Lynch Syndrome
(Hereditary Non-Polyposis Colorectal Cancer)

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BACKGROUND INFORMATION

It is estimated that one out of every three Americans will develop cancer sometime during their lifetime. Individuals in the general population have a lifetime risk of developing colorectal cancer of approximately 6%. While it is difficult to determine the exact cause of cancer in an individual, the majority of cancer is thought to be due to a combination of factors such as chance events, the aging process, or environmental exposures. About 5-10% of cancer cases are caused by a hereditary predisposition that is passed on within a family.

Inherited traits are characteristics, such as eye color or hair texture, that are passed from one generation of a family to the next. These traits are passed on in the form of genes. Genes are located on structures called chromosomes. Individuals typically have 46 chromosomes in every cell of the body, and they come in pairs. The chromosome pairs numbered 1 through 22 are the same between men and women and the last pair determines our gender: XX for female and XY for male. One copy of each chromosome pair (and therefore each gene) comes from our mother and the other from our father. Similarly, we pass on one copy of each chromosome pair to our children.

There are hundreds of genes located on each chromosome. Genes make proteins that are necessary for the proper growth and development of the body. Each gene is made up of DNA, which is the information that codes for a particular trait or condition. If you think of a gene as being a very large book, DNA is like the alphabet that makes up the words and sentences in the book. When a gene is altered, it simply means there is a typographical error (typo) in the book. This alteration makes the gene unable to function properly. Alterations can be as large as an entire chapter missing from the book, or as small as a single letter change within a word.

GENETICS OF LYNCH SYNDROME

We know of a few genes that when altered, may give an individual in increased chance to develop certain types of cancer. These types of genes are called cancer predisposition genes. Some families with an inherited predisposition to colorectal cancer have a condition called Lynch Syndrome or Hereditary Non-Polyposis Colorectal Cancer (HNPCC). Alterations (or "mutations") in four mismatch repair genes – *MLH1*, *MSH2*, *MSH6,* and *PMS2* – account for the majority of all Lynch syndrome cases. Recently, a fifth gene called *EPCAM* (or TACSTD1) was found to account for approximately 1-3% of Lynch syndrome cases. The *EPCAM* gene sits right next to (neighbors) the *MSH2* gene on the chromosome.

These mismatch repair genes are responsible for correcting mistakes that occur during DNA replication. Individuals who carry an alteration in one of these genes have a greater risk to develop certain types of cancer than those who do not have an alteration. However, not everyone who has an altered gene will develop cancer. There are other known genes that can cause a predisposition to colon cancer. Research is ongoing to discover other cancer predisposition genes.

There are two copies of the *MLH1, MSH2/EPCAM*, *MSH6,* and *PMS2* genes in each cell of your body. Recall that one copy is received from your mother and the other copy is received from your father. During the course of an individual's lifetime, these genes can acquire alterations and stop functioning properly. Gene alterations can be acquired for a variety of reasons, including the aging process, chance, etc. If one copy of a gene pair in a cell becomes altered, that cell will remain healthy because there is still one copy of the gene pair that is working properly. However, as the cell ages, it is possible that the working copy of the gene pair may also acquire an alteration. At this point, both copies of the gene in the cell no longer work and the cell could become a cancer cell and grow into a tumor. This is called "sporadic" cancer and is the way most cancers develop (see Figure 1). An individual is born with two working copies of the gene and both need to be altered in order for the cell to become a cancer cell.

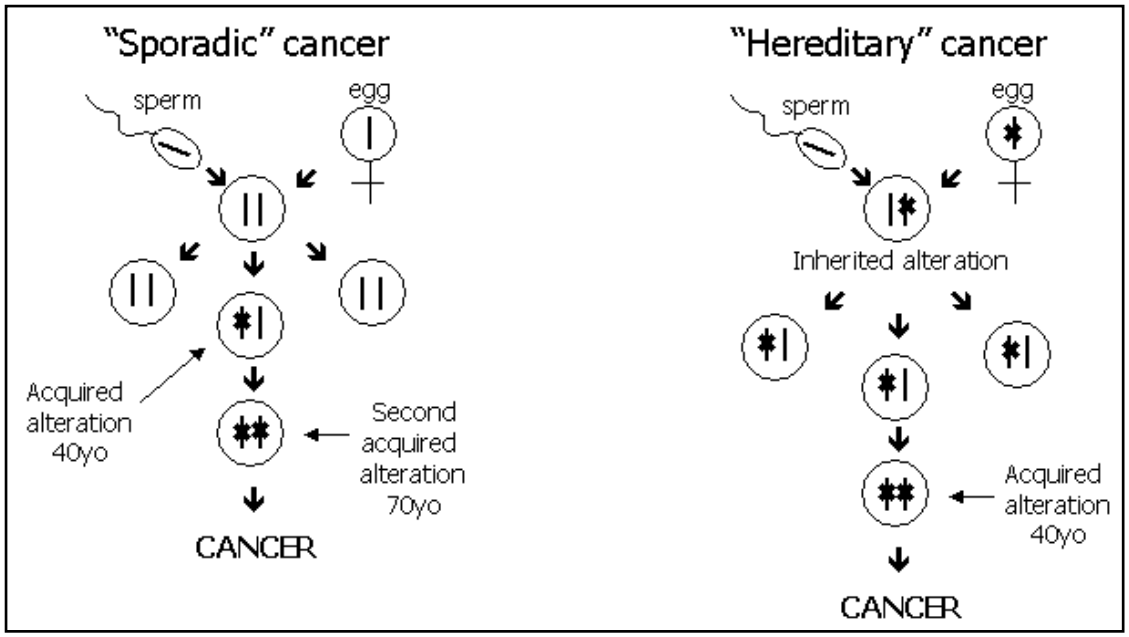

Figure 1: "Sporadic" cancer vs "Hereditary" cancer

Some individuals are born with one altered copy of the *MLH1, MSH2/EPCAM*, *MSH6,* or *PMS2* gene, and therefore have only one working copy of the gene in all of the cells of their body. The altered gene could have come from either the egg or the sperm. These individuals only require one alteration in the working gene to occur for the cell to become a cancer cell. This explains why individuals with "hereditary" cancer tend to have cancer at an earlier age and may develop more than one cancer during their lifetime because only one alteration is needed to develop cancer (see Figure 1). Individuals with hereditary cancer are *predisposed* to developing cancer, but some may never acquire an alteration in the working gene and therefore never develop cancer.

We look for several features in families to try to determine whether or not there is a hereditary cancer predisposition in the family. These include:

- Multiple family members affected with the same cancer (such as colon cancer) or related cancers (such as colon and uterine cancer)
- Earlier than average ages of diagnosis

- Multiple primary cancers in the same individual (such as two diagnoses of colon cancer)
- Cancer occurring in multiple generations

INHERITANCE

If an individual is found to have an alteration in the *MLH1, MSH2/EPCAM*, *MSH6,* or *PMS2* there is a 1 in 2 (or 50%) chance that each child could inherit the altered gene (see Figure 2). Both men and women can have alterations in these genes and have a chance to pass on the alteration to a child.

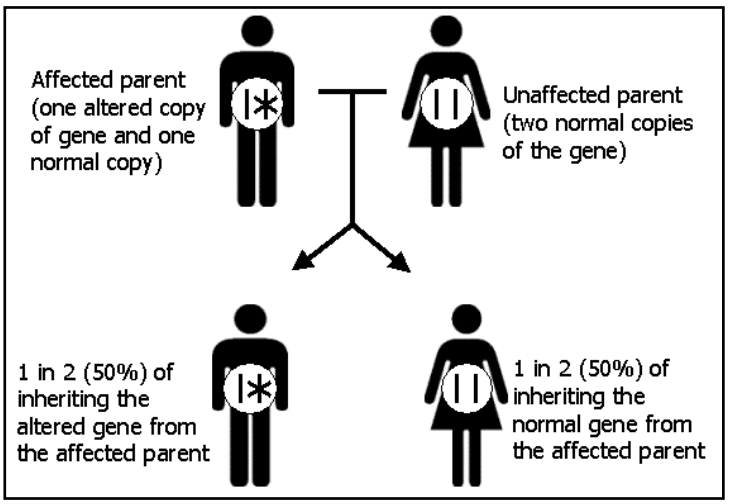

Figure 2: Autosomal dominant inheritance

GENETIC TESTING

Genetic testing involves taking a blood sample and checking the DNA pattern of a gene for an alteration. The cost of genetic testing is often covered by health insurance, but is dependent upon the individual insurance plan. Coverage information can usually be determined prior to proceeding with the test. Results of genetic testing are most informative if an individual who has been diagnosed with cancer is tested first. Genetic testing for cancer predisposition gene mutations should be accompanied by genetic counseling to determine the appropriateness of genetic testing based on the personal and family history of cancer, as well as the pros, cons, and limitations of testing.

CANCER SUSCEPTIBILITY

The cancer risks associated with an *MLH1, MSH2, MSH6*, or *PMS2* alterations are listed below. The cancer risks associated with an *EPCAM* mutation are believed to be the same as those associated with an *MSH2* mutation. The percentages cited are estimates and may change as more research is performed, particularly with regards to the *EPCAM* and *PMS2* genes.

Individuals with an altered *MLH1* and *MSH2* gene have up to an 80% lifetime risk of developing colorectal cancer. Men with an altered *MSH6* gene have up to a 70% lifetime risk of colorectal cancer, and women have up to a 30% lifetime risk. Individuals with a *PMS2* mutation may have up to a 20% lifetime risk for this cancer type. In comparison, individuals in the general population have a lifetime risk for colorectal cancer of approximately 6%.

Women with an *MLH1*, *MSH2,* or *MSH6* gene alteration have an up to 70% lifetime risk of developing endometrial (uterine) cancer, whereas women with a *PMS2* mutation may have up to a 15% lifetime

risk for this cancer type. There is also a 9-12% lifetime risk of developing ovarian cancer for women with an MMR mutation. In comparison, the general population risk for uterine cancer is 3% and for ovarian cancer 1-2%.

There may be an increased chance of developing cancer at other sites for both men and women with an *MLH1, MSH2/EPCAM, MSH6*, or *PMS2* mutation, including the stomach, small intestine (duodenal and jejunum), pancreas, gall bladder and bile duct, urinary tract (including kidney cancer and ureter cancer), skin (sebaceous cysts/neoplasm), and on rare occasion the brain (glioblastomas).

OTHER ISSUES

There are advantages and disadvantages to having genetic testing for *MLH1, MSH2/EPCAM, MSH6,* or *PMS2* alterations. These issues will affect individuals differently, which is why we encourage you to consider the possible ramifications before proceeding with genetic testing.

Potential advantages

- The results of the test can help individuals tailor their cancer screening and management appropriately. For example, an individual who has a positive test result may be recommended to have more frequent screening or prophylactic surgery.
- Results can also help family members clarify their risks of developing cancer and alter their current screening, if indicated.
- The uncertainty of potentially having a gene alteration can also be alleviated by genetic testing results.

Potential disadvantages

- Individuals may be more anxious if they find they have a *MLH1, MSH2/EPCAM, MSH6,* or *PMS2* gene alteration because of the uncertainty of when and if cancer will develop.
- An individual's test result can have an impact on other family members and might lead to strained relationships within the family.
- While insurance companies will often cover the cost of testing for alterations in the genes associated with HNPCC, the test can be quite expensive if an individual is responsible for covering all or part of the cost of testing.

Another concern for some individuals is the possibility of genetic discrimination. Genetic discrimination is the misuse of genetic information (*MLH1, MSH2/EPCAM, MSH6, PMS2* test results, for example) by employers, health insurers, life insurers and disability insurers. To date, there have been no documented cases of individuals suffering from genetic discrimination due to hereditary cancer syndrome genetic testing in terms of health insurance. There are laws (both national and state) that provide protection against genetic discrimination in heath insurance and employment. Unfortunately, these laws do not yet protect against genetic discrimination in life insurance, disability insurance, or long-term care insurance.

If you are interested in scheduling an appointment to discuss this information with a genetic counselor, at Lahey Clinic please call 781-744-3982

Familial Cancer Risk Assessment Center