Neglected aspects of false positive findings of mammography in breast cancer screening: analysis of false positive cases from the Stockholm trial

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Abstract

***Objectives*—To examine the implications of false positive results of mammography in terms of the time lag from screening and complete mammography to the point when women with false positive results are declared free of cancer; the extra examinations, biopsies, and check ups required; and the cost of these extra procedures.**

***Design*—Review of women with false positive results from the Stockholm mammography screening trial.**

***Setting*—Department of Oncology, South Hospital, Stockholm.**

***Subjects*—352 and 150 women with false positive results of mammography from the first and second screening rounds of the Stockholm trial.**

***Main outcome measures*—Extra examinations and investigations required and the cost of these procedures.**

***Results*—The 352 women from the first screening round made 1112 visits to the physician and had 397 fine needle aspiration biopsies, 187 mammograms, and 90 surgical biopsies before being declared free of cancer. After six months 64% of the women (219/342) were declared cancer free. The 150 women in the second round made 427 visits to the physician and had 145 fine needle aspiration biopsies, 70 mammograms, and 28 surgical biopsies, and after six months 73% (107/147) were declared cancer free. The follow up costs of the false positive screening results were Kr2.54m (£250 000) in the first round and Kr0.85m (£84 000) in the second round. Women under 50 accounted for about 41% of these costs.**

***Conclusions*—The examinations and investigations carried out after false positive mammography —especially in women under 50—and the cost of these procedures are a neglected but substantial problem.**

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Introduction

In 1986 the Swedish National Board of Health and Welfare published guidelines on breast cancer screening with mammography and recommended that all women aged 40-74 years should be screened—every 18 months for women aged 40-55 and every two years for women aged 56-74.[1] Mammography screening programmes have developed since then, and in many parts of Sweden women are screened from 40 years of age. The guidelines also stated that benign lesions must be investigated immediately to avoid the anxiety created by unnecessary check ups and inconclusive information.[1]

A review of five completed randomised trials of mammography screening in Sweden showed a significant 29% reduction in breast cancer mortality among women aged 50-69 years but a nonsignificant 13% reduction among women aged 40-49.[2] The benefits of mammography screening remain controversial, though other randomised studies have also shown that a significant reduction in breast cancer mortality can be achieved by screening women over 50.[3,4]

Some workers have raised the issue of whether a reduction in mortality will balance the potential negative effects of mammography screening.[5-7] This is especially relevant in women under 50, who have a lower incidence of breast cancer and in whom mammography has a lower specificity and sensitivity.[8] False positive mammograms may induce psychological problems. For example, Gram *et al* reported that women with false positive findings suffered increased anxiety about breast cancer.[9] Lerman and Rimer reported that an abnormal screening result might lead to distress and anxiety that could continue even after further work up positively excluded cancer. Lerman and Rimer also suggested that in some women an abnormal mammogram might lead to extreme levels of distress.[10] Cockburn *et al* highlighted the negative consequences of recall for further investigation after a screening mammogram and encouraged the use of a questionnaire to measure the psychological consequences of screening mammography.[11]

Several studies have examined the cost effectiveness of mammography for breast cancer screening.[12-19] These, however, have not dealt explicitly with the cost of false positive findings but have included this aspect in the overall cost of screening. van der Maas *et al* and de Koning *et al* conducted several studies on the cost effectiveness of breast cancer screening. They concluded that two yearly screening of women aged 50-70 years was cost effective but that screening women aged 40-49 years was not cost effective.[20,21] They, however, also failed to analyse the cost of false positive findings separately.

We reviewed all women with false positive findings from the Stockholm mammography screening trial. We paid particular attention not only to the numbers of surgical biopsies performed after the false positive result but also to other examinations and check ups carried out and the time lag before the women were finally declared cancer free. In calculating the overall cost of the extra examinations and investigations performed we costed each item separately.

Subjects and methods

In 1981 a randomised breast cancer screening trial with mammography began in one part of Stockholm county. The trial was conducted with women aged 40-64 years. Figure 1 presents a flow chart of the two screening rounds in the trial. The first round was completed in 1983 and the second round in 1985. The control population was invited for screening in 1985.

This study is concerned with 352 and 150 women

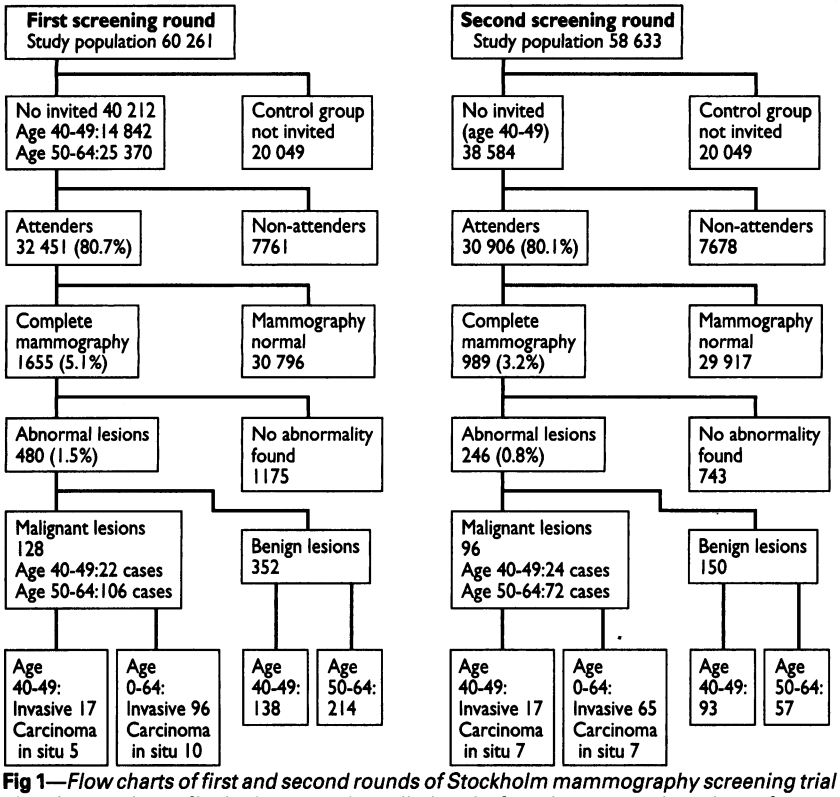

Fig 1—*Flow charts of first and second rounds of Stockholm mammography screening trial showing numbers of invited, screened, recalled, and referred women and numbers of cancer cases. Age groups represent age at entry*

with false positive mammograms in the first and second screening rounds from 1981 to 1985 who underwent further investigations after complete mammography (see fig 1). These women did not have breast cancer detected in the next screening round and therefore were confirmed false positive cases. All were referred to the department of oncology at South Hospital for the further investigations.

We divided the women into two groups based on age at first screening—namely, 40-49 years and 50-64 years—and analysed the numbers of examinations and investigations performed in each group. We particularly wished to know the extent to which the women needed extra procedures such as surgical biopsies, check up mammography, fine needle aspiration biopsies, and palpation check ups before finally being declared cancer free. In addition, we estimated the costs of these procedures and recorded the time lag from screening to being declared cancer free.

Hospital records were missing for 10 women from the first round and seven from the second round. We therefore reviewed the records of the remaining 342 and 143 women for all examinations till they were declared cancer free. The cost estimates are based on the type and frequency of the examinations of these women. The cost of each examination refers to its actual cost (1993 price level) at the hospital where it was performed. Indirect costs, such as the costs of sick leave, travel, and patient time, are not included. We also excluded costs related to examinations other than those directly related to the diagnostic work up generated by the findings of mammography. The cost of the whole screening programme was based on the net cost of single view mammography in 1993 (Kr180).

Results

Among the women referred to the oncology department in the first screening round there were 113 invasive cancers, 15 carcinomas in situ, and 352 benign lesions (false positive cases) (fig 1). In the second round there were 82 invasive cancers, 14 carcinomas in situ, and 150 benign lesions (fig 1). Table 1 shows the numbers and types of examinations performed in women with false positive findings stratified by age (40-49 and 50-64 years).

Most invasive cancers detected in the two screening rounds (85% (96/113) and 79% (65/82)) were in women aged over 50 (fig 1). One third and one half of the carcinomas in situ detected in the two rounds were in younger women (fig 1). In the first screening round 39% of the women with false positive findings (138/352) were below age 50 at entry and in the second round 62% of these women (93/150) were below age 50 (table 1). Table 2 shows the ratio of benign to malignant breast lesions detected in different age groups in the two rounds.

Table 1—*Examinations and costs of positive cases in different age groups (age group at entry) of women at first and second screening rounds including 32 451 and 30 906 screened women respectively*

		First screening round (352 women)				Second screening round (150 women)			
		Age 40-49 (n=138)		Age 50-64 (n=214)		Age 40-49 (n=93)		Age 50-64 (n=57)	
	Cost/ examination (Kr)	No	Kr	No	Kr	No	Kr	No	Kr
Visits to physician		418		704		230		197	
First visit	735	135	99 225	207	152 145	93	68 355	50	36 750
Second or later visit	459	283	129 897	497	228 123	137	62 883	147	67 473
Fine needle aspiration biopsy (by palpation)	582	115	66 930	144	83 808	58	33 756	38	22 116
Fine needle aspiration (stereotaxic)	873	38	33 174	100	87 300	23	20 079	26	22 698
Mammography	526	62	32 612	125	65 750	30	15 780	40	21 040
Surgical conference	877	38	33 326	53	46 481	17	14 909	13	11 401
Blood sampling	Various	41	2 757	64	5 163	0	0	1	150
Excision biopsy	16 170	39	630 630	51	824 670	16	258 720	12	194 040
Lung radiography	525	9	4 725	33	17 325	0	0	2	1 050
Telephone calls						3	378	1	126
Total cost of investigations of false positive cases			1 033 276		1 510 765		474 860		376 844
Mean cost per woman with false positive findings			7 488		7 060		5 106		6 611
Cost of false positive cases per cancer discovered			46 967		14 252		19 786		5 234
No of cancers (invasive and carcinoma in situ) discovered		22		106		24		72	
Cost of false positive cases per 1000 screened women aged 40-64:		First round Kr78 400, second round Kr27 560.							
Cost of screening programme (one view mammography plus complete mammography after recall):		First round Kr6.7m, second round Kr6.1 m.							

Table 2—*Ratio of benign to malignant breast lesions detected in different age groups (age at entry) in first and second screening rounds*

	First screening round			Second screening round		
Age (years)	Benign	Malignant	Ratio	Benign	Malignant	Ratio
40-44	72	8	9·0	49	12	4·1
45-49	66	14	4·7	44	12	3·7
50-54	72	20	3·6	21	12	1·8
55-59	68	42	1·6	20	24	0·8
60-64	74	44	1·7	16	36	0·4
Total	352	128	2·8	150	96	1·6

Figure 2 shows the time lag from screening till the women were declared cancer free. At six months 64% (219/342) and 73% (107/147) of the women with false positive findings in the first and second rounds were declared cancer free.

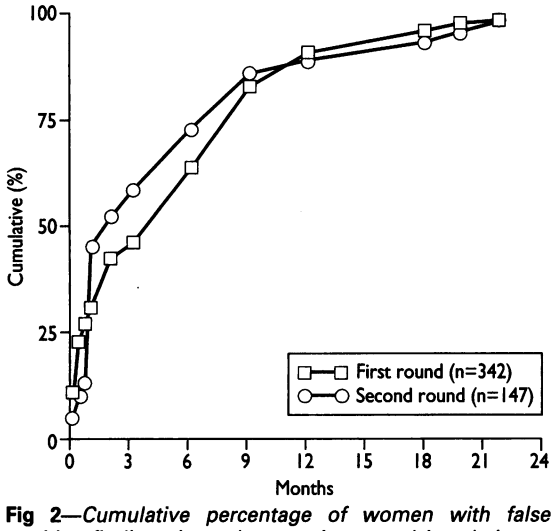

Fig 2—*Cumulative percentage of women with false positive findings in each screening round in relation to time (months) till they were declared cancer free. Hospital records were missing for 10 women in first round and seven women in second round*

The total costs of the examinations and investigations of women with false positive mammograms were Kr2.54m (£250 000) in the first screening round and Kr0.85m (£84 000) in the second round. Of the total costs in the first round, 41% referred to women under 50 (table 1). Table 1 summarises the costs of the false positive findings per 1000 screened women and per cancer detected and the cost of the whole screening programme.

Discussion

Women with false positive findings in the Stockholm mammography screening trial have undergone many diagnostic procedures often over prolonged periods before being declared cancer free. The cost of examinations alone due to false positive findings is substantial. A total of 32 451 women accepted the invitation for screening in the first round of the trial and 30 906 accepted in the second round. The total costs of screening these women, including follow up by three view mammography, were Kr6.7m (£663 000) in the first round and Kr6.1m (£604 000) in the second round. However, the need to investigate women with false positive findings till they could be declared cancer free generated a further Kr2.54m and Kr0.85m in the two rounds. This is a generally neglected aspect of the total costs of screening with mammography.

Studies of the cost effectiveness of screening with mammography have shown great variation in the cost per year of life saved. This variation has been due to several factors—for example, differences in the prevalence and incidence of breast cancer between different countries and ethnic groups, the age groups of the women screened, the intervals between screens, the methods of calculation, and the costs assessed.[12] Studies show that screening is least cost effective in women under 50 because of the lower incidence of breast cancer and reduced effectiveness of mammography in younger women. It is also reportedly less cost effective to screen women over 75 because of the potentially fewer years of life left to save.[13-16] Yearly screening has been shown to be less cost effective than two yearly screening, though yearly screening makes it possible to detect some cancers at an earlier stage and reduce mortality to some extent.[17]

Except for reports of the numbers of surgical procedures performed for benign lesions, no major screening trial or programme has included an analysis such as the one presented here.[22-25] We therefore do not know whether such extensive clinical follow up is relevant only to the Stockholm trial. In Swedish mammography screening programmes the ratio of benign to malignant lesions subjected to biopsy has reportedly been kept low. In the two county study the ratio was 1:1 in the first round and 1:3 in the second, and the corresponding ratios in the Stockholm trial were 1:1.4 and 1:3.4.[26,27] These ratios are much more favourable than those reported from Canada and the United States.[18,28] We cannot exclude the possibility that the low benign to malignant biopsy ratios in Sweden are related to more extensive follow up of the women with inconclusive findings.

We did not study the possible adverse psychological consequences of the false positive mammograms in these women. But given the considerable time lag and the many examinations and investigations needed before they could be declared cancer free (fig 2, table 1) it would seem reasonable to conclude that they suffered substantial stress. A woman told that she might have breast cancer suffers the same anxiety whether she turns out to have cancer or not.[29] It is usually claimed that fear of delaying the diagnosis of breast cancer is greater in the United States than in Europe[30] and leads to more benign biopsies in American screening series. Our study indicates that this is not so. Hospital records showed that the repeated check ups were to reassure radiologists and oncologists that nothing pathological was going on in the women's breasts. However, subjecting women to repeated biopsy and continued monitoring may have adverse psychological effects, but few studies have examined this issue. Currently we have no evidence to show which is worse for the women.

BENEFITS VERSUS POSSIBLE NEGATIVE EFFECTS

The benefits of screening are a reduction in breast cancer mortality and more breast conserving operations. However, to justify mammography screening these benefits must outweigh any negative effects. A seven year follow up from the Stockholm trial showed an overall non-significant 29% reduction in mortality in the study group.[31] The subgroup of women aged 40-49 years showed no reduction in mortality after seven years. However, seven years is too short a time to draw firm conclusions and the subgroup of younger women was small. The overview of Swedish randomised trials showed a mortality reduction of 13% among women aged under 50 but the mortality curves did not diverge until after eight years.

Figure 1 shows that comparatively few invasive cancers were found among women under 50 in the two screening rounds but that among malignant lesions in this age group comparatively high proportions were

Key messages

- Women who have false positive results of mammography may suffer needless anxiety and generate extra costs
- These extra costs come from the examinations and investigations required during follow up—for example, repeated biopsy of benign tissue—before the patient is declared cancer free
- In this series the costs of following up women with false positive mammograms were almost one third of the cost of screening all women in the randomised Stockholm mammography trial
- These extra costs and other negative aspects of false positive results of mammography—especially in women under 50—are a neglected but substantial problem
- The benefits of mammography must be carefully weighed against the potential negative aspects, especially in women under 50

carcinomas in situ (23% (5/22) and 29% (7/24)). Detection of carcinoma in situ is not considered to be a goal of a screening programme; ductal carcinoma in situ left without operation might never threaten life.[32]

The proportion of benign lesions selected for further investigation between the first and second screening rounds decreased more for women aged 50 and over at entry than for younger women (table 2). With repeated screening of women aged over 50 the recall rate can be kept low, as in the Stockholm programme at South Hospital; 1·5% of screened women were recalled for complete mammography, of whom 0·81% underwent further investigation and 0·41% were finally diagnosed as having cancer.[33] Such a favourable decrease in the recall rate probably cannot be expected with repeated screening of younger women (table 2).

This study was focused on a screened population. Whether non-screened women have a similar pattern of examinations and investigations remains to be determined. Our objective was to present facts and draw attention to the time, volume, and costs of diagnostic procedures and the related implications of these procedures associated with false positive findings in mammography screening programmes. We believe that a similar analysis should be done in other mammography screening programmes, giving opportunities to compare how different units deal with false positive findings and thus encouraging efforts to minimise the problem.

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ONE HUNDRED YEARS AGO

The Woman Who Wouldn't. A Novel by LUCAS CLEEVE. (London: Simpkin, Marshall, Hamilton, Kent and Co. 1895. Demy 8vo, pp. 233. 3s. 6d.)—This one volume novel is a contribution to "the eternal sex question," a question which cannot fail to be more and more discussed as the eyes and minds of women are opened by education. Never, however, since the Kreutzer Sonata was written, were sexual matters, not usually mentioned in fiction, quite so plainly treated as in the volume before us. "The woman who wouldn't" learnt, however, as others have done, that in surrender to the physiological needs of humanity her reward was the crown of motherhood. That women will marry later in life than their grandmothers did, and that many women will not marry at all, are the inevitable results of granting them education, intellectual occupation, freedom, and wider life interests; but if in marrying they accept marriage rationally, knowing beforehand its physical penalties, its risks and obligations, happier unions are more likely to be made than when a girl thinks the wedding ring admits to a paradise, to discover afterwards that her god has feet of clay and a heart of brass. In this story very *risqué* matters are treated with considerable deftness and delicacy. Though the light from within must in each individual be the guide to deliver from the pitfalls of sensuality, it may be well that the conscience of some be aroused on the possible prostitution of marriage.

(*BMJ* 1896;i:28.)