

## False-Positive Results in the Randomized Controlled Trial of Mammographic Screening from Age 40 (“Age” Trial)

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### Abstract

**Background:** False-positive recall is a recognized disadvantage of mammographic breast screening, and the rate of such recalls may be higher in younger women, potentially limiting the value of screening below age 50.

**Methods:** Attendance and screening outcome data for 53,884 women in the intervention arm of the U.K. Age trial were analyzed to report observed false-positive recall rates during 13 years of trial fieldwork. The Age trial was a randomized controlled trial of the effect of mammographic screening from age 40 on breast cancer mortality, conducted in 23 National Health Service screening centers between 1991 and 2004. Women randomized to the intervention arm were offered annual invitation to mammography from age 40 or 41 to age 48.

**Results:** Overall, 7,893 women (14.6% of women the intervention arm and 18.1% of women attending at least one routine screen) experienced one or more false-positive screen during the trial. The rates of false-positive mammography at first and subsequent routine screens were 4.9% and 3.2%, respectively. The cumulative false-positive rate over seven screens was 20.5%. Eighty-nine percent of women who had a false-positive recall at their previous screen attended their next invitation to routine screening.

**Conclusions:** The rates of false-positive recall in the Age trial were comparable with the national screening program; however, the positive predictive value of referral was lower. Experiencing a false-positive screen did not seem to lessen the likelihood of re-attendance in the trial.

**Impact:** The question of greatly increased false-positive rates in this age group and of their compromising re-attendance is refuted by the findings of this study. *Cancer Epidemiol Biomarkers Prev*; 19(11); 2758–64. ©2010 AACR.

### Introduction

The effectiveness of mammographic screening in reducing mortality from breast cancer in women ages 50 to 69 is widely accepted (1). However, debate continues about the risks and benefits of mammography, especially for women in their forties. Disadvantages of screening, which need to be weighed against any benefit, include false-positive results—the recall of women for further investigations that do not result in a diagnosis of breast cancer. False-positive recall can result in inconvenience, increased anxiety, particularly in the

short-term, and will usually lead to further investigations, involving biopsy in some instances. Collectively, these contribute significantly to the overall cost of screening programs.

False-positive rates of screening mammography tend to decrease with age, but reported rates vary widely, ranging from 0.9% to 6.5% in published randomized trials, case-control studies, and demonstration studies of annual mammography in women ages 40 to 64 (2). European organized breast screening programs tend to have relatively low false-positive rates, whereas U.S. rates are higher. The U.K. breast screening program recorded false-positive rates of 7.9% and 3.2% at first and subsequent routine screens, respectively, between 1999 and 2005 (3). In contrast, the Netherlands breast screening program reported false-positive rates of only 2% at both initial and subsequent screens for women ages 50 to 69 between 1990 and 1995 (4).

Importantly, false-positive results may discourage women from re-attending for screening. This seems to vary considerably between countries. In the United States, women were more likely to return for screening after a false-positive result, whereas in Canada, they were less likely to re-attend, and in Europe, no significant

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effect of false-positive screens on re-attendance was seen (5). Many studies have sought to address the psychological consequences of false-positive mammograms and, although some have suggested lasting effects, most found that anxiety returns to previous levels once the outcome is known (6).

The U.K. Age trial was the only trial designed specifically to investigate the effect of annual invitation to mammography starting at age 40. It has recently been announced that the U.K. National Health Service Breast Screening Programme (NHSBSP) will lower the minimum invitation age for its 3-yearly screening from 50 to 47 by 2012. Information from the U.K. Age trial, which invited women up to age 48, has therefore assumed increased relevance for the NHSBSP. In 2006, we reported mortality results from the U.K. Age trial after 10 years of follow-up (7). The present article reports information on false-positive recalls at routine mammographic screening among women in the intervention arm of the Age trial during 13 years of fieldwork between 1991 and 2004.

## Materials and Methods

### The trial

The Age trial was conducted in 23 NHS breast screening units in England, Wales, and Scotland. The design of the study has been previously described in detail (8). Briefly, between 1991 and 1997, 160,921 women ages 39 to 41 years were randomized to an intervention arm and a control arm at a ratio of 1:2. The intervention arm provided information on 53,884 women for this analysis. Women in the intervention arm were offered annual screening by mammography up to and including the calendar year of their 48th birthday, whereas those in the control arm received standard medical care. All women in the intervention arm, including previous nonresponders, were re-invited annually unless they specifically requested not to be invited again.

The analysis included trial screening occurring between date of entry to the trial and December 31, 2004. All screening in the trial had been completed by this date.

### Screening and breast cancer incidence data

Individual-level data on screening invitation, attendance, and procedures performed and their outcomes were downloaded from the National Breast Screening Computer System at participating screening units using an extraction software written specifically for the trial. In this analysis, "ever attenders" are defined as women who attended at least one routine screen, and "regular attenders" are those who attended seven or more routine trial screens.

Data on breast cancer diagnoses in the trial population were obtained from cancer registries, pathology laborato-

ries, breast screening units, and the Office for National Statistics.

### False-positive screens

True-positive screening episodes were those where initial mammographic findings led to recall for further procedures and breast cancer (*in situ* or invasive) was found. False-positive screens were defined as routine trial screens where initial mammographic findings led to recall for additional procedures, but further assessment did not result in a diagnosis of breast cancer at that episode. Recalls on the basis of technically inadequate films were not included as positive mammographic results.

### Cumulative false-positive recall rate

The cumulative false-positive recall rate over seven screens was calculated for a subgroup of women who attended at least seven routine screens during the trial (i.e., regular attenders). The number of women in this group who experienced at least one false-positive recall in their first seven screens was expressed as a proportion of the total number of women in the group. False-positive rates in the regular attenders were extrapolated to estimate a cumulative false-positive rate over 10 screens. The additional number of women who would be expected to have a false-positive result was derived for rounds 8 to 10 from the average number of regular attenders who experienced their first false-positive result at screens 4 to 7.

The cumulative independent risk over seven screens was defined by:

$$1 - \text{probability of never having a false-positive recall over seven screens} = 1 - [(1 - p(\text{FPS1})) \times (1 - p(\text{FPSS}))^6]$$

where  $p(\text{FPS1})$  is the probability of false-positive recall at the first screen and  $p(\text{FPSS})$  is the probability of false-positive recall at subsequent screens (2 to 7).

### Socioeconomic status

The socioeconomic status of the study population was estimated using the Townsend index of social and material deprivation (9); a summary score was calculated using unemployment, car ownership, owner occupation, and overcrowding variables derived from the 1991 census. Precalculated Townsend values by enumeration district (10) were mapped to each woman's postcode of residence at the time they entered the trial. Data from the 1991 census data were most current for the period of trial entry, which took place between 1991 and 1996. Townsend quintiles used in analyses were defined according to the distribution of scores for the whole of England and Wales.

### Statistical tests

All statistical tests were conducted using STATA (version 10.0, Stata Corporation) statistical software. Differences

**Table 1.** Number of false-positive screens per woman (screening rounds 1 to 10)

No. of false-positives	All intervention arms No. of women (%)	Ever attenders ( $\geq 1$ attendance) No. of women (%)	Regular attenders ( $\geq 7$ attendances) No. of women (%)
At least 1	53,884 (100.0)	43,709 (100.0)	23,245 (100.0)
0	7,893 (14.6)	7,893 (18.1)	5,272 (22.7)
1	45,991 (85.4)	35,816 (81.9)	17,973 (77.3)
2	6,779 (12.6)	6,779 (15.5)	4,417 (19.0)
3	963 (1.8)	963 (2.2)	723 (3.1)
4	137 (0.3)	137 (0.3)	121 (0.5)
5	11 (<0.1)	11 (<0.1)	8 (<0.1)
6	3 (<0.1)	3 (<0.1)	3 (<0.1)

between proportions were assessed by  $\chi^2$  tests. A *P* value of 0.05 (two-sided) was considered statistically significant in all analyses.

## Results

### False-positive rates

Of the 53,884 women randomized to the intervention arm of the trial, 7,893 (14.6%) experienced one or more false-positive recall during the course of their routine trial screening and 1,114 (2.1%) experienced two or more, equivalent to 18.1% and 2.5% in the ever attenders. Among the regular attenders, 5,272 women (22.7%) experienced at least one false-positive recall and 855 (3.7%) had two or more (Table 1).

Table 2 shows the number of false-positive screens in women as a proportion of screens attended and the additional procedures performed. There were 2,134 (4.9%) false positives at first screens and 7,041 (3.2%) at subsequent screens; the overall false-positive rate at routine screens was 3.5%. At first screens, 237 women with false-positive recalls (0.5% of first screens; 11.1% of false-positive first screens) had cytology and 86 women (0.2% of first screens; 4.0% of false-positive first screens) underwent surgical or nonsurgical biopsy. These proportions decreased at subsequent screens when 346 women (0.2% of subsequent screens; 4.9% of false-positive subsequent screens) had cytology and 214 (0.1% of subsequent

screens; 3.0% of false-positive subsequent screens) underwent biopsy.

### Cumulative false-positive rates

Among the 23,245 women who were regular attenders, 4.7% had a false-positive finding at their first screen and 3.2% at subsequent screens (2.9-3.3% with no evidence of a decrease with increasing round number). Over their first seven attendances for routine mammographic screening, women in this group had a 20.5% risk of experiencing at least one false-positive recall. Calculated on the basis of independent probability, the cumulative risk of false positive was 21.6% over seven screens.

The average number of regularly attending women experiencing their first false-positive screen at rounds 4 to 7 was 581 per round. Using this estimate as the number expected at rounds 8 to 10 gives a total of 6,505 false-positives in the regular attenders, a 28.0% risk of experiencing at least one false-positive recall over 10 attendances for routine mammographic screening.

### Impact of false-positive results on re-attendance for screening

Table 3 shows the effect of a false-positive recall on subsequent re-attendance. Uptake of the routine invitation following a false-positive screen was 88.8%. Uptake of the routine invitation following a true-negative screen was 88.5% in women who had never had a false-positive result, compared with 91.5% in women who had prior

**Table 2.** Cytology and biopsy procedures in women with false-positive results

Routine screen	No. of screens	False-positive screens* n (%)	Cytology n (%)	Biopsy n (%)	Cytology and biopsy n (%)
First	43,709	2,134 (4.9)	237 (0.5)	86 (0.2)	32 (0.07)
Subsequent	216,930	7,041 (3.2)	346 (0.2)	214 (0.1)	52 (0.02)
Total	260,639	9,175 (3.5)	583 (0.2)	300 (0.1)	84 (0.03)

\*Includes 21 screens (14 first, 7 subsequent) where mammography was positive, but the women failed to attend for further procedures at the trial screening unit. None of these 21 women were diagnosed with breast cancer in the following 5 y.

**Table 3.** Impact of false-positive result on uptake of next routine invitation

	No. invited	Uptake (%)
Invitation following a false-positive screen	7,852	88.8
Invitation following a true-negative screen		
No history of false-positive screen	194,806	88.5
History of false-positive screen	18,977	91.5
Total	213,791	88.8

experience of a false-positive ( $P < 0.0001$ ; 88.8% among all women). There was also no difference in re-attendance after false-positive compared with true-negative screens when uptake was calculated as a proportion of the number of women in each group, as opposed to the number invited in each group.

#### False-positive results and measures of socioeconomic status

Table 4 shows the cumulative false-positive status of regular attenders by deprivation group. There was no significant difference in risk of at least one false-positive screen between the lowest and highest Townsend quintiles (risk ratio, 0.94; 95% CI, 0.86-1.03;  $P = 0.20$ ).

#### Discussion

A review for the American College of Physicians (ACP) concluded that routine mammographic screening in women ages 40 to 49 years reduced the risk of death from breast cancer but led to an increase in additional clinical procedures and anxiety (11). Rates of false-positive mammographic screening vary widely, but tend to be lower in organized breast screening programs. To our knowledge, the only data on false-positive results for mammographic screening in women under age 50 in Europe are from Navarra, Spain, reporting prevalent screen false-positive rates of 23%; however, initial screening was by single view mammography and recall was frequently limited to the requirement for a second view (12).

The sensitivity and specificity of mammography decrease with increasing breast density. In a study of

women ages 40 to 44 (13), 10% of women with very dense breasts had a false-positive recall, compared with 4% of women with fatty breasts, and mammography sensitivity was 62% and 88%, respectively. As women in their forties have denser breasts than women over 50, false-positive results might be expected to be higher in the Age trial than in the U.K. national program (NHSBSP), which currently invites women ages 50 to 70. The false-positive rates of 5% and 3% at first and subsequent screens in the trial compare favorably with the rates of 8% and 3% reported for equivalent rounds in the NHSBSP (3); however, the difference in breast cancer incidence rates in women of different ages will affect the overall rate of recall for assessment. The positive predictive value of recall, which also reflects the specificity of the screening test, may provide a better measure for comparing false-positive results between different age groups. The positive predictive value of recall for assessment in the trial was 2% at first screens (first invitation) and 3% to 5% at subsequent screens, increasing with age. The NHSBSP positive predictive value is 8% at first screens (first invitation) and 16% at subsequent screens (3).

By 2012, the NHSBSP will be inviting women for their prevalent screen from age 47. Only 356 women in the Age trial received their first trial screen at age 47, and these screens will not be typical of prevalent screens in this age group because the women involved will have been previous nonattenders. More informative for the new national policy is to compare the incident round false-positive rate in Age trial women ages 47 or above with the rate of false-positives at NHSBSP incident

**Table 4.** Cumulative false-positive status and socioeconomic status among regular attenders

False-positive status	Townsend quintile					Not known n (%)	Total n (%)
	1 (least deprived) n (%)	2 n (%)	3 n (%)	4 n (%)	5 (most deprived) n (%)		
Yes (1 or more)	1,595 (23.2)	1,207 (23.1)	926 (21.3)	817 (22.9)	507 (21.9)	220 (23.6)	5,272 (22.7)
No	5,281 (76.8)	4,010 (76.9)	3,419 (78.7)	2,743 (77.1)	1,806 (78.1)	714 (76.4)	17,973 (77.3)
Total	6,876 (100.0)	5,217 (100.0)	4,345 (100.0)	3,560 (100.0)	2,313 (100.0)	934 (100.0)	23,245 (100.0)

NOTE: Townsend deprivation score 1991 based on the earliest postcode of residence during the trial.

screens in women ages 50 to 54 (currently the youngest age group). These women will have had their prevalent round NHSBSP screen before age 52. The incident screen false-positive rate among these women between 1999 and 2005 was 3.56% (data from the Department of Health routine statistics provided annually by breast screening units). The Age trial incident round false-positive rate in women ages 47 or above was 3% (in 40,355 screens), suggesting that no great increase in false-positive results should be expected from the policy of inviting younger women.

The ACP review concluded that the psychological consequences of false-positive screens were greater among women who underwent biopsy than women with further imaging only (11). Only a small number of studies have reported the rates of extra diagnostic procedures arising from false-positive screens. In a U.S. study, 631 false-positives led to a 26% increase in outpatient visits, 89% more imaging procedures, and 20% more biopsies (14). In the Stockholm trial, in women ages 40 to 49, 231 false-positives resulted in 648 physician visits, 234 fine-needle aspiration cytologies, 92 extra mammograms, and 55 (24%) excision biopsies (15). The U.K. Million Women Study showed that 15% of false-positives in women ages 50 and above had a negative biopsy (fine-needle aspiration, wide-bore needle, or surgical biopsy; ref. 16). In our data, it was not possible to distinguish between surgical and nonsurgical biopsies, but of the total 9,175 false-positive screens, the proportion undergoing additional invasive procedures was relatively low at 6% and 3% for cytology and biopsy, respectively.

Recent literature, both in the media and in peer-reviewed journals, has emphasized the need for more information on the potential harms of breast screening to be made routinely available to women (17, 18). The NHSBSP is currently revising the information provided to women invited for screening, which will include more information on the issues of overdiagnosis, overtreatment, and false-positive recalls.

The observed cumulative risk of a regularly attending woman experiencing a false-positive recall over seven routine Age trial screens was 20% and estimated to be 28% over 10 screens. This is higher than the cumulative false-positive rates over 10 screens of 8% to 21%, predicted on the basis of 3 to 5 screening rounds in women ages 50 to 69 in Denmark (19), and higher than the 21% risk over 20 years of biennial screening for women ages over 50 in Norway (20). The Age trial rate is also higher than the 10% to 11% cumulative false-positive rate estimated from NHSBSP cancer detection and cumulative assessment rate data for four screening rounds at five units published by Wallis et al. (21). However, the Age trial rate is significantly lower than most reported rates for U.S. women ages under 50, which are of the order of 34% after five screens for women ages 40 to 49 (22).

There is an ongoing debate about whether the risk of having a false-positive screen depends, at least in part, on previous screening history (19). The independent rate

may be an overestimate if access to previous mammograms aids interpretation and reduces the chance of unnecessary recall. Conversely, the existence of a previous false-positive screen might reflect characteristics that place a woman at higher risk of a further false-positive result, for example, having particularly dense breast tissue. In the trial, the observed cumulative risk of one or more false-positive recalls over seven screens was 20%, compared with an independent probability of 22% over the same period. This suggests that in this trial, previous experience of a false-positive result does not make another any more likely.

Evidence of the influence of a false-positive experience on subsequent screening attendance is contradictory, ranging from women being less likely to return for routine screening to being unaffected to being more likely to attend future screens (23-26). A study of women ages 50 and above invited by the U.K. NHSBSP in East Anglia found that 83% of women with a false-positive result re-attended compared with 96% of women with true-negative results (27). By contrast, a study of women ages 40 and above in Washington state, United States, reported a 1.2-fold increase in attendance at the next scheduled screen for women with a false-positive versus women with a true-negative result (28). Based on re-invitation, Age trial women who experienced a false-positive result were just as likely to attend their next screen as those who had had a true-negative result. Indeed, uptake of invitation following a true-negative result was higher (91%) among women who had had a false-positive screen in the past than among women who had never experienced a false-positive recall. The study by McCann et al. (27) identified that it was only when re-attendance was based on the number of women, rather than the number re-invited, that lower re-attendance following false-positive recall was apparent. When this method was applied to the Age trial data, there was no difference in uptake following a false-positive screen compared with overall uptake following a true-negative screen.

In the Age trial, as has been reported for the NHSBSP (29, 30), there was an inverse relationship between screening attendance and socioeconomic status (31). Because the number of attendances will influence whether a woman ever receives a false-positive result in her cumulative screening history, the effect of deprivation was examined in this study for the regular attenders only. Among women who attended at least seven routine trial screens, the likelihood of experiencing a false-positive screen was not related to socioeconomic status.

### Methodologic issues and limitations

The cumulative false-positive recall rate over a given number of screens has been calculated using data for women who attended at least seven screens. Women accepting all or almost all their invitations are a selected group, and thus cumulative estimates based on their experience might not be valid for all women (19). However,

in this trial, we found that the risk at each screen was independent of previous false-positive experience.

No information was collected on the level of increased anxiety caused by false-positive recalls in the Age trial.

The relationship between false-positive recalls and subsequent interval cancer diagnosis is not covered here but will be addressed by a future article.

The fact that the trial was set completely within the NHSBSP framework should ensure the applicability of the results to the U.K. program. The Age trial can therefore provide useful information on the rates of false-positive recall to be expected among women at the youngest end of the age range once the NHSBSP begins inviting women from age 47.

## Conclusions

Results from the Age trial do not suggest that the new national policy of inviting women for breast screening from age 47 by 2012 will result in a large increase in false-positive results. Experiencing a false-positive screen did not seem to prevent women from re-attending, but the negative psychological effect should not be discounted. False-positive recalls are a disadvantage of breast cancer screening, and their likelihood and implications should be fully communicated to the target population to allow women to make an informed choice about whether or not to attend screening. Whether screening should be implemented in this age group is a separate issue, but the question of greatly increased false-positive rates in this age group and of their compromising re-attendance is refuted by the findings of this study and should be taken into account when determining screening policy.

## Appendix

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