INHERITED BREAST CARCINOMA

Prospective findings in 1 194 women at risk

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According to preset criteria, 1 194 women at risk for inherited breast carcinoma were selected and subjected to examination. Six hundred and three women were examined once, 591 were followed for a mean of 1.8 years. Twenty infiltrating cancers (median age 49 years) and 16 precancers (median age 44 years) were found, demonstrating that breast carcinoma continued to occur in the selected families as expected under the hypothesis of dominant inheritance. At first round, 14 (1.2%) infiltrating carcinomas and a total of 22 (1.8%) cancers or precancers were found. Incidence rates of 0.58% pr. year for infiltrating cancers, and 1.04% pr. year for cancer or precancer were calculated. This confirms the tentative conclusions that were drawn in our previous report. These are the first prospective reports documenting how to delineate a high risk group for premenopausal breast cancer, and how to diagnose cancer at an early stage. All but two affected women had cancer without lymph node metastasis. Although a longer observation time is needed, we cautiously conclude that the results are in keeping with our aim of providing safety for those at risk. Clinical use of predictive genetic testing may be implemented within these families.

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Since the description in 1866 of autosomally, dominantly inherited breast cancer occurring in young adults (1), knowledge about the condition has accumulated. The condition is frequent enough to have a bearing on the overall mortality of young women. Within the affected families, close on half the women contract the disease.

Two distinct genes (BRCA1 and BRCA2) may each separately cause the disease (2, 3), and it has become evident that mutations in BRCA1 are the cause of most cases of inherited ovarian cancer as well (4). About 5% of all breast cancer occurs within affected families (5). Breast cancer screening has resulted in a 25–30% reduction in mortality from breast cancer in women aged 50 years and upwards (6, 7). Median age of onset of inherited breast cancer from the retrospective studies currently available is below 50 years (4). Thus, the majority of inherited breast cancer cases occur at an age where no programme has proved to cause reduced mortality (7). The conclusion is that breast cancer screening, such as is offered to older women so far, is not a suitable approach to the inherited form of the disease.

On the other hand, there are numerous reports describing the treatment and cure of women with inherited breast cancer. All our knowledge indicates that early treatment may increase the probability of cure. Thus, identifying the women at high risk and subjecting them to regular examinations aiming at diagnosing early signs of disease are logical steps in testing the hypothesis to increase cure rate.

This paper describes how we define women at risk from family history, our protocols for genetic work-up of the families, counselling, examination protocols, practical organization for running the programmes, and our findings so far.

Material and Methods

Our clinical criteria for defining women at risk have been previously published (8), and are summarized in Table 1. The population was informed through the media about our activity, and written self-referral to genetic counselling for women at risk was accepted. Information about our activity was spread to all hospitals dealing with breast cancer and to GPs. A written family history was obtained from all women included in the study. Reports of operated breast cancer in close relatives were accepted (5). All other relevant diagnoses were verified by copy of medical files and histopathology, whenever possible. All women included were invited to genetic counselling by a medical geneticist.

The 1 194 women who were eligible for the study had no history of breast cancer and no symptom of breast cancer at the time of inclusion. All women at risk were examined according to our previously published protocol (8) (Table 2) with clinical mammography in institutions capable of performing triple diagnostic procedures without delay.

Mean sojourn time (MST, time in preclinical detectable stadium) is presented in Swedish reports for women aged 40 and upwards (6); the younger the women the shorter the MST. These were used to calculate observation time underlying the first observation. We used the MST for women aged 40–49 years for all women below 50 years of age. Actual follow-up for women examined more than once was calculated as time between first and last examination. The findings were grouped as atypical hyperplasia (AH), carcinoma in situ (CIS), and as infiltrating carcinoma (CA). CA was grouped as with or without affected axillary lymph node(s), judged by microscopy.

Results

As of June 1996, mean age at inclusion was 42.9 years (SD 11.4). Stratification of included women according to selection criteria is given in Table 3. No single criterion or

Table 1

Criteria for inclusion

Abbreviation	Description
CM1[1]	Four diseased[2] first or second degree relatives
CM2[1]	Two diseased relatives, both diseased < = 55 years of age. The diseased should be first degree relatives or second degree relatives related through a male.
CM3	One diseased first degree relative with bilateral breast cancer < = 60 years of age.
CM4	One diseased first degree relative with breast cancer and another cancer, the breast cancer diagnosed < = 60 years of age.
CM5	One first degree relative diseased 46–50 years of age.
CM6	One first degree relative diseased 41–45 years of age.
CM7	One first degree relative diseased < = 40 years of age.
CMO1[1]	One first degree relative with ovarian cancer who has a first degree relative (or a second degree relative through a male) with breast cancer 60 < = years, or vice versa.
CMO2[1]	One first degree relative with both ovarian and breast cancer, the breast cancer diagnosed < = 60 years of age.
CO[1]	One diseased first degree relative with ovarian cancer who has a first degree relative (or a second degree relative through a male) with ovarian cancer.

[1] Second degree relative through a male also accepted
[2] Diseased = breast cancer

Table 2

Examination protocol

1. Clinical mammography (clinical examination + mammography) annually from 35 to 55 years of age—from 25 years in families with early onset of disease. Examination every second year after age 55.
2. The examinations are supplemented with ultrasound, aspiration cytology and/or surgical biopsy whenever necessary. These facilities should be present in the institution to which the patient is referred.

Table 3

Number of women included, according to selection criteria met and number of abnormal findings in each group. For interpretation, see results

Selection criteria[1]	No. of women meeting criterion				No. of women meeting the given criterion but not any other criteria			
	All	AH	CIS	CA	All	AH	CIS	CA
CM1	94	2		3	33			2
CM2	270	4	1	3	39		1	
CM3	88	1			14			
CM4	36	1			7			
CM5[2]	138	1	2	2	58		2	
CM6[2]	252	1	1	2	95		1	2
CM7[2]	200	1	1	5	92	1	1	2
CMO1	304	1	1	6	134			2
CMO2	64			1	9			
CO	213	1	1	4	99			
Other[3]	138	1	3	4	138	1	3	4

[1] See Table 1 for use of abbreviations. A given patient will meet one or more criteria.
[2] Criteria CM5, CM6 and CM7 are not overlapping—they indicate the youngest affected in the family.
[3] Not meeting any preset criteria, but thought to be at high risk and included.

Table 4

Number of women examined according to age, women-years for each age group calculated as MST[1] and actual follow-up, expected numbers of sporadic breast cancer in each age group calculated from Norwegian incidence rates, and observed numbers of AH, CIS, CA, and their calculated incidence rates pr. year

Age group	No.	Woman-years	Expected sporadic cancers	Observed (incidence pr. year)			
				AH	CIS	CA	Sum
-29	152	353	0.02	0	0	0	
30-39	381	797	0.21	1	2	5(0.0062)	8
40-49	360	1 163	1.41	4	6	5(0.0043)	15
50-59	200	857	1.19	2	0	6(0.0070)	8
60-69	82	358	0.67	0	0	3(0.0084)	3
70-	19	74	0.18	0	1	1(0.0135)	2
Sum	1 194	3 602	3.68	7	9	20(0.0058)	36(0.0104)

[1] See text

group of criteria seems to be more efficient than the others. Compared with a previous report (5) on the first 537 women (who were also included in this study), we continue to select women of the same age and with the same distribution on the ascertainment criteria.

A total of 1 194 women were examined at least once, and 591 of them were followed for a mean of 1.84 years. The distribution of age and women-years in each age group calculated as the sum of MST and actual follow-up are presented in Table 4. Number of abnormal findings and the calculated incidence/year for each age group are also given, together with the calculated number of expected sporadic breast cancers. Median age for infiltrating cancer demonstrated was 49 years (range 34–72), median age for AH or CIS demonstrated was 44 years (range 32–73). Observed number of CA was 20 compared with 3.68 expected sporadic cancers (x^2 with Yates' correction = 68, 1 df, $p < 0.000001$).

Abnormal findings stratified at first round and follow-up are summarized in Table 5. Fourteen CA (1.2%) and a total of 22 (1.8%) CA, CIS or AH were found in the first round. The sum of MST was 2 515 years, and the sum of actual follow-up was 1 087 years, giving a ratio of 2.3. The observed ratio between CA found at first round and at

Table 5

Abnormal findings stratified on first examination and follow-up, for AH, CIS and CA separately, and with median age at diagnosis and range for each group

Finding	First round		Follow-up	
	No.	Median age (range)	No.	Median age (range)
CA	14	50(37–72)	6	58(34–62)
CIS	2	38(32–44)	7	43(39–73)
AH	6	48(37–51)	1	44

follow-up was 2.3. The ratio between all abnormal findings at first examination and at follow-up was 1.6. At first examination, 8 precancers (AH + CIS) and 14 CA were found, versus 8 and 6, respectively, at follow-up (Fisher's exact $p = 0.16$).

Women with abnormal findings were selected by all the criteria employed as selection basis (Table 3). Numbers in each subgroup are still small, and more detailed analyses have to await future expansion of the study. It is intriguing, however, that the highest prevalences of CA as well as of CIS were found in the 'others' group—that is in families after extensive genetic examination considered to have possible inherited cancer, but without meeting any preset criteria. For capacity reasons, inclusion criterion CM5 (one first degree relative diseased 46–50 years old) has now been omitted. Table 3 may be interpreted like this: The columns under the heading 'meeting criterion' can be read as pick-up numbers and affected found by this criterion alone if the other criteria had not been employed, for each criterion given. The other columns under the heading 'meeting this criterion but not meeting any other criteria' may be read as what had not been found if this single criterion had not been used, for each criterion given.

All but two cancers were lymph node negative. The two had one affected axillary lymph node each, and they were both found at first examination. No cancer with lymph node metastasis at follow-up has so far been found.

All results given above and in the tables are events. Three women had two events each (= bilateral abnormal findings). They were CIS-CA, AH-CIS and CA-CA, respectively. These numbers are too small to allow discussion.

Discussion

The criteria employed were effective for delineation of women at risk for breast carcinoma. This was the conclusion in our first report (5), and is now confirmed by this report.

The results also show that our examination programme was able to demonstrate cancers at early stage. Empirical figures for morbidity and mortality for women included having to await many years of follow-up. However, data regarding staging may soon be clear, from which prognostic expectations may be derived. Our aim is to provide safety for the women included, and we regard early detection to be in keeping with this goal. A programme with documented benefit for those included is an ethical prerequisite for progressing to predictive mutation testing. Based on our experience so far, we consider that such testing should now be offered to these families.

Most of the women were self-referred. Some had been to various follow-up regimens before entering our programme. Because of wide variation in examination methodology and intervals, it was found impossible to generate records on previous examinations. Previous examinations may explain why no advanced cancer was found in the first round. For those who had been examined shortly before inclusion in our programme, the given MST as observation time underlying our first examination would have been too long. Also, the MST used for women under 40 years of age is thought to be too long. Thus, the calculated incidence rates in Table 3 may be minimum estimates.

Having defined women at high risk for breast carcinoma, we face the problem of protocols for treatment of abnormal findings (9). Protocols from previous screening programmes in low-risk groups may be inappropriate for many reasons. One reason is the cost/benefit calculations underlying many suggested actions. In the high risk group, false positive results have low prevalence as a mathematical function of the high a priori risk at inclusion. Furthermore, almost all women attending our programme prefer safety. The problem of false positive results may be regarded as a price paid for safety, and is dealt with in the genetic counselling session prior to examinations. It does not emerge as an unexpected event in unprepared patients.

AH and CIS may be the precancerous lesions (10). The breast, being a clonal expansion of a few predetermined cells in puberty, may contain more such lesions than the one demonstrated in any given patient. Reports on this subject are many, and are in keeping with the empirical data that women with AH in breast cancer kindreds have a high propensity for breast cancer after removal of AH (11). Our aim is to disclose clinically significant precancerous lesions, and to treat the precancerous breast so that infiltrating cancer does not occur. There should be further discussion on how to define and treat AH and CIS.

For the evaluation of programmes like ours, the interpretation of AH and CIS is essential. As an example, we mention the extreme situation when we may find only precancers, removing them and thereby avoiding all cancers. If precancers are not considered as an endpoint of follow-up, then the conclusion will be that the criteria employed did not define persons at risk because no cancers were found. It means that the highest success possible for a programme like this might spuriously be interpreted as a total failure. The biological problem of classifying precancers, as well as the statistical problems associated with considering precancers as an endpoint in studies like ours, should receive proper attention.

To us it is also rational to suggest that in breast-ovarian cancer kindreds, estrogen receptor positive breast carcinoma should be treated with surgical oophorectomy. Ovarian cancer has a median age of onset 10 years later than breast cancer in the affected families (4), and the probability for contracting ovarian cancer among those who have breast cancer is high (12). Oophorectomy furthermore reduces the risk for breast cancer/spread of breast cancer. Adjuvant antiestrogens (tamoxifen) for

breast cancer within such families may leave the patient with a substantial risk for ovarian cancer as compared with oophorectomy. Our suggestion of therapeutic oophorectomy in patients with demonstrated breast cancer does not include prophylactic castration of healthy young women in affected families.

The similar fractions of cancers found in our study in the first round and in the actual follow-up indicate that the calculation of women-years using MST was reasonable. The findings at actual follow-up are free from the possible errors on disease status at inclusion which have a bearing on interpretation of the results from the first round of examination. The figures are still too small to allow firm conclusions, but the findings are in keeping with an interpretation that a high incidence rate of cancer continues to occur in the families, and we have detected the cancer at an early stage.

Sisters and daughters of BRCA1 or BRCA2 mutation-carrying females are expected to be born with a 50% risk of being mutation carriers, and about 85% of the carriers are expected to contract breast cancer. This gives an incidence rate of about 2% pr. year from 30 years of age and onwards for mutation carriers in such families, and we understand that CIS is included in this figure (4). Half that incidence is expected in sisters and daughters not tested for carrying status. The calculated incidence rates of 0.58% for CA, and of 1.04% for CA, CIS or AH, indicate that our selection criteria are more than 50% specific for delineating families with inherited breast cancer.

Previous reports indicate a drop in incidence rate between 50 and 60 years of age (4). As seen in Table 4, we found increasing incidence rates with increasing age. From our data, follow-up is indicated also from 50 to 70 years. Future determination of mutation carrier status in healthy young women will increase risk in those selected, and further strengthen the need to offer the best programme available to keep mortality as low as possible in these families.

No abnormal findings were recorded in women below 30 years of age. We conclude that the selection criteria and examination protocol used, gave the result of 1.2% incidence pr. year of abnormal findings, including 0.64% infiltrating cancer pr. year from 30 years on. Median age at onset of disease was below 50 years. All but two cancers in the first round and all cancers at follow-up were without lymph node metastasis. No previous prospective study has demonstrated such a high incidence of premenopausal breast cancer. So far, the figures are consistent with our aim of providing a follow-up regimen for women at risk for inherited breast carcinoma. We may now progress to the clinical use of preclinical testing for mutation carrier status within the group described.

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