



Genetics of Breast Cancer A Review for Primary Care Providers

Introduction

In the United States, breast cancer is the most frequently occurring cancer among women, with a lifetime risk of 1 in 8. Studies suggest that approximately 9% of all breast cancer in the United States is accounted for by a positive family history of breast cancer¹. Familial clustering of breast cancer may be a coincidence, or it may be due to an underlying genetic risk inherited in a polygenic, multifactorial or single gene pattern. Hereditary breast cancer is real and may produce dramatic familial aggregations of breast cancer. At least eight identified genes have been associated with inherited breast cancer susceptibility (summarized by Greene²). Others are likely to be found. BRCA1 and BRCA2 are currently the most important of these but account for less than 5% of all breast cancers.

Many women with a family history of breast cancer are concerned about their own risk of developing cancer and medical management options that might reduce this risk. They will turn to their family physicians for accurate information. In response, primary care physicians must be familiar with cancer risk assessment, hereditary syndromes, the usefulness of predictive genetic testing and referral mechanisms to make appropriate patient management decisions.

Family history taking and cancer risk assessment

Multiple epidemiological studies have documented that a reported history of breast cancer among relatives is a reproducible predictor of breast cancer risk. Data suggest that, for the vast majority of women with a positive family history of breast cancer (1 or 2 affected relatives), the relative risk for breast cancer is increased 2-3 fold³. The risk escalates dramatically, however, for families with premenopausal breast cancer, bilateral disease and multiple affected family members.

Identifying women with a positive family history is an important first step to providing accurate cancer risk assessment. It is vital to gather information regarding both the maternal and paternal side of the family. For each family member with cancer the following information should be documented:

- the site of origin of all reported primary cancers
- whether the tumor was bi- or unilateral in paired organs
- age at diagnosis
- lineage (either maternal or paternal) and degree of relationship

When reviewing the completed family history, families can be assigned to lower or higher risk categories. Lower risk families typically present with fewer than three cases of breast cancer, absence of ovarian cancer and an older age of breast cancer onset (greater than 50 years old). An hereditary syndrome (or higher risk family) should be suspected if the following are noted:

- a history of breast or ovarian cancer in two or more first degree relatives in either paternal or maternal lineage
- early age of onset (<50)
- bilateral or multifocal breast cancer
- specific constellation of tumors that comprise a known breast cancer syndrome, e.g.
 - breast, ovarian, prostate and colon (hereditary breast cancer)
 - breast, brain, adrenocortical tumors, sarcoma, leukemia (Li Fraumeni syndrome)
 - breast, lymphoma, and pancreatic cancer
 - (ataxia telangiectasia)
 - breast, thyroid and skin (Cowden syndrome)

- absence of environmental influences

Lower risk families

The primary care provider may help allay the inappropriate fears expressed by many patients simply by (a) pointing out the relative rarity of truly hereditary breast cancer, (b) **reminding patients that "familial" and "hereditary" are not the same**, and (c) providing a description of the features of hereditary breast cancer (which only applies to a small minority of patients with a family history of breast cancer.) Even in the absence of clear proof of efficacy, a common-sense set of recommendations for "good breast health" can also be offered, and includes:

- maintaining ideal body weight
- participating in regular aerobic exercise
- consuming a diet that emphasizes fresh fruits, vegetables, chicken and fish, and de-emphasizes beef
- moderating alcohol consumption
- minimizing radiation exposure to the breasts (particularly in teenagers)
- thoughtful deliberation over decisions regarding use of oral contraceptives, estrogen replacement therapy and the appropriateness of tamoxifen. (Results from the Breast Cancer Prevention Trial suggest that tamoxifen may have an important role to play in reducing breast cancer incidence in carefully selected, appropriately informed women at increased risk of breast cancer⁴).

For some patients, fears do not subside until additional information is given. Providing patient-specific cancer risk assessment to these individuals may prove beneficial. A comprehensive evaluation may be indicated, especially for women who have had an abnormal mammogram or biopsy indicating a precancerous lesion. This may best be completed by a multidisciplinary team which can assess cancer risk, review cancer risk factors and make recommendations about appropriate prevention and screening.

Among unaffected relatives from lower risk families, cancer risk assessment is not standardized. In addition to family history, a personal health history as well as occasional laboratory and radiographic studies must be considered and interpreted. Sophisticated mathematical models can be employed to estimate risk of developing breast cancer for unaffected relatives in families in which there is not a significant history of cancer in extended members.

One such model, published by Claus et al.⁵, predicts the cumulative risk of breast cancer at specific ages. Presented in detailed tables, this model takes into account the age of onset for affected relatives and the age of the patient. It does not account for other breast cancer risk factors.

Another model, published by Gail et al.⁶, does incorporate breast cancer risk factors including age at menarche and number of previous breast biopsies into its mathematical formula. Although valuable in predicting risk in women undergoing annual mammography, this model is limited by considering only first degree relatives and not accounting for age of diagnosis of breast cancer.

Higher risk families

To obtain the most up-to-date information about the role that susceptibility genes play in the development of cancer and to accurately assess cancer genetic risk, high risk families should be referred to a program which specializes in managing hereditary cancer. These clinics include education and counseling about cancer risk, cancer risk reduction, and effective screening and prevention options. Genetic counseling is essential to ensure that patients understand the information presented, appreciate potential medical and psychological implications of hereditary cancer and have an opportunity to explore the limitations and benefits of available testing options.

BRCA1 and BRCA2

Overall, 52% of breast cancer families with at least four cases of breast cancer are linked to BRCA1. Cumulative breast cancer risk among gene carriers is approximately 80% by age 70. This figure may be high due to an ascertainment bias of particular populations or of high risk families. The risk of developing cancer may be lower in women with less dramatic family histories or in women whose mutations are identified via population screening^{7,8}.

Among BRCA1 mutation carriers with a first breast cancer, the risk of contralateral breast cancer may be as high as 65% by age 70. The risk of ovarian cancer in these same women has been estimated between 30-65% by age 70^{7,9,10}. Colon cancer is estimated to occur four times more frequently among BRCA1 mutation carriers than expected from general population rates: the absolute risk is 6% by age 70 (1-2% in non-carriers). Prostate cancer may occur 3.3 times more often than expected in male BRCA1 mutation carriers, with an absolute risk of 8% by age 70⁹.

The prospect that the cloning of BRCA1 would quickly lead to a simple genetic test has been thwarted by the gene's large size and the enormous number of distinct, disease-related mutations which have been identified to date. Over 200 BRCA1 mutations have been documented, some of which seem specific to particular populations. Appropriate testing for the first member of most families in which mutation status is unknown is to offer full gene sequencing.

Of those families which have an inherited predisposition to developing breast cancer, about 35% appear to be linked to a second breast cancer susceptibility gene, BRCA2¹¹. Male breast cancer seems to be part of the BRCA2 tumor spectrum (although it is observed in occasional BRCA1 families as well) and is estimated to occur in approximately 6% of mutation carriers¹¹. Lifetime risk of breast cancer in women with BRCA2 mutations is similar to those with BRCA1.

In contrast, the cumulative lifetime risk of ovarian cancer, while still higher than that in the general population, appears to be 10-20% lower than that of women who have a BRCA1 mutation^{7,11,12}. Like BRCA1, multiple distinct mutations in BRCA2 have been identified, scattered rather evenly throughout this large gene.

It has been long appreciated from breast cancer case-control studies that Jewish women are at mildly increased risk of breast cancer compared to non-Jewish women. One of the more intriguing observations regarding BRCA1 and BRCA2 has been the recognition that three specific mutations (185delAG, 5382insC and 6174delT) occur with a very high frequency (>2%) among persons of Ashkenazi Jewish extraction. These three mutations have been reported in approximately 25% of site specific breast cancer families and up to 90% of breast and ovarian cancer families¹³. In light of these data, women of Ashkenazi Jewish ancestry who have at least one first degree relative with premenopausal breast cancer or ovarian cancer are appropriately referred to a high risk breast cancer clinic.

Predictive testing for BRCA1 and BRCA2 mutations

The issue as to when to offer predictive genetic testing for BRCA1 and BRCA2 is proving remarkably contentious. None of the cancer susceptibility tests currently available appears to be appropriate for screening asymptomatic individuals in the general population, although the population-specific mutations described among Ashkenazi Jews may reach that status in the future.

The evaluation of individuals from high risk families with well defined syndromes is far less clear. Most academic, professional and government organizations that have addressed this issue have concluded that it is premature to offer BRCA1 and BRCA2 testing as a routine clinical service. The American Society of Clinical Oncology (ASCO) has published a position paper on this subject¹⁴. This statement and the companion comments provide an excellent summary of the issues:

The basic elements of informed consent for germline DNA testing are complex and extensive. Patients must be given: (1) information on the specific test being done; (2) implications of a positive and negative test; (3) possibility that the test will not be informative; (4) options for risk evaluation without genetic testing; (5) risk of passing a mutation to children; (6) technical accuracy of the test; (7) fees involved in testing and counseling (up to \$2500); (8) risk of psychological distress; (9) risk of employment and insurance discrimination; (10) need for confidentiality; and (11) options and limitations of medical surveillance and screening after testing.

The Breast Cancer Linkage Consortium data base and mathematical models developed by Shattuck-Eidens et al.¹⁵, Parmigiani et al.¹⁶, Couch et al.¹⁷ and Frank et al.¹⁸ can be used to compute estimated probabilities that a BRCA1 and BRCA2 mutation will be found in women of various ages, cancers and relationship combinations. When included in the discussion of predictive gene testing, this information may enhance informed decision making regarding BRCA1 and BRCA2 testing.

What benefits might accrue to those who undergo predictive genetic testing? In the context of testing members of a family known to carry a BRCA1 or BRCA2 mutation, most persons tested will achieve knowledge of their gene status, thereby, eliminating pre-test ambiguity. In that setting, for those who do not have the mutation seen in other members of their family, additional potential benefits include:

- relief from fear of genetic cancer risk, both for themselves and their children
- elimination of the need to consider prophylactic breast and/or ovarian surgery
- the ability to make choices regarding exogenous hormone use without concern about genetic interactions
- general improvement in their sense of well-being

For those who test positive, one might anticipate:

- more accurate quantification of cancer risks
- less uncertainty about the potential benefits of prophylactic surgery
- the ability to elect more intensive, site-specific cancer surveillance
- enhanced motivation to make prudent lifestyle change which might reduce cancer risk

Operating counter to this cautious approach to the introduction of predictive testing are the commercial interests that hold the patents on the tests to be marketed and that stand to profit enormously if the tests are widely used. Several commercial laboratories currently market BRCA1 and BRCA2 testing. They are, to their credit, making an effort to ensure that testing is being done as part of a comprehensive genetic testing/counseling program, but the ultimate responsibility will rest with busy clinicians who are relatively ill-equipped to present the subtleties and complexities of cancer genetic risk assessment and predictive genetic testing. It is important to remember that commercial availability of a genetic test does not automatically mean it is suitable for routine general use.

Based on the data presented, guidelines for referring a patient to discuss predictive genetic testing include:

- a woman with breast cancer diagnosed younger than age 30
- a woman with breast or ovarian cancer diagnosed younger than age 50 who has a sister, mother, or daughter with breast or ovarian cancer diagnosed younger than age 50
- an affected woman from a family with two or more breast cancers and one or more ovarian cancers
- an unaffected first-degree relative of someone with a known mutation in BRCA1 or BRCA2
- an Ashkenazi Jewish woman with breast cancer diagnosed at less than age 40 or ovarian cancer diagnosed at any age

Ideally, in a family which has not previously been shown to have a disease-related mutation, genetic testing should start with a family member who has had cancer.

Summary

While the process of cancer risk assessment and predictive genetic testing is complex, much of the basic information regarding the clinical characteristics of hereditary breast cancer, the relative rarity of BRCA1 and 2 mutations, and sensible recommendations for breast health can be managed by primary care providers.

Currently, predictive genetic testing is best done through specialty referral. We are at the beginning of an exciting period in genetic oncology, but much remains to be learned. To the greatest extent possible, genetic testing for cancer susceptibility should be made available to selected patients as part of preventive oncologic care only in conjunction with appropriate patient education, informed consent, support and genetic counseling. Patients may benefit greatly from accurate cancer risk assessment even when genetic testing is not undertaken.

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