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Hereditary Breast Cancer in Northern Ireland

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SUMMARY

The aim of this investigation was to document hereditary breast cancer in Northern Ireland. Family history details from over nine hundred women were obtained by postal survey and one hundred and twenty nine home visits were carried out to collect pedigree information. The families documented varied in the number of affected women from three, which was the minimum criteria for inclusion, to a maximum of nine and many families described other features of hereditary disease such as bilateral breast cancer, ovarian and gastrointestinal malignancies.

INTRODUCTION

A family history of breast cancer is recognised as one of the most important risk factors for the disease.[1,2] In the majority of women breast cancer is due to a multifactorial combination of environmental and genetic factors. However breast cancer in some women is due to a major genetic influence. Several epidemiological[1,2,3] studies have suggested that an autosomal dominant gene may be present in approximately three per thousand individuals, and that this is responsible for a substantial proportion of the familial clustering of breast cancer in the population. It is now established that in some families the high incidence of breast cancer is due to a mutation in a gene, known as BRCA1, which is located on the long arm of chromosome 17.[4,5]

Hereditary breast cancer has a number of distinguishing features[6] which include early age of onset of breast cancer, an autosomal dominant pattern of inheritance, an association with other malignancies, an excess of bilateral disease and a better prognosis. It was decided to undertake a study to document hereditary breast cancer families within the community.

METHODS

Suitable families were identified by selecting pre-menopausal women who had developed breast cancer. In addition, specialist breast clinics, a charity cancer screening organisation and general practitioners were involved in identifying families containing at least three women who had developed breast cancer.

All women in Northern Ireland who developed pre-menopausal breast cancer in the five years between January 1986 and January 1991 were identified through pathology records. Patients with a diagnosis of invasive breast carcinoma, either ductal or lobular, were selected. Most histopathology records are computerised but manual documentation was necessary in two of the hospitals in Northern Ireland.

Details of women with a family history of breast cancer were obtained from three sources.

1. 'At risk' patients attending specialist breast clinics in either the Royal Victoria or Belfast City Hospitals.
2. General Practitioners were contacted by letter and referral of suitable families requested.
3. Women attending 'Action Cancer' for breast cancer screening within the period January 1986 - January 1991 were ascertained, although

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the medical records for a longer period were available.

All women identified were sent a postal questionnaire requesting details regarding family history of breast and other cancers. The returned questionnaires were manually checked and details were stored on computer (Amstrad Locofile) which prevented inclusion of any family already identified, and avoided multiple ascertainment.

Those families which fulfilled the criteria of at least three affected women were contacted and a home visit was arranged to obtain a pedigree and clinical details necessary for pathological verification of diagnosis.

RESULTS

The numbers of women identified from the various sources are shown in Table I. There was a total of 3425 new patients with breast cancer diagnosed in Northern Ireland within the five year period, of which 727 were aged 47 years or less. For 632 of these patients we were able to establish a name and address; the remaining 95 women could not be contacted as hospital records had insufficient information.

TABLE I

Number of pre-menopausal women with breast cancer: source of referral, number identified and number with at least three affected women.

Source of Patients	*Number identified*	*Number with three affected relatives*
Pre-menopausal women	632	47
Clinical referral	87	35
General practitioner referral	13	4
Action Cancer records	170	78
Total	902	164

From other sources two hundred and seventy women were identified and in total nine hundred and two women were sent a questionnaire. Six hundred and forty-seven questionnaires were returned, (58%) and one hundred and sixty-four families fulfilled the criteria of three or more affected women.

One hundred and twenty-nine women were visited at home. Of the remaining thirty-five families, twenty-one were reluctant to take any further part in the study, and nine who did not include a telephone number in their returned questionnaire failed to respond to a posted request to arrange a home visit. In five instances although the family agreed to a home visit, various family circumstances prevented this during the study period. In four families the death of a family member from breast cancer meant that the family were too distressed to discuss details of the pedigree. One family moved to another part of

TABLE II

Number of families identified with number of affected women per family *

Number of affected women in family	*Number of families identified*
3	63
4	37
5	12
6	12
7	2
8	1
9	2
	Total 129

* Previously published data – Br J Surg 1995; 82: 1086-1088.

TABLE III

Additional features of hereditary disease in the families

Additional Feature	*Number of families affected*
Bilateral breast cancer	38
One ovarian malignancy	18
Two or more ovarian malignancies	4
One gastrointestinal malignancy	10
Two or more gastrointestinal malignancies	17
Male breast cancer	3

the United Kingdom before a visit could be arranged. Pedigree details are shown in Table II. Many families revealed additional features in their pedigree suggestive of hereditary disease. These include bilateral breast cancer, other malignancies in the family and male breast cancer (Table III).

Families were also classified into three groups depending on age at onset of disease. There were forty-six families in which all affected women in the family were aged 47 years or less at diagnosis. There was a group in which the majority, but not all, of the breast cancers developed in the pre-menopausal period. This group, which contained fifty-four families, was described as Mixed. Twenty-nine families showed predominantly post-menopausal onset of breast cancer.

DISCUSSION

Five hundred and nine women with hereditary breast cancer have been identified in Northern Ireland using multiple sources of ascertainment. The sources used are similar to those reported in other studies although many of these relied on a single source of ascertainment and a realistic comparison between methods of family identification is not possible.

The majority of breast cancers develop in the post-menopausal period; pre-menopausal disease normally accounts for approximately 20% of the total.[7] This is borne out in our study from histopathology records in which 727 (21%) women developed pre-menopausal disease. Previous studies have shown that 20% of women who develop pre-menopausal breast cancer will have another relative with breast cancer.[7, 8] Analysis of pedigrees in this study allowed identification of 28% hereditary breast cancer families. However from the total 632 pre-menopausal breast cancers it might have been expected to identify more than the 47 (7.5%) families (Table I).

Action Cancer provided an important source of breast cancer-prone women, contributing more than 50% of the total families identified as containing three or more affected women. Women attending Action Cancer are often self-referrals for breast cancer screening. This suggests that the availability of a Breast Cancer Family clinic will attract concerned families. The number of referrals from the general practitioners was low and this possibly reflects the use of a manual system for medical records in some practices which would prevent rapid, easy identification of families containing several members with cancer.

The criteria for inclusion in the study of three or more affected family members has been used in most other studies. However breast cancer is common in Northern Ireland (142 per 100,000)[9] and three affected members within a family could also result from the clustering of sporadic breast cancers. There is evidence from local genetic analysis studies that some families with three affected members do trace susceptibility to the gene BRCA1.[10] These families which contain only three affected members demonstrate the difficulties associated with genetic analysis when the pedigree shows a nuclear family pattern.

It may be that some families containing a smaller number of affected members represent the effect of environmental influence in combination with the incomplete penetrance documented for BRCA1.[5] It is also possible that there are several BRCA1 mutations in the population with variation in expression depending on the degree of penetrance of some mutations.

The majority of families (78%) described either three or four affected women but twenty-four families contained either five or six affected women. Despite such a high incidence of disease less than 30% of unaffected women from these families attended either Action Cancer or a specialist breast clinic. Both the families containing nine affected women were identified through the attendance of an unaffected relative at a specialist breast clinic but even in these families many unaffected women, despite the availability of such a facility, do not attend for surveillance. This may seem surprising but a study of breast cancer families has shown that a common reaction to the serious threat of breast cancer is denial. This type of denial reaction is associated with a reluctance to attend for surveillance, and a delay in seeking medical attention when a breast lump is discovered.[8] A more recent study reports that many women from breast cancer prone families underestimate their risk of breast cancer and despite counselling feel that their risk of breast cancer is only slightly greater than that of the general population.[11]

The development of bilateral breast cancer is very suggestive of hereditary disease[6] and a study has shown that a woman with unilateral hereditary breast cancer has almost a 50% risk of developing a second breast cancer if she survives over a

twenty year period.[8] In addition women who develop breast cancer when aged less than fifty years have more than five times the risk of developing a second breast cancer than those women who exhibit post-menopausal disease.[8] In our study 38 families showed evidence of bilateral breast cancer although this trait was not confined to the families with particularly large numbers of affected women. However there did seem to be more bilateral disease in the families in which the majority of women had developed pre-menopausal disease, in that all of the women with bilateral breast cancer were from families classified as either pre-menopausal or mixed age at onset of disease.

In 22 families at least one woman had developed ovarian cancer. Although there is some evidence that a small number of families with multiple breast and ovarian cancers are not linked to BRCA1 most publications suggest that BRCA1 is responsible for disease in the majority of these families.[4, 5] If appropriate surveillance is undertaken then clearly women in such families must be offered regular monitoring for gynaecological neoplasia. It is recommended that unaffected women from these families have six monthly pelvic ultra-sound surveillance.[6]

Twenty-seven families (25%) contained at least one relative with a gastrointestinal cancer. Large bowel cancer is common in Northern Ireland with approximately 620 new cases per year[12] and the prevalence of gastrointestinal cancers amongst relatives in these families may be due to a common sporadic disease.

Early onset of disease is perhaps the most characteristic feature of hereditary breast cancer[2] and there were forty-six families in which all affected women were aged less than 47 years at diagnosis. In a study including combined results from ten different centres throughout the United States and Europe involving 214 families in which DNA analysis was used to investigate familial susceptibility to BRCA1, there was strong evidence for an association between early onset breast cancer prone families and BRCA1 but little evidence for families showing post-menopausal onset of disease.[5]

In this study twenty-nine families showed predominantly late-onset of breast cancer. A similar study noted 19 late-onset families.[5] However, the majority of reports made no comment on late-onset disease. This may be due to family identification methods, as clinical referral may select early-onset breast cancer families. A Swedish study in which there was a number of late-onset families used a postal survey system to ascertain families.[13] It is possible that in families with late onset of breast cancer another gene may be involved, for example a region on chromosome 6[14] or indeed on another as yet unidentified gene.

Those families which were classified as mixed, in which the majority of women showed pre-menopausal breast cancer but one or more women developed breast cancer post-menopausally may represent variation in penetrance of hereditary breast cancer genes, or the post-menopausal cases may be due to the development of sporadic breast cancer within a hereditary breast cancer family which has been documented.

There are many undiscovered families in the community, as evidenced by a continued accumulation of families through Action Cancer and clinical referral. If the frequency of BRCA1 in the general population is 0.003[1, 2, 5] then it would be expected that in the population of Northern Ireland of roughly one and a half million there will be approximately 2250 female carriers. If 5%[6] of breast cancers are hereditary, then in Northern Ireland about 30 women could be expected to develop breast cancer each year as a result of a major gene.

CONCLUSION

Women with a family history of breast cancer, whether linked to BRCA1 or to some other gene, have a high risk of developing the disease.[1, 2, 5] Frequently these women are young, and they have the added risk of bilateral disease.[5, 15, 16] Little information from controlled clinical trials is available as to the effectiveness of screening for breast cancer in young, high-risk women and it may be very difficult to obtain.[17]

There are increasing requests for information, counselling and surveillance from patients and general practitioners. The rapid development of molecular genetic diagnostic techniques and general public awareness through media publicity demand an organised team approach.

It is suggested that this demand is best served by a breast cancer family clinic where women with a family history of breast cancer can obtain accurate risk counselling from a medical geneticist with back up from a molecular genetic laboratory.

In addition appropriate surveillance requires a specialist breast surgeon, with the availability of both cytopathology and radiology breast imaging services.

Apart from families who were identified either through attendance at specialist breast clinics or 'Action Cancer' breast screening we found little evidence that breast cancer-prone women attend for genetic assessment or screening investigation. When the possibility was discussed, usually when obtaining a pedigree, many women expressed an interest in attending a breast cancer family clinic but at present this type of service is unavailable in Northern Ireland. This study shows that families and women can be identified in the Northern Ireland community who are at risk of developing breast cancer and who may benefit from such a clinic.

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