Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial

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Summary

Background Age-specific effects of mammographic screening, and the timing of such effects, are a matter of debate. The results of the UK Age trial, which compared the effect of invitation to annual mammographic screening from age 40 years with commencement of screening at age 50 years on breast cancer mortality, have been reported at 10 years of follow-up and showed no significant difference in mortality between the trial groups. Here, we report the results of the UK Age trial after 17 years of follow-up.

Methods Women aged 39–41 from 23 UK NHS Breast Screening Programme units years were randomly assigned by individual randomisation (1:2) to either an intervention group offered annual screening by mammography up to and including the calendar year of their 48th birthday or to a control group receiving usual medical care (invited for screening at age 50 years and every 3 years thereafter). Both groups were stratified by general practice. We compared breast cancer incidence and mortality by time since randomisation. Analyses included all women randomly assigned who could be traced with the National Health Service Central Register and who had not died or emigrated before entry. The primary outcome measures were mortality from breast cancer (defined as deaths with breast cancer coded as the underlying cause of death) and breast cancer incidence, including in-situ, invasive, and total incidence. Because there is an interest in the timing of the mortality effect, we analysed the results in different follow-up periods. This trial is registered, number ISRCTN24647151.

Findings Between Oct 14, 1990, and Sept 25, 1997, 160 921 participants were randomly assigned; 53 883 women in the intervention group and 106 953 assigned to usual medical care were included in this analysis. After a median follow-up of 17 years (IQR 16·8–18·8), the rate ratio (RR) for breast cancer mortality was 0·88 (95% CI 0·74–1·04) from tumours diagnosed during the intervention phase. A significant reduction in breast cancer mortality was noted in the intervention group compared with the control group in the first 10 years after diagnosis (RR 0·75, 0·58–0·97) but not thereafter (RR 1·02, 0·80–1·30) from tumours diagnosed during the intervention phase. The overall breast cancer incidence during 17 year follow-up was similar between the intervention group and the control group (RR 0·98, 0·93–1·04).

Interpretation Our results support an early reduction in mortality from breast cancer with annual mammography screening in women aged 40–49 years. Further data are needed to fully understand long-term effects. Cumulative incidence figures suggest at worst a small amount of overdiagnosis.

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Introduction

Population-based screening for breast cancer by mammography is well established in many countries, although the target age range for invitation varies and the appropriate age range at which to invite women for screening continues to be an area of debate. Although some service screening programmes begin offering screening at age 40 or 45 years,[1] most begin offering it from age 50 years.[1] In England, the lower age limit for invitation is being reduced to 47 years, which means that when this extension is complete, all women will receive their first invitation before the age of 50 years. This change is being made with an experimental design that will allow assessment of its effect in the service screening environment,[2] but the results will not be available for many years.

A recent review[3] by the International Agency for Research on Cancer concluded that there was limited evidence for the efficacy of screening women aged 40–49 years by mammography. However, it has been argued that evidence[4] from randomised controlled trials does not provide a strong basis for determining the effectiveness of mammography in women in their 40s compared with that in older women, and evidence[5,6] from service screening programmes supports a more optimistic view of the benefits of mammography in women aged 40–49 years. Although most US organisations recommend annual mammography for

Research in context

Evidence before this study

Several previous randomised trials of mammographic screening included women aged younger than 50 years. A meta-analysis including these studies done for the US Preventive Services Task Force (USPSTF), published in 2009, identified a relative risk reduction in breast cancer mortality of 15% in women, aged 39–49 at randomisation, invited for screening, similar to that for older women, but a lower absolute reduction and greater number needed to invite. This meta-analysis included the first mortality results of the UK Age trial, and also the results of the Canadian trial (NBSS-1), the only other trial designed to study women younger than 50 years. A Cochrane review published in 2013 identified a 13% reduction in mortality in an analysis of only three of the eight trials included in the USPSTF meta-analysis, and a 16% reduction including all eight trials at 13 years of follow-up. Evidence from some service screening programmes supports a benefit of mammography in women younger than 50 years.

Estimates of overdiagnosis as a result of mammographic screening vary widely, largely because of differences in the methods used. Particularly, failure to allow for adequate follow-up will lead to an overestimate of overdiagnosis because of lead time. As a result, little reliable evidence exists about the extent of overdiagnosis in this age group.

Added value of this study

The UK Age trial is the only trial designed specifically to study the effect of mammographic screening starting at age 40 years. This study reports breast cancer mortality and incidence at a median of 17·7 years of follow-up, an increase of 7 years from the previous publication.

Implications of all the available evidence

The evidence supports a reduction in breast cancer mortality as a result of mammographic screening in women younger than 50 years at least in the first 10 years of follow-up. Further analysis of all the trials might clarify the long-term effects of early screening. No evidence for an increased amount of overdiagnosis in this age group was noted.

women in their 40s, in 2009, the US Preventive Services Task Force (USPSTF) revised its 2002 recommendations that women in their 40s should undergo mammography screening every 1–2 years, and now recommends against routine screening mammography for women in this age group based mainly on what it judged to be an uncertain balance of benefits and harms.[7] Its systematic review[8] noted that although the relative risk reductions in women aged 50–59 years (14%) and 40–49 years (15%) were similar, the absolute risk reduction was greater for women aged 50–59 years than for those aged 40–49 years, leading to a number needed to invite to screening of 1339 compared with 1904 for the younger age group.

See Online for appendix

The USPSTF meta-analysis[7] included the first mortality results from the UK Age trial,[9] which were based on breast cancer mortality at a mean of 10·7 years (SD 1·6) of follow-up and showed a non-significant reduction in women invited to screening (relative risk 0·83, 95% CI 0·66–1·04), with an absolute risk reduction of 0·40 per 1000 women invited, equivalent to a number needed to invite of 2512. The UK Age trial was a randomised screening trial established in 1991 to determine the effectiveness of annual mammographic screening commencing at age 40 years compared with the UK national policy at the time, which was to commence from age 50 years. The UK Age trial is unique in that it included women aged 39–41 years at entry and is the only trial of mammography specifically designed to study the effectiveness of commencing screening at age 40 years. We aimed to assess the effect on breast cancer incidence and breast cancer mortality after long-term follow-up of the UK Age trial.

Methods

Study design and participants

The design of the UK Age trial has been described elsewhere.[10] Briefly, women aged 39–41 years from 23 UK NHS Breast Screening Programme (NHSBSP) units (appendix) were identified from the general practitioners' (GP) lists of patients held in health authority databases. Women in the intervention group received an information leaflet about the trial with their letter of invitation and acceptance of the invitation to attend screening was taken to be informed consent to participate. The uninvited control group were unaware of their inclusion in the trial, which was deemed acceptable because this is no different to a geographically distinct population that are followed up to monitor cancer and mortality and who are receiving the usual standard of care. Ethical approval for this study was obtained from London Central Research Ethics Committee.

Randomisation and masking

Individuals in the UK Age trial were randomly assigned (1:2) to either the intervention group or the control group. From 1992 onwards, randomisation and allocation to trial group were done 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 generated from the health authority. Randomisation was stratified by GP practice.

Procedures

Women in the intervention group were invited for screening by the centres up to and including the calendar year of their 48th birthday, although screening ceased

early in three centres because of insufficient resources. Screening was by two-view mammography at first screen and single view thereafter, unless otherwise indicated.

All screening in the trial was completed by 2006. Women in both groups of the trial became eligible for their first invitation to screening as part of the NHSBSP between the ages of 50 and 52 years, with invitations every 3 years thereafter. Data for screening invitations and attendances were obtained from the individual screening centres, up to and including the first NHSBSP invitation in both groups of the trial. Additionally, data were obtained from all NHSBSP screening units for the first NHSBSP invitations for women in the trial, including data for women who had moved outside the trial areas.

All women in the trial were followed up through the NHS Central Register (NHSCR) to establish breast cancer incidence and mortality, mortality from all causes, and information about emigration.

Outcomes

The primary outcome measures were mortality from breast cancer (defined as deaths with breast cancer coded as the underlying cause of death on the death certificate), and breast cancer incidence, including in situ, invasive, and total incidence.

Statistical analysis

We originally designed the trial to recruit 190 000 women to have 80% power to detect a 20% reduction in breast cancer mortality at 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. The revised power, on the basis of the original estimates of breast cancer mortality in the control group of 3·3 per 1000, was 72%. Later estimates based on a lower expected mortality rate in the control group identified a power of 90% to detect a 20% reduction over 14 years.[10] The present analysis was based on follow-up to Dec 31, 2011.

The primary analysis compared breast cancer incidence and breast cancer mortality between groups using Poisson regression. We calculated p values using the Wald test. We calculated cumulative hazards using the Nelson-Aalen method.[11] The primary analysis was based on an intent-to-treat principle and included all women assigned to randomised groups who could be traced by the NHSCR and who had not died or emigrated before entry. We compared all-cause mortality between groups to check randomisation.

With increasing time after the end of screening in the trial, the reported effect on breast cancer mortality will be diluted by the inclusion of breast cancers diagnosed after the end of screening,[12] including those detected by screening from age 50 years in the NHSBSP. The primary analysis was therefore restricted to breast cancer deaths in women with breast cancer diagnosed during the intervention phase, during which the intervention group was invited to screening and the control group was not, defined as the period up to but not including the date of first NHSBSP invitation. Breast cancer deaths in women with a date of breast cancer diagnosis before their date of entry to the trial were excluded from the analysis.

We did further prespecified analyses by period from randomisation, analyses of breast cancer deaths specific to all periods of diagnosis, and an analysis including all breast cancer deaths irrespective of date of diagnosis. We also did a secondary analysis to estimate the effect of screening in women who accepted their first invitation, which approximates a per-protocol analysis, with the assumption that the underlying breast cancer mortality in acceptors is equivalent to that in the control group adjusted for the rate in the non-acceptors.[13]

Cumulative breast cancer incidence was analysed for all follow-up and for cancers diagnosed up to the date of first NHSBSP invitation. For women who received their first NHSBSP invitation after the age of 52 years, the age of first NHSBSP invitation was indicated as 53 years. For women for whom no date of first NHSBSP invitation was available, we estimated this as the date at which they attained the average age of women at this invitation (51·03 years [SD 0·97]). Analyses were done both excluding and including cancers diagnosed at the first

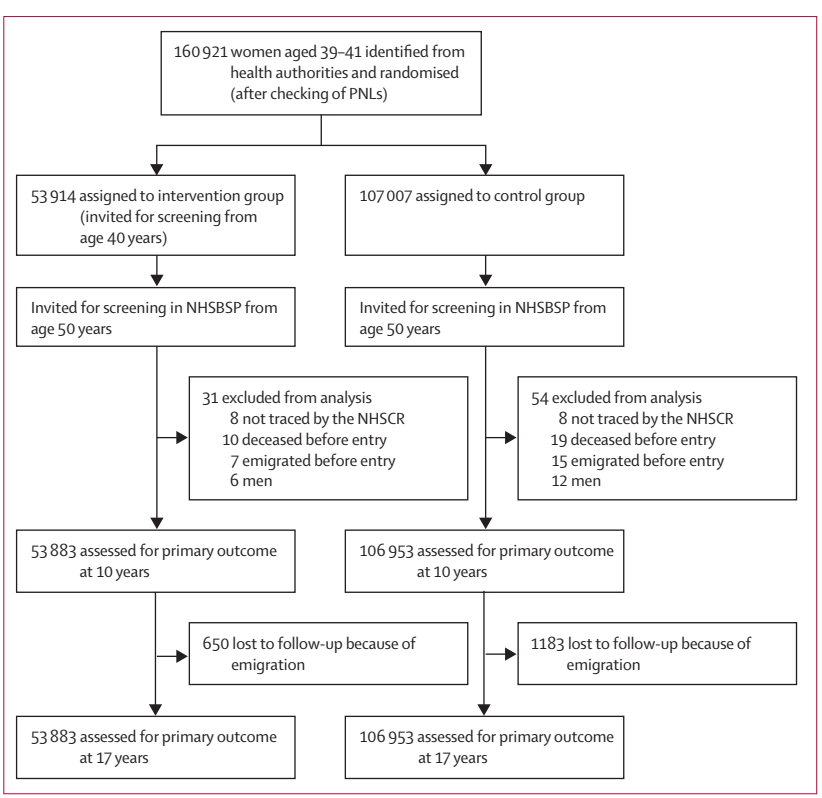


Figure 1: **Trial profile**
PNL=prior notification list. NHSBSP=National Health Service Breast Screening Programme. NHSCR=National Health Service Central Register.

	Number of women	0–10 years after randomisation					More than 10 years after randomisation				
		Women-years*	Breast cancer deaths	Rate per 1000 women-years	Rate ratio (95% CI)	Absolute risk reduction per 1000 women (95% CI)	Women-years†	Breast cancer deaths	Rate per 1000 women-years	Rate ratio (95% CI)	Absolute risk reduction per 1000 women (95% CI)
Intervention	53 883	532 747	83	0·156	0·75 (0·58 to 0·97)	0·51 (0·08 to 0·94)	408 221	99	0·243	1·02 (0·80 to 1·30)	−0·03 (−0·47 to 0·41)
Control	106 953	1 058 322	219	0·207	1·0	..	810 395	193	0·238	1·0	..

*Calculated from date of randomisation to 10 years after randomisation or end of follow-up, whichever was earliest; median follow-up of 10·0 years (IQR 9·9–10·0). †Calculated from 10 years after randomisation to end of follow-up. Median follow-up of 7·7 years (IQR 6·9–8·9).

Table 1: **Mortality from breast cancers diagnosed during the intervention phase by time since randomisation**

	Number of women	Women-years*	All-cause deaths			Breast cancer deaths†			
			n	Rate per 1000 women-years	Rate ratio (95% CI)	n	Rate per 1000 women-years	Rate ratio (95% CI)	Absolute risk reduction per 1000 women (95% CI)
Intervention	53 883	940 969	2127	2·26	0·98 (0·93 to 1·03)	182	0·193	0·88 (0·74 to 1·04)	0·47 (−0·14 to 1·09)
Control	106 953	1 868 717	4320	2·31	..	412	0·220	..	..

Rate ratio and absolute risk reduction are for intervention versus control group.*Calculated from date of randomisation to end of follow-up; median follow-up of 17·7 years (IQR 16·8–18·5). †Restricted to deaths of women with breast cancer diagnosed in the intervention phase.

Table 2: **Mortality from all causes and from breast cancer in the intervention and control groups for a 17 year follow-up**

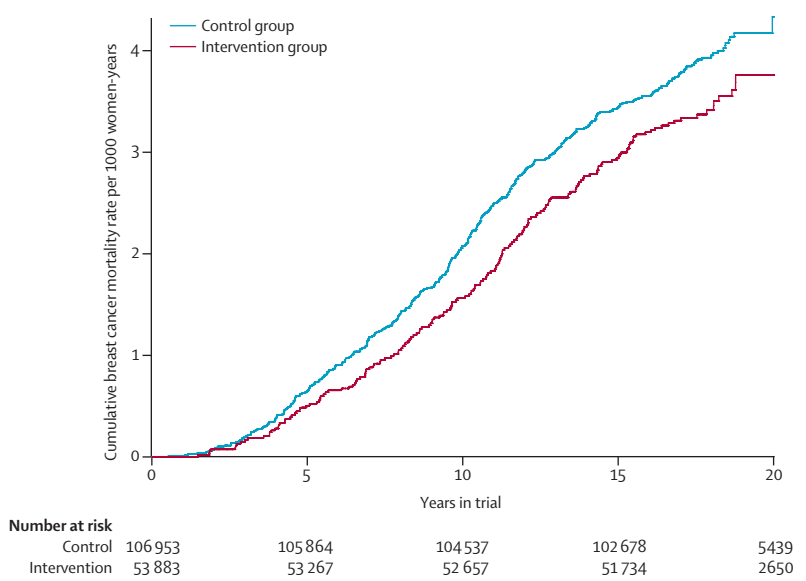


Figure 2: **Nelson-Aalen estimate of cumulative breast cancer mortality (restricted to deaths from breast cancers diagnosed in the intervention phase)**

NHSBSP screen (defined as cancers recorded as screen-detected on the screening centre system, 95% of which occurred within 6 months of the date of screen).

Women-years for analyses of mortality were calculated from date of trial entry to Dec 31, 2011, or to death or loss to follow-up because of emigration, whichever was earliest. Women-years for breast cancer incidence were also censored at date of diagnosis.

All statistical analyses were done with Stata version 12.1. This study is registered, number ISRCTN24647151.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SMM, CW, and SWD had access to raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between Oct 14, 1990, and Sept 24, 1997, 160 921 women were randomly assigned to the intervention and control groups. More than 99·9% of women were successfully identified by the NHSCR; 85 women (31 in the intervention group and 54 in the control group) were excluded from the analysis because they either could not be traced by the NHSCR, they had died or emigrated before entry, or were mistakenly identified men (figure 1). Four women have been identified as having emigrated or died before date of entry since our previous analysis.[9] 1833 women (650 in the intervention group and 1183 in the control group) were lost to follow-up after randomisation because of emigration. 53 883 women in the intervention group and 106 953 in the control group were included in the analysis. The median follow-up was 17·7 years (IQR 16·8–18·8). 3944 (3%) women received their first NHSBSP invitation after the age of 52 years (1245 in the intervention group and 2699 in the control group). For 11 728 (7%) women, no date of first NHSBSP

	Intervention			Control			Rate ratio (95% CI)	Absolute reduction per 1000 women-years (95% CI)	Absolute risk reduction per 1000 women (95% CI)
	Women-years*	n	Rate per 1000 women-years	Women-years	n	Rate per 1000 women-years			
0–4 years	267 864	27	0·10	532 104	69	0·13	0·78 (0·50 to 1·21)	0·03 (−0·02 to 0·08)	0·14 (−0·10 to 0·39)
5–9 years	264 884	56	0·21	526 220	152	0·29	0·73 (0·54 to 0·99)	0·08 (0·006 to 0·15)	0·38 (0·03 to 0·74)
10–14 years	261 163	98	0·38	518 223	185	0·36	1·05 (0·82 to 1·34)	−0·02 (−0·11 to 0·07)	−0·09 (−0·54 to 0·36)
More than 15 years	147 057	61	0·41	292 170	109	0·37	1·11 (0·81 to 1·52)	−0·04 (−0·17 to 0·08)	−0·12 (−0·47 to 0·24)
Total	940 969	242	0·257	1 868 717	515	0·276	0·93 (0·80 to 1·09)	0·02 (−0·02 to 0·06)	0·32 (−0·38 to 1·02)

Rate ratio and absolute risk reduction are for intervention versus control group. *Women-years in each time period from randomisation.

Table 3: **Breast cancer mortality by period in trial**

invitation was available (4115 in the intervention group and 7613 in the control group).

Of the women randomly assigned to the intervention group, 36 622 (68%) of 53 883 were screened at the prevalent screen; the mean number of routine screens attended was 4·8 (SD 3·3). Overall 43 709 (81%) women in the intervention group attended at least one routine screen.[14]

594 breast cancer deaths occurred from 2684 tumours diagnosed during the intervention phase. Table 1 shows the breast cancer mortality by trial group and time period after randomisation. A significant reduction in breast cancer mortality occurred in the first 10 year period (rate ratio [RR] 0·75, 95% CI 0·58–0·97) restricted to deaths in cancers diagnosed in the intervention phase, but not thereafter (RR 1·02, 0·80–1·30).

Table 2 shows the deaths from all causes and from breast cancers in the two trial groups for all follow-up. The RR of all-cause mortality in the intervention group relative to the control group was 0·98 (95% CI 0·93–1·03). When restricted to deaths due to breast cancers diagnosed in the intervention phase, the RR was 0·88 (95% CI 0·74–1·04). The absolute mortality reduction in the intervention group was 0·04 per 1000 women-years or 0·47 per 1000 women, equivalent to a number needed to invite of 2108, or number needed to screen of 1366 (based on the average uptake of 65%[14]). Figure 2 shows cumulative breast cancer mortality for this analysis estimated by the Nelson-Aalen method.

There were 5761 breast cancer diagnoses (invasive and in situ) and 757 breast cancer deaths from cancers diagnosed at any time during follow-up. Table 3 shows the breast cancer mortality irrespective of date of diagnosis by trial group in successive 5 year periods from date of randomisation. During the first 10 years after randomisation (when all but two deaths were from cancers diagnosed in the intervention phase), a significant mortality reduction was noted (RR 0·75 [95% CI 0·58–0·96]), and attenuated with longer follow-up, similar to that seen in table 1.

Including all follow-up, breast cancer mortality per 1000 women-years was 0·257 (242 of 940 969) in the intervention group and 0·276 (515 of 1 868 717) in the control group giving an RR of 0·93 (0·80–1·09). Figure 3 shows a graph of the cumulative breast cancer mortality estimated by the Nelson-Aalen method.

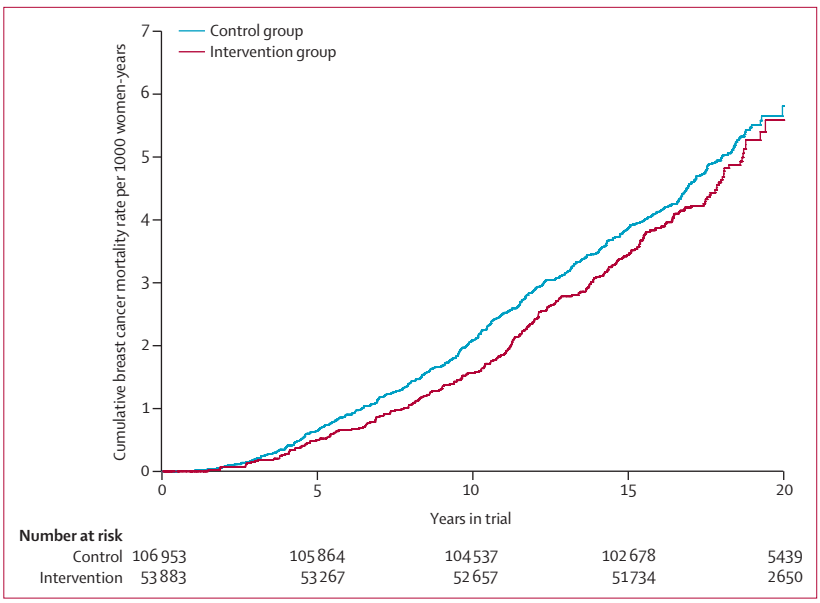


Figure 3: **Nelson-Aalen estimate of cumulative breast cancer mortality (all dates of diagnosis)**

In the first 10 years of follow-up, breast cancer mortality for women attending their first round screen was reduced compared with the control group (RR 0·64 [95% CI 0·45–0·94]). Table 4 shows the comparison of all cause and breast cancer mortality for women in the intervention group who did or did not attend their first invited screen.

Figure 4 shows the RR in the intervention group for breast cancer mortality, restricted to deaths in cases diagnosed within different number of years from randomisation; the RR reaches a minimum of 0·82 (95% CI 0·65–1·02) when restricted to deaths in cases diagnosed in the first 7 years. We also did analyses in which deaths from breast cancer were restricted to those in cases diagnosed within 12, 24, and 36 months of date of last invitation (and before first NHSBSP screen), to allow for varying estimates of lead time. For women in the control

	Number of women	Women-years	All cause deaths		Breast cancer deaths		
			n	Rate per 1000 women-years	n	Rate per 1000 women-years	Rate ratio (95% CI) attenders versus control group*
Breast cancer deaths restricted to cancers diagnosed in the intervention phase							
Attenders for screening	36 540	642 865	1130	1·76	123	0·19	..
Non-attenders for screening	17 343	298 104	997	3·34	59	0·20	0·83 (0·65–1·06)
Breast cancer deaths restricted to cancer diagnosed in the intervention phase, censored at 10 years of follow-up							
Attenders	36 540	362 952	415	1·14	49	0·14	..
Non-attenders	17 343	169 796	424	2·50	34	0·20	0·64 (0·45–0·94)

*Adjusted for rate in those who did not attend screening in the intervention group.

Table 4: **All cause and breast cancer mortality in attenders and non-attenders at first screen in the intervention group**

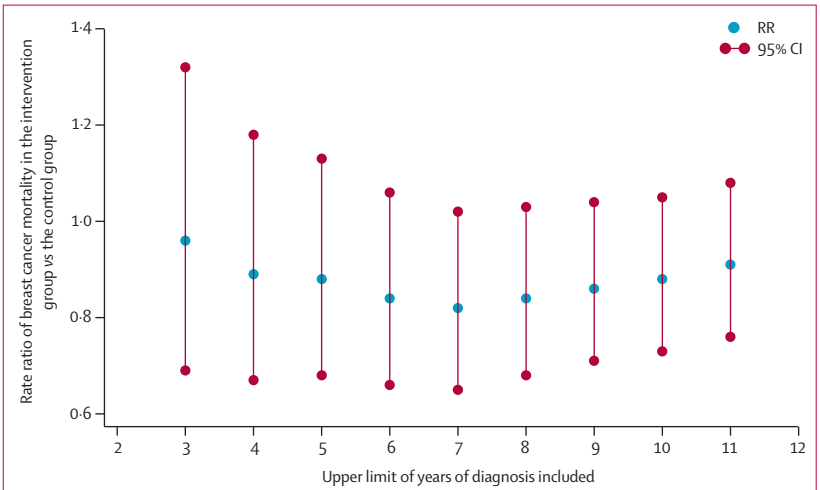


Figure 4: **Rate ratio of breast cancer mortality in the intervention group, according to period of diagnosis of breast cancer**

group, the date used was based on the date of last invitation of the participant in the intervention group closest to the same age within the same screening centre. The RRs for the three analyses were 0·88 (95% CI 0·72–1·08), 0·88 (0·73–1·07), and 0·90 (0·75–1·08).

The cumulative incidence of all breast cancer diagnoses and by subtype are shown in table 5 and figure 5. The absolute differences for in-situ and invasive cancer (table 5) are equivalent to an additional 0·25 in-situ cancers and 0·93 fewer invasive breast cancers per 1000 women invited for screening. For breast cancers diagnosed up to but excluding the first NHSBSP invitation, a significant increase was noted in both in-situ and overall incidence, equivalent to 1·23 and 0·28 additional cancers per 1000 women invited; however, with inclusion of breast cancers diagnosed at the first NHSBSP screen, only the increase in in-situ disease remained significant (table 5).

Of those cancers in the intervention group diagnosed in the intervention phase, 171 (42%) of 406 grade 1 and 2 cancers were screen-detected compared with 76 (23%) of 330 grade 3 cancers.

Discussion

The long-term results from the UK Age trial presented here show a significant reduction in the risk of breast cancer mortality in the intervention group compared with the control group in the first 10 years, followed by no difference between the groups thereafter, when analysis was restricted to breast cancers diagnosed during the intervention phase. The absolute effect of mammographic screening in this age group is difficult to assess when we include deaths from cancers diagnosed after the intervention phase of the trial, when both groups are receiving the same care, and at ages older than 50 years, when underlying incidence and mortality are substantially increased.

The overall RR was 0·88 (95% CI 0·74–1·04) during a median of 17 years of follow-up and was not significant. Previous results of this trial showed a non-significant RR of 0·83 (0·66–1·04) for breast cancer mortality in the intervention group compared with the control group at a mean of 10·7 years (SD 1·6) of follow-up.[9]

The reported difference in breast cancer mortality peaked when the analysis was restricted to breast cancers diagnosed up to 7 years of follow-up, despite the fact that at this point in time, there was an excess of breast cancer incidence in the intervention group, which would tend to introduce a bias against screening as some of this excess will be due to the effect of lead time—ie, the analysis includes deaths from cancers in the intervention group whose equivalent in the control group are excluded because they will be diagnosed after the 7 year period. The dilution of effect seen in figure 4 as breast cancers diagnosed beyond year 7 or 8 are included represents the fact that the two groups have essentially the same screening regimen from this point in time.

The difference between the long-term effect restricted to deaths from cancers diagnosed in the intervention phase and that reported in table 3 including all cancers irrespective of period of diagnosis shows how a reduction in mortality with screening can be obscured by the inclusion of deaths from cancers diagnosed outside the screening period. This observation further casts doubt on some negative results of analyses of published mortality rates that include deaths from cancers diagnosed outside the screening period—ie, cancers that could not have been affected by the intervention.[15,16]

In women who attended screening in response to the first invitation compared to the control group, the rate ratio for breast cancer mortality was 0·83 (95% CI 0·65–1·06) overall when restricted to cancers diagnosed in the intervention phase. Previous estimates of the extent of screening in the control group suggest that screening was limited, with only 4% of a sample of 2000 women

	Intervention group		Control group		Rate ratio (95% CI)	Absolute difference per 1000 women-years (95% CI)	Absolute difference per 1000 women (95% CI)
	n	Rate per 1000 women-years	n	Rate per 1000 women-years			
Breast cancer incidence to Dec 31, 2011 (end of follow-up)							
In-situ	252	0·27	473	0·26	1·06 (0·91 to 1·23)	0·02 (−0·03 to 0·06)	0·25 (−0·45 to 0·95)
Invasive	1654	1·78	3382	1·84	0·97 (0·92 to 1·03)	−0·05 (−0·16 to 0·05)	−0·93 (−2·72 to 0·87)
Total cancers (women-years)*	1906 (927 249)	2·06	3855 (1 842 857)	2·09	0·98 (0·93 to 1·04)	−0·04 (−0·15 to 0·08)	−0·67 (−2·59 to 1·25)
Breast cancer incidence to date of first NHSBSP screen, excluding cancers diagnosed at first NHSBSP screen							
In-situ	118	0·21	103	0·09	2·27 (1·75 to 2·96)	0·12 (0·07 to 0·16)	1·23 (0·79 to 1·66)
Invasive	835	1·47	1628	1·44	1·02 (0·94 to 1·11)	0·03 (−0·10 to 0·15)	0·28 (−1·00 to 1·55)
Total (women-years)†	953 (569 016)	1·67	1731 (1 129 491)	1·53	1·09 (1·01 to 1·18)	0·14 (0·01 to 0·27)	1·50 (0·16 to 2·85)
Including cancers diagnosed at first NHSBSP screen							
In-situ	155	0·27	226	0·20	1·36 (1·11 to 1·67)	0·07 (0·02 to 0·12)	0·76 (0·23 to 1·29)
Invasive	970	1·70	2021	1·79	0·95 (0·88 to 1·03)	−0·08 (−0·22 to 0·05)	−0·89 (−2·28 to 0·50)
Total (women-years)†	1125 (569 016)	1·98	2247 (1 129 491)	1·99	0·99 (0·93 to 1·07)	−0·01 (−0·15 to 0·13)	−0·13 (−1·62 to 1·35)

Rate ratio and absolute risk reduction are for intervention versus control group. NHSBSP=NHS Breast Screening Programme. *Calculated to end of follow-up, censored at date of diagnosis of breast cancer; median follow-up 17·6 years (IQR 16·6–18·8). †Calculated to date of first NHSBSP screen or end of follow-up if earlier, censored at date of diagnosis of breast cancer; median follow-up of 10·6 years (IQR 9·8–11·4).

Table 5: **Breast cancer incidence for all follow-up and to date of first NHSBSP screen**

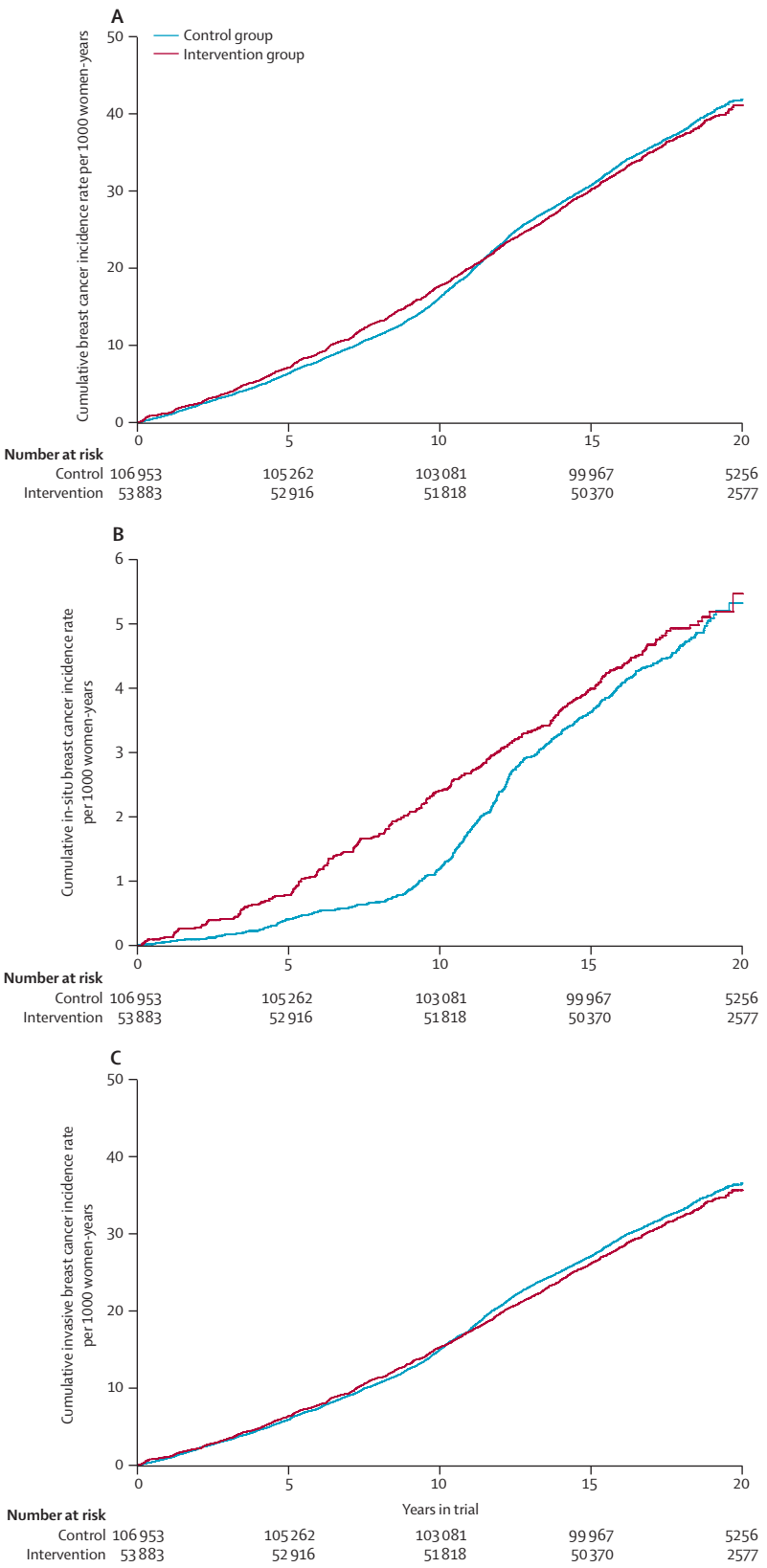
reporting a mammogram other than for symptomatic reasons within the previous 3 years. Such contamination is therefore likely to have had little effect on the outcome of this trial. Although according to the trial protocol, women in the intervention group were invited for screening up to and including the calendar year of their 48th birthday, women who moved to an area not covered by the trial would no longer have been invited for screening. Additionally, three of the 23 centres ceased screening in the trial prematurely because of insufficient resources to maintain the extra workload. As a result, by the seventh screening round less than 55% of women in the intervention group were actually screened.[14] The reported effect at later follow-up will therefore be less than would be observed with population screening.

To explore this further, we did analyses in which deaths from breast cancer were restricted to those in cases diagnosed within 12, 24, and 36 months of date of last invitation to allow for varying estimates of lead time. The RRs ranged from 0·88 (95% CI 0·72–1·08) to 0·90 (0·75–1·08). However, even at 36 months after last invitation, a 15% excess of cancers in the intervention group occurred, which would result in some dilution of the effect of screening.

The NHSBSP now routinely uses two-view mammography at all screens, which has resulted in improved detection, and lower recall, together with a lower incidence of interval cancers.[17,18] The improved detection rates apply particularly to ductal carcinoma in situ and invasive cancers of size less than 15 mm. Use of two-view mammography in younger women would be likely to result in a similar benefit. Thus if the UK Age trial were done now, the intervention might have a greater effect because of the improved detection of ductal carcinoma in situ and small invasive tumours.

An increased threshold for recall and biopsy of microcalcifications might have contributed to a lower detection of ductal carcinoma in situ than in present screening programmes, in which the detection of ductal carcinoma in situ is generally around three times that reported in this trial. A review[19] of interval cancers occurring in the trial noted that granular microcalcification was the most common feature on the screening mammograms of false-negative interval cancers. An increased detection of ductal carcinoma in situ in this trial might have led to a greater mortality reduction, and those cases of ductal carcinoma in situ leading to death would be more likely to cause death in the long term.

We estimated a number needed to screen of around 1400 women to prevent one death during 10 years. This contrasts with a number needed to invite of 1904 (sometimes incorrectly interpreted as number needed to screen) estimated by the USPSTF.[7] These results raise the question of why the mortality advantage in the intervention group is reduced after 10 years from entry, even when restricted to cancers diagnosed in the intervention phase of the trial. In an analysis of deaths of participants diagnosed in the intervention phase stratified by histological grade, the intervention group shows lower case fatality in women with grade 1 and 2 cancers in the periods both before and after 10 years from entry, suggesting that the intervention is achieving sufficiently early detection of these tumours to affect long-term prognosis and probably achieving complete cure in a large proportion of these. In women with grade 3 cancers, the intervention only confers lower case fatality in the first 10 years, suggesting that in most of the patients with these tumours, the early detection is postponing rather than completely preventing breast cancer death. This notion is consistent with the fact that in the intervention group, 42% of grade 1 and 2 cancers



diagnosed in the intervention phase were screen-detected compared with 23% of grade 3 tumours.

We did not collect treatment data for women diagnosed with breast cancer in either group of the trial because these data were not routinely available; however, any imbalance in treatment between groups would be more likely to have an effect on long-term follow-up, rather than short-term outcomes that are more dependent on stage at diagnosis.[20]

In women with grade 3 tumours, prolonging life, even if eventual death is from breast cancer, is a worthwhile achievement. With present screening, enhancement of our ability to prolong life in such cases should be possible. The sensitivity of screening in the national programme has substantially improved since the time of the screening in this trial, with detection rates rising from four to six per 1000 in the 1990s to seven to eight per 1000 today.[21] This improvement in detection is likely to be because of the use of two views at each screen (unlike in this study) and greater use of double reading. Also, digital mammography is now in general use, which will confer substantially improved screening sensitivity in this age group who have higher mammographic density than older women.[22,23]

Our results differ substantially from those of the Canadian National Breast Screening Study (NBSS-1), which saw no reduction in breast cancer mortality in the mammography group.[24] However, participants in the NBSS-1 trial were aged 40–49 years at entry, and received an initial breast physical examination and instruction on breast self-examination before randomisation. Whether cancers detected at this initial screen are included or excluded, the potential to show an effect of initiation of mammography screening at a younger age will be diluted. This trial was volunteer-based rather than population-based and reservations have been expressed about adherence to its design, specifically the unexpectedly high rate of palpable, advanced breast cancers in the invited group in the first round of screening;[25,26] the authors have responded to these criticisms, for example, by doing analyses excluding cancers diagnosed at the prevalent screen,[24,27] which still showed no significant mortality reduction. Results of the Swedish trials (in Ostergotland, Malmo, and Gothenburg) restricted to women aged 40–44 years at randomisation have shown a 15% reduction in breast cancer mortality at an average follow-up of 14·7 years.[28] This long-term follow-up of the Swedish trials concluded that, generally, the absolute effect increased up to 12 years after randomisation, after which it was maintained.

An analysis of service screening in Sweden comparing women invited to screening at ages 40–49 years from 1986 to 2005 with those not invited identified an estimated reduction in breast cancer mortality of 26% at an average follow-up of 16 years.[5] In this analysis, done

Figure 5: **Cumulative incidence of in-situ and invasive breast cancer (A), in-situ breast cancer alone (B), or invasive breast cancer alone (C)**

on the basis of refined mortality in cancers diagnosed at 40–49 years, the cumulative mortality from breast cancer continued to diverge between the groups up to 15 years of follow-up. However, a major difference from our trial is that some women in this study would have been close to age 50 years at first invitation. In other trials, some evidence exists for an effect on mortality after 10 years in women aged 40–49 years at randomisation, although again this finding is complicated by the fact that these analyses will include cancers diagnosed after age 50 years.[29,30] In our study, all women will have received their last invitation before reaching age 50 years, thus avoiding this issue. We understand that an overview of the mammography trials is underway under the aegis of the Early Breast Cancer Trialists Collaborative Group. The collective data for epoch of and age at diagnosis might resolve this, by providing greater numbers of participants for long-term follow-up restricted to similar age ranges to ours.

Correct estimates of overdiagnosis need sufficient follow-up to allow time for the compensatory drop after the end of invitation to screening.[31] In our trial, estimates of overdiagnosis will be affected by the fact that women in the control group were invited to screening in the NHSBP starting at ages 50–52 years. Nevertheless, the long-term incidence of all breast cancers, including those diagnosed after entry to the NHSBSP, is slightly lower in the intervention group. Thus, our results provide no evidence that screening in the trial resulted in any overdiagnosis in addition to any occurring as a result of NHSBSP screening, which cannot be assessed because of lead time. The absence of a marked excess of invasive cancers in the intervention group at the start of the trial represents the shorter lead time at younger ages, which has also been reported by others.[29] At the time of completion of the first NHSBSP screen, a significant excess of in situ disease in the intervention group was noted, balanced by a reduction in invasive disease, which was non-significant. The overall excess of breast cancer in the intervention group before the first NHSBSP screen of 0·14 per 1000 women-years is as compatible with a small lead time effect as it is with overdiagnosis. No excess incidence was reported in the intervention group at final follow-up, which is qualified by the fact that both study and control groups will have been offered screening in the NHSBSP at this time. However, because the intervention group, with 260 638 more screening episodes than the control group, showed no excess incidence after entry to the NHSBSP, it suggests that overdiagnosis is at worst a very minor occurrence. Figure 5 shows that during the intervention phase when only the intervention group was being screened, the difference in incidence was small, and even a potential short lead time would rule out substantial overdiagnosis.

Overall, these results support an early reduction in mortality from breast cancer with annual mammography screening in women aged 40–49 years. Synthesis of results from all the trials, and further data from modern service screening might clarify long-term effects. Cumulative incidence figures suggest at worst a small amount of overdiagnosis.

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. CW, SMM, and SWD analysed the data. SMM, SWD, and RS drafted the report. All authors have participated in interpretation of the results and have seen and approved the final version.

Declaration of interests

SMM received funding from the National Institute for Health Research Health Technology Assessment, American Cancer Society, Cancer Research UK, Department of Health, Medical Research Council, and the US National Cancer Institute, during the conduct of the study. All other authors declare no competing interests.

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