PAPERS

UKCCCR multicentre randomised controlled trial of one and two view mammography in breast cancer screening

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Abstract

Objective—To compare one view (oblique) and two view (oblique and craniocaudal) mammography in breast cancer screening.

Design—Randomised controlled trial.

Setting—Nine breast screening centres in England.

Subjects—40 163 women aged 50-64 attending their first breast screening examination.

Interventions—Women were randomised to have one view mammography, two view mammography, or two view mammography in which one view was read by one reader and both views were read by another.

Main outcome measures—Prevalence of cancer detected, recall rates, cost per cancer detected, and marginal cost per extra cancer detected.

Results—Two view mammography detected 24% more women with breast cancer (95% confidence interval 16% to 31%) than one view mammography. Prevalence of detected cancer was 6·84 with two view mammography and 5·52 per 1000 women with one view. The proportion of women recalled for assessment was 15% lower (95% confidence interval 6% to 23%) with two view (6·97%) than with one view (8·16%) mammography. The cost of two view screening was higher (£26.46 compared with £22.00 per examination) but the average cost per cancer detected was similar (£5330 compared with £5310) and the marginal cost per extra cancer detected with two views was similar to the average cost (£5400).

Conclusion—Two view mammography is medically more effective than one view; it detects more cancers and reduces recall rates; it is also similarly cost effective financially.

Introduction

It is unknown whether breast cancer screening should be performed with one or two x ray views of each breast. An oblique view is necessary, but the extra value of a craniocaudal view is uncertain.[1-4] Two retrospective studies (examining films from women who had two views—one first, then both together)[5 6] suggested 9% extra detection with two view mammography. Such studies could underestimate the advantage of the second view because readers were presented with a higher proportion of breast cancer cases than would be seen in ordinary screening and may have "played safe" by recommending higher recall rates than in normal screening practice. Similar prospective studies with a typical prevalence of breast cancer may not avoid the problem because the reader of the single view knows that no action will be taken until the second view has been examined. Some readers may disregard suspicious findings, underestimating one view detection. Others may recommend recalling more

cases, knowing that the second film reading could correct the high recall rate.

To resolve the matter we, with the support of the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) conducted a randomised trial allocating women to one view or two view mammography to determine (a) the additional breast cancer detection achievable with two views instead of one at the first screening examination, (b) the recall rates for the two policies, and (c) the economic implications of the two policies.

Patients and methods

A total of 40 163 women were recruited between 1990 and 1994 from nine centres in England (West London 10 610, Brighton 8048, Worthing 6564, North London 4260, Liverpool 3858, Reading 3141, Winchester 2388, Leeds 1060, and Southampton 234). Twenty one national breast screening programme film readers took part. All but two were radiologists. Women aged 50-64 were eligible for the trial at their first screening examination if they had not had breast surgery and could give consent. To be eligible for the trial, centres must have screened at least 5000 women as part of a general screening programme and identified at least four breast cancers for every 1000 women screened, with a recall rate of less than 10%, and have at least two film readers (X and Y).

In each centre women were randomised to one of three groups in the ratio 1:1:2 by means of a computerised random numbers generator. Group 1 had oblique view mammography alone, interpreted by film reader X; group 2 had two view mammography, interpreted by film reader Y; and group 3 had two view mammography, interpreted independently by X (reading the single view) and Y (reading both views). Women were entered into the trial before allocation was made and consent obtained from those allocated to two view mammography except in one centre, in which consent was given before randomisation. Readers reported results as positive (recall for assessment) or negative (no action to be taken). To avoid reader bias the two readers at each centre rotated, each reading the single views of women in groups 1 and 3 for one month (reader X), then switching to reading two views for the women in groups 2 and 3 (reader Y) for the next month.

The primary analysis of recall rates was between groups 1 and 2, and comparison of the rates of recommended recalls by readers X and Y in group 3 was a secondary analysis. The primary analysis of cancer detection was between the cancers detected by X and Y in group 3 (this maximised statistical power by removing between woman variation). Comparison of cancer detection in groups 1 and 2 was a secondary analysis.

Groups 1 and 2 were necessary to allow assessment of

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recall rates and avoid bias in the comparison of rates in group 3, in which the reader of the single view knew that another reader was examining two views. In the trial readers did not know to which group women were allocated, and one quarter of the women whose films were read by X would not receive a second view. Readers' performance was therefore likely to be typical of normal practice.

In group 3 a woman was recalled if either reader found a positive result. For the trial, if the one view reader recommended recall and the two view reader did not, the discordant interpretation was recorded as the study result. It was judged unnecessary and unethical to recall a woman for a second view when this had already been taken. The craniocaudal film was then shown to the single view reader, who gave a two view opinion. This second opinion was acted on, though the original recommendation was used in the statistical analysis. An "intention to treat" analysis was thereby preserved. The trial's design comparing the benefits and costs of two views with those of one view, followed by a second view when necessary, was preserved. The approach was therefore appropriate and ethical.

A random effects model[7] was used in some analyses, when appropriate, to account for heterogeneity between study centres. Analyses in groups 1 and 2 were based on an intention to treat analysis. Comparisons in group 3 were restricted to 16 677 women for whom both one view and two view opinions were available. This excluded 17% (3446/20 123), almost all because the women declined two views or had large breasts, making two view mammography impracticable. In no case was exclusion linked to detection being better with one view or two. All P values were two tailed. The study was originally designed to recruit 100 000 women with 50 000 in group 3. This would yield 85% power of detecting an 8% difference in cancer detection at the 5% level of significance assuming a 5% random error in film reading. Funding was provided in two stages. Before claiming the second portion we found that the observed effect was greater than expected; a clear result had emerged and so the trial was stopped.

The costs of initial screening and of follow up diagnostic procedures were assessed separately for the one and two view procedures and the average cost estimated for each. The unit cost of film processing, clinical examination, cytology, biopsy, single view mammography, and the percentage of costs ascribed to overhead and capital expenditure were obtained from the Scottish Home and Health Department's 10 year study on economic costs of screening for breast cancer,[8] updated to 1992-3 values. Extra initial screening costs incurred for the second view were estimated by using survey data from the 251 timings of radiographers' screening by one and two views, from the time taken to read 470 one and two view films by five radiologists, extra film and processing, and overhead and capital costs. A questionnaire concerning travel and time costs incurred at the recall appointment was completed by 338 women at nine screening centres to assess differences in personal costs. Follow up referral costs to the health service per woman screened were assessed by applying the unit cost of each procedure (including overhead and capital costs) to the proportion of screened women who received the procedure, and summing over all procedures for groups 1 (one view) and 2 (two views) separately.

Results

MEDICAL

The mean age of women in the three groups was similar (57 years), and 0.1% were lost to follow up. A total of 10 058 women were randomised to group 1, 9982 to group 2, and 20 123 to group 3.

Primary analysis of recall rates based on groups 1 and 2 (table I) yielded a recall rate of 8·16% in group 1 (one view) and 6·97% in group 2 (two views), an absolute difference of −1·20% (95% confidence interval −1·93% to −0·47%; P=0·001) or a proportional difference of 15%. Taking account of statistical heterogeneity between centres in the estimates of the difference in recall rates (χ^2_8=28)[7] yielded virtually the same difference (−1·26%) but with a wider 95% confidence interval (−2·69% to 0·16%; P=0·08). Recall rates in group 3 were 8·45% for one view and 6·30% for two view mammography. This difference was also significant (χ^2_8=94; P=0·013). The two sets of results (group 1 versus group 2 and within person comparison in group 3) indicated that the reduced recall rate achieved by two view mammography was unlikely to be due to chance.

The primary analysis of cancer detection based on group 3 (table II) showed no heterogeneity in cancer detection between centres. Statistically, the most powerful comparison relies on the discordant results between the two readers. There were 24 such cases, 23 detected by the two view reader only and one detected by the one view reader only (91 were concordant—that is, detected by both). This result (23:1 instead of an expected 12:12 if there was no advantage to two view mammography) was unlikely to have arisen by chance (P<0·0001; McNemar's test).

TABLE II—*Cancers detected among women in group 3 (two views: one read by one reader, both read by other reader) who received two views (16 677 women)*

	No of women
Cancer detected by both one view and two views	91
Cancer detected by two views only	23
	(12 expected if no difference)
Cancer detected by one view only	1
	(12 expected if no difference)
Total	115
Cancer detected by two views	114 (91+23)
Cancer detected by one view	92 (91+1)
Proportional increase in cancers detected	24% (22/92 [114-92/22])

Twenty seven women with breast cancer in group 3 were excluded—19 because only one view was taken and eight because the one view report was not recorded. Failure to record such opinions seemed random, occurred in all centres, and was unlikely to have introduced bias.

To estimate the impact of two view mammography, all the data in group 3 (concordant as well as discordant sets) were examined. A total of 114 cases were detected with two views and 92 with one view, a 24% (95% confidence interval 16% to 31%)[9] greater prevalence of screen detected cancer (6·84 versus 5·52 cases per 1000 women respectively). Absolute rates were similar to those in group 2 (two views, one reader) and group 1 (one view, one reader) (6·51 and 5·57 per 1000 respectively). The difference in prevalence of screen detected breast cancer between groups 1 and 2 was not significant, illustrating the greater statistical power

TABLE I—*Numbers of recalls and cancers detected in groups 1 (one view, one reader) and 2 (two views, one reader)*

	No randomised	No of scheduled recalls	Recall rate (%)	No of women who had biopsy	No of women with cancer†	Prevalence of screen detected cancer/1000
Group 1	10 058	821	8·16	75	56	5·57
Group 2	9 982	695	6·97	74	65	6·51

†Based on biopsy in all cases except one, in which diagnosis was based on cytology alone. There were two cases of bilateral breast cancer.

Cost of first screening round	One view (group 1) (£)	Two views (group 2) (£)	Two views minus one view (£)
Screening†	15·63	20·79	5·16
Recall, assessment, and diagnosis‡	6·37	5·67	−0·70
Total cost of screening to health service	22·00	26·46	4·46
Personal costs of recall per woman screened§	1·47	1·25	−0·22
Grand total	23·47	27·71	4·24

†Includes cost of repeat mammograms due to technical faults.
‡Average cost of assessment £78·08 (one view) or £81.43 (two views); £6.37=£78.08×8·16%; £5.67=£81.43×6·97%.
§Costs to screenee, her companion, and employers incurred by attending recall clinic (average cost £17.97 per woman recalled).

TABLE IV—*Average cost per breast cancer detected and marginal cost per extra cancer detected for one view and two view mammography expected in typical screening practice*

	One view	Two views	Difference
Prevalence of detected cancer per 1000 women:			
At first examination (all ages)	5·52	6·84	1·32 (+24%)
At first examination (ages 50-52)	3·62†	4·49‡	0·87 (+24%)
At subsequent examinations (ages 53-64)	3·68§	4·56‖	0·88 (+24%)
Recall rate (%):			
At first examination (all ages)	8·16	6·97	−1·20 (−15%)
At subsequent examinations (all ages)	4·13¶	3·52††	−0·61 (−15%)
Health service cost per screening examination (£):			
At first examination (all ages)	22.00	26.46	4.46 (+20%)
At subsequent examinations (all ages)‡‡	18.85	23.66	4.80 (+25%)
Average cost per breast cancer detected (£)	5310	5330	16.84 (+0·3%)
Marginal cost per extra breast cancer detected by two view mammography		5400	

†Observed prevalence of detected cancer in 50-52 year age group in this study.
‡Based on 24% increase in detection with two view mammography (1·24×3·62).
§67%[10] of 5·52 per 1000 (one view prevalence of detected cancer).
‖Based on 24% increase in detection with two view mammography (1·24×3·68)
¶51%[10] of 8·16% (one view recall rate).
††51%[10] of 6·97% (two view recall rate).
‡‡By using screening cost in table III (£15.63 or £20.79) plus assessment cost (£78.08 or £81.43) times corresponding percentage recall rate (above).

TABLE V—*Estimated cost attributable to screening per life saved and per year of life saved for one view and two view mammographic screening*

	One view	Two views	Absolute difference (%)†	Marginal costs/ benefits with two view mammography
Estimated lives saved among 100 000 women aged 50 (see text)	412	510	99 (+24)	99
Cost per life saved (£)‡	23 600	23 700	+74.95 (+0·3)	24 000
Cost per year of life saved (assuming 20 years of life saved per life saved)	1 180	1 190	+3.75 (+0·3)	1 200

†Numbers in this column may differ from those calculated from numbers in previous two columns because of rounding.
‡Based on costs of first screening examination and four subsequent screening examinations.
In estimating extra reduction in breast cancer mortality we assumed that two view mammography will yield same proportional increase in detection rate at each of four subsequent three yearly screening examinations between ages of 50 and 64 as at first (see text).

of the within person analysis in group 3. Twenty times more women would have been required in a between person comparison to have the same statistical power.

On comparing groups 1 and 2 (stratified Mantel-Haenszel exact test) two view relative to one view mammography was also shown to be associated with (a) fewer women having assessment films at the recall visit (62% of women versus 84%; P<0·0001), (b) a higher proportion of women having a biopsy proving to have a malignant lesion (86% versus 73%; P=0·032), (c) a lower benign biopsy rate (1·00 versus 1·99 biopsies per 1000 women; P=0·070), (d) a similar proportion of tumours detected (bilateral cancers counted as two) that were invasive (that is, not carcinoma in situ; 45/56 for one view, 59/67 for two views), and (e) the same proportion (25%) of cancers that were 1 cm or less in diameter.

ECONOMIC

Table III shows the estimated average costs for one and two view mammographic screening. The estimated cost to the health service when using one

view at the first screening examination was £22.00 per woman screened. By comparison two views at the first examination cost £26.46 per woman screened. The lower personal costs to women in the two view group (owing to the lower recall rate) reduced the difference between the two groups to £4.24 per woman screened (1992-3 values, including capital and overhead costs).

The average extra time taken for two view mammography was 1 minute 54 seconds per woman (1 minute 20 seconds of which was due to the extra mammography time). The average extra time reading the second view was six seconds.

In established screening programmes the first screening examination will mainly include women entering the age range for screening (50-52) and subsequent examinations will be limited to women aged 53-64. Our results refer to women who were first screened at ages 50-64 because it was conducted when the screening programme was launched in Britain and all women aged 50-64 were invited. To allow for the difference in age we used the age specific prevalence of detected cancer to estimate the rate in the 50-52 year age group (see table IV) as well as the rate at subsequent examinations. We allowed for the observation that the prevalence of detected cancer in subsequent examinations is two thirds the rate at the first examination.[10]

We found that the recall rates at the first examination did not vary materially with age. Data from the national programme[10] showed that subsequent screening examinations were associated with half the recall rate of the first examination. Based on these estimates, table IV shows that the average cost of screening per breast cancer detected (cost of initial screening plus cost of recall, assessment, and diagnosis in 1000 women, divided by the number of cancers detected) was £5310 with one view mammography and £5330 with two view mammography. The marginal cost per extra cancer detected (that is, the extra cost of each extra cancer detected) by two view mammography compared with one view was £5400 when using the difference in average screening cost of each method divided by the difference in the number of cancers detected by each method.

Discussion

Breast cancer screening by means of two view rather than one view mammography at the initial examination led to 24% more cancers being detected. If two view mammography detects all breast cancers this would mean that one view would detect only 81%. The recall rate was reduced by 15% with two view compared with one view mammography. The odds of a recalled woman having breast cancer were 1:10 with two view mammography and 1:14 with one view mammography (for groups 1 and 2 in table I). Two view mammography at the first screening examination is more effective than one view mammography.

The overall prevalence of detected cancer (6·6 cases per 1000 women screened) was similar to that in the British breast screening programme[10] in 1993-4 (5·7 cases per 1000) among women aged 50-64 attending the first screening examination. The overall recall rate in the trial (7·6%) was somewhat higher than the corresponding rate in Britain (5·9%); this may be due, at least in part, to the double reading of films in many centres in the national programme. In the trial as a whole the proportion of tumours 1 cm or less in diameter was also similar (24%) to that in the national programme (23%). Our results therefore reflect typical screening practice.

The estimated long term implications of screening with two view mammography are summarised in table

V. Three yearly one view mammography between the ages of 50 and 64 (five examinations) would be expected to reduce breast cancer mortality by 27% in screened women. This is derived from the 31% reduction in a meta-analysis of screening trials[11]—some using one view, some two and the 24% increase in detection in our trial (with the assumption that the 24% extra detection with two view mammography results in a 24% reduction in mortality). This is equivalent to 412 lives saved over 15 years per 100 000 women screened with one view mammography and 99 extra lives saved per 100 000 screened by two view mammography over all screening examinations. The average costs per life saved with one view and two views are similar (table V).

A recent review of breast cancer screening trials showed no significant difference in breast cancer mortality between trials using two view mammography and those using one view mammography in the age group 50-74 years,[12] and the authors concluded that there was no advantage with two view mammography. However, the analysis was liable to between trial confounding. If centres using one view mammography (for example, the Swedish two counties study, which found a 28% reduction in breast cancer mortality) had, for reasons unrelated to the number of views taken, a better screening performance than centres using two views (for example, Malmo, which found a 14% reduction in breast cancer mortality) we should be liable to falsely conclude that two views were worse than one. Our results, though not based on mortality, compare the effects of one and two view mammography directly within the same programme in an unbiased way.

Routinely using two view mammography instead of one view increases overall costs by about 24%, but when the higher detection rate is taken into account such screening is as cost effective as one view mammography. Even if the lower limit of the 95% confidence interval on the estimated extra detection with two view mammography were used (16%) the increase in cost per case detected would still be small (6·8%).

The lifetime risk of breast cancer arising from the extra radiation with two view mammography compared with one view over five screening examinations is minimal (one to two cancers per 100 000 women screened)[13] and substantially less than the lives saved by the higher detection rate.

Our results are based on the first screening examination. The availability of a previous film for comparison at subsequent examinations is not a substitute for a second view. It is unlikely to increase detection materially, as all one of the 23 cancers missed with one view were interpreted as "normal appearance" without mention of a radiological abnormality. Hence it was rare to find a lesion that could be looked for in an earlier film to see if it had progressed. A previous film could, however, reduce the false positive rate, and hence the recall rate, by showing that a suspicious finding in a current film was present three years before, allowing it to be discounted as benign and avoiding an assessment. This effect could diminish the reduction in the recall rate resulting from the use of two concurrent views if the lesions thereby confirmed as benign tended to be those confirmed as benign in a previous view. Even at the extreme, if all benign lesions seen in a concurrent view were present in a previous film and the false positive rate reduced accordingly the extra cost per year of life saved with two view mammography would be only 2%.

Two view mammography improves the discrimination between women with and without cancer. Unless the presence of a previous film completely duplicates the extra information from a concurrent second view, which is implausible, there will continue to be a

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Key messages

- Breast cancer screening in which women aged 50-64 are invited for a mammographic examination is an effective way of reducing mortality from this disease

- Taking two mammographic views of the breast instead of one increases the detection of breast cancer by 24% and reduces the number of women recalled for further investigation by 15%

- Two view mammography is financially cost effective

- Two view mammography should be used instead of one view mammography at the first screening examination and is also likely to confer screening benefits at subsequent screening examinations

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medical benefit in using two view mammography at subsequent screening examinations, though the size of the benefit is less certain. Even with a small benefit the cost per case detected, or the cost per year of life saved, would be similar to that with one view mammography at all screening examinations.

We conclude that (a) two view mammography increases the prevalence of cancers detected by about 24%, a difference that is likely to be similar at subsequent screening examinations; (b) two view mammography is expected to reduce breast cancer mortality by 34% in screened women compared with a reduction of 27% with one view; (c) two view mammography reduces the false positive rate, and therefore the recall rate, by about 15% at the first screening examination (it is also likely to be reduced at subsequent examinations, though the magnitude of this reduction remains uncertain); and (d) the cost per life saved with routine two view mammography will be similar to that with one view mammography. It is reasonable, therefore, that two view should replace one view mammography in breast cancer screening.

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Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women

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Abstract

Objectives—To examine the association between androstenedione, total and bioavailable testosterone, oestrone, and total and bioavailable oestradiol concentrations and the risk of death from cardiovascular and ischaemic heart disease.

Design—19 year old population based prospective study with 99·9% follow up.

Setting—Rancho Bernardo, California.

Subjects—651 postmenopausal women, none taking oestrogen.

Main outcome measures—Concentrations of plasma sex hormones measured by radioimmunoassay in an endocrinology research laboratory. Cardiovascular and ischaemic heart disease deaths assessed by death certificate; 85% of 30% sample validated by record review.

Results—Age adjusted concentrations of sex hormones did not differ significantly in women with and without a history of heart disease at baseline and did not predict cardiovascular death or death from ischaemic heart disease. Most 95% confidence intervals for the age adjusted relative risk of cardiovascular death or death from ischaemic heart disease were narrow, and all included one. Endogenous oestrogen concentrations were not associated with significantly more favourable risk factors for heart disease, and testosterone was not associated with less favourable risk factors.

Conclusion—These prospective data do not support a causal or preventive role for endogenous oestrogens or androgens and cardiovascular mortality in older women.

Introduction

At every age women have less heart disease than men, and this difference is not explained by any of the classic risk factors for heart disease.[1] In countries with very different death rates from heart disease, diets, and lifestyles, the sex ratio for fatal coronary heart disease in men and women aged 45-69 years shows a surprisingly consistent 2·5 to 4·5-fold excess risk in men,[2] suggesting an endogenous protective trait in women. One obvious candidate is oestrogen.

A cardioprotective role for oestrogen is supported by the observation that the excess risk of cardiovascular disease in women who underwent oophorectomy in young adulthood is prevented by oestrogen.[3] In addition, a large body of observational data shows a significant reduction in the risk of heart disease in women who take oestrogen after a non-surgical menopause.[4 5] The apparent prevention of heart disease in women using exogenous oestrogen is seen when

pharmacological doses are given by mouth. It is not known whether physiological concentrations of oestrogen are also associated with a reduced risk of cardiovascular disease. A prospective study of premenopausal women, who are at low risk of cardiovascular disease and have cyclic hormone concentrations, would be difficult. Postmenopausal women have more heart disease and more stable concentrations of their primary oestrogen, oestrone, such that a single assay should reflect hormonal state well enough for epidemiological studies.[6 7]

Only one cross sectional study has reported the relation of circulating oestrone concentrations to heart disease in postmenopausal women; no association was found.[8] To our knowledge, no prospective study has reported the relation of endogenous oestrogen or androgen to cardiovascular disease in women. We describe the absent association of endogenous sex hormones and cardiovascular death in a prospective population based study of postmenopausal women who were followed for 19 years.

Methods

Between 1972 and 1974 all adult residents in Rancho Bernardo, California, were invited to participate in a study of risk factors for cardiovascular disease, and 82% did so. Participants were seen between 7 30 and 11 00 am after a requested 12 hour fast. A standardised questionnaire was completed which included questions about personal and family history of heart disease (heart attack or heart failure), history of cigarette smoking, and current use of oestrogen. Blood pressure was measured with a mercury sphygmomanometer after the participant had been seated for at least five minutes. Height and weight were measured with the participants wearing lightweight clothing without shoes; body mass index (weight (kg)/height (m)^2) was used to estimate obesity. Total plasma cholesterol concentration was measured in a Centers for Disease Control standardised lipid research clinic laboratory with an AutoAnalyzer; lipoprotein concentrations were not determined at baseline. Fasting plasma glucose concentration was measured in a hospital diagnostic laboratory with a hexokinase method. Plasma for endogenous sex hormone assays was obtained and frozen at −70°C.

Between 1984 and 1986 sex hormones were measured in an endocrinology research laboratory (S S C Yen) by radioimmunoassay with thawed specimens obtained from postmenopausal women at the 1972-4 venepuncture.[9] Previous work in this laboratory demonstrated no hormone deterioration over 15 years when samples were frozen and stored in

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