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The incidence of breast cancer from screening women according to predicted family history risk: does annual clinical examination add to mammography?

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Abstract

In breast cancer, mutations of predisposition genes such as *BRCA-1/2* and other genes as yet uncharacterised are manifest in up to 10% of cases. Although the prior probability of the presence of a breast cancer predisposing gene can be calculated for individual women, there is no published evidence to justify predicted risk as a selection criteria for screening. This study aims to define which patient groups with a significant family history should be screened, and whether clinical examination is necessary in addition to mammography. The Claus model was used to predict breast cancer risk in women with a family history. Women were divided into two groups according to their predicted risk: group I consisted of women at standard risk (lifetime risk less than 1:6) and group II with moderate/high risk (lifetime risk greater than or equal to 1:6). Women were cancer-free at the point of entry, and screening consisted of annual clinical examination and mammography from the age of 35 years. This study consisted of 1500 women in group I and 1078 in group II. The period of observation was 5902.0 and 4327.8 women years, respectively. A total of 31 cancers were detected, 12 in group I and 19 in group II. The median age at diagnosis in group II was 45 years (range 26–66 years) compared with 54.5 years (range 38–63 years) in group I ($P=0.03$). The relative risk of developing breast cancer in group II was 2.6 (95% confidence interval (CI) 1.2–5.8). When compared with breast cancer incidence in the normal population, the standardised incidence ratio in group II was significantly higher at 2.8 (95% CI: 1.7–4.2). The standardised incidence ratio of women in group I was similar to that of the general population (1.1 (95% CI: 0.6–1.8)). A total of 26/31 (84%) cancers detected were palpable, of which 14 (54%) were not visible on mammography. Approximately one-third of all palpable cancers were detected at routine follow-up. Mammography correctly identified 17/31 cancers (55%), but 29% of these were not palpable. Family history screening programmes are effective and women should be selected for screening according to predicted risk. The younger age of diagnosis in group II justifies screening from an earlier age using both annual clinical examination and mammography.

Keywords: Family history; *BRCA-1*; Breast cancer; Breast screening; Mammography

1. Introduction

Family history is an established major risk factor in the pathogenesis of breast cancer [1,2]. The risk of an individual developing breast cancer can be predicted by various models, most of which have been derived having first identified an index case [3,4]. In breast cancer, high-risk germ-line mutations in cancer predisposing genes are manifest in 5–10% of women [5,6]. Approximately half of these genes can be attributed to *BRCA1* or *BRCA2*, with a life-time risk of developing cancer of 51% by age 50 years and 85% by age 70 years in high risk families [7], and approximately 37–50% by age 70 years in population-based studies [8,9]. Most randomised trials of screening women in the general population using mammography have shown a significant reduction in mortality from breast cancer [10–13], while other studies show no survival benefit [14,15]. Meta-analysis

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of the Swedish trials on screening women over the age of 50 years show a reduction in breast cancer mortality of greater than 30% compared with women who were not screened [16]. Screening women in the general population unselected for risk under the age of 50 years remains controversial [17,18], although more recent studies with longer follow-up demonstrate a survival benefit [19,20].

The Breast Diagnostic Unit (BDU) at the Royal Marsden NHS Trust in London was established in 1968 as a Well Woman Clinic that screened patients preceding the National Health Services Breast Screening Programme (NHSBSP). As it evolved, it included women with a wide range of risk from family history. This enabled us to review our data to provide information on patient selection for screening according to predicted risk, with the aim of addressing whether cut-offs can be drawn to justify screening women truly at risk, while reassuring and discharging those with a low risk family history. We also assessed the value of annual clinical examination to detect breast cancer in addition to annual mammography alone.

2. Patients and methods

Women were referred to the BDU by their general practitioners for a family history of breast cancer. A full clinical and family history were taken and recorded on pro forma notes at the first attendance. The Claus model was used to predict risk, calculated using data from the Cancer and Steroid Hormone Study [6], that takes into account the number of affected close relatives with breast cancer and age of diagnosis. The life-time risk of developing breast cancer in the United Kingdom general population remains approximately 1:12 or 8%. In this study, only women with a family history of breast cancer were included, and divided into two groups according to predicted risk. Group I consisted of women of standard risk (lifetime risk less than 1:6 or 16%) and group II consisted of women at moderate and high risk group (lifetime risk greater than or equal to 1:6 or 16%). Within group II, 233/1078 (21.6%) had a predicted life-time risk of developing breast cancer of greater than 1:4 or 25%.

Screening consisted of annual clinical examination and annual mammography from the age of 35 years. If the index case developed breast cancer under the age of 40 years, the unaffected relative was screened from 5 years younger than the earliest diagnosis within the family, with a lower limit of 25 years. All screening was undertaken by senior clinicians (medical and nursing) with extensive experience in breast examination and diagnostic methods. The risk allocation for women accepted into the family history programme is summarised in Table 1.

Relative risks were calculated from standardised incidence rates, with analysis of standardised incidence ratios according to the method of Breslow and Day [21]. Breast cancer incidence rates in England and Wales were obtained from the Office of National Statistics [22]. The cohort studied consisted of a pre-existing group of patients that had previously attended the BDU for screening and were cancer-free on 1 June 1993. As entry criteria depended on being well on 1 June 1993, incidence and follow-up data were calculated from this date to avoid lead-time bias of individuals who developed breast cancer in the screening programme up to that point in time. The results of this study therefore provide true incidence data on breast cancer development in women stratified according to their family history risk, together with information on methods of detection, tumour variables and outcome following treatment.

3. Results

Group I and II consisted of 1500 and 1078 women, respectively. The period of observation was 5902.0 and 4327.8 women years in each group, respectively. Both groups in this study of consecutive women had similar characteristics (Table 2). Thirty-one cancers were detected, 12 in group I and 19 in group II. Of the 31 cancers detected, two were found to be DCIS only without

Table 1
Stratification of family history risk into standard risk (group I) and moderate and high risk (group II) by age of onset of breast and associated cancers

Group I (lifetime risk $<16\%$)	Group II (lifetime risk $\geqslant 16\%$)
One first or second degree relative with breast cancer diagnosed >40 years	One first degree relative with breast cancer diagnosed $\leqslant 40$ years
Two first or second degree relatives with breast cancer diagnosed median age >60 years	Two first or second degree relatives with breast cancer diagnosed median age $\leqslant 60$ years Three or more relatives with breast cancer diagnosed median age $\leqslant 70$ years Four relatives with breast cancer diagnosed at any age Breast and ovarian cancer combinations First degree bilateral breast cancer diagnosed $\leqslant 60$ years First degree male breast cancer diagnosed $\leqslant 60$ years

Table 2
Cancer incidence data in women followed up for family history risk

	Group I	Group II
Women with family history risk (*n*)	1500	1078
Women years follow-up	5902.0	4327.8
Median number of screens	3.9	4.0
Median age at 1.6.1993 (years)	48.0	44.2
Total cancers detected (*n*)	12	19
Invasive cancer	12	17
DCIS	0	2
Cancers detected per 1000 visits	2.0	4.4
Median (range) age at diagnosis (years)	54.5 (38–63)	45[a] (26–66)

DCIS, ductal carcinoma *in situ*.
[a] Significantly lower age at diagnosis in group II compared with group I, Mann–Whitney test, $P = 0.03$.

Table 3
Breast cancer detection by clinical examination and/or mammography according to predicted risk in each of groups I and II

	Palpable lump	
	Yes	No
Mammographic abnormality		
Yes		
Group I	6	2
Group II	6	3
No		
Group I	4	0
Group II	10	0

invasive cancer and both these were in the moderate/high risk group. The median age at diagnosis in group II was 45 years (range 26–66 years), significantly younger than the median age of women in group I at 54.5 years (range 38–63 years) ($P = 0.03$, Mann–Whitney test).

The relative risk of developing breast cancer in the moderate/high risk group was significantly higher at 2.6 (95% confidence intervals (CI) 1.2–5.8) compared with the low risk group. When compared with the population incidence rates derived from Office of National Statistics data, the development of breast cancer in the standard risk group was not significantly different from the population incidence with a relative risk of 1.1 (95% CI: 0.6–1.8). The relative risk in group II compared with population incidence rates, however, was significantly higher at 2.8 (95% CI: 1.7–4.2).

A total of 26 of the 31 cancers (84%) were palpable, and of these 14 (54%) were palpable, but not visible on mammography (Table 3). Mammography correctly identified 17 out of the 31 cancers (55%). Five of the 17 (29%) were visible only on mammography and not palpable. Of the 26 cancers that were clinically detectable, 17 (65%) were felt by the patient and nine (35%) found by the clinician. The patient-detected clinical abnormalities presented as 15 interval cancers, while 2 patients waited for their routine outpatient appointments to report their findings. All radiological and clinician detected lumps were identified at routine visits. Fine needle aspiration cytology confirmed the pretreatment diagnosis in 27 patients, and a pretreatment diagnosis was achieved in the remaining women on core-cut biopsies for histology.

The pathological variables of the cancers detected in this cohort are summarised in Table 4. In group I, nine out of 12 cancers (75%) were T1 tumours 20 mm or smaller in diameter, while 14 out of 17 (82%) cancers detected in group II were 20 mm or smaller. The majority of the cancers were grade 2 or 3 and 60% of the patients overall were lymph-node negative. These cancers were treated according to standard hospital protocols in place at the time of diagnosis after multidisciplinary review (Table 5). All patients who had grade 3 cancers and who were lymph node-positive had chemotherapy. Radiotherapy to the breast with a boost to the tumour bed was given to all patients after breast conservation surgery. Women who had mastectomies and who were node-positive routinely received radiotherapy to the chest wall. Tamoxifen was given to all women who were oestrogen receptor (ER)-positive. Two women in group I developed distant metastases (one has since died), and one patient in group II died of distant disease.

4. Discussion

Greater awareness of breast cancer and the recognition of family history as an important risk factor have led to increasing numbers of women referred to breast and genetics clinics. As breast cancer is a common condition, many women could potentially attend for assessment because of a cancer history that may have occurred by chance. Diagnostic testing for breast cancer predisposition gene mutations is usually only offered after full genetic counselling when a prior probability of the presence of the breast cancer predisposition gene being tested in the family is far greater than 10% [23,24]. Most women referred to breast clinics for family history assessment do not meet this criterion.

The options for women at high risk of developing breast cancer include breast surveillance, chemoprevention or prophylactic mastectomy. Although the National Surgical Adjuvant Breast and Bowel Project showed tamoxifen chemoprevention to reduce the risk of breast cancer by 49% with a median follow-up of 55 months [25], interim analysis of two European trials did not confirm this finding [26,27]. Powles and colleagues included women with a family history of breast cancer with comparable risk factors to our study, and despite a median follow-up of 70 months, found that chemoprevention cannot be currently recommended to mem-

Table 4
Pathological variables of invasive breast cancers ($n = 29$) detected at incidence screens

	Group I	Group II
Pathological type		
Invasive ductal (IDC)	10	13
Invasive lobular (ILC)	1	0
Invasive mixed	1 (IDC + ILC)	2 (1 tubular + IDC; 1 mucinous + IDC)
Unknown	0	2 (1 patient had a complete response to primary chemotherapy; 1 had an occult primary presenting with axillary metastasis)
Size		
10 mm	2	4
10–20 mm	7	10
21–30 mm	3	1
> 30 mm	0	0
Unknown	0	2 (1 patient had a complete response to primary chemotherapy; 1 had an occult primary presenting with axillary metastasis)
Grade		
1	1	1
2	6	6
3	5	8
Unknown	0	2 (1 patient had a complete response on primary chemotherapy; 1 had an occult primary presenting with axillary metastasis)
Lymph node status		
Negative	6	9
Positive	4	6
Unknown	2 (both clinically node-negative: 1 had radiotherapy to the axilla; 1 had distant metastasis at presentation)	2 (1 patient had a complete response to primary chemotherapy; 1 patient had nodes left electively at primary surgery, but recurred at 3 months and was positive on axillary dissection)
Oestrogen receptor (ER) status		
ER +	10	10
ER−	2	5
Unknown	0	2 (1 patient had a complete response to primary chemotherapy; 1 patient was treated elsewhere)

bers of high risk groups [26]. The efficacy of prophylactic mastectomy in a retrospective study of 639 women with a family history of breast cancer is estimated to reduce the incidence of breast cancer by at least 90% [28], but acceptance of this aggressive intervention amongst cancer predisposing gene carriers may be variable.

The value of screening asymptomatic women with a family history is controversial [29–31]. Kollias and colleagues presented the results of screening women under the age of 50 years with a family history of breast cancer in Nottingham. Prevalent and incident cancers are combined in their results, and of 1371 women screened with a mean follow-up of 22 months, 29 cancers (23 invasive and six *in situ*) were detected [30]. Lalloo and colleagues reported the Manchester experience of 1259 women with a predicted life-time risk of 1:6 and a median follow-up of 30 months. In that study, 16 breast

Table 5
Treatment modalities used in the 31 cases of breast cancer detected

	Group I ($n = 12$) n (%)	Group II ($n = 19$) n (%)	Comments
Surgery	11 (93)	18 (95)	Surgery was not performed in two patients: 1 patient in Group I had distant metastasis at presentation; 1 patient in Group II had complete response after primary chemotherapy and had radical radiotherapy with tamoxifen.
Chemotherapy	7 (58)	10 (53)	All patients with grade 3 or node positive cancers had adjuvant chemotherapy.
Radiotherapy	10 (83)	15 (79)	Adjuvant radiotherapy was given to all patients after breast conservation surgery. Radiotherapy was given to the chest wall if lymph node positive.
Endocrine therapy	12 (100)	14 (74)	Tamoxifen was given to all women with oestrogen receptor positive invasive cancers and some with oestrogen receptor negative cancers, according to practice at the time. Patients who had DCIS alone did not have tamoxifen.

DCIS, ductal carcinoma *in situ*.

cancers were detected seven of which were prevalent and nine incident, including two interval cancers [31]. In both these studies, the prevalent cancers amounted to approximately 40% of their cases [30,31]. Our study consisted of a larger cohort of women screened with longer follow-up, and included only true incident cancers, as the prevalent screening rounds had already been completed prior to entry. As expected, the incidence of breast cancer in our moderate/high risk group (group II) was significantly higher compared with group I. The relative risk of developing breast cancer in the standard risk group was similar to that of the general population. The low incidence of cancer in group I is related to weak family histories that are likely to have occurred simply by chance.

Mammography as a screening tool under the age of 50 years has a lower overall accuracy than in postmenopausal women [32]. The sensitivity of mammography in our study in picking up breast cancer was 55%. Of the 31 breast cancers detected, 26 (84%) were palpable. Seventy-one per cent of the cancers detectable only on clinical examination were in the high risk group (Table 3). In this study, 14 out of 31 cancers (45%) would have been missed if mammography alone had been done without clinical examination, ten of which were in the moderate/high risk group. Only five cancers visible on mammography were not palpable (16%). Family history screening clinics for women at risk of developing breast cancer should therefore consist of clinical examination as well as mammography. Of the clinically detected cancers, 17 out of the 26 were found by patients, while the remainder were detected by clinicians at routine screening visits. The Canadian National Breast Screening Study-2 randomised women aged 50–59 years into annual screening by mammography and physical examination compared with physical examination without imaging and found that the addition of mammography to physical examination had no impact on mortality [15]. Family history and other risk factors were not considered in this population-based breast screening programme which were also targeted at older women compared with our higher risk younger population.

Approximately 80% of the invasive cancers detected in our study were 20 mm or smaller in diameter (Table 4). This is likely to translate into a survival benefit with longer follow-up, as has been demonstrated in general breast screening programmes in women over 50 years [16]. The relatively short follow-up of this and other studies [30,31] suggest that no firm conclusions can be drawn on the survival benefit of screening moderate/high risk women. Surprisingly, only two cases of DCIS were detected in this study. Although this may be because mammography has a lower sensitivity in the age group studied, highly penetrant genes such as *BRCA-1* and *BRCA-2* may be associated with an increased cancer risk, but lower incidence of DCIS [33]. The significance of detecting non-invasive malignancy remains controversial, although the estimated risk of developing invasive cancer following DCIS is estimated to be up to 50% at 10 years [34,35].

An important consideration in breast screening is the high cost of introducing a programme to younger women. Patient selection according to predicted risk of developing breast cancer from their family history, however, facilitates targeting a population that requires to be screened. The incidence of breast cancers detected in our moderate/high risk group was 4.4 per 1000 visits (Table 2). The NHSBSP detects breast cancer in the incident screen of approximately 3.8 cancers per 1000 visits in women aged over 50 years screened by 3-yearly mammography [36]. If breast screening of the general population over the age of 50 years is considered acceptable, our results suggest that screening women under the age of 50 years who are at moderate/high risk of developing breast cancer has a similar breast cancer detection rate. The guidelines recommended by the British Association of Surgical Oncology suggest that screening of relatives with a significant family history should start at age 35 years [37], and data from our study would support the implementation of these recommendations.

In conclusion, our study supports the effectiveness of a screening programme for women with a family history, selected according to prior probability. The younger age of diagnosis in the moderate/high risk group justifies screening from an earlier age than that offered by the NHSBSP, by clinical examination in addition to mammography. Women in the standard risk group do not need special screening and should be encouraged to attend routine national breast screening. As criteria for family history screening can now be set, this task should be taken on by adequately funded specialist clinics, with quality assurance established along the lines of the national screening programme.

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