ORIGINAL ARTICLE

Establishing a Family Risk Assessment Clinic for Breast Cancer

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■ **Abstract:** Breast cancer is the most common cancer affecting European women and the leading cause of cancer-related death. A total of 15–20% of women who develop breast cancer have a family history and 5–10% a true genetic predisposition. The identification and screening of women at increased risk may allow early detection of breast cancer and improve prognosis. We established a family risk assessment clinic in May 2005 to assess and counsel women with a family history of breast cancer, to initiate surveillance, and to offer risk-reducing strategies for selected high-risk patients. Patients at medium or high risk of developing breast cancer according to NICE guidelines were accepted. Family history was determined by structured questionnaire and interview. Lifetime risk of developing breast cancer was calculated using Claus and Tyrer-Cuzick scoring. Risk of carrying a breast cancer-related gene mutation was calculated using the Manchester system. One thousand two hundred and forty-three patients have been referred. Ninety-two percent were at medium or high risk of developing breast cancer. Formal assessment of risk has been performed in 368 patients, 73% have a high lifetime risk of developing breast cancer, and 72% a Manchester score ≥16. BRCA1/2 mutations have been identified in 14 patients and breast cancer diagnosed in two. Our initial experience of family risk assessment has shown there to be a significant demand for this service. Identification of patients at increased risk of developing breast cancer allows us to provide individuals with accurate risk profiles, and enables patients to make informed choices regarding their follow-up and management. ■

Key Words: breast cancer, family history, genetic testing, surveillance

In Europe in 2006 breast cancer accounted for 29% of new cancer cases in women and 18% of cancer-related deaths, making it not only the leading type of cancer, but also the most common cause of cancer-related death in European women (1). Breast cancer rates vary widely in Europe (41–91/100,000), however, most countries have reported an increasing incidence during the last decade. Increased incidences of breast cancer have been matched by improved survival rates that in part reflect the presence of organized cancer screening programs. Variability in survival among countries with similar incidence rates suggests the need for greater screening efforts and earlier identification of women at increased risk of developing breast cancer (1). National screening programs meet the needs of the population as a whole but may not cater for those who have an increased risk of developing breast cancer and who are too young for entry into screening. In Ireland, for example, one-quarter of all new breast cancers are diagnosed in women aged <50 years (2).

Familial breast cancer occurs in women whose families have experienced more cases of breast cancer than would have been expected to occur by chance alone. Increased rates of breast cancer within families reflect genetic susceptibility and shared environmental factors. Approximately 15–20% of women diagnosed with breast cancer have a family history. In addition, 1–2% of women have a family history that suggests a true genetic risk due to the presence of a high penetrance gene conferring up to 80% lifetime risk of developing breast cancer. The gene mutations that are known to predispose to the development of breast cancer are BRCA1, BRCA2, and TP53 and may be found in up to 5–10% of women who develop breast cancer (3). The population lifetime risk of developing breast cancer is 11%. Using data from empirical studies or using statistical models, the cancer risk for an individual with a particular family history may be calculated and classified as low (10-year risk of <3% for

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women aged 40–49 years or lifetime risk <17%), moderate (10-year risk of 3–8% for women aged 40–49 years or lifetime risk of 17–29%), or high (10-year risk of >8% for women aged 40–49 years or lifetime risk >30%). Patients with a 20% or greater chance of carrying a BRCA1, BRCA2, or TP53 gene mutation are also classified as high risk (4).

Appropriate early screening of women who are at increased risk of developing breast cancer may facilitate early detection or allow the introduction of risk-reducing strategies, and ultimately reduce breast cancer-related morbidity and mortality. We established a specialist family risk assessment clinic to cater for these needs. Our aims were to identify women who are at increased risk of developing breast cancer due to familial association or genetic risk; to provide women with a reliable estimate of their risk and to offer them appropriate counseling; to detect breast cancer at an early stage through regular surveillance of women at increased risk; and when appropriate to offer risk reduction strategies. Women at medium or high risk according to NICE guidelines were deemed suitable for referral (4). Herein, we report our experience to date.

PATIENTS AND METHODS

Patient Selection

Patient triage was based on NICE guidelines (Table 1) (4). Patients were classified as low, medium, or high risk depending on the number of family members with breast cancer and their age at diagnosis. All patients were contacted and their family history verified. Patient details were entered prospectively into a dedicated computerized database. Those confirmed to be at low risk were reassured, discharged to the care of their general practitioner, and advised to participate in the national breast cancer screening program at age 50 years. Women at medium or high risk were selected for further assessment and formal evaluation of risk (4).

Risk Evaluation

Patients were contacted and supplied with an information pack which included a detailed family history questionnaire. Patients were subsequently interviewed by a specialist nurse. During this initial consultation, the family tree was reviewed and written verification of cancer occurrence in affected relatives obtained. The consultation also included a discussion of inheritance patterns of BRCA genes, lifestyle risks, and breast awareness. The individual patient's risk of carrying a breast cancer gene mutation, and their lifetime risk of developing breast cancer were then calculated using Manchester, Claus, and Tyrer-Cuzick scoring (5–8). Patients were reviewed by a specialist nurse and a consultant breast surgeon for clinical assessment and detailed discussion of cancer risk.

Management

Risk reduction strategies were established based on individual patients' risks and requirements. Options included intensive surveillance comprising regular clinical assessment and mammography, genetic testing, participation in clinical trials, and risk-reducing surgery. The option of genetic screening for BRCA1 and BRCA2 mutations was discussed for individuals with a Manchester score >16 (threshold established by the

Table 1. Family risk assessment patient selection protocol

Low risk	Medium risk	High risk
No family history of breast cancer One first-degree relative with breast cancer >40 One second-degree relative with breast cancer at any age Two first- or second-degree relatives diagnosed with breast cancer >50 (on different sides of the family)	One first-degree relative with breast cancer <40 Two first- or second-degree relatives with breast cancer at an average age >50 Three first- or second-degree relatives with breast cancer at an average age >60	Two first- or second-degree relatives with breast cancer <50 Three first- or second-degree relatives with breast cancer <60 Four relatives with breast cancer at any age Two first- or second-degree relatives diagnosed with breast or ovarian cancer plus any of the following: Additional relative(s) with breast or ovarian cancer Breast cancer diagnosed before the age of 40 Ovarian cancer diagnosed before the age of 50 Bilateral breast cancer Breast and ovarian cancer in the same woman Ashkenazi Jewish Ancestry Breast cancer in a male relative First- or second-degree relative diagnosed with sarcoma at age 45 or younger One member of a family where a breast cancer gene has been identified

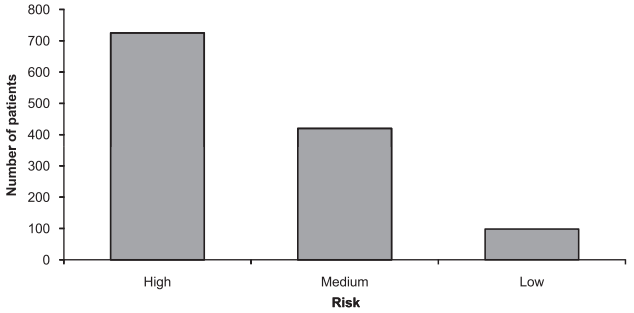

Figure 1. Risk stratification according to NICE guidelines of 1243 patients referred for family risk assessment.

National Centre for Medical Genetics). In this study, we report our findings for all patients referred between May 2005 and October 2008.

RESULTS

During the three-and-a-half year study period 1243 women were referred to the family risk assessment clinic. According to NICE guidelines 98 were at low risk, 420 at medium risk, and 725 at high risk (Fig. 1). Seventy-eight percent of patients were aged 50 years or less. Patients were referred from our own rapid diagnostic breast clinic (46%), directly from general practitioners (30%), by family members already attending the clinic (10%), and from other sources (14%) including private clinics, gynecology, oncology, and other hospitals (Fig. 2).

Five hundred and eighty-four patients (403 high risk; 181 medium risk) have undergone first assessment (Fig. 3). Of these 584 patients, 368 have had complete assessment and a management plan formulated. Of the 368 patients who have had a complete assessment, 270 have been designated as at high lifetime risk of developing breast cancer. To date 83 patients (75 high risk; 8 medium risk) have attended for subsequent follow-up assessment.

Of the 270 designated high-risk patients who have undergone complete assessment, 194 had a Manchester score ≥16 and 76 patients had a score <16 (Fig. 4). Fifty-six patients were referred for genetic screening for BRCA1/2 mutations and of those who have had complete assessment eight were diagnosed BRCA1 mutation carriers and six BRCA2 mutation carriers Three of these patients subsequently opted for prophylactic surgery in the form of bilateral mastectomy with immediate tissue expander reconstruction. A further three patients are undergoing preoperative evaluation, and the remainder have opted for intensive screening.

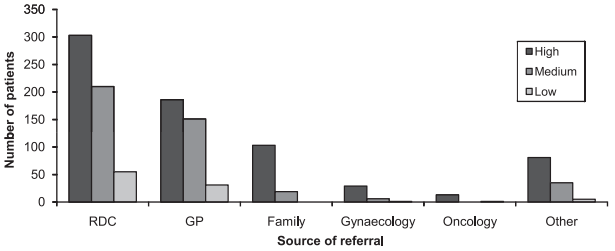

Figure 2. Source of patients referred for family risk assessment with risk stratification according to NICE guidelines (RDC, rapid diagnostic breast clinic; GP, general practitioner).

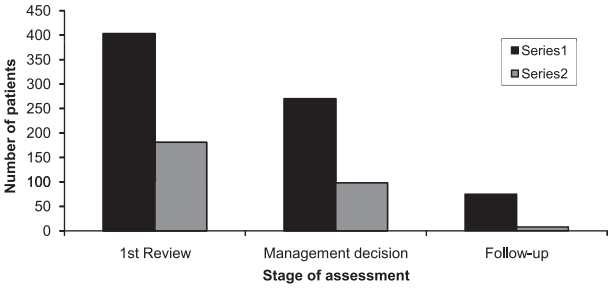

Figure 3. Management stage of medium- and high-risk patients who have undergone formal assessment.

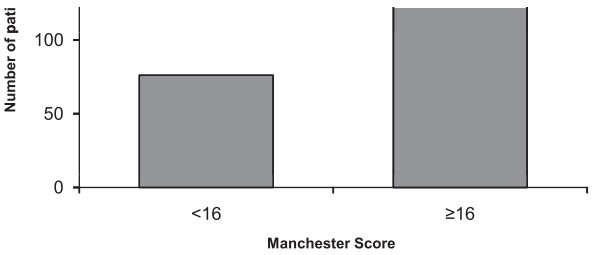

Figure 4. Manchester scores for 270 high-risk patients who have undergone formal assessment.

Individual surveillance programs were established according to individual patient characteristics and risk profiles. For patients at medium risk (lifetime risk: 1 in 6 to 1 in 4) surveillance comprises clinical breast examination and mammography at 12- to 24-month intervals depending on individual characteristics. Those aged >50 years are discharged to the national breast screening program (Breast Check), and their general practitioner. For patients at high risk (lifetime risk >1 in 3 or Manchester score >16) management options include intensive screening, referral to clinical trials, referral for genetic testing, and risk-reducing surgery.

To date two patients have been diagnosed with breast cancer. In one patient pathological analysis following prophylactic bilateral mastectomy showed duc-

tal carcinoma in situ. A second patient was found to have a breast lump at scheduled follow-up and was subsequently diagnosed with invasive breast cancer.

DISCUSSION

A family history of breast cancer is a recognized risk factor for the development of breast cancer. We established a breast cancer family history risk assessment clinic to meet the needs of those individuals who are at increased risk but who prior to that had no available means of assessing and managing their risk. Through the use of objective scoring systems we are able to provide patients with information that allows them to make informed decisions regarding their care. Since the inception of the clinic we have been referred over 1200 women, and fully assessed almost 400. Of those assessed, three-quarters have been found to be at high lifetime risk of developing breast cancer, or of carrying a breast cancer gene mutation. Of patients referred for genetic screening, almost half have been found to carry BRCA mutations. Risk-reducing strategies, comprising intensive screening and in selected cases risk-reducing surgery, may enable us to detect breast cancer at an earlier stage or prevent its onset and ultimately improve survival in this patient group.

Methods of Risk Assessment

The assessment of an individual's risk of developing breast cancer and their subsequent optimal counseling requires the use of several models of risk estimation. Two types of model that provide complimentary information may be used. Firstly, those that provide estimates of an individual's lifetime risk of developing breast cancer; and secondly probability tools that estimate the likelihood of identifying a gene mutation for a given individual. A number of scoring systems are in place for estimating an individual's breast cancer risk including Gail, Claus, and Tyrer-Cuzick, while models that facilitate selection for BRCA testing including Couch, Frank, BRCAPRO, Adelaide, Family History Assessment Tool, and Manchester (8–10). Each system has advantages and disadvantages. In particular, none of the models have been extensively validated and some may be overly simplistic in their risk estimates. These models do, however, allow calculation of risk based on complex family histories and this is their main advantage over the alternative, case–control studies, which give estimates of risk for common patterns of family risk only. For their overall usability and applicability to our population, we initially chose to employ the Claus and Manchester scoring systems. The Claus scoring system incorporates maternal and paternal histories as well as first- and second-degree relatives, and also weights for the age of diagnosis and any other family history of breast cancer (7). However, the tables are based on the assumption of prevalence of high penetrance genes for susceptibility to breast cancer and are limited to specific combinations of affected relatives. Such a system may not be applicable to all combinations of affected relatives and may underestimate risk in certain family lineages. For these reasons, we have within the last year used the Tyrer-Cuzick model as an adjunct to Claus scoring in calculating lifetime risk (8). This system allows both for a greater number of affected relatives and also for individual risk factors such as menstrual and reproductive history.

Manchester scoring was developed by Evans et al. (5) as user friendly scoring system for use by clinicians to calculate the likelihood of identifying a BRCA1 or BRCA2 mutation in a family. This system was designed to improve on deficiencies in existing manual models and to be less time consuming than computer models. Furthermore, the Manchester system has the advantage of accounting for a family history of other malignancies associated with BRCA gene mutations. The Manchester scoring system was designed to predict pathogenic mutations at the 10% likelihood level with a score of 10 points for each gene equating to a greater than 10% probability of a mutation in BRCA1 and BRCA2. Further development resulted in an updated scoring system, where a combined Manchester score of 15 indicates a 10% threshold for BRCA1/2 testing (6).

These systems have advantages and disadvantages, and results should be interpreted in the context of the individual patient. A reliable estimate of familial risk can only be obtained when all sources of data are taken into account, and is dependant on appropriate interpretation by experienced clinicians and family history counselors (9).

Verification of Family History

When gathering data regarding family history it is essential that incidences of breast and other cancers are verified. Although unreliable reporting for a family history of breast cancer appears to be of less significance than for other cancers, inaccuracies in reporting may nevertheless lead to bias toward increased familial risk estimates (11,12). Indeed, some studies suggest

that of all cases of breast cancer reported by families, only 56% are ultimately verified (13). This may lead to unnecessary or inappropriate screening efforts and referrals for genetic testing. Conversely, false-negative results and underestimation of family risk represents a missed opportunity for early intervention (9,11,14). In order to minimize this bias in our patients we sought to verify diagnoses in the form of pathology reports or death certificates in all family members reported to have breast, ovarian, pancreatic, prostate, gastric, and colonic cancer by women referred to our clinic. Only women who had undergone this formal assessment were included in our final figures. This process can, however, frequently pose significant difficulties for patients and lead to protracted and drawn out assessments.

Challenges in Family Risk Assessment

While family risk assessment clinics appear to be useful means of identifying patients at increased risk of developing breast cancer, a number of issues arising from our experience should be highlighted. Following assessment most patients will opt for intensive surveillance in the form of self-examination, clinical examination, and mammography. For those women who go on to develop breast cancer early detection appears to confer a survival advantage (15). While intensive surveillance will be appropriate for the majority of patients, the type and frequency of screening that should be employed for the young women in their teens and 20s, who account for a significant proportion of our patients is unclear. Secondly, patients found to be at high risk of being gene mutation carriers are faced with the considerable dilemma of choosing for or against genetic screening and the implications it raises for both the individual and her family. Thirdly, the provision of a service of this type has considerable implications for available resources. The assessment of patients followed by long-term surveillance places a significant demand on medical, specialist nurse, radiology, and other support services. It has recently been calculated that the cost alone of verifying a single family history and subsequent patient review is between 100 and 150 Euro (16). Furthermore, previous studies have shown that despite being at high risk a substantial number of patients fail to adhere to their recommended screening protocol (17). Currently demand for our service far out-weighs our ability to assess and follow-up patients, and the number of yearly referrals is steadily increasing. Referrals from general practitioners have in particular increased with the number more than doubling in 2007 when compared with the preceding year. Analysis of our referral patterns suggests a high level of awareness of referral criteria among referring physicians—only 8% of patients were classified as low risk. Maintaining awareness and on-going education of general practitioners will be critical in ensuring the efficient use of this service. General practice based software packages and online tools may facilitate physicians further in selecting patients appropriately for family risk assessment (18). Lastly and most importantly, for those patients deemed to be at high risk of developing breast cancer and for whom long-term surveillance is unacceptable, the only prophylactic treatment option available is surgical in the form of bilateral mastectomy and/or oophorectomy. Prophylactic bilateral mastectomy will reduce risk of developing breast cancer by at least 90% (19,20), while prophylactic bilateral salpingoophorectomy (BSO) has been shown to reduce the risk of breast cancer in BRCA mutation related breast cancer (21,22). Previous studies have shown uptake of risk-reducing surgery in females, who are at moderate or high risk to be low (approximately 5%) and is more likely to be considered by those with multiple affected relatives, those of older age, and those with BRCA mutations (23). Long-term follow-up indicates a 74% reduction in emotional concern regarding risk of developing breast cancer, but carries negative impact on feeling of femininity and satisfaction with body appearance (25% and 36% dissatisfaction, respectively) (24). In women from high-risk families with BRCA mutations who are diagnosed with breast or ovarian cancer the uptake of prophylactic mastectomy (contralateral or bilateral) is approximately 35%, and 50% for BSO (25). While chemoprophylaxis through the use of medications such as tamoxifen represents a potential prophylactic treatment option, its use remains under evaluation and is neither established nor clearly defined (26–29). As our understanding of the molecular and genetic etiology of breast cancer expands it is our hope that we will be able to offer patients less invasive treatment options to reduce their risk.

CONCLUSION

Women with a significant family history of breast cancer have an increased risk of themselves developing

breast cancer. Appropriate assessment allows us to provide individual patients with accurate risk profiles that enable them to make informed choices regarding their follow-up and management. Furthermore, the identification and treatment of women at increased risk of developing breast cancer represents an opportunity for early diagnosis and ultimately a reduction in breast cancer-related morbidity and mortality. Our experience has shown there to be a significant demand for this service; however, establishing a family risk assessment clinic is not without challenges and places a significant demand on existing resources.

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Disclosure

The authors have no conflicts of interest to declare.

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