Annual mammographic screening to reduce breast cancer mortality in women from age 40 years: long-term follow-up of the UK Age RCT

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Scientific summary

Long-term follow-up of the UK Age RCT

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Background

The effect of mammographic screening on breast cancer mortality in women aged < 50 years has been a matter for discussion for several decades. A lesser effect of screening on breast cancer mortality has been observed for women aged < 50 years in randomised controlled trials, partly because this age group has more radiologically dense breast tissue than those aged ≥ 50 years, and possibly also because of the more rapid progression of cancers diagnosed in younger women.

There is continuing disagreement and uncertainty on the magnitude of the major desirable effect of screening in this age group, the reduction in breast cancer mortality and on some major adverse effects, notably overdiagnosis of breast cancer. In this context, overdiagnosis is the diagnosis of breast cancer as a result of screening that would not have occurred in the person's lifetime if they had not been screened.

Objectives

The primary objective was to determine the effect of annual mammographic screening on breast cancer mortality for those aged 40–49 years. We also aimed to estimate the effect on other-cause and all-cause mortality, and the effect on breast cancer incidence, to assess the implications for overdiagnosis of breast cancer.

Methods

A total of 160,921 women were randomised in a 1 : 2 ratio to the intervention group or the control group. After exclusions, the trial included 160,836 women who had data available for analysis. Recruitment took place between October 1990 and September 1997. Individual randomisation was performed, stratified by general practice so that one-third of the women in any practice were allocated to the intervention group. Women were aged 39–41 years at time of entry to the trial. The trial was conducted in 23 NHS Breast Screening Programme units in England, Wales and Scotland. Women in the intervention group were sent a letter of invitation and an information leaflet that clearly stated that the woman was being asked to participate in a research trial, and that her acceptance of the invitation was taken to be her informed consent to participate. Women in the intervention group were invited for annual mammography screening until the calendar year of their 48th birthday. At 50 years, both they and the women in the control group became eligible for 3-yearly invitation to screening as part of the NHS Breast Screening Programme, and received their first invitation between the ages of 50 and 52 years.

Screening in the trial was by two-view mammography at the first screen, with single-view mammography thereafter unless otherwise indicated. Mammograms were double-read. All women, including non-attenders, were reinvited annually unless they requested otherwise. Women who moved to areas that were not covered by the trial were not reinvited 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) because of the inability of the centres to manage the additional workload with the available resources.

Women were flagged for follow-up by the NHS Central Register (a responsibility now belonging to the Office for National Statistics with data collation by NHS Digital), and the triallists were notified of all breast cancers, breast cancer deaths and deaths from all other causes up to 28 February 2017.

Mortality data from breast cancers, other causes and all causes were analysed by Poisson regression for significance testing between the intervention and the control groups, and for the estimation of relative rates and confidence intervals on these. In addition, we calculated Nelson–Aalen estimates of cumulative hazard.

The primary end point was mortality from breast cancers diagnosed in the intervention phase of the trial, before the first National Programme invitation. In estimating the effect on mortality from cancers diagnosed in the intervention period of the trial, there is a potential bias against the intervention because the intervention group will include deaths from cancers diagnosed at screening whose time of diagnosis would have been at or after the first NHS Programme invitation, and which 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. We therefore performed a secondary analysis redefining the intervention period cancers as those diagnosed up to and including the first NHS Programme screen in both groups.

We compared incidence between the intervention and control groups before the first National Programme screen, up to and including the first National Programme screen and up to the final follow-up at 28 February 2017. We also derived tentative estimates of overdiagnosis using Markov process models.

Results

At 10 years, there was a statistically significant 25% reduction in mortality (relative rate 0.75, 95% confidence interval 0.58 to 0.97; $p = 0.03$). For ≥ 10 years, there was no reduction observed (relative rate 0.98, 95% confidence interval 0.79 to 1.22; $p = 0.9$). Overall, there was a 12% reduction in breast cancer mortality, which was not statistically significant (relative rate 0.88, 95% confidence interval 0.74 to 1.03; $p = 0.1$).

For the corresponding breast cancer mortality figures for the secondary analysis of cancers diagnosed up to and including the first NHS Programme screen in both groups, the 10-year results were identical to the primary analysis: a statistically significant 25% reduction in mortality (relative rate 0.75, 95% confidence interval 0.58 to 0.97; $p = 0.03$). For ≥ 10 years, a small, statistically non-significant reduction was observed (relative rate 0.95, 95% confidence interval 0.77 to 1.17; $p = 0.6$). At complete follow-up, there was a 14% reduction in breast cancer mortality that was of borderline statistical significance (relative rate 0.86, 95% confidence interval 0.73 to 1.01; $p = 0.07$).

After adjustment for selection bias, the effect of actually being screened was estimated as a statistically significant 34% reduction in breast cancer mortality up to 10 years after randomisation (relative rate 0.66, 95% confidence interval 0.46 to 0.95; $p = 0.02$), a statistically non-significant 2% reduction after 10 years (relative rate 0.98, 95% confidence interval 0.75 to 1.27; $p = 0.9$) and a statistically non-significant 16% reduction overall (relative rate 0.84, 95% confidence interval 0.68 to 1.04; $p = 0.1$).

There was no difference between intervention and control groups in mortality from other causes than breast cancer (relative rate 1.02, 95% confidence interval 0.97 to 1.07; $p = 0.4$) or from all-cause mortality (relative rate 1.01, 95% confidence interval 0.96 to 1.05; $p = 0.8$).

There was an excess of cancers (total invasive and in situ) up to the time of the first National Programme screen, which was not present thereafter. Tentative formal estimation of overdiagnosis

suggested that 80 breast cancers were overdiagnosed in the intervention phase of the trial, 8.5% of cancers diagnosed in this period in the intervention group, and an absolute rate of 0.2% over eight annual screens. However, the equalisation of incidence at the time of the first National Programme screen indicates that these would have been diagnosed by screening after the age of 50 years in any case.

Conclusions

Annual mammographic screening at 40–49 years conferred a reduction in breast cancer mortality. The relative reduction is attenuated after 10 years, possibly because of a lesser effect of screening in some aggressive grade 3 tumours in this age group. There was no evidence of overdiagnosis in addition to that which already results from the National Programme carried out at later ages. These results pertain to the epoch before digital mammography and universal two-view imaging, so the effectiveness nowadays may be greater than that observed here.

Trial registration

This trial is registered as ISRCTN24647151.

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