

Efficacy of Early Diagnosis and Treatment in Women with a Family History of Breast Cancer

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ABSTRACT: **BACKGROUND:** Surveillance programmes for women at increased genetic risk of breast cancer are being established worldwide but little is known of their efficacy in early detection of cancers and hence reduction in mortality.

METHODS: Data were contributed from seven centres participating in the EU Demonstration Programme on Clinical Services for Familial Breast Cancer. All breast tumours (n = 161) detected prospectively, from the time of enrolment of women in a screening programme, were recorded. Analysis took account of age at diagnosis, whether tumours were screen-detected or not, their pathological stage and outcome by Kaplan—Meier survival plots.

RESULTS: Mean age at diagnosis was 48.6 years. Overall, 75% of tumours were detected in the course of planned examinations. For women under age 50 at diagnosis, this figure was 68%. Eighteen percent were mammographically negative, (23% in patients under age 50). At first (“prevalence”) round and at follow-up screening, 16% and 22% of tumours respectively were carcinoma in situ (CIS) while 27% and 22% respectively had evidence of nodal or distant spread (CaN+). Comparison of screen-detected and other tumours showed that the latter were more frequently mammogram-negative and CaN+. Overall five-year survival was 89% and five-year event-free survival 86%. Five-year event-free survival was 100% for CIS, 88% for invasive cancer without nodal or distant spread and 67% for CaN+.

CONCLUSIONS: The majority of cancers arising in women at increased genetic risk of breast cancer can be detected by planned screening, even in those under

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age 50. Surveillance should include regular expert clinical examination and teaching of "breast awareness" as well as mammography. Attention to the logistics of screening programmes may improve still further the proportion of tumours that are screen-detected. The trend towards earlier pathological stage in tumours detected during follow-up rounds and the preliminary findings on survival analysis suggest that this approach will prove to be of long-term benefit for breast cancer families.

KEYWORDS: Inherited, familial, breast cancer, prognosis, stage, diagnosis, survival, screening, mammography

INTRODUCTION

Familial breast cancer has been recognised at least since 1866 as a dominantly inherited trait characterised by early onset of disease and high mortality [1]. In many centres, systematic risk assessment and screening are now offered to female members of breast cancer families but there is little evidence from which to judge the effectiveness of these programmes. The few published reports have recorded small numbers of tumours prospectively diagnosed, documenting clinical and pathological stage but with no information on survival [2–5].

The demonstration that germline mutations in BRCA1 or BRCA2 underlie a substantial proportion of inherited breast cancers has made possible predictive testing to identify women at particularly high risk. This has stimulated debate on the relative merits of systematic screening versus prophylactic mastectomy as protective strategies [6].

The European Union has funded a multi-centre collaborative Demonstration Programme to evaluate clinical services for familial breast cancer. In all centres women are defined as eligible to receive these services if their genetic risk is at least twice that of the general population, based on the Claus model [7] (i.e. at least one first degree relative with breast cancer diagnosed before age 40 or one first degree and one second degree relative with breast cancer, mean age of diagnosis > 55 years, or more than two close relatives affected — one first degree). We have described the surveillance programmes offered in the different centres [3,4,8]. Here we report the findings with respect to breast cancers diagnosed within these programmes, their means of detection, pathological stages and preliminary data on survival.

MATERIALS AND METHODS

Women were included in the present study if they were at sufficiently high genetic risk, as defined above, and, at enrolment, had no signs or symptoms suggestive of breast cancer (previous or concurrent). Numbers contributed from each centre are specified in Table 1. The period of study for each centre was from the time of establishment of a surveillance programme until the end of the latest month for which complete data are available. The date of enrolment for each woman was the date on which she was accepted for inclusion in a surveillance programme. In some centres, for logistic reasons, there could be a delay of several months between registration and first clinical/mammo-

Table 1
Numbers of tumours reported by centres

| | Tumours |
|------------------------|---------|
| Norway | 50 |
| Dundee | 29 |
| Manchester | 27 |
| Leiden | 20 |
| Aberdeen | 19 |
| Edinburgh | 14 |
| Guy's Hospital, London | 2 |
| Sum | 161 |

graphic examination.

Until very recently, entry to surveillance programmes in all the participating centres has been based on family history alone, since the availability of molecular diagnosis has been limited and DNA analysis has been applied mainly to families already enrolled in the programmes. The number of women with known BRCA1 or 2 mutations is still too small to be used as a grouping variable. They are therefore not treated separately in the analyses. All screening protocols include mammography (usually annually) from age 35 to 50 years, starting at a younger age if there has been very early onset disease in the family. This has been combined with regular expert clinical examination and instruction on self-examination of the breasts ("breast awareness"). For women over age 50, screening intervals in some centres have been longer (18 months or two years).

All centres have interpreted indications for cytology (fine needle aspiration and core biopsy) in this high-risk population liberally, placing the need for enhanced sensitivity ahead of concern for specificity. The frequency of invasive investigations has been evaluated for three of the participating centres. Rates were similar (3.9–7.3% of all examinations) and the extra demands on pathology services have been minimal [9].

Two of the participating centres have previously reported on prospectively detected cancers [3,4]. These series (updated) are included in the present report. Cancers were classified as carcinoma in situ (CIS), invasive carcinoma without evidence of spread (CaN₀) or invasive carcinoma with nodal or distant spread (CaN₊), based on pathological findings after excision. Follow-up period was recorded as the time between definitive diagnosis and latest clinical examination. Tumours were designated "screen-detected" cancers if they were found on mammography, clinical examination, or both, within a planned surveillance programme. Those presenting outside a planned surveillance examination were either "interval" tumours (i.e. where there had been a previous negative screening examination) or "others" (to include those presenting clinically before a planned first

screening examination was actually undertaken). The existence of this last group emphasises that evaluation of surveillance protocols for those at high risk must be based on "intention to screen" since delays in implementation of that intention, as well as unintended prolongation of screening intervals, may have adverse effects on programme performance.

Tumours were considered mammogram-negative if interpretation of the mammogram did not lead to additional investigations and/or if the radiologist could not confirm any suspicion of cancer raised by the clinical examination. Ten tumours (seven of which were non-screen-detected cancers) were excised without prior mammography. In calculating the proportion of mammogram-negative tumours, the denominator includes those not examined mammographically, unless otherwise stated. Contra-lateral breast cancer was treated as a separate tumour in recording stage at diagnosis, so nine patients were counted twice. However each patient was counted once only (using first tumour) for survival analysis, using Kaplan—Meier plots in the SPSS statistical PC programme. For overall survival, death was the event scored. For event-free survival, tumour spread (loco-regional, nodal or distant) or cancer-related death were recorded as events. For patients with metastatic disease at diagnosis, only death was scored as an event. No breast cancer patient in this series experienced any event (spread or death) which was not related to the first breast cancer recorded.

Age-specific mean sojourn time (MST or "lead time"), i.e. the time that a breast cancer may be detectable on examination before presenting clinically, was derived as follows. The average MST for breast cancer in this age group, (1.25 years) from published Swedish population studies [10,11], was applied to estimate the observation period covered by the first examination (the "prevalence round") and hence to deduce the annual incidence rate for our total high-risk population. The validity of this calculated rate was then tested by comparing it with the observed incidence rate on follow-up.

Predicted numbers of cancers were derived from local age-specific incidence rates. Statistical

associations were tested by Fisher's exact *p* (one sided).

RESULTS

One hundred and sixty-one breast cancers in 152 women were observed prospectively in women enrolled in formal surveillance programmes because of perceived genetic risk. This is by far the largest series reported from any such study. Mean age at diagnosis was 48.6 years, range 28 to 71 years, with 91 (57%) being under age 50, including 31 (19%) under age 40.

Table 2 records the characteristics of all the tumours observed, categorised by pathological stage, mammographic findings and whether they were screen-detected or not. Table 3 gives figures for women diagnosed before age 50 separately, but no statistically significant differences were seen between outcome in patients under and over 50 years of age.

We have previously published that annual incidence rate in the Norwegian series was 0.0064 calculated, as indicated above, from findings in the first round, and 0.0086 observed

at follow-up [3]. Data from the Manchester series [4] allowed similar calculations, resulting in annual incidence rate 0.0025 derived from first round, and 0.0024 observed at follow-up. The closeness of agreement between calculated and observed data indicates that the assumed Mean Sojourn Time (MST) of 1.25 years is accurate.

Forty tumours (24.8%) presented clinically and were detected by the patients themselves. Two tumours were found on planned examinations outside the specific programme and, for the purposes of analysis, were classified as screen-detected. Among the 40 self-detected tumours, 2 (5%) were CIS, 22 (55%) were CaN₀ and 16 (40%) were CaN+. Compared with screen-detected tumours, interval and "other" cancers were less often CIS (*p* = 0.01) and more frequently CaN+ (*p* = 0.006). Thirteen out of 33 (39%) non-screen-detected cancers were mammographically negative (when examined on clinical presentation), versus 15 of 118 (13%) screen-detected (*p* = 0.001). Overall, 6 of 32 (19%) CIS, 16 of 87 (18%) CaN₀ and 6 of 32 (19%) CaN+ cancers were mammographically negative.

The proportion of CIS tumours was higher on

Table 2
Results stratified on CIS, CaN₀ and CaN+ for first round and for follow-up separately. Mammographic negative tumours (mimneg) and interval cancers (interval) in each row are specified. Percentages in parentheses were calculated as number in cell divided by sum for row

| | CIS | CaN ₀ | CaN+ | Sum | Mamneg | Not screen-detected |
|-----------------------|-----|------------------|----------|-----|----------|-----------------------|
| First round | 8 | 29 | 14 (27%) | 51 | 8 (16%) | 11 (22%) ¹ |
| Of these - mamneg | 2 | 4 | 2 (38%) | 8 | | 5 (63%) ¹ |
| - not screen-detected | 0 | 6 | 5 (45%) | 11 | 5 (45%) | |
| Follow-up | 24 | 62 | 24 (22%) | 110 | 20 (18%) | 29 (26%) |
| Of these - mamneg | 4 | 12 | 4 (20%) | 20 | | 8 (40%) |
| - interval | 2 | 16 | 11 (38%) | 29 | 8 (28%) | |

¹ After filed "intention to screen" at genetic counselling, before first examination — time delay up to one year in some parts of the series.

Table 3
Results from follow-up (after first round) for patients aged less than 50 years considered separately

| | CIS | CaN ₀ | CaN+ | Sum | Mamneg | Not screen-detected |
|-------------------|-----|------------------|----------|-----|----------|---------------------|
| Follow-up | 15 | 32 | 15 (24%) | 62 | 14 (23%) | 20 (32%) |
| Of these - mamneg | 1 | 9 | 4 (29%) | 14 | | 5 (36%) |
| - interval | 1 | 11 | 8 (40%) | 20 | 5 (25%) | |

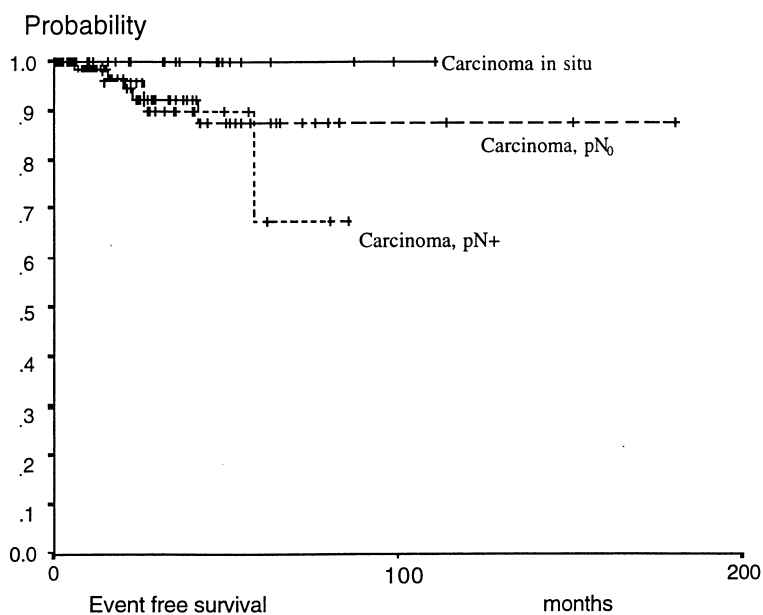


Fig 1. Event-free survival according to stage at diagnosis. CIS n = 32, CaN₀ n = 91, CaN₊ n = 38.

follow-up than in the first screening round (22% vs. 16%); conversely, the proportion of CaN₊ tumours was lower on follow-up (22% vs. 28%) but these differences did not reach statistical significance.

All deaths in the observation period were breast cancer related. Five year overall survival was 0.89 (SE 0.05). Five year event-free survival for the whole group of women with tumours was 0.86 (SE 0.06). Five year event-free survival for patients with CIS was 1; for those with CaN₀ it was 0.88 (SE 0.06) and for those with CaN₊, 0.67 (SE 0.20) (Figure 1).

DISCUSSION

Women aware of their increased genetic risk of breast cancer have to make a difficult choice between enrolment in a surveillance programme, participation in a chemoprevention trial or prophylactic mastectomy. In the families described, few have actively pursued the last option but a recently published retrospective review [6], showing that surgery can reduce cancer incidence by 90%, has generated considerable interest and adds urgency to the

question of how effective the alternatives may be, particularly in view of lack of empirical results for efficacy of mammographic and clinical follow-up examinations in premenopausal women at risk.

This study demonstrates conclusively that surveillance programmes for women whose family histories suggest they may be at increased risk can detect the majority of breast tumours, including those arising at an early age. Over 75% of tumours were detected in the course of planned screening examinations. Attention to the logistics of service provision might improve this figure still further: Eleven of the forty non-screen-detected cancers presented symptomatically in the period between registration of the patient for surveillance and institution of clinical/mammographic screening. In addition, seven of 11 (64%) interval cancers with spread at follow-up were detected more than 6 months after the previous examination (data not shown), indicating the possibility of reducing the numbers of pathologically advanced tumours by reducing the interval between screening examinations.

Sixty percent of non-screen-detected cancers were still node-negative at diagnosis. This may be interpreted as a success for the policy of

encouraging regular self-examination or “breast awareness”. Nevertheless it is lower than the corresponding proportion of screen-detected tumours (82%) and is comparable to the figure for tumours in unscreened women under age 50 from the Swedish two counties trial [12]. Overall, twenty-eight tumours (18%) were negative on mammography despite the fact that the attention of the radiologist could be drawn to suspicious areas detected on clinical examination. This figure was higher (23%) for the tumours diagnosed under age fifty, though the difference is not statistically significant. These findings emphasise the need to include regular expert clinical examination as a component of screening for this high-risk group.

Rates of CIS were higher than expected in both the first and subsequent screening rounds (Table 2). The high frequency of CIS at follow-up was first noted in the Norwegian data [3] and is confirmed in the additional series reported here. If CIS was not associated with genetically-caused infiltrating cancers, the ratio of CIS to infiltrating cancers should have been relatively low in our cohort, enriched for women at increased genetic risk. The findings suggest that CIS is indeed associated with familial breast cancer and that, in the high-risk population, new CIS lesions are continuing to arise at an appreciable rate. In this setting, CIS is presumably a precursor of invasive cancer, in which case, one feature of an effective screening programme should be the trend observed here, namely an increasing proportion of tumours detected at the stage of CIS and a decrease in those with nodal or distant spread. This concept has parallels with inherited colon cancer where invasive cancer arises within the dysplastic adenomatous polyp and removal of the polyp protects against cancer [13]. It is also in keeping with a previous report that abnormal proliferation of the breast epithelium segregates as a dominant trait in breast cancer kindreds [14].

In this series, stage-specific 5-year survival was similar to that reported for sporadic breast cancer [15], while the overall 5-year survival was better. This again indicates that prognosis is related to stage at diagnosis, and that the effect of

our intervention was mediated through diagnosis at an early stage.

The actual tumour incidence rates were much higher than age-specific rates for the general population but differed considerably between two centres (eight times higher in Norway, two and a half times higher in Manchester), which probably reflects differences in the risk profiles of the two clinic populations, given that a substantial proportion of Norwegian breast cancer families have subsequently been shown to carry founder mutations in BRCA1 [16], while there have been no comparable findings in Manchester. The only inference drawn from this part of the study was that familial breast cancer has the same age-related MST as sporadic cancer. Applying 1.25 year lead time [10,11] and comparing the outcome in this series with historical reports for BRCA1 mutation carriers [17,18], follow-up results to date are encouraging although several more years of observation will be required before the benefits of planned surveillance in this genetically high-risk group can be fully evaluated.

Inherited breast cancer is clearly not homogenous with respect to phenotypic appearance and prognosis. For example, there is evidence that tumours arising on a background of BRCA1 mutations are characterised by histopathological signs associated with poor prognosis, including low frequency of CIS [19]. If so, BRCA1 mutation carriers may need more frequent follow-up examinations because of a shorter “time-window” for diagnosis before spread. Our continued monitoring of the patients described, and determination of their carrier status for relevant mutations, may clarify this. The same problems of possible different effects of intervention for distinct genetic subgroups, also apply to any alternative strategy to prevent or cure inherited breast cancer.

While there remains a great need to match management strategies to more precise definitions of risk, women with family histories of breast cancer can now choose, on the basis of real data, between prophylactic surgery [6] and regular surveillance. It is interesting to compare these data with the predictions upon which a

published decision analysis [20] was based. The presumption that prophylactic mastectomy would confer 85% protection now appears slightly conservative, while the estimate that a screening programme would detect 80% of tumours at the node-negative stage (and 20% after metastatic spread) has yet to be confirmed, though these figures seem attainable. The conclusions that, “on average, 30 year old women who carry BRCA1 or BRCA2 mutations gain from 2.9 to 5.3 years of life expectancy from prophylactic mastectomy” and that “gains in life expectancy decline with age at the time of prophylactic surgery”, are likely to prove accurate.

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