Living with
HEREDITARY Colorectal Cancer

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Introduction

Colon cancer is the second most common cause of cancer death in the United States as well as most western countries. It affects men and women equally. About 140,000 new cases of colon cancer are diagnosed and about 55,000 patients die from it each year in the US. Many of those deaths could be prevented through appropriate cancer screening and early detection.

Colon cancer is so common that a person can have two or more relatives affected with colon cancer due to chance alone; however, in some families it is hereditary. The most common form of hereditary colon cancer is referred to as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also termed Lynch Syndrome. HNPCC accounts for 5-10% of all colon cancer cases. Scientists have identified at least five genes associated with HNPCC. It is likely there are other, as yet unidentified, genes associated with HNPCC.

In families with HNPCC, multiple members are affected with colon cancer often at a young age, with the average age of onset being 45. Cancers of the endometrium (the lining of the uterus), ovary, urinary tract, upper GI system and biliary tract also occur more often in these families. A person who has a mutation in a gene associated with HNPCC would have a much higher chance of developing colon cancer, as well as other cancers, than a person who does not have a gene mutation.

The purpose of this booklet is to review what is known about HNPCC and how this disease is passed down in families. The risks and benefits of genetic testing will also be presented. We hope that this information will provide you with the necessary knowledge to make a personal choice regarding genetic testing.

Development of Cancer

Cancer is defined as the uncontrolled growth of abnormal cells. It is the result of a change in the code of multiple genes that normally have some control over cell growth. There are three major classes of "cancer" genes, which have a normal function that is lost when mutated (a change in the code of the gene):

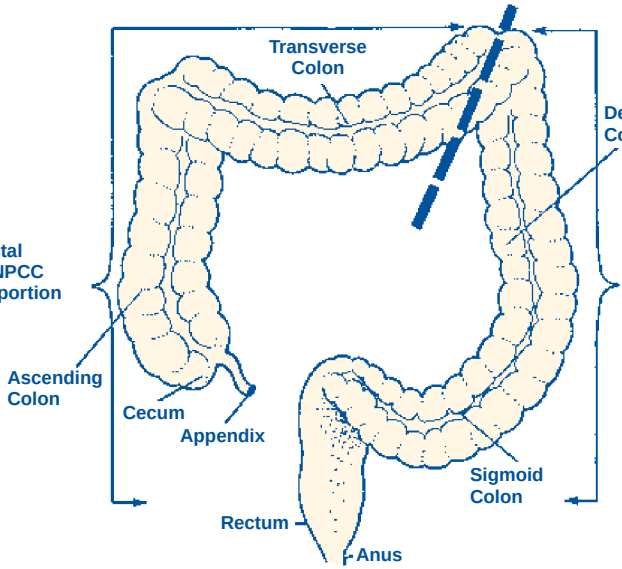
- **Oncogenes** normally promote the growth of cells when needed and are turned off when not needed. A mutation in an oncogene can allow it to be turned on when it should not be.
- **Tumor suppressor genes** act like the brakes slowing down or stopping cell growth when it is no longer needed. A mutation in a tumor suppressor gene can interfere with that braking function and cell growth continues without control.
- **DNA repair genes** repair mistakes in the code of other genes. A mutation in a DNA repair genes allows the accumulation of mutations in other genes.

The cancers that occur in the general population are called sporadic cancers. Sporadic cancers occur as the result of a series of mutations in several cancer genes within a group of cells in a specific tissue. These mutations may be the result of spontaneous errors in the DNA code or of exposure to a carcinogen such as tobacco. Hereditary cancers are those that occur in generation after generation of a family. They are the result of a mutation in a cancer gene that is present at conception and thus reproduced in every cell in the body plus a series of mutations in a group of cells within the specific tissue.

The Colon (Large Intestine)

The colon extends from the end of the small intestine (ileum) to the anus and looks like a large question mark. The term "colorectal" refers to the entire colon including the rectum.

HNPCC
2/3 of colorectal cancers in HNPCC occur in this portion of the colon.



General Population
2/3 of the colorectal cancers in the general population occur in this portion of the colon.

The colon's primary function is to absorb water from digested food that enters from the small intestine. It also holds solid waste until it is convenient to eliminate.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

The classic features of HNPCC are:

1. Colon cancer occurs in multiple family members in more than one generation.
2. The average age of colon cancer diagnosis is 45 which is 15 to 20 years earlier than in sporadic colon cancers.
3. The cancers occur more often on one side of the colon than the other (see picture on page 4).
4. The chance of having more than one cancer is greater than in the general population. For example, some people with HNPCC have cancer in more than one organ such as endometrium and colon or in more than one place within the colon.

Basic Genetics

To explain how one inherits an increased risk of developing colorectal cancer, we will review some basic genetics. Genes provide instructions in the form of a code for the body to develop, grow and maintain itself. There are thousands of genes and each provides a specific instruction.

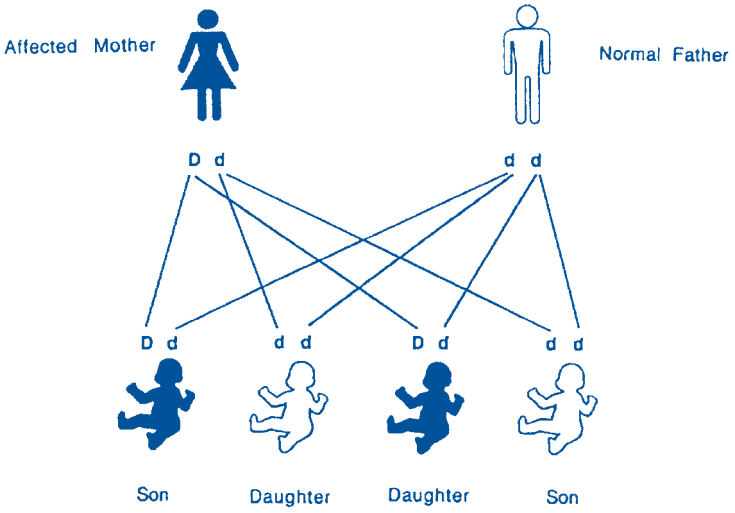
We have pairs of genes; one from each pair comes from an individual's mother and the other from the father. Genes within a pair may not code for exactly the same product. The product of some genes may not be apparent unless there are two copies with the same code; these genes are said to be recessive. The products of other genes are always apparent, and these genes are said to be dominant. An example of this is eye color. An individual with two genes for blue eyes will have blue eyes, while an individual with one gene for blue eyes and one gene for brown eyes will have brown eyes. The gene for blue eyes is recessive and the gene for brown eyes is dominant.

An alteration in the code of a gene that results in a medical problem is called a mutation. HNPCC is the result of a mutation in one of a pair of mismatch repair genes; therefore the mutation is said to be dominant. An individual with HNPCC would have inherited a mutated gene from one parent and a normal gene from the other parent.

Sometimes a child looks so much like one parent that it seems that the child must have received more genes from that parent, but the child has received the same number of genes from each parent. Similarly, it may be assumed that if a child takes after the side of the family with HNPCC, the child will also have colon cancer, but that

is a false assumption. The genes associated with HNPCC are not associated with an individualís appearance.

In the diagram below, the gene with the mutation for HNPCC is represented by a "D" and the normal gene by a "d". The mother is shown as being affected, she has one gene with the mutation and one normal gene; the father has two normal genes. When they have children, the father will always pass on a normal gene from that pair. There is a 50% chance the mother will pass on the HNPCC mutation and a 50% chance she will pass on the normal gene regardless of whether it is to a boy or a girl. This 50% chance remains the same for each of the offspring.



Mutation Testing

It is possible to do a blood test to learn if a person has a mutated gene. This test is only offered to individuals in families that are known to have an HNPCC mutation or to individuals with a history of cancer in families that are very likely to have HNPCC. The test result provides information about cancer risk related to mutations in these particular genes, but not any other diseases. The recommended age for genetic testing is 18 years and older based on the legal age for providing informed consent.

Implications of a Positive Test Result:

A male who has a mutation in one of the HNPCC genes has an 80% to 85% lifetime risk of colon cancer. For a female with a mutation there is a risk of 54 to 85% of colon cancer, 30 to 69% of endometrial cancer and 12% of ovarian cancer. Males and females also have an increased risk for urinary tract, biliary tract and upper GI cancers.

Implications of a Negative Test Result:

In a family with an HNPCC mutation, persons who do not have a mutation have the same risk for developing colon cancer as other people in the general population (about 5% over a lifetime). Individuals who do not have the mutation cannot pass it down to their children.

Risks and Benefits of Genetic Testing

Risks of Testing:

1. People with a negative result may experience a sense of guilt about being so fortunate when others in the family were not.

2. People with a positive result may experience a negative psychological response such as increased anxiety or depression.

3. Genetic testing may reveal that family relationships are different than had been assumed, such as indicating that a parent could not be the biologic parent of a son or daughter.

4. A positive result may affect a person's insurability or employability. There may be increased insurance premium payments, decreased coverage, or a loss of insurance. Because of insurance concerns, a person may be locked into a job; or an employer may discriminate because of concerns about the expense of employing someone with a high risk for cancer.

Benefits of testing:

1. Cancer risk can be more clearly defined not only for the person who is tested but also for that person's children.

2. Recommendations for cancer surveillance and prevention can be made based on a person's gene status. For a person with a gene mutation, this may result in early identification of cancer when treatment is most effective. For those with a negative result, unnecessary surveillance may be avoided.

3. Some people believe that the relief from the uncertainty about their gene status is desirable no matter what their test result.

Surveillance Recommendations

FOR INDIVIDUALS AT HIGH RISK BASED ON FAMILY HISTORY OR FOR INDIVIDUALS WHO HAVE A MUTATED HNPCC GENE

Colonoscopy:

Colonoscopy should be initiated between the ages of 20 and 25 and performed annually thereafter. This young age for starting screening is recommended because of the early onset of colon cancer in HNPCC. A full colonoscopy is required because HNPCC cancers are more likely to occur in the right side of the colon, which would be missed by a sigmoidoscopy.

A colonoscopy requires a cleansing preparation of the colon the day before the procedure so that the colon can be fully visualized. The colonoscopy involves the insertion of a colonoscope (a long tube with a light at the end) into the rectum and passed the full length of the colon to the other end. This allows the physician to examine the entire colon. If a polyp is detected it can be removed before cancer develops.

The frequency of every year or at least every other year is necessary since the evolution of a colon cancer from a polyp generally takes 2 to 3 years in HNPCC as opposed to 8 to 10 years in the general population.

Endometrial and ovarian screening:

Endometrial and ovarian cancer screening are initiated at age 30. The recommended screening procedures are annual endometrial aspiration and transvaginal ultrasound and twice yearly CA125. An endometrial aspiration is performed by passing a very thin instrument through the cervical opening into the uterus and suctioning a small amount of fluid with cells from the lining of the uterus for evaluation. A transvaginal ultrasound is done by inserting the ultrasound probe into the vagina in order to get the best view of the endometrium and the ovaries; it is similar to the ultrasound that is often done early in a pregnancy. Color doppler flow is a part of this exam and enables the ultrasonographer to view the pattern of the blood vessels increasing the likelihood of detecting a tumor. CA125 is a blood test for a tumor marker, which may be elevated in the presence of ovarian cancer. Although ovarian cancer screening with CA125 and ultrasound is not very effective in detecting early cancers, they are the best tests at this time, and may help detect up to 30% of ovarian cancers.

Prevention Options

FOR INDIVIDUALS WHO HAVE A MUTATED HNPCC GENE

Some individuals will not follow surveillance or screening recommendations because of the discomfort of actual test procedures, the cost of tests and concerns about insurance coverage, fear of insurance discrimination, or fear of cancer being detected. Consideration of prophylactic surgery (surgical removal of an organ before cancer develops) may be appropriate for these individuals.

Prophylactic colectomy is the surgical removal of virtually the entire colon to prevent the occurrence of colon cancer. This procedure is offered as an option to individuals with an HNPCC mutation. Current surgical methods (subtotal colectomy with ileorectal anastamosis) can avoid the need for a bag. The remaining small portion of the rectum requires annual screening after the prophylactic surgery.

Prophylactic hysterectomy and oophorectomy is the removal of the uterus and ovaries to prevent cancer in those organs. This procedure is offered as an option for women with a mutation who have completed childbearing. Even with complete hysterectomy and oophorectomy, there is still some tissue similar to ovarian tissue that lines the inside of the abdominal cavity, and cancer can develop in this tissue. The risk of developing this type of cancer after prophylactic removal of the ovaries in women at high risk is approximately 3 to 5%, and is referred to as peritoneal carcinoma.

Chemoprevention denotes the use of drugs or other substances to prevent cancer growth. Aspirin and other nonsteroidal anti-inflammatory agents, usually used for the treatment of arthritis, have been shown to reduce the incidence of colon cancer in the general population. The effectiveness of these agents in reducing colon cancer in HNPCC is being studied. There are also studies of hormones and other agents in reducing the incidence of endometrial and ovarian cancers.

Issues to Consider Prior to Genetic Testing

There are many issues to be considered prior to making a decision about testing. Some of these are:

1. Psychological: Each individual has to determine for her or himself whether they would be better off knowing whether they have the mutation. It is especially important for parents and spouses not to pressure someone to make one decision or another. Some people report not wanting to be tested because a positive result would make them worry more. Others know that the uncertainty about their status is worse than knowing that they do have the mutation. Some have identified with the high risk for cancer in their family so strongly that they have a difficult time accepting a negative result.

2. Functional: Some will be more likely to follow through with screening if they know they have the mutation. For others the anxiety and worry about finding a cancer during screening will interfere with their ability to follow through.

3. Family: Parents who receive a positive result tend to worry about their children, often feeling guilty when they had no control over what was passed onto them. Sometimes family members do not feel as close to other members who have received a different result than their own. Occasionally an adult child wants to be tested but their parent does not. If the child receives a positive result, the parent's status is revealed. Respect for each other, open communication and compromise usually lead to mutually satisfying resolution of these differences.

4. Personal Goals: Career and family plans may be impacted by both positive and negative test results. Not knowing one's status may make it very difficult to make life decisions for some. It can

continued next page

be important to discuss such issues with others who will share in those decisions

5. Discrimination: Health and life insurers may use genetic test results to make decisions about coverage and premiums to charge. Employers may prefer to not take the chance of employing someone who has a high risk of cancer. Very few people who have undergone genetic testing have encountered such problems, but it is good to have an awareness of that possibility and to consider how to protect the privacy of your genetic test results. It may be helpful to ask your physician how he/she would protect your test results from being revealed inadvertently before you share the result. There are federal and state laws to help protect you from discrimination. If you want more information about the protections available to you can find it on the Internet at: **http://www.healthinsuranceinfo.net**.

Conclusion

We have covered a great deal of information in this booklet. Hopefully, this information will be helpful to members of your family. Our goal is to provide adequate education in order for you to make an informed decision regarding genetic testing. Hopefully you found it helpful and thought provoking. Research brings new information everyday. We hope to continue to provide you with updated information that might be of benefit to persons at high risk for colon cancer whether it is for you or for future generations in your family.

If you or anyone else in your family has any questions or wishes to discuss any of the issues presented in this book please contact:

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