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Research Article

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Assessing the Amount of Unscheduled Screening ("Contamination") in the Control Arm of the UK "Age" Trial

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Abstract

The UK Age Trial of mammographic screening from age 40 has reported a nonsignificant 17% reduction in breast cancer mortality calculated on an "intention to treat" basis. High levels of ad hoc screening in the control arm could potentially have diluted the estimated effect.

Objectives: To estimate the level of unscheduled mammography in the control arm of the UK Age Trial.

Methods: Data were obtained from questionnaires sent to a random sample of 3,706 women at five centers in the control arm of this trial. Questions included in the Office for National Statistics Omnibus Surveys about the timing of and reasons for any breast screening provided comparable data. The overall response rate was 58.8%.

Results: Overall, 24.9% (95% confidence interval, 23.0-26.8) of Age Trial controls responding reported ever having had a mammogram, 18.2% reported a mammogram for symptomatic reasons, and 8.4% reported unscheduled mammography. Overall, 4.0% and 1.8% of women reported symptomatic and unscheduled mammography, respectively, within the previous 12 months. Results from the Omnibus surveys were similar, 14.2% of women reported previous mammography for symptomatic reasons or follow-up after breast cancer and 6.8% reported unscheduled mammography.

Conclusions: The level of contamination due to mammographic screening in the control arm of the Age Trial was low and will have had a minimal effect on the estimated reduction in mortality from breast cancer.

Impact: Estimating the extent of screening in the control arm in randomized trials of screening is important to inform interpretation of the results. *Cancer Epidemiol Biomarkers Prev; 19(4); 1132–6. ©2010 AACR.*

Introduction

Randomized controlled trials are considered the "gold standard" for the evaluation of cancer screening, and are principally analyzed on an "intention to treat" basis, i.e., the end point (usually cause-specific mortality) is compared between the intervention and uninvited arms. However, such analyses potentially underestimate the effect of screening in subjects actually screened, due both to noncompliance in the intervention arm and ad hoc screening ("contamination") in the control arm (1). Although data on noncompliance are usually routinely available, estimating the extent of contamination by screening outside the trial is likely to require additional effort and data collection (2).

In 1991, a national, multicenter randomized controlled trial (the Age Trial), was set up to evaluate the effect of annual mammographic screening of women, starting at ages 40 to 41, on mortality from breast cancer. At that time, there were concerns that screening of women in the control arm might dilute any observed benefit.

The trial was originally designed to detect a 20% reduction in breast cancer mortality in the intervention arm as a whole, analyzed on an intention to treat basis. With uptake in the intervention arm of 70%, in the absence of selection bias, an observed mortality reduction in the intervention arm of 20% would be equivalent to a reduction of 28.6% in those actually screened. If 10% of the control arm were screened with the same level of benefit, the observed reduction in the intervention arm as a whole would be 18%; with 50% contamination, this would decrease to 7%. Selection bias due to different levels of risk between those screened and not screened would alter these estimates.

The aim of the present study was to assess the amount of unscheduled screening (i.e., contamination) taking place in a sample of the control arm of the trial, in order to determine any dilution in breast cancer mortality reduction that might be observed in the trial.

The design of the trial has been described in detail elsewhere (3). In summary, the trial recruited 160,840 women

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Note: Professors H. Cuckle, A. Evans, Drs. L. Bobrow, E. Kutt, S. Moss, C. Record, and B. Thomas are also members of the Trial Management Group. See Appendix.

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Table 1. Mammography reported by responders at six centers in the Age Trial control arm

Responders who have	*n* (%)	Median (range)
Never had a mammogram	1,535 (75.1)	74.9 (65.0-83.1)
Had a mammogram due to breast problems	372 (18.2)	18.5 (10.6-26.7)
Had an unscheduled type mammogram	172 (8.4)	8.6 (6.7-11.4)
Have had both types of mammograms	35 (1.7)	1.6 (0.8-3.1)
Have had any type of mammogram	509 (24.9)	25.1 (16.9-35.0)

NOTE: Results from all usable questionnaires (n = 2,044).

ages 40 to 41, such that 53,884 formed an intervention arm and the remaining 106,956 women a control arm. The population was recruited from 23 of the established National Health Service Breast Screening Programme centers performing routine screening in women ages 50 and over. Women in the intervention arm were invited for annual screening by mammography, and become eligible for the National Health Service Breast Screening Programme after age 50. Those in the control arm were not offered screening as part of the trial, or informed of their inclusion in the trial population, but would become eligible for screening in the national program at age 50.

Materials and Methods

Data were gathered from randomly selected samples of women in the control arm using a postal questionnaire asking for details such as number, approximate date, location of, and reason for all previous mammograms.

Between November 1990 and August 1991, the questionnaire was piloted in three centers on samples of 200 women who were ages 41 or 42 before the trial commenced, and were therefore ineligible for inclusion in the trial. As a result of these pilot surveys, the layout of the questionnaire was changed and questions on symptomatic and asymptomatic mammograms were separated. These surveys were included in the original protocol for which ethical approval was obtained (MREC 98/2/40).

Between April 1996 and August 1997, questionnaires were sent to random samples of 10% of the control arm (women who were born between 1950 and 1954) in four centers (Avon, Bromley, Derby, and Guildford). A total of 2,251 questionnaires were sent. Women known to have moved, emigrated, or died, and those who were known to have breast cancer were excluded from the survey. A return of 1,500 questionnaires was expected based on 65% compliance predicted from the pilot surveys.

Additional surveys were conducted in Edinburgh (December 2000) and Derby for a second time (February 2001) when the women were in their late forties. Due to lower than expected compliance in two of the earlier surveys, the sample size was increased to 15% of the control population of each center (a total of 1,455 women born from 1951 to 1954). Women in Edinburgh born in 1950 were excluded as they had reached age 50 and were eligible for screening in the National Health Service Breast Screening Programme. Women in Derby who had previously been sent questionnaires were also excluded. The questionnaire was revised slightly to include a question on whether the respondent had ever had a breast X-ray.

Questionnaires were electronically scanned into a database; only those questionnaires that were returned from women who had had a mammogram were entered. A total of 71 questionnaires were illogically completed and were excluded from the analysis.

In conjunction with the national office of the NHS Cancer Screening Programmes, data were also collected on questions relating to female screening from the Office for National Statistics (ONS) included in their Omnibus surveys. An Omnibus survey is a means of providing quick results from a relatively short and simple set of questions. A module of questions on "women's health" was included in nine ONS Omnibus Surveys conducted between February 2005 and March 2007 at approximately 3-month intervals. Data relating to 3,333 women between 40 and 74 y of age were sent to the coordinating center. For purposes of comparison with the Age Trial, data were analyzed separately for women ages 40 to 48 and for women ages 49 to 74 at the time of the survey. Those in the younger age group were between 20 and 48 y when they underwent mammography and some of those ages 49 or over when questioned were younger than 49 at mammography. For some, their age at mammography was not known.

Results

A total of 3,706 women were sent questionnaires, of whom 2,115 (57.1%) responded. The average age of the women sent questionnaires was 44.5 years in the first four surveys and 48.7 years in the final two. The response rate ranged from 45.4% to 71.3% between centers. A total of 2,044 questionnaires (55.2%) were suitable for analysis (range, 43.6-68.2%). The response rate in 1996 was 70%, but this decreased to 58% in 1997 and to 47% in 2000 to 2001.

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Table 1 shows a summary of mammography reported by women who participated in these surveys. Overall, 24.9% (95% confidence interval, 23.0-26.8) of all women less than 50 years old had had a mammogram; 18.2% reported having had a mammogram for symptomatic reasons, and 8.4% of women having had a routine-type screening mammogram.

The proportion reporting any mammogram was significantly higher in Guildford than in other centers, and higher in Scotland and Bromley than in Avon and Derby; differences between centers were greater in the proportion of symptomatic than in screening mammograms.

The interval since the last mammogram is reported in Table 2. Overall, 4.0% of women screened reported having symptomatic screening within the last 12 months, whereas 1.8% had a routine type screen in the same period. Within the last 3 years, 8.8% had had a symptomatic mammogram and 3.9% had a routine screening mammogram. Table 2 also shows the frequency of reported mammography. Approximately 15% had one or two symptomatic mammograms whereas only 6.9% had one or two routine mammograms.

Of the 172 responders (8.4% of the total number of usable questionnaires) who reported unscheduled routine screening, 58 (2.8%) attended a private clinic and 17 (0.8%) said that they had a mammogram at their workplace. Fifty-five (2.7%) women reported that they attended the hospital and 27 (1.3%) described the venue for the mammogram as the NHS. Eleven (0.5%) women were screened in a mobile unit and the remaining four women did not specify the location of the unscheduled screening.

Of the 3,333 women interviewed in the Omnibus surveys, 984 (29.5%) were aged 40 to 48 at the time of the survey. Of these, 946 (96.1%) responded with information on their history of breast screening and this is summarized in Table 3. Overall, 23.6% had had a breast screen, and 13.8% had a symptomatic screen. If follow-up screening

Table 2. Time since last mammogram and number of mammograms reported by individual women in the Age Trial control arm

Time since most recent mammogram due to breast problems (y)	No.* (%)	Range at centers (%)
(A) Mammography due to breast problems		
≤1	81 (4.0)	0.4-6.0
1.1-3	99 (4.8)	3.2-7.8
>3	170 (8.3)	3.6-14.8
Missing data	22 (1.1)	0-1.9
Total	372 (18.2)	10.6-26.7
Number of mammograms due to breast problems		
1	237 (11.6)	7.7-16.2
2	74 (3.6)	1.8-5.2
3	32 (1.6)	0.5-2.9
≥4	27 (1.3)	0.5-2.4
Missing data	2 (0.1)	0-0.4
Total	372 (18.2)	10.6-26.7
(B) Unscheduled mammography		
Time since most recent unscheduled mammogram (y)		
≤1	36 (1.8)	0.4-2.9
1.1-3	43 (2.1)	0.4-3.6
>3	65 (3.2)	2.1-4.8
Missing data	28 (1.4)	0-3.9
Total	172 (8.4)	6.7-11.4
Number of unscheduled mammograms		
1	111 (5.4)	3.4-8.3
2	31 (1.5)	0.8-2.4
3	17 (0.8)	0.4-1.6
≥4	11 (0.5)	0.2-1.2
Missing data	2 (0.1)	0-0.4
Total	172 (8.4)	6.7-11.4

NOTE: Results from all usable questionnaires (n = 2,044).

*These numbers include a total of 35 women who were screened for both breast problems and for unscheduled mammography.

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Table 3. Women reporting previous mammography in ONS Omnibus Surveys (February 2005 to March 2007; women ages 40-48 y at survey date)

	No. (%)
Number who have had a previous mammogram	
Yes	223 (23.6)
No	723 (76.4)
Not known	0 (—)
Total	946 (100)
Time since most recent mammogram (y)	
≤1	61 (6.4)
1.1-3	49 (5.2)
>3	77 (8.1)
Not known	36 (3.8)
Total	223 (23.6)
Reason	
Referral (symptomatic)	131 (13.8)
Follow-up after treatment for breast cancer	4 (0.4)
Unscheduled or routine (nonsymptomatic)	30 (3.2)
Family history	16 (1.7)
Private	18 (1.9)
Other	12 (1.3)
Not known	12 (1.3)
Total	223 (23.6)

NOTE: Results from responders (n = 946).

after treatment for breast cancer is included, this increased to 14.2%, and if routine, private, family history, and other mammography are combined, 8.0% of all women participating who were ages 40 to 48 had routine screens.

Discussion

Overall, 24.9% of women surveyed in the Age Trial reported having had a breast X-ray but only around a third of these (8.4%) were for nonsymptomatic reasons. These findings are in line with the analysis of data from the ONS Omnibus Surveys. The age range for women participating in the Omnibus surveys spans mammography from 20 to 48 years as compared with an age range of 42 to 49 for women on the Age Trial. The sample size of the Omnibus survey was also rather limited.

The response rate in the surveys decreased between the first and second phases, possibly due to the fact that the women included in the latter were slightly older. Reporting of mammography seemed to be slightly higher in the southeastern centers and in Scotland, but it is not possible to determine whether this was an effect of increased awareness. Routine screening may take place as part of health insurance checks, or as a result of the availability of "Well Woman Screening" in the workplace. Women who are aware of an increased risk due to family history may also seek screening.

There is little published evidence on the extent of contamination in randomized control trials of breast screening, In one center of the Canadian National Breast Screening Study (4), health insurance claims for mammography were reported for 21.8% of control arm women ages 40 to 49, and 16.7% of those ages 50 to 59, the proportion for screening mammograms being 14.1% and 10.5%, respectively (5). An earlier article reported that 26% of the control group ages 40 to 49 received a mammogram, but 14.5% had only a single examination. Unlike the Canadian trial, which recruited volunteers, in the Age Trial, women in the control arm were not informed of their inclusion, and there was minimal prior publicity to avoid high levels of contamination.

We have no information on the diagnostic follow-up or outcomes of screening in the control arm; less complete follow-up of positive screens may result in such screening being less effective (6). Although 25% of women reported at least one mammogram, only 8% reported mammography probably for screening purposes, and the majority only had a single mammogram as compared with the average of six screens in women ever screened in the intervention arm. Only 7% of women in the intervention arm were only screened once, and 50% attended six or more screens. Any effect of contamination in the control arm is therefore likely to be minimal compared with the effect of screening in the intervention arm.

In conclusion, the level of contamination reported in the present trial is unlikely to have resulted in a marked dilution of the true effect of mammographic screening in the trial on breast cancer mortality.

Appendix A. Trial Management Group

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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