Genetic testing for inherited breast and ovarian cancer syndromes: important concepts for the primary care physician

M R G Taylor

Abstract

The remarkable advances in the area of genetic testing are transforming the way clinical medicine is practised. In the case of the inherited breast-ovarian cancer syndrome the ability to engage in genetic testing of BRCA genes has raised novel issues over caring for patients who are at increased risk for these malignancies. The primary care physician is likely to play a pivotal role in identifying such persons. As only 10–15% of all breast cancers are caused by directly heritable mutations, cultivating the ability to identify those who may be at increased risk is an important skill for the primary care physician. Once it is established that an individual is at risk of BRCA mutation, the physician must understand the potential benefits and drawbacks of the various genetic BRCA tests. Taking such factors into account leads to the development of an appropriate plan for evaluation. Careful attention must also be paid to social and psychological issues that may affect patients and their families.

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Recent advances in the field of genetics have led to improved understanding of the inherited cancer syndromes. This progress has stimulated the development of genetic tests for predicting cancer susceptibility, and several such tests are already available commercially (for example, tests for hereditary retinoblastoma, colon cancer, and breast-ovarian cancer syndromes). Generalists and specialists alike may be unfamiliar or feel uncomfortable with recommending or interpreting genetic tests,¹ yet the impressive advances in this field are difficult to ignore. The combination of increasing availability of genetic testing coupled with expanding public awareness of such testing options is challenging primary care physicians to cultivate their knowledge of these diseases. One such syndrome, the familial breast-ovarian cancer syndrome, has received widespread attention and is the subject of this review.

The hereditary breast-ovarian cancer syndrome

Breast cancer has the notorious distinction of being the most common non-skin cancer detected in women in the United States. Approximately 180 000 new cases of breast

cancer are diagnosed each year. As such, it ranks second—with 45 000 annual deaths—behind lung cancer as a cause of cancer death.² Roughly 12% of all women will develop breast cancer in their lifetime. Effective public health campaigns by the American Cancer Society have raised awareness of the disease and made this “one in nine” statistic familiar to many women (although the statistic is now closer to one in eight). Surprisingly, although heart disease is responsible for substantially more deaths in women, American women are far more likely to identify breast cancer as the disease they fear most.³ Ovarian cancer is substantially less common than breast cancer and is newly diagnosed in over 26 000 women annually in the United States. It is the most deadly gynaecological malignancy and results in nearly 15 000 deaths each year.⁴

Early descriptions of families suffering from multiple cases of breast cancer date back centuries. The first comprehensive description was provided by Paul Broca, a French surgeon, who, in 1886, characterised the presence of breast cancer in his wife’s family through four generations.⁵ Many other families have since been well described. Ovarian cancer and other malignancies also affect these families. Although these pedigrees are striking when encountered, it must be remembered the majority of cases of both breast and ovarian cancer are sporadic. The breast-ovarian cancer syndrome accounts for an estimated 10–15% (or 18–25 000) of the cases of breast cancer diagnosed in the United States each year.^{5–6} In many cases the primary care physician is in an opportune position to distinguish patients with heritable cancers from the multitude of sporadic cases. In the past decade an understanding of two important breast cancer genes, BRCA1 and BRCA2, has helped make this distinction possible.

Inherited cancer syndromes and tumour suppressor genes

BRCA1 and BRCA2 are “tumour suppressor genes” (fig 1). The exact details of the tumour suppressor model are beyond the scope of this review, but some basic points can be made. Cancers can be considered in the context of a multistep model, where a handful of mutations are necessary for cancer to occur. Tumour suppressor genes code for proteins along the multistep pathway. These proteins are intimately involved in controlling cellular growth and differentiation. When they are absent or mutated to an extent that their function is compromised, proper regulation of these func-

Division of Genetics,
Children’s Hospital,
1056 E 19th Avenue
B300, Denver,
Colorado 80218, USA

Correspondence to:
Dr Taylor
matthew.taylor@uchsc.edu

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Figure 1 The tumour suppressor model in setting of BRCA1. Normally (left), individuals have two functioning copies of the BRCA1 genes in each cell. Each gene produces a BRCA protein product that ensures tight control of cell growth and differentiation. Somatic mutations in wild type BRCA genes that eradicate BRCA function are possible. In the case of a somatic mutation occurring in a normal individual (middle), the end result is that only one copy of a normal BRCA protein is made. This single BRCA copy retains the ability to regulate cellular functions. Such mutations are very rare, and the probability that a second mutation will inactivate the remaining wild type copy in that particular cell is remote. In contrast, individuals with germline mutations in a BRCA gene are functionally hemizygous (only one active copy) in all of their cells. Now a single somatic mutation that inactivates the wild type copy of the BRCA gene in any cell eliminates BRCA activity. Without normal BRCA function the cell is predisposed to develop malignant characteristics.

tions is impaired. Individuals with hereditary cancer syndromes have a germline mutation in one copy of a tumour suppressor gene. Consequently all of their cells have only one functioning copy. Over time a mutation that inactivates the remaining copy can occur and render that cell at risk of developing into cancer. The requirement for at least two mutations to occur to lead to tumorigenesis was originally described by Knudson in the setting of retinoblastoma; it is now referred to as "Knudson's two hit hypothesis."⁷ This model does not reduce the multistep process of cancer development to just two events. Rather, it serves to emphasise the importance of the loss of both copies of a given tumour suppressor gene in tumorigenesis.

The majority of mutations in the BRCA genes have been described in extended family pedigrees where the causative mutation can be followed through several generations. The pattern of inheritance is autosomal dominant; a history of breast cancer in a patient's paternal aunt must therefore carry the same weight as a similar history in the maternal grandmother, as both are second degree relatives. Spontaneous new mutations in BRCA genes must also arise, although it remains unclear exactly what the new mutation rate is. At the present time, most mutations are identified through recognition of compelling family histories, and consideration of testing for such mutations in sporadic cases is seldom a clinically relevant issue. However,

when faced with an individual with very early onset breast or ovarian cancer, or with multiple cancers of this type, approaching BRCA testing may be appropriate even if the family history is not compelling.

BRCA mutations and the risks of cancer

Mutations in BRCA1 and BRCA2 confer a lifetime risk of breast cancer as high as 80% by the eighth decade.⁸ These mutations are common in early onset breast cancers and in women with bilateral disease. BRCA2 has been linked with cases of male breast cancer.^{9,10} Ovarian cancers are also more prevalent in people with BRCA mutations, with lifetime risks of 25–85% and 10% for BRCA1 and BRCA2, respectively.⁹ Cancers of the colon and prostate appear to be slightly increased as well (6% and 8% by age 70 for BRCA1).^{2,8} Cases of these cancers are important because they can occur in male family members. In a family where many of the relatives are male, finding several cases of early onset colon or prostate cancer can strengthen suspicions of a hereditary syndrome.

The BRCA1 and BRCA2 genes

The BRCA1 gene is one of the largest genes described to date. Located on chromosome 17, its 22 coding regions (exons) are dispersed over 100 000 base pairs of DNA. The protein produced is large, containing 1863 amino acids, is targeted to the nucleus, and does not

show significant homology to any other described protein.⁸ Over 300 unique mutations have been documented in BRCA1. Most of these mutations result in a shortened, presumably non-functioning, protein product. BRCA2 is also a large gene—in fact the final protein product is nearly twice as long as BRCA1. As with BRCA1, over 100 mutations have been documented, and the number continues to increase. BRCA2 does not show marked sequence similarity to any other protein, including BRCA1. To date, all the mutations in BRCA2 have resulted in a shortened protein product.

Testing for BRCA1 and BRCA2 mutations

Several things should be considered when deciding to offer BRCA testing. Finding a BRCA mutation in a woman does not guarantee that she will inevitably develop breast or ovarian cancer (after all, an 85% lifetime chance of having breast cancer is still a 15% chance of not developing the malignancy). Geneticists use the term “penetrance” to describe how frequently a given phenotype (in this case cancer) is seen with a particular genetic mutation. Furthermore, one should allow for the fact that not all women who develop breast cancer die from it, and that many breast cancers detected at an early stage may be curable. There is even some evidence that the cancers resulting from BRCA1 or BRCA2 mutations may be less virulent than sporadic breast and ovarian cancers.⁴ Although both patient and physician may be justifiably relieved by a true negative mutation result, neither should make the mistake of believing that the absence of a BRCA mutation is “protective” against developing cancer. Sporadic breast cancer, for example, still affects 12% of women, and sensible recommendations for annual mammography and regular clinical breast examinations should not be disregarded on the basis of a negative test result.

Testing for BRCA1 and BRCA2 is still relatively new, and guidelines for determining exactly who should and should not be offered tests are still being debated. The Cancer Genetics Study Consortium (organised in part by the Human Genome Project),¹² the Stanford program in genomics, ethics, and society,¹³ and the American College of Obstetrics and Gynecology¹⁴ have all published guidelines on BRCA testing. As more is learned about the clinical implications of specific BRCA mutations, these guidelines are likely to evolve further.

When deciding to pursue genetic testing in a patient with a history suggestive of breast-ovarian cancer syndrome, the eventual result should not be interpreted in the context of a simple positive or negative model. Importantly, not all mutations can necessarily be viewed as conferring equivalent risks for tumorigenesis. A few mutations have been well characterised because they are more common and show clear association with cancer. Several mutations have only been described in one or two families, and the implications for other families with these

less well understood mutations are not straightforward. Other “mutations” have not been proven to be pathogenic and may just represent silent genetic changes that do not confer an increased risk of breast cancer. Interestingly, location of the mutation may be somewhat predictive of the eventual phenotype. Some mutations have been described in families predominantly affected by breast cancer, while others have been linked to families with proportionally more cases of ovarian cancer; yet others appear to be found in families which are clearly affected by both types of cancer. It will probably take several more years to determine the significance of each particular mutation in these genes.

Who should be tested for BRCA1/BRCA2 mutations?

It is now well established that BRCA tests should not be offered to all women as a routine screening procedure.¹² BRCA mutations are thought to be uncommon in the general population (much less than 1% harbour a mutation). The tests are also expensive, ranging from \$300 to \$2400. These facts, along with the lack of clearly beneficial treatment for BRCA mutation carriers, argues forcefully against population based screening. Even comprehensive screening of all women with breast cancer cannot be recommended, as the majority of breast cancers are sporadic in nature. In the Ashkenazi Jewish population, where 1% of individuals have one of three BRCA mutations, population screening is being considered. A specific testing panel targeted at members of this population is available.

Only 10–15% of all breast cancers are manifestations of the breast-ovarian cancer syndrome, and for the majority of women suffering from breast cancer, genetic testing for BRCA mutations is not likely to be revealing. The primary care physician has the daunting task of distinguishing those patients who are at high risk of BRCA mutations from those who have sporadic cancer. To determine whether BRCA testing is appropriate, a detailed personal and family history takes centre stage. One should not only pay attention to cases of breast and ovarian cancer, but a history of other cancers (for example, of colon and prostate) should also be sought. In keeping with the pattern of other inherited cancer syndromes, one should look for evidence of early age of cancer onset, bilateral disease, the presence of multiple cancer types (for example, breast and ovarian cancer in one individual), and an autosomal dominant pattern of inheritance.¹¹ Unusual cancers such as male breast cancer should also raise suspicions of a breast-ovarian cancer syndrome. Once a patient at risk for a BRCA mutation is identified, it is advisable to provide some form of detailed genetic counselling before proceeding with any genetic testing.

Understanding BRCA testing

Before engaging in genetic testing, both the physician and the patient should possess some level of understanding about what particular BRCA tests are available. As around 85% of

cancer causing BRCA mutations lead to shortened protein products, “protein truncation” assays are often done first. The shortened protein migrates at a different speed on an electrophoretic gel and can be distinguished from normal BRCA protein. Single strand conformation analysis (SSCA) is another technique that relies upon differences in DNA structure between mutant and non-mutant DNA. Single stranded DNA does not exist in a long-linear configuration; instead it folds upon itself to form complicated three dimensional structures. Mutations create folding that is different from wild type DNA. SSCA can detect even single base pair changes between mutant and wild type DNA. Although these tests are useful in establishing rapidly that a mutation is present, they cannot specifically characterise a mutation.

More focused testing can search for specific mutations. This is desirable when testing Ashkenazi Jewish patients, for example, as three specific mutations appear to account for upwards of 90% of the BRCA mutations in this group.

Finally, the technology to sequence the entire gene has now been realised. Not surprisingly, sequencing is the most expensive of the current tests, though it appears to provide the most comprehensive information.

Limitations of current genetic testing

Powerful as these genetic tests can be in defining patients with hereditary breast-ovarian cancer syndromes, there are nevertheless important limitations. DNA sequencing can theoretically miss major mutations that are outside the boundary of the sequenced DNA, and it also has the power to identify alterations in sequence that can be a source of uncertainty and anxiety. Often it is not possible to predict the clinical implications of such changes. How does one counsel a patient who carries a change in her BRCA1 gene that has not yet been strongly linked to cancer, or has only been reported in one family previously? Is her risk the same as for other well described mutations, or could it be less pathogenic or even phenotypically silent?

Different problems are encountered when a BRCA mutation is suspected but none can be found. In these cases the negative BRCA test results can be difficult to interpret. If the person tested has breast or ovarian cancer, then the negative test result has three possible explanations. First, the result could be a true negative, in the sense that there really is no BRCA mutation affecting that family, and all cases represent only sporadic cases. Second, a BRCA mutation could be causing the excess of cancers in that family, but the mutation is not detectable by the genetic test that was used. Finally, it is possible that there is no mutation in BRCA1 or BRCA2, but that the family is still at increased risk for cancers on the basis of other, as yet undiscovered, breast-ovarian cancer genes.

These complexities may be further worsened when an unaffected family member is tested. If this asymptomatic individual tests positive for a

well understood BRCA mutation, then the test result may be said to be informative. However, if the individual tests negative, then the problems mentioned above may still apply. In addition, there is the possibility that a BRCA mutation is segregating in a family, but the unaffected person tested may not have inherited that mutation. This last point emphasises the importance of making every effort to test an affected family member before testing an asymptomatic individual.

Diagnostic v predictive testing

Effective counselling of patients regarding BRCA testing involves a thorough explanation of the potential of the tests and their limitations. It is particularly important to explain that testing provides “predictive” rather than “diagnostic” information.¹⁵ Diagnostic testing refers to procedures that definitively diagnose a particular condition. A needle biopsy of a malignant breast lump or an x ray of a broken bone can generally be said to provide diagnostic information. Many genetic tests fall into the category of diagnostic testing. Examples would include documenting an extra chromosome 21 in the diagnosis of Down’s syndrome or finding abnormal haemoglobin segregation in the case of sickle cell anaemia. Huntington disease—a lethal neurodegenerative disorder—provides another example of diagnostic DNA testing, in that all the individuals who have a Huntington disease mutation will develop the disease as they age. Tragic though a positive test may be, it is “diagnostic” in that it affirms with a high degree of certainty that the individual will be affected.

A positive result from a predictive tests reveals that a patient’s risk of developing a disease is increased but it cannot predict whether or not that individual will be affected. BRCA testing is predictive because a given BRCA mutation does not inevitably lead to cancer in a given individual. A BRCA mutation markedly increases the likelihood of developing breast and ovarian cancer, but other genetic factors and environmental influences also contribute to the phenotype; thus a positive result does not mean that cancer is inescapable. Consider the patient who has two first degree relatives with breast cancer. Her risk of breast cancer is increased above the population risk because of her two affected relatives. Showing that she carries a BRCA mutation predicts a higher lifetime risk for cancer but does not make that diagnosis a certainty. Similarly, a true negative result predicts that her risk of cancer is not markedly increased over that of the average woman in the population. The opportunity for misunderstanding in this area has generated concern that some women from high risk families who are found to be negative for BRCA mutations may interpret such a result as suggesting that they are “protected” from ever developing breast cancer. In point of fact, such women are clearly not immune from developing sporadic breast cancer.

Table 1 Recommendations for management of carriers of BRCA1 and BRCA2 gene mutations (adapted from Burke *et al.*¹²)

Topic	Recommendation (expert opinion)
Breast self examination	Education regarding monthly examination
Clinical breast examination	Annually beginning at age 25–35
Mammography	Annually beginning at age 25–35
Transvaginal ultrasound (with colour Doppler)	Annually beginning at age 25–35
Bilateral mastectomy	Insufficient evidence to recommend for or against*
Bilateral oophorectomy	Insufficient evidence to recommend for or against
Oestrogen replacement	Insufficient evidence to recommend for or against*
Chemoprevention (for example, tamoxifen)	Insufficient evidence to recommend for or against*

*There is evidence that these interventions may reduce the risk of cancer in individuals at high risk of breast or ovarian cancer, but data specific to patients with BRCA mutations are lacking.

Other issues in genetic testing

The impact of breast and ovarian cancers on patients and their families can be sizeable. Exploring a patient's emotional and psychological concerns before initiating tests is recommended. An early concern in the realm of testing for Huntington disease was that patients receiving positive results would be at risk for severe depression or suicide. Fortunately, several studies have tempered these concerns. Similar investigations into the emotional impact of breast cancer testing have been undertaken. In general, genetic counselling and subsequent genetic testing for BRCA mutations has not been shown to lead to undue psychological stress.¹⁶

The complexities surrounding BRCA testing explain why many guidelines recommend that it may be appropriate for patients to receive formal genetic counselling before testing.¹³ Primary care physicians—who are likely to be among the first to have the opportunity to identify patients with worrying family cancer histories—can assume an important role in identifying patients who could benefit from BRCA testing. Some initial counselling on the part of the primary care physician can help determine if the patient is interested in testing. Once this is established, patients can be offered formal genetic counselling where a comprehensive pedigree analysis, calculation of specific BRCA mutation risks, and a thorough explanation of genetic testing is achievable.

Once a patient is found to have a BRCA mutation, the physician must develop a reasonable management plan. As BRCA genes have only been recognised in the past decade, definitive prospective data to clearly establish the optimal management of these conditions are lacking. At present one must rely on expert recommendations. Clinical breast and ovarian cancer screening examinations should be done on a routine basis and are initiated at an earlier age than is suggested for the general population. Similarly, an earlier initiation for screening mammography and ovarian ultrasound is suggested. The cancer screening marker CA-

125 is also used by some as an ovarian cancer screening tool¹²; however, its efficacy in the setting of BRCA mutations has not been conclusively demonstrated. Published recommendations addressing these cancer surveillance strategies are available (table 1). These guidelines also provide information about prophylactic surgical interventions (that is, mastectomy or oophorectomy) which may reduce the cancer morbidity in patients with BRCA mutations.^{12, 17}

Finally, the issue of genetic testing and confidentiality should be broached with patients interested in undergoing testing. Legislation protecting patients from genetic discrimination is present in many states in the USA, but the laws are not comprehensive and may not have been tested in court. The possibility of encountering discrimination when pursuing future employment or seeking health insurance should be discussed. A positive BRCA test result might be interpreted legally as a "pre-existing condition" that must be disclosed in certain circumstances. Some have even suggested that patients only seek testing in established clinical trials that can provide confidentiality and anonymity.

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