MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Breast & Ovarian Cancer Genetics

Cancer in general

Cancer is a common disease. It is expected that one in every three people in the U.S. will develop cancer over their lifetime. The vast majority of cancers are not primarily due to an inherited factor. Individuals can develop cancer due to "sporadic factors" such as chance events, environmental exposures or lifestyles. Mainly inherited factors (altered cancer susceptibility genes) are responsible for only a small number of cancer cases, approximately 5-10%.

There are several features that are seen in a family when there is an inherited alteration in a cancer susceptibility gene. These include:

1) Multiple family members affected with the same (such as breast cancer) or other possibly related cancers (such as breast and ovarian)
2) Young ages of onset for the cancers (breast cancer which occurs at a younger than average age)
3) Individuals in the family may have multiple cancers such as two separate, primary breast cancers or breast and ovarian in the same person
4) Cancer occurring in multiple generations

Genetics

It is important to understand what "inherited" means. Inherited traits are passed from one generation of a family to the next. These traits, like eye color or hair texture, are passed on in the form of genes. Genes are located on structures called chromosomes. There are 46 chromosomes in every cell of our body, and they come in pairs. The chromosome pairs are numbered 1 through 22 and the 23rd pair is the sex chromosomes: XX for female; XY for male. One copy of each chromosome pair comes from our mother and the other from our father. Similarly, we pass on one copy of each chromosome pair to our children.

Each chromosome contains many hundreds of genes. Because we have two copies of each chromosome, we therefore have two copies of each gene. Each gene is made up of DNA, which is the information that codes for a particular trait or condition. The sequence of DNA is very specific and if there is an alteration (or change) in the DNA pattern in any gene, this may cause the gene to not function properly. Alterations in certain genes can lead to a higher susceptibility to specific disease. A gene that could lead to a higher susceptibility to cancer is called a cancer predisposition gene.

Massachusetts General Hospital Cancer Center
Center for Cancer Risk Analysis: Cancer Genetics
55 Fruit Street, YAW 9
Boston, MA 02114

Breast / Ovarian Cancer Genetics

A few genes are responsible for an inherited predisposition to breast, ovarian and other cancers. Two of these genes are called BRCA1 and BRCA2 (BReast CAncer 1 and 2). The majority of families with inherited predisposition to breast and/or ovarian cancer have inherited alterations in these two genes. However, there are other genes (some known, others unknown) that can cause a predisposition to breast and ovarian cancer.

BRCA1 is located on chromosome pair #17. BRCA2 is located on chromosome pair #13. A woman who has an alteration in BRCA1 or BRCA2 has an increased chance of developing both breast and ovarian cancer in her lifetime. An altered BRCA gene may also increase the risk of male breast cancer. Not all individuals with BRCA1 or BRCA2 alterations develop cancer during their lifetime. Even so, they are still at risk of passing the altered gene to their children.

What does it mean when it is said that a gene is "altered"? If you envision each gene as being a very long book, you can then think of the DNA that makes up the gene as the letters that go into making the words and sentences in the book. When a gene is "altered", it simply means that there is a typographical error (typo) in the book. This typo can be as large as an entire chapter missing from the book, or as small as a single letter change within a word (e.g. "cat" vs. "rat").

Although a typo (alteration) will be the same within a single family, different families (most often) will have different alterations. For example, the Smith family may have an alteration on page 225 of the BRCA1 gene, and the Jones family may have an alteration on page 67 of the BRCA1 gene. There are exceptions to this rule. Namely, certain ethnic populations share common alterations.

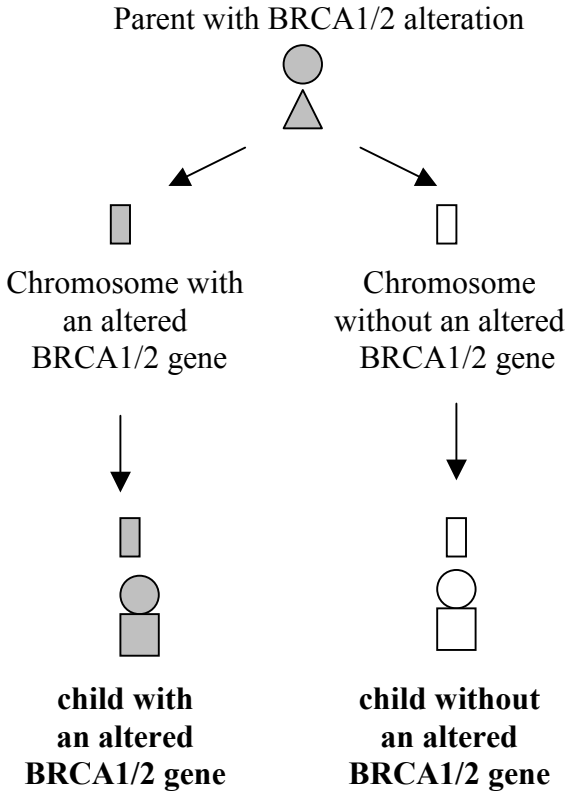
There are three alterations in the BRCA1 and BRCA2 genes that are more common in individuals of Eastern European (Ashkenazi) Jewish descent. There are two alterations in the BRCA1 gene (185delAG and 5382insC) and one alteration in the BRCA2 gene (6174delT) that represent the vast majority of BRCA alterations in Ashkenazi Jewish families. It is estimated that 1 out of 50 (2%) Ashkenazi Jewish individuals in the U.S. have one of these three alterations. If a Jewish individual has a personal history of breast and/or ovarian cancer, the likelihood that he/she has one of these alterations is higher.

Inheritance of BRCA1/2 alterations

What is the chance that a person with an altered BRCA1 or 2 gene will pass it on to their children? Remember that each of us have two copies of every gene. If a person is identified as having an altered BRCA1 or 2 gene, we would assume that the other copy of the gene is working because it is extremely unlikely that an individual is born with both copies of a gene altered. Remember also that we pass on only one copy of each gene to each of our children. There is a 50% or 1 in 2 chance that each child would inherit an altered gene and a 50% chance that each of them would inherit a working gene.

Massachusetts General Hospital Cancer Center
Center for Cancer Risk Analysis: Cancer Genetics
55 Fruit Street, YAW 9
Boston, MA 02114

Figure 1: Inheritance



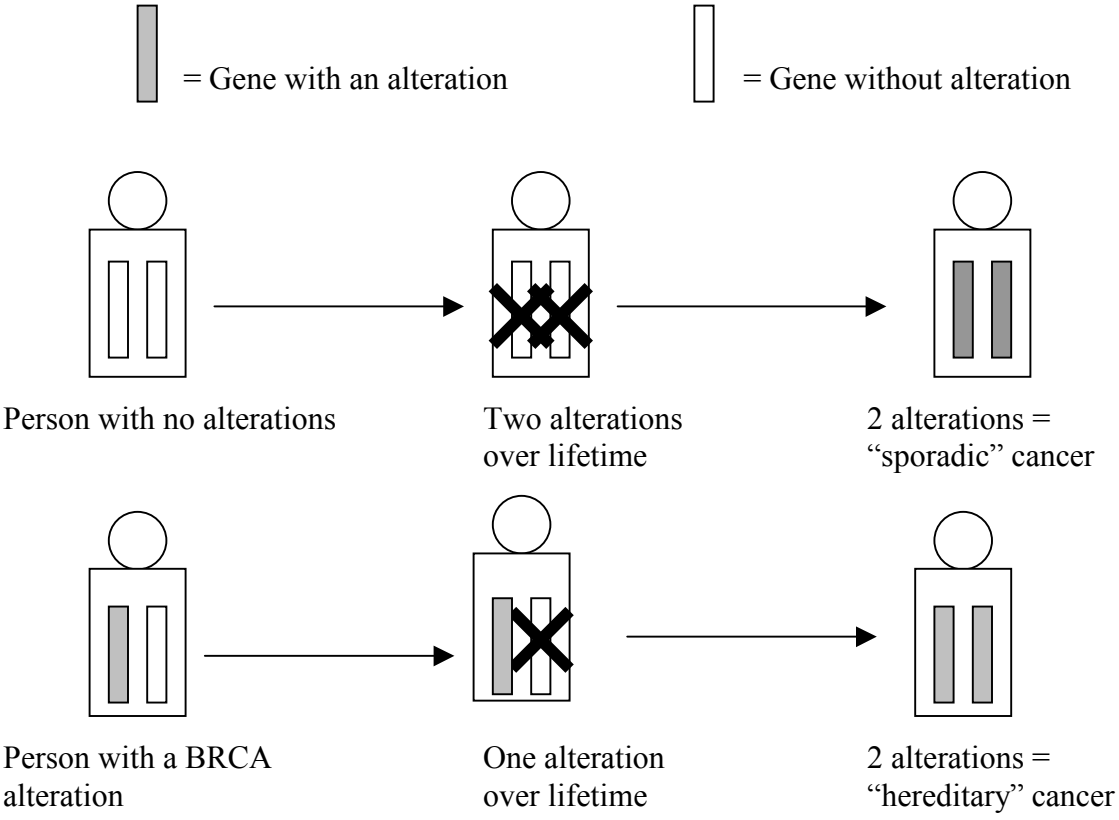
Conclusion: 1 in 2 or 50% chance for each pregnancy to inherit an altered gene

BRCA1 and BRCA2 Function

The function of the BRCA1 and BRCA2 genes is not completely understood. However, it is believed that these genes prevent cancer. As you recall, each person should have two BRCA1 and two BRCA2 genes. These genes can become altered (and stop functioning properly) over one's lifetime, for many complicated reasons (the aging process itself, chance, etc.). If one copy of a gene pair in a cell becomes altered, that cell will remain healthy and not become a cancer cell because there is one copy of the gene pair that is still working properly. However, as that cell gets older, the working copy of the gene pair may become altered as well. This cell would no longer have any gene working properly, and could develop into a cancer cell and grow into a tumor. This is the way most cancers develop: a person is born with two working copies of a gene and both need to be altered in order for the cell to become a cancer. This is called "sporadic" cancer.

Massachusetts General Hospital Cancer Center
Center for Cancer Risk Analysis: Cancer Genetics
55 Fruit Street, YAW 9
Boston, MA 02114

Figure 2: "Sporadic" cancer vs. "Hereditary" cancer



People who are born with one altered copy of the BRCA1 or BRCA2 gene, however, only have one working copy of the gene in each of their cells. These people only require the other copy of the gene to become altered in a cell for the cell to become a "hereditary" cancer (see figure 2). This is why people with inherited alterations in BRCA1 or BRCA2 tend to have cancer at an earlier age. Because only one more alteration is needed to develop cancer, instead of two, this may take less time and, in general, cancers occur at younger ages when there is a hereditary cause. This also explains why most but *not all* individuals with inherited alterations develop cancer.

Genetic testing

It is possible to test someone's BRCA1 and 2 genes for inherited alterations. Genetic testing is done by taking a blood sample and checking the DNA pattern of a gene to look for an alteration in the gene (i.e. proofreading the gene). Results of genetic testing are most informative if a person who has been diagnosed with cancer is tested first. If an altered gene is identified in that person, the individual's blood relatives can be tested easily and the results are informative. That is, if the relative had the altered gene known to cause the cancer in the family, he/she would have an increased risk of developing cancer. If the relative did not inherit this altered gene, his/her risk of developing cancer would be the same as an individual in the general population.

Massachusetts General Hospital Cancer Center
Center for Cancer Risk Analysis: Cancer Genetics
55 Fruit Street, YAW 9
Boston, MA 02114

Other Considerations

There are many issues that one needs to consider before having genetic testing. Genetic information can have many emotional consequences for the person being tested. Individuals may feel anxiety and or depression as they await their result, and may experience many different emotions once they receive their result. In addition, this information can have widespread implications for other family members, and it may be difficult to inform relatives if an alteration is identified.

The threat of genetic discrimination is of concern for some individuals. Genetic discrimination is the use of genetic information (e.g. BRCA1/BRCA2 test results) by health insurers, employers, life insurers and disability insurers. There are no documented cases of individuals suffering from genetic discrimination due to hereditary cancer syndrome genetic testing in terms of their health insurance at this point. In addition, it is *illegal* in the state of Massachusetts to discriminate based on genetic information in health insurance and employment. Life insurance is not protected by this law. It is legal for a life insurance company to adjust your premiums and/or choose not to insure you if they found out about this type of information.

Testing Logistics

It is important that genetic testing for BRCA1 and BRCA2 alterations occur with appropriate genetic counseling and education. At MGH, testing for BRCA1 and BRCA2 alterations involves two visits with a genetic counselor and nurse practitioner or oncologist team at the MGH: a pre-test education session and a result disclosure session. There is no cost for the genetic counseling visits, but the cost of the lab test is the responsibility of the person being tested. The laboratory charges a fee of $2975 for full gene testing. Individuals of Jewish descent will most likely be tested only for those three alterations that are more common in their ethnic group, and the cost is $415. When an alteration has previously been identified in an individual, the cost of subsequent testing for their family members is $350. In many cases, this fee is covered (in full or in part) by insurance. We are happy to assist in looking into insurance issues but we cannot guarantee coverage.

If you are interested in pursuing genetic testing or have further questions regarding testing, please call the Massachusetts General Hospital Breast/Ovarian Cancer Genetics Program at 617-724-1971.

Massachusetts General Hospital Cancer Center
Center for Cancer Risk Analysis: Cancer Genetics
55 Fruit Street, YAW 9
Boston, MA 02114