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Cancer genetics for the clinician: Recommendations on screening for *BRCA1* and *BRCA2* mutations

ABSTRACT

Mutations in the *BRCA1* and *BRCA2* genes confer a greatly increased risk of breast cancer, ovarian cancer, and other malignant diseases. This paper offers recommendations about who should be screened for *BRCA* mutations, and insights into the ramifications of *BRCA* testing.

KEY POINTS

BRCA1 and *BRCA2* are tumor-suppressor genes; mutations that cause them to lose their function confer susceptibility to cancer in an autosomal-dominant fashion.

In general, genetic testing is indicated only if the prior probability of abnormalities is at least 10%, as revealed by family and clinical history.

Before testing, patients should undergo counseling and give their informed consent.

Patients found to carry mutations in *BRCA1* or *BRCA2* should be encouraged to commit to an intensive, lifelong program of cancer surveillance. Some may wish to take the extreme step of undergoing prophylactic mastectomy and oophorectomy, although these measures remain controversial.

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THE DISCOVERY that mutations in the *BRCA1* and *BRCA2* genes increase the risk of breast and ovarian cancer[1,2] raises difficult questions for clinicians and patients. Who should undergo genetic testing? How should we counsel patients who have abnormal results? What is the proper screening regimen to detect early cancers? And perhaps most difficult, what preventive therapy—such as prophylactic mastectomy or oophorectomy—is appropriate for these patients?

This paper briefly reviews clinical and ethical implications of testing for mutations in *BRCA1* and *BRCA2* and the biology of familial and hereditary cancers.

CALCULATING BREAST CANCER RISK

Of the known risk factors for breast and ovarian cancer, age and family history of the disease are the most important. A woman's risk of developing breast cancer by age 30 is only 0.04%, and the risk by age 75 is 9%. However, some cases of breast (and ovarian) cancer do occur in younger women, and many of these are due to a genetic predisposition.

One can use two empiric tools to calculate a woman's risk of breast cancer:

The Gail model[3] uses the woman's current age, age at which she first gave birth, age at menarche, number of first-degree relatives with breast cancer, and number of biopsies she has undergone for suspected breast cancer.

The Claus model[4] uses the number of first-degree and second-degree relatives with breast cancer and the age at which these relatives developed cancer.

Neither model is perfect, but of the two, the Claus model is more appropriate for women with inherited breast cancer. The Claus model is too complex to reproduce here, but the original report[4] contains a variety of tables that can help a clinician estimate risk. The Gail model is not as accurate for younger women with a positive family history, since it does not consider breast cancer in second-degree relatives or cases of ovarian cancer in the family. In families with inherited breast or ovarian cancer, both models underestimate the risk for women who carry a mutation in a cancer gene, and both overestimate the risk for women who do not carry the mutation.

GENETICS OF CANCER

Approximately one person in five will develop cancer in his or her lifetime. As high as this figure is, some people inherit a much higher risk, owing to a genetic predisposition. These persons account for 5% to 10% of cases of cancer.

Researchers have identified a number of genes that, if inherited in a mutated form, confer an increased risk of cancer. The Human Genome Project, now nearly completed, should increase our knowledge in this area tremendously.

Cancer is always a genetic disease

All cancer is considered a genetic disease, although most cases are not inherited. This genetic basis of cancer is rooted in the cell cycle and the different genes that regulate the growth and death of cells.

A number of genes determine when the cell will grow and divide. Some genes, called oncogenes, code for proteins and enzymes that promote growth and division. Another type of gene, called tumor-suppressor genes, keeps growth and division in check. A third class, called mismatch-repair genes, edits and corrects errors that occur when DNA replicates.

Mutations in any of these classes of genes can push the cell in the direction of developing a neoplasm, but in different ways. Mutations in oncogenes promote accelerated cell division. In contrast, mutations in tumor-suppressor genes remove the natural controls on cell division. And mutations in mismatch-repair genes can lead to further mutations in oncogenes and tumor-suppressor genes.

Tumor-suppressor genes and predispositions for cancer

Suppose a person inherits two normal alleles of a tumor-suppressor gene. (Keep in mind that we have two of each gene, except for those on the Y chromosome.) If, in the course of this person's life, one of these alleles in one of the person's billions of cells is damaged or sustains a mutation (and the cell's mismatch-repair genes cannot repair the damage), the other, undamaged allele can still prevent unregulated cell growth and division.

Now suppose another person inherits one normal allele of the same tumor-suppressor gene and one nonfunctional allele. If her single functioning copy of the gene becomes damaged—either by a toxic chemical, by radiation, or by a random transcription error—this person has no backup system.

Thus, compared with people with two normal alleles of the gene, she has an increased risk of developing cancer, and at an earlier age and in multiple sites. This "two-hit" hypothesis, in which the first "hit" is inheriting a damaged gene and the second hit is damage to a normal gene, was originally proposed by Knudson in 1971,[5] and explains how inherited gene mutations could confer susceptibility to cancer.

Risk models underestimate risk in mutation carriers

Oncogenes promote uncontrolled growth

With oncogenes, the situation is different. Only one copy of an oncogene need be mutated to push the cell toward unregulated growth and division, if the mutation causes the gene to be more active than normal.

In general, these are not germline mutations that are inherited, primarily because they can cause the carrier to develop cancer before reaching reproductive age.

BRCA1: A TUMOR-SUPPRESSOR GENE

Studies of families with high incidences of breast and ovarian cancer and patients with early-onset breast cancer led to the discovery of the first breast cancer gene, *BRCA1*, located on chromosome 17 at band q21.

BRCA1 behaves as a tumor-suppressor gene, as shown by its pattern of inheritance. Persons who carry a mutation in *BRCA1* are heterozygous for the mutation—ie, they inherit one normal copy and one abnormal copy.

However, when these persons develop tumors, the tumor cells show a loss of heterozygosity, ie, both copies are abnormal. This suggests that some event (a second hit) has occurred to disable the normal gene. Another bit of evidence that suggests that *BRCA1* is a tumor-suppressor gene is that about 80% of the mutations identified are loss-of-function mutations. Such loss of function in a tumor-suppressor gene allows unregulated growth to proceed, while loss of function of an oncogene would not accelerate growth.

According to some studies,[6,7] people who inherit a mutation in this gene have the following chances of developing cancer by age 70:

- Breast cancer—85%
- Ovarian cancer—45% to 60%
- Colon cancer—6%
- Prostate cancer (men)—8%.

More recent population-based studies[8] suggest the risk may be a bit lower: a 73.5% risk of breast cancer by age 80, and a 28% risk of ovarian cancer. Mutations in the *BRCA1* gene account for 45% of hereditary breast cancers and up to 80% of hereditary ovarian cancers.

Ask about all first- and second-degree relatives for three generations

In the laboratory, *BRCA1* is hard to screen for mutations, for several reasons. First, it is large, with approximately 100,000 base pairs of genomic DNA. Furthermore, mutations occur throughout the gene, and only approximately one third of them are recurrent. Many families have a unique or "private" mutation, which is different from other mutations in other families. This situation differs from simpler genetic defects which are much easier to detect, such as the sickle cell trait, which involves the mutation of just one base pair which is the same in all carriers.

BRCA2: SIMILAR TO *BRCA1*

The second breast cancer gene identified is *BRCA2*, located on chromosome 13 at band q12.

BRCA2 is similar to *BRCA1* in several ways. Like *BRCA1*, it is a tumor-suppressor gene, as shown by loss of heterozygosity of the wild-type allele in tumor tissue from carriers of *BRCA2* mutations. As with *BRCA1*, carriers of mutations in *BRCA2* also have an increased risk of breast cancer and ovarian cancer, although the percentages are a bit different: an 85% risk of breast cancer by the age of 70,[9] but only a 20% risk of ovarian cancer.[10] Of interest, *men* who carry a mutation in this gene have a 10% risk of breast cancer. Mutations in the *BRCA2* gene account for 35% of hereditary breast cancers.

Like *BRCA1*, *BRCA2* is hard to screen for mutations, for the same reasons. *BRCA2* is large, with approximately 70,000 base pairs, and mutations have been found throughout the gene; most of them are loss-of-function mutations, and some are recurrent.

RECOGNIZING HEREDITARY CANCER SYNDROMES

Not all cancer patients with a positive family history have a hereditary cancer syndrome.

Familial cancers are cases in patients with a family history of cancer. The relationship may be due to a common genetic heritage, a common environment, or merely chance.

Hereditary cancer susceptibility syndromes, on the other hand, are transmitted as a Mendelian dominant trait, owing to a germline mutation in an oncogene, tumor-suppressor gene, or DNA mismatch-repair gene. Hereditary cancer susceptibility syndromes are characterized by high penetrance or risk of the disease over a lifetime.

Hereditary cancer syndromes have the following general characteristics:

- The cancer appears at an unusually early age
- The cancer develops at multiple foci at one site or at bilateral paired sites
- The patient has more than one primary tumor
- One or more family members has had the same type of cancer
- The family has a high prevalence of cancer of a specific type.

Examples of hereditary cancer susceptibility syndromes are the breast-ovarian cancer

syndrome (due to *BRCA* mutations), hereditary nonpolyposis colon cancer (HNPCC), Li-Fraumeni syndrome, and familial medullary thyroid carcinoma.

Interestingly, although *BRCA* mutations increase the risk of both breast cancer and ovarian cancer, in some families with *BRCA* mutations nearly all the cases of cancer are "site-specific," ie, either one or the other, but not both. Site-specific ovarian cancers account for 5% to 10% of epithelial ovarian cancers. These are predominantly serous tumors.

WHO SHOULD BE TESTED FOR *BRCA* MUTATIONS?

Testing for mutations in the BRCA1 and BRCA2 genes is available commercially from Myriad Genetic Laboratories (Salt Lake City, UT). A complete test involves sequencing the entire lengths of both *BRCA1* and *BRCA2*, takes approximately 1 month, and costs approximately $2,600.

In general, genetic testing is appropriate if the patient's prior probability of having a *BRCA* mutation is 5% to 10% or greater. Models have been developed that take into account the age of onset of breast or ovarian cancer, number of affected relatives, and ethnic origin.[11,12] A high risk of developing breast cancer based on the Claus or Gail model does not necessarily mean a woman has an increased probability of having a *BRCA* mutation.

In practical terms, testing is reasonable if, after taking a complete family history that includes all first-degree and second-degree relatives over three generations, any of the following are true:

- Three or more first-degree or second-degree relatives on the same side of the family have had cancer, regardless of the age at diagnosis
- The patient has had breast or ovarian cancer diagnosed at age 45 or younger
- A family member has a known mutation in the *BRCA1* or *BRCA2* genes
- One or more family members developed ovarian cancer at any age and one or more family members on the same side of the family developed breast cancer at any age
- The patient or a family member has or had multiple primary or bilateral breast cancers
- The patient is a man with breast cancer or has a male relative with breast cancer
- The patient is a woman of Ashkenazi Jewish descent and has one or more relatives with breast or ovarian cancer at any age. (Three specific mutations in the *BRCA1* and *BRCA2* genes have been found in the Ashkenazi population: 185delAG and 5382insC in the *BRCA1* gene, and 6174delT in the *BRCA2* gene. These mutations are found in 2.5% of Ashkenazi individuals and account for 30% to 50% of cases of early-onset breast or ovarian cancer.)

WHAT PRETEST COUNSELING IS NEEDED?

If a patient is identified as being at risk for a hereditary cancer susceptibility syndrome, the clinician should discuss the issues surrounding genetic testing, its benefits, and its burdens. Pretest education should provide sufficient information to allow the patient to make an informed choice, and should cover the following topics:

- The patient's risk status as determined by her personal and family history
- How cancer susceptibility syndromes are inherited
- The risks, benefits, and limitations of testing
- The meaning of possible test results, including positive, negative, and uninformative
- The limitations of surveillance and prophylactic therapy
- Psychosocial issues surrounding genetic testing
- Issues relating to insurance, employment, and confidentiality
- Alternatives to genetic testing.

Give posttest counseling in person

If the patient has not had breast or ovarian cancer, a living-affected relative should be tested first. If a living-affected relative cannot be tested first, a negative test result may not be informative because the patient may still be at risk of a hereditary cancer syndrome caused by a mutation in a gene other than *BRCA1* or *BRCA2*.

HOW TO DISCUSS THE TEST RESULTS

Posttest counseling should be given in person. If the patient has a positive result the physician should explain the issues in full, along with the options for surveillance and clinical management. The limitations of screening modalities should be discussed. Negative results do not mean a woman is free of cancer risk—she still has the same background risk as the general population.

Professional societies have published guidelines and protocols to be used when doing predisposition testing for late-onset disorders such as hereditary cancer syndromes in adults.[13,14]

SURVEILLANCE FOR CANCER IN *BRCA* MUTATION CARRIERS

Women with *BRCA* mutations must commit to an intensive, lifelong program of surveillance for cancer. To detect breast cancer, they must:

- Do a breast self-examination every month beginning at 18 years of age
- Have a clinical breast examination once or twice a year beginning at age 25
- Have a mammogram every year beginning at age 25

Women with a *BRCA* mutation should begin mammography at age 25

The efficacy of screening for ovarian cancer among *BRCA* mutation carriers is less well established. Nevertheless, we recommend:

- A pelvic examination once or twice a year beginning at age 25 to 35
- Transvaginal ultrasonography with color Doppler and a CA-125 measurement once or twice a year beginning at age 25 to 35.

PREVENTIVE MEASURES ARE CONTROVERSIAL

The clinical management of *BRCA1* and *BRCA2* mutation carriers is controversial.

Prophylactic oophorectomy

Prophylactic oophorectomy remains controversial. Arguments in favor: there is no good way to screen for ovarian cancer, survival rates are poor among women with ovarian cancer, and women who are *BRCA* mutation carriers are at a high risk of ovarian cancer.[15] On the other hand, evidence that prophylactic surgery reduces ovarian cancer risk is lacking; peritoneal carcinomas remain a concern, even in patients who have had a prophylactic oophorectomy.

Oral contraceptives and estrogen replacement

Oral contraceptives have been shown to lower the ovarian cancer risk in the general population. A recent study by Narod et al[16] suggested that *BRCA* mutation carriers can lower their risk of ovarian cancer by 60% by using oral contraceptives for 6 years or more. However, this raises the controversial issue of using estrogens in a genetically susceptible population of women, and one study has suggested that the risk of breast cancer may be increased in mutation carriers who use oral contraceptives.

Although postmenopausal users of hormone replacement therapy had a relative risk of breast cancer of 1.5 in some studies, first-degree relatives of patients who developed breast cancer while using hormone replacement did not seem to be at increased risk if they also used hormone replacement. Some clinicians therefore believe the benefits of estrogen replacement therapy in preventing cardiovascular disease and osteoporosis are worth the risk, even in high-risk women.

Prophylactic mastectomy

There are a number of reasons why a woman who is a mutation carrier would consider prophylactic mastectomy. If she has had breast cancer already, she is at increased risk for developing breast cancer again in the same or the other breast. Risk reduction strategies and surveillance methods have not yet been shown to be effective in long-term trials. Some women consider the surveillance recommendations burdensome and distressing. For women with dense breast tissue, neither clinical evaluation nor mammography may be adequate for surveillance. Finally, a recent study[17] suggests that prophylactic mastectomy may reduce the risk of breast cancer by as much as 90%. Prophylactic mastectomy should not be offered without genetic and psychological counseling.

Chemoprevention

In a large landmark trial,[18] women at high risk of breast cancer (as determined by the Gail model) decreased their risk by nearly half by taking tamoxifen. In fact, the trial was stopped early once the benefit was established. On the other hand, no one knows whether tamoxifen can prevent breast cancer in *BRCA* mutation carriers, and its side effects include an increased risk of endometrial cancer and thromboembolism.

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