis. DP and LJ were responsible for study informatics. RAS and PDS contributed oversight of statistical analysis and interpretation of results. SWD produced the first draft of the manuscript. All authors participated in interpretation of the results and have seen and approved the final version of the manuscript.

#### Declaration of interests

SWD reports grants from the National Institute for Health Research, in addition to that for this trial. PDS reports grants from the National Institute for Health Research, during the conduct of the study; and personal fees from GRAIL, outside the submitted work. SMM reports grants from the National Institute for Health Research Technology Assessment, the American Cancer Society, Cancer Research UK, the Department of Health, the Medical Research Council, and the US National Cancer Institute, during the conduct of the study. All other authors declare no competing interests.

#### Data sharing

Individual participant data are held under a data sharing agreement with NHS Digital, and any requests for individual participant data will be forwarded to NHS Digital. All other data may be shared subject to our institute's data sharing policy, available at: https://www.qmul.ac.uk/wolfson/about-us/centres/ccp/data-sharing. Requests should be made to the corresponding author (SWD).

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