Pergamon

European Journal of Cancer, Vol. 34, No. 6, pp. 878–883, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)00365-1

Original Paper

Screening Women Aged Less than 50 Years with a Family History of Breast Cancer

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Family history is an important breast cancer risk factor and is a common reason for referral to specialist breast clinics for consideration of breast screening. The aims of this study were to determine cancer detection rates and prognostic features of breast cancers identified in women aged less than 50 years at increased risk of breast cancer who attend a Family History Breast Screening Clinic (FHC). Between January 1988 and December 1995, 1371 asymptomatic women aged less than 50 years underwent annual clinical breast examination and biennial mammography due to a family history of breast cancer. A total of 29 cancers (23 invasive and 6 *in situ*) were detected or presented as interval cancers during a mean follow-up of 22 months (range 0–96 months). This gave a relative risk for invasive breast cancer in this high-risk group of 5 when compared with an age-matched female population in the U.K. The cancer screening detection rates were similar to those of women aged 50 years or over undergoing population screening in the NHS Breast Screening Programme (NHSBSP)—FHC prevalent screen 8 per 1000 screening visits versus NHSBSP 6.5 per 1000, FHC incident screen 3.3 per 1000 screening visits versus NHSBSP 3.8 per 1000. A higher proportion of *in situ* cancers were detected in the FHC screened group compared with cancers identified in symptomatic patients from an age-matched risk group (21% versus 4%). No differences were demonstrated for invasive tumour size, grade or lymph node stage between symptomatic and screened women. The early results of this study suggest that young women at risk of breast cancer due to a family history may benefit from regular breast screening due to the early detection of *in situ* lesions. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, screening, family history
Eur J Cancer, Vol. 34, No. 6, pp. 878–883, 1998

INTRODUCTION

FAMILY HISTORY is an established risk factor in breast cancer [1–4]. Concerns regarding breast cancer risk have led to an increasing number of young asymptomatic women being referred to specialist breast clinics for counselling and risk assessment. Breast screening using regular breast examination and mammography is often offered to women at risk attending such clinics, but as yet there is no evidence of any resultant survival benefit. Results from randomised trials of population-based breast screening using mammography have shown a reduction in mortality from breast cancer in women aged over 50 years of greater than 30% [5]. The results of screening women under 50 years of age have not shown a statistically significant benefit.

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Received 14 Jan. 1997; revised 21 Jul. 1997; accepted 22 Jul. 1997.

The Nottingham City Hospital Family History Breast Clinic (FHC) commenced screening in October 1988 for asymptomatic women under 50 years of age at increased risk because of their family history of breast cancer. The aims of this study were: (1) to confirm the predicted higher incidence of breast cancer in this high risk group; (2) to compare breast cancer detection rates in these women with those of population screening of women aged 50–65 years in the NHSBSP; (3) to compare the prognostic features of all cancers arising in the screened group with those arising in women of the same age with a family history but who had not attended the FHC prior to the detection of their cancer.

PATIENTS AND METHODS

Between October 1988 and December 1995, 1371 asymptomatic women aged < 50 years were offered screening at a special weekly FHC at the Nottingham City Hospital. The

Table 1. *Eligibility criteria for asymptomatic patients offered Family History breast screening*

- Entry age < 50 years
- Screening commences at age 10 years younger than youngest affected relative
- One or more affected first-degree relatives aged < 60 years
- Multiple affected relatives aged < 60 years such that lifetime breast cancer risk is at least 1 in 9

eligibility criteria for acceptance for screening are summarised in Table 1. The minimum requirement for screening was for a woman to have one first-degree relative with breast cancer whose age of onset was less than 60 years or multiple affected relatives with age of onset less than 60 years; under these circumstances, the lifetime risk of breast cancer in women accepted to the FHC is at least 1 in 9. Cumulative lifetime risks are assessed using risk tables according to Claus and associates [6].

The median age of patients accepted for FHC screening during the study period was 41 years (range 18–49 years). Using the Claus risk tables, the median breast cancer lifetime risk for the screening cohort was 16.5% (range 11–45%) and the median calculated relative risk was 2.3 (range 1.5–6). The characteristics of the patients' family histories are summarised in Table 2, with the majority having a history of only one affected first-degree relative.

Breast screening commences at an age no more than 10 years younger than the youngest affected relative. This consists of annual clinical examination in the FHC and biennial mammography. There was no minimum age of entry, although only 31 patients (2%) were undergoing regular clinical examination before the age of 25 years. In general, mammography was not routinely performed until the age of 35 years unless the family history suggested multiple affected relatives with very early age of onset. In these unusual circumstances, an individualised screening plan was made for each patient after consultation with the breast radiologist. Craniocaudal and mediolateral mammogram views were taken at the first screening visit (prevalent screen) and oblique views taken subsequently. All mammogram films were read by radiologists experienced in breast imaging. Patients received instructions in breast self-examination and were offered open direct access to the clinic should they find a breast problem between routine clinic visits.

The histological features of tumour size, lymph node stage, tumour grade and tumour type were reported using standard criteria [7, 8] for all invasive cancers identified and the Nottingham Prognostic Index (NPI) calculated for each [9]. The NPI identifies groups of patients with invasive breast cancer who have significantly different survival outcomes according to tumour size, histological grade and lymph node stage. Patients in the good prognostic group (GPG) have a 15 year survival of over 80%, only marginally lower than an age-matched population. Patients with ductal carcinoma *in situ* (DCIS) or invasive cancers in the GPG thus represent a group at low risk of death from breast cancer, whilst patients within the moderate (MPG) or poor (PPG) prognostic groups are likely to die as a result of their breast cancer.

The overall invasive breast cancer incidence for FHC screened patients in this study was compared with that of an age-matched population in the U.K. [10]. Breast cancer detection rates at prevalent (first visit) and incident screens (subsequent scheduled visits) were compared with those in women 50 years of age and over, attending the population-based United Kingdom National Health Service Breast Screening Programme (NHSBSP) [11].

Between November 1988 and December 1995, 238 women aged less than 50 years (median age 43 years, range 28–49 years) presented to the Nottingham City Hospital with symptomatic primary operable breast cancers. Of these, a subgroup of 54 women would have been eligible for family history screening according to our protocols based on their family history of breast cancer. None of these women had undergone previous breast screening. The prognostic features of the 54 'symptomatic' cancers were compared with screen-detected cancers identified in women under 50 years of age attending the Family History Clinic. The family history details of the symptomatic group are summarised in Table 2.

Statistical differences between groups were evaluated using the Chi square or Fisher's exact tests.

RESULTS

The mean time for which the patient group had been attending the FHC was 22 months (range 0–96 months). Twenty-nine cancers (6 DCIS and 23 invasive) were diagnosed in 1371 women screened (median age 44 years, range 31–49 years). This gave an incidence for invasive breast cancer in this high risk group of women of 7.9 per 1000 women-years. The incidence of breast cancer in England and Wales for an age-matched female population is 1.6 per 1000 women-years [10] such that the risk of breast cancer in the FHC screened group was five times that of the general

Table 2. *Family history/risk factor characteristics and breast cancers of* 1371 *women aged* < 50 *years attending FHC screening between October* 1988 *and December* 1995 *and* 54 *patients aged* < 50 *years with symptomatic breast cancer matched for family history during the same time interval*

Family history characteristics	FHC screened women (%)	Cancers in FHC screened women (%)	Cancers in non-screened women with family history (%)
Two first-degree relatives	80 (6)	4 (14)	1 (2)
One first- and one second-degree relative	278 (20)	3 (10)	9 (17)
One first-degree relative	776 (57)	18 (62)	29 (54)
Three or more relatives	206 (15)	3 (10)	9 (17)
Two second-degree relatives	24 (2)	0	6 (11)
Atypical hyperplasia	6 (< 1)	1 (4)	0
Atypical hyperplasia and family history	1 (< 1)	0	0
Total	1371	29	54

Table 3. Prevalent screen breast cancer detection rates in women aged < 50 years attending Family History screening and women aged 50–64 attending the U.K. NHS Breast Screening Programme (Trent region)

	Prevalent screen FHC Age < 50 years ($n = 1371$)	Prevalent screen NHSBSP Age 50–64 years ($n = 72\,773$)
Overall cancers	8/1000	6.5/1000
DCIS only	2.2/1000	1.2/1000
Invasive cancers only	5.8/1000	5.3/1000

population. A total of 8 cancers were detected in women aged < 40 years and 21 in women aged 40–49 years.

The nature of the family history in those who developed breast cancer compared with the entire study group is shown in Table 2. The proportion of women developing cancer was similar for each family history risk category.

Of the 29 cancers diagnosed, 19 were detected at routine screening visits: 11 (38%) at the first clinic visit (prevalent screen) and 8 (28%) at routine follow-up visits (incident screen). Ten cancers (34%) were diagnosed at interval appointments made because a lump was discovered by the patient incidentally or by routine breast self-examination. Mammography demonstrated 23/29 cancers (79%). A preoperative tissue diagnosis was made in 23 cases (79%) with 6 patients having required open biopsy to confirm the diagnosis of malignancy. During the period of study, 24 open biopsies were performed for benign disease giving a ratio of benign open biopsies:number of cancers detected of 1:1.2.

Prevalent screen

Eleven cancers (8 invasive, 3 *in situ*) were detected in 1371 asymptomatic women whose median age was 41 years (range 35–49 years). Two cancers were mammographically occult. The cancer detection rate for the prevalent screen was compared with that for women aged 50–64 years who accepted invitations to attend the NHSBSP. The overall cancer detection rate in the FHC was 8 per 1000 compared with 6.5 per 1000 in the NHSBSP (Table 3). The breast cancer detection rates for invasive breast cancer were similar between the two screened groups, but more *in situ* cancers were detected in the FHC.

Incident screen

Eight cancers (6 invasive, 2 *in situ*) were detected in 1360 asymptomatic women during 2438 routine follow-up visits. All cancers were demonstrated on screening mammography. The cancer detection rate was therefore 3.3 cancers/1000 screening visits using annual clinical examination and 2-yearly mammography. This compares with the incident cancer detection rate of 3.8 cancers/1000 screening visits in women aged over 50 years attending the NHSBSP who are screened 3-yearly by mammography [11].

Interval cancers

During the follow-up period, 302 extra visits were made by patients between routine clinic visits. Ten cancers were detected at these interval visits. Six cancers developed within 12 months of a normal reported mammogram—two were mammographically occult at diagnosis and one was evident on the previous film (false-negative). Three cancers developed between 12 and 24 months of a normal reported mammogram—two were mammographically occult at diagnosis. 1 patient who developed an interval cancer at age 31 years had not undergone a preliminary mammogram and presented between routine clinical visits. The FHC interval cancer rate in the first 12 months after a routine screening mammogram was 2.2 per 1000 yearly intervals, and 3.4 per 1000 yearly intervals in the second 12 months (after routine clinical examination). Overall, the interval cancer rate in the 24 months after mammography was 2.5 per 1000 women screened.

Prognostic features of breast cancers

The histological features of the cancers detected in the FHC group were compared with those of 54 patients in the non-screened family history group (Table 4). A significant difference was seen in the proportion of cases of DCIS between screened and symptomatic patients (21% versus 4%: $P = 0.01$, Fisher's Exact test). Of the six cases of DCIS detected in the screened group, 5 (83%) were of high-grade comedo subtype. No differences were demonstrated for invasive tumour size, histological grade or lymph node stage between screened and symptomatic patients. In the FHC screened group, a higher proportion of cancers were in the combined DCIS/good prognostic group according to the NPI in comparison with non-screened patients (41% versus 30%)

Table 4. Histological features of cancers in women attending the Family History screening clinic and cancers in symptomatic women with a family history

Histological features		FHC screening (%)	Symptomatic (non-screened) (%)	*P* value
DCIS		6 (21)	2 (4)	0.01
Invasive cancers		23 (79)	52 (96)	
Size	0–2 cm	15 (65)	33 (63)	0.8
	> 2 cm	8 (35)	19 (37)	
Grade	I	2 (9)	3 (5)	
	II	9 (39)	19 (37)	0.8
	III	12 (52)	30 (58)	
Lymph node status	negative	15 (65)	31 (60)	0.8
	positive	8 (35)	21 (40)	
Tumour type	NST	13 (46)	41 (78)	
	special type	3 (10)	3 (6)	0.1
	lobular	7 (24)	6 (12)	
	atypical medullary	0	2 (4)	
Total		29	54	

Table 5. Prognostic features of all cancers detected in women attending Family History screening and cancers in symptomatic women with a family history ($\chi^2 = 0.80$, $P = 0.37$)

Prognostic features	FHC screening ($n = 29$)	Symptomatic ($n = 54$)
DCIS/good prognosis (NPI ≤ 3.4)	12 (41%)	16 (30%)
Moderate/poor prognosis	17 (59%)	39 (70%)

NPI, Nottingham Prognostic Index.

although the numbers were too small to reach statistical significance ($\chi^2 = 0.80$, $P = 0.37$) (Table 5).

DISCUSSION

Family history is an important risk factor in breast cancer [1–4]. A heightened awareness of breast cancer and risk factors has led to increasing numbers of young asymptomatic women being referred to specialist breast clinics for risk assessment and counselling. This referral trend is evident at the Nottingham City Hospital Breast Unit where the number of women referred by general practitioners because of a family history increased from 243 in 1992 to 466 in 1995.

The recent discoveries of breast cancer susceptibility genes such as *BRCA1* [12], *BRCA2* [13], *Ataxia telangiectasia* [14] and *TP53* [15] have led to much medical, media and community interest. Further advances in molecular genetics with gene mutational analysis are likely to lead to specific recommendations regarding breast cancer prevention in affected families. It has been estimated that less than 5% of breast cancer is due to highly penetrant dominant genes [16], whereas up to 20% of women have a family history of breast cancer [17]. Despite being in a moderate or high risk group according to epidemiological studies, most women are unlikely to harbour germline mutations in the readily identifiable breast cancer susceptibility genes.

Possible management options for women at increased risk include prophylactic mastectomy, chemoprevention [18] and breast screening. Regular clinical examination and mammography are often recommended for women at increased risk [19–21]. In a recent survey carried out from our unit of 91 breast surgeons associated with the NHSBSP, 37 of the 45 (82%) who replied stated that they routinely offered screening to women under 50 years of age with a family history of breast cancer. The practice of screening young asymptomatic women at increased risk of breast cancer due to their family history has been questioned because there is no scientific evidence of benefit [22].

In breast screening, the absolute reduction in the risk of death from breast cancer is the product of the relative risk reduction and the baseline risk of death from breast cancer [23]. Population-based breast screening using mammography has shown a highly significant one-third reduction in breast cancer related mortality in women aged 50–70 years [5]. In comparison, a 10–13% reduction was seen in women under 50 years of age which failed to reach statistical significance. Furthermore, the number of breast cancers detected in younger screening populations is less which further brings into question the efficacy of breast screening in younger women. Although the relative reduction in breast cancer mortality of 10–20% is still likely to exist for screened women aged less than 50 years with a family history, the absolute reduction in breast cancer deaths is likely to be greater than a general screened population under 50 years of age because the baseline incidence of breast cancer in the family history screened group is much higher. This study has shown that the incidence of breast cancer in women aged less than 50 years offered FHC screening is indeed up to five times greater than that of an age-matched population.

One way of assessing the quality of a new screening programme is by comparing it with an already established one. The breast cancer detection rates at the prevalent screen in women aged less than 50 years attending the family history clinic are similar (indeed higher) to those recently published by the U.K. NHSBSP [11] for women aged 50 years or older. The incident screen cancer detection rates were also similar, although the nature of the screening schedule was different (yearly clinical examination and 2-yearly mammography versus 3-yearly mammography). A better comparison of prevalent and incident screen cancer detection rates is likely when results are available from the MRC mammography screening age trial in women aged 40–49 years. The interval cancer detection rate was higher than that reported by our unit for women over 50 years of age attending the U.K. NHSBSP (2.5 per 1000 intervals versus 0.8 per 1000 intervals) [24], but approached interval cancer rates in Northwest England (1.6 per 1000 intervals) [25] and the Stockholm trial (1.9 per 1000 intervals) [26] for women aged over 50 years. Because the underlying incidence of breast cancer in FHC screened women is much higher than an age-matched population and, indeed, higher than women aged 50–64 years, the higher interval cancer rates are not surprising. The interval invasive cancer rates expressed as a percentage of the underlying incidence for the FHC screened patients were 29% in the first 12 months and 44% in the second 12 months after mammography. This compares with the screening results of Tabar [27] where the interval cancer rates expressed as a percentage of the underlying incidence for women aged 40–49 years was 45% in the first 12 months and 62% in the second 12 months after mammography.

A major risk of screening mammography in young women is the consequence of false-positive mammographic findings which leads to unnecessary biopsy. Results of a recent study by Kerlikowski and associates have suggested that the positive predictive value of screening mammography in women under 50 years of age is highest for those with a family history and is similar to that for population screening in women aged 50 years or older [28]. The results from the present study show that the benign:malignant breast biopsy ratio in patients under 50 years of age attending FHC screening is approximately 1:1 and compares with the current quality assurance guidelines for surgeons involved in breast screening in the U.K. for women aged 50 years or older [29].

The histological features of breast cancer differ according to age groups [30]. In order to assess the histological and prognostic features of cancers detected at family history screening, a symptomatic comparison group was matched according to age, family history and date of diagnosis. Most cancers were of high histological grade in both FHC and symptomatic groups. No differences were demonstrated for tumour size or lymph node stage in women with invasive cancers. The mammographic screening interval in women under 50 years of age may be important. Tabar has suggested that a yearly mammographic screening interval is recommended for younger women because the mean sojorn time

for cancer detection is less than 2 years for that age group [31]. The efficacy of the 2-year mammographic screening interval used for FHC screening could therefore be questioned, and perhaps be assessed in a randomised trial compared with yearly mammographic screening.

There was a significant difference in the proportion of cancers detected as *in situ* cancers in screened versus symptomatic patients (21 versus 4%). The clinical importance is that 5 of the 6 cases of DCIS were of high-grade comedo subtype, 3 of which were > 4 cm in extent. The reported risk of subsequent invasive breast cancer following a biopsy that revealed DCIS is 30–50%, almost invariably within 10 years [32]. The risk increases to 75% after a biopsy revealing comedo subtype with a mean interval to developing breast cancer of 4 years [33]. The reported association between high-grade DCIS and high-grade invasive breast cancer [34] suggests that detection of DCIS through screening may be an important mechanism of reducing breast cancer mortality in this group of women prone to high-grade invasive breast cancer.

Histological prognostic features can serve as surrogate predictors of survival in women with breast cancer. The long-term survival of patients with DCIS or NPI-Good Prognostic Group invasive cancers is only marginally less than that of an age-matched population and represent a group that are potentially 'cured' after local treatment alone. The results of this study show that 41% of the cancers arising in women attending FHC screening were DCIS or good prognosis cancers compared with 30% of the non-screened group.

The results of this study are unique because there have have been few prospective studies addressing the issue of screening young women at increased risk of breast cancer due to their family history. Our results confirm a higher breast cancer incidence in this high-risk group compared with age-matched women in the U.K. Breast cancer detection rates through screening are similar to those of women aged 50–64 years attending screening through the NHSBSP. The prognostic features of cancers in women attending the FHC appear to be better than those of an age-matched risk group, principally due to a significantly higher proportion of cancers detected as DCIS. In this way, a survival advantage over a non-screened group is anticipated.

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