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Repeated screening for breast cancer

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SUMMARY In a screening service for breast cancer the results of routine repeat tests of women will contribute more than the results of their initial tests. A comparison of first and subsequent screens in a group of high risk women suggests that the sensitivity of screening declines between first and subsequent visits, whereas its specificity improves. Despite improved specificity, the ratio of benign biopsies to cancer was worse at repeated screening (21 to 1) than at first screening (6 to 1). This was because between first and subsequent screens the yield of cancers fell to a greater extent than the yield of benign disease. The patients with breast cancer diagnosed during this study were remarkable for their good prognosis, 92% being still alive and 86% free from recurrence at their last follow up, the follow up intervals ranging from four to eight years.

In the West London feasibility study of different screening methods for breast cancer a self selected group of women aged 40 and over were screened on four successive occasions. Information was collected on the sensitivity, specificity, and cost of screening by clinical examination alone, mammography alone, and by these two modalities combined. Previous reports have described the results of each screening modality at the initial visit[1–3] and of the four repeated screens grouped together.[4] The present paper compares the yield of both breast cancer and benign breast disease at the first screen with that at subsequent screens and discusses how the validity of the tests alters between first and subsequent screens. Follow up information on the survival and disease free interval of all patients with cancer diagnosed during the course of this study is also presented.

Method

A breast screening clinic set up in 1973 was open to any woman aged 40 or over who lived in the London Borough of Ealing. Apart from a small group known to have a family history of breast cancer, women were not personally invited but learnt about the clinic through general publicity. A total of 2484 attended for screening and each was reinvited at intervals of six months, 12 months, and 24 months after her first attendance. Screening was by clinical examination and mammography, each of these modalities being reported without knowledge of the result of the other. Any woman in whom a breast abnormality was suspected was referred, through her general practitioner, to a hospital outpatient breast clinic for surgical assessment. All patients diagnosed as having breast cancer have been followed up through the hospital concerned. In addition an attempt was made to follow up all other women in the survey for 12 months after their last screening attendance to determine any subsequent breast disease that occurred in this time. Forms were sent to their general practitioners asking if any breast disease had been diagnosed within a year of the date of their last screening attendance. Out of 2437 forms sent out 1704 (77%) were returned and one further case of breast cancer was reported.

Results

COMPLIANCE

Attendance rates for repeated screening were high, as would be expected in this population of women, most of whom had self selected themselves for screening. After excluding women who were diagnosed as having breast cancer during the course of the survey and 12 women who died of other causes, 91% attended the second visit, 88% the third, and 86% the fourth.

YIELD OF DISEASE

Table 1 shows the breast abnormalities that were detected by each of the four successive screens,

expressed as a rate per 1000 women screened. The high rate of disease on the first occasion reflects the prevalence of preclinical breast abnormalities in this group of women, presumably including a range of durations of disease from some very early cases that had just become detectable to others of much older duration that were probably about to present clinically. The prevalence of breast cancer was 9.7 per 1000 on first screening, but at repeated screens the yield fell to around 1 per 1000. The latter were presumably new incident cases arising in the interval between screens to a detectable but still asymptomatic stage. Some additional patients with breast cancer (not included in table 1) presented with symptoms during the intervals between screens and these cases, missed by the screening programme, are discussed further below.

Table 1 *Rate of diagnosis of breast cancer and other breast abnormality per 1000 women, at each screening attendance*

	1st screen	*2nd screen*	*3rd screen*	*4th screen*
Breast cancer	9·7	0·9	1·4	0·5
Benign abnormality:	128·9	54·7	42·5	40·0
Biopsied	62·0	21·1	17·5	20·0
Not biopsied	66·8	33·6	25·0	20·0
No of women screened	2484	2232	2163	2105

The prevalence of benign disease was nearly 130 per 1000 at first screening and the yield thereafter fell to around 45 per 1000. Not all of this benign disease found at repeated screening was new; some was persistence of a chronic condition. Sixty four women were referred twice with a benign abnormality, 12 were referred three times, and one was referred after all four screens. Twenty three women had benign biopsies after two different screening visits.

SENSITIVITY

It is a common convention in cancer screening to regard cancers presenting symptomatically in the interval between one screen and the next as false negative results to the previous screen. Sensitivity is defined by the number of cancers detected at a screen expressed as a proportion of those detected at the screen plus those that present symptomatically before the next screen is due. Table 2 shows that screening detected 24 out of 25 cancers at first screening (sensitivity 96%) but only six out of 10 cases at subsequent screens (sensitivity 60%). Of these six cases, two were found at the second visit, three at the third, and one at the fourth. The remaining five cancers presented symptomatically, one being diagnosed four months after the first screen, two at intervals of six months, one at an interval of four months after the third screen, and one at an interval of two months after the fourth screen. A substantial proportion of cancers would have been missed by screening if either clinical examination or mammography had been omitted. At the first screen either modality alone would have detected only 70% of cancers. Clinical screening found only three out of the subsequent ten cancers, and mammography only four.

Table 2 *Method of diagnosis of cancers*

	1st screen	*Subsequent screens**
Detected by screening:		
X ray alone	6	3
X ray + clinical	11 (24)	1 (6)
Clinical alone	7	2
Interval cases	1	4
Total cancers	25	10

*Includes cancers diagnosed up to 12 months after fourth screen.

SPECIFICITY

The high yield of benign abnormality reflects the lack of specificity of these tests. Specificity—the test's ability correctly to classify women without cancer as negative—is defined by the number of women with negative results expressed as a proportion of all women not diagnosed as having breast cancer before the next screen is due. Specificity increased between the initial and subsequent screens from 87% to 96%. This improvement may be partly due to the surgical removal of prevalent benign disease detected at the first screen and partly to increasing experience of the screening staff in deciding on the degree of abnormality necessitating referral. Approximately half of these referrals required a surgical biopsy to establish the correct diagnosis, and there was no significant difference in this proportion between those referred from the first and those referred from subsequent visits. Another measure of the extent to which screening results in possibly unnecessary biopsies is given by the ratio of benign biopsies to cancers. Despite the improved specificity of subsequent screens, this ratio deteriorated from six benign to one malignant at the initial screen to an average of 21 to one at subsequent screens. This was because the yield of benign disease at repeat screening fell less than the yield of cancer.

The benign referrals from each modality are listed in table 3, indicating that mammography is much

more specific than clinical examination, a fact which contributes to its superior cost efficiency.[3] In subsequent screens there is remarkably little agreement between mammography and clinical examination, suggesting a difference in criteria for referral.

Table 3 *Non-malignant referrals from mammography and clinical examination at first and subsequent screens*

	1st screen	*2nd screen*	*3rd screen*	*4th screen*
No without cancer referred:	320 (13%)	122 (5%)	92 (4%)	84 (4%)
X ray alone +ve	50 (4%)	26 (1%)	23 (1%)	22 (1%)
X ray and clinical +ve	48 (11%)	6 (4%)	3 (3%)	2 (3%)
Clinical alone +ve	222	90	66	60
No without cancer screened (100%)	2459	2230	2157	2103

STAGE DISTRIBUTION OF CANCER PATIENTS

Table 4 shows that most breast cancers in this study were diagnosed at an early stage. The small numbers detected at subsequent screens and in the interval between screens do not permit conclusions on whether they tend to be diagnosed earlier or later than those detected at first screening.

Table 4 *Stage distribution of breast cancers according to time of diagnosis*

	$T_0 - T_3$ *Node −ve*	$T_1 - T_3$ *Node +ve*	T_3 *Node +ve −ve or metastases*	*Total*
First screen	14*	9	1	24
Subsequent screens	4	2	—	6
Interval cases	4	—	1	5
Total	22	11	2	35

*In four cases the nodes were clinically negative but were not histologically examined.

SURVIVAL OF PATIENTS WITH CANCER

All the 35 patients with breast cancer have now been followed up for at least four years, some of them for as long as eight years from the date of diagnosis. Only three of the 35 have died. One was an interval case already metastatic at the time of diagnosis who died two years later. The other two patients were both diagnosed by the first screen, one had a T_2 node positive tumour and died three and a half years later and the second a T_3 node positive tumour and died six years later. Two further patients whose cancers were detected at the first screen have developed metastatic disease, six and a half years and seven and a half years after diagnosis. Thus 32 out of 35 patients (92%) were alive and 30 (86%) were free from disease at their last follow up. The six cases detected at repeated screening are all in the latter category, their follow up periods ranging from 53 months (a patient who moved away and was lost to follow up) to 89 months.

Discussion

The population of women included in this study was a self selected high risk group,[1] and the mammography technique was probably of poorer quality and the diagnostic criteria less well defined than those used today. These facts, together with the small size of the sample, mean that the actual levels of prevalence, sensitivity, and specificity cannot be extrapolated to predict the results of screening a general population of middle aged women. Nevertheless, this is one of the few studies that has compared the results of initial screening with those of subsequent screens, and the difference found may well apply more generally.

In a continuous screening service for breast cancer women would probably be offered screens every one to three years throughout middle and old age. In such a situation the results of repeated screens would contribute more than those of the initial screen, which would apply only to the small proportion who entered the eligible population each year. It is therefore important to understand how repeated screening affects not only the yield of cancers detected but also the efficiency of the screening modalities used.

In the HIP study in New York the yield of cancers on first screening an unselected group of women was 2.7 per 1000 falling to 1.5 per 1000 at subsequent annual screens.[5] In the BCDDP study, involving a volunteer population, the initial prevalence was 4.8 and the subsequent annual yield 1.9 per 1000.[6] The particularly high prevalence of both cancers and benign disease in the present study was related to the self selection of women to attend this clinic, since 20% (40% of those with cancer) had symptoms when they first attended.

This study would suggest that the sensitivity of the screening tests in detecting cancer was greater at the initial screen than subsequently, and this is also borne out on a much larger scale in the BCDDP results where sensitivity fell from 85% to 77%.[6] A fall in sensitivity with repeated screening may be explained either by increased observer error due to the

monotonous nature of the task or by a different case mix of preclinical lesions available for detection. In a previously unscreened population it can be expected that some preclinical cases will be of relatively long duration and hence by implication may be larger and more easily detectable than the new cases available for detection at subsequent screens, whose duration can be no longer than the screening interval. The denominator used for estimating sensitivity includes all cancers detected at screening and all interval cases presenting before the next screen. Even if the number and behaviour of interval cases is the same after the first and subsequent screens they form a smaller proportion of the total number of cancers when considering the first screen with its high yield than in subsequent screens. Hence, sensitivity estimates based on initial screening may give an overoptimistic view of the proportion of cancers that can be detected by screening in continuous service.

The low specificity in this survey was partly caused by the self selection of participants with symptoms and partly by the study design in which referral for surgical opinion was based on the independent verdict of any of the screeners without consultation between them. No other studies that we are aware of have reported the specificity of subsequent screens. It is of interest that, although specificity improved substantially from the initial value, the ratio of benign to malignant biopsies became worse, because the yield of benign abnormalities did not fall to the same extent as that of cancers. If this finding is borne out by population based studies now in progress[7] it will have implications both for the way in which women are told of the need for biopsy, and for calculating the total cost of the screening programme.

The patients found to have breast cancer in this study are remarkable for their very good prognosis. It is invalid, however, to make a comparison between cancers detected by screening with others, because of the biasses of lead time, length bias, and patient selection.[8] One might expect that the interval cases would represent faster growing cancers with a poor prognosis, but this applied only to one of the five, the remaining four being alive with no recurrence at follow up five to seven years after diagnosis. The fact that these four were at an early stage at the time of diagnosis may indicate that this group of women had a heightened awareness of breast abnormalities and knew of the need to take action. The good prognosis for screening detected cancers is certainly not proof of the value of screening but is consistent with the hope that it may be effective in saving lives.

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