Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Division of Human Genetics
University of Cape Town

What Is HNPCC?

Bowel/colorectal cancer generally refers to cancer of the large bowel (which is made up of the colon and the rectum). HNPCC is an inherited form of bowel cancer characterized by early onset, usually before the age of 50 years. Colon and rectum cancers most likely develop slowly over a period of several years. These cancers begin as a polyp (a growth of tissue into the centre of the colon or rectum). People with HNPCC are much more likely to develop these polyps than people without HNPCC. Early removal of these polyps may prevent them from becoming cancer. Over 95% of colon and rectal cancers are adenocarcinomas. These are cancers of the cells that line the inside of the colon and the rectum.

How Common Is It?

The lifetime risk of colorectal cancer (CRC) in the general population (to age 75) is 2%. HNPCC accounts for between 3% and 5% of all CRC.

What Causes It?

The causes of HNPCC are complex and involve interactions between genetic and environmental factors. The cancer is the result of faults (called mutations) in genes. These genes, called mismatch repair genes, normally instruct the cell to grow and divide in an orderly manner. When these genes contain a fault, the cell can grow out of control and a cancer may develop. These faults occur for largely unknown reasons, although it is known that as we age, changes in the genes are more likely to occur. Other factors that may play a role in causing these faults in the control genes may include exposure to various poisons, radiation, lifestyle and diet.

Five genes have been associated with HNPCC. Two of these genes, *MLH1* and *MSH2*, are responsible for the majority of HNPCC. We all have an *MLH1* and an *MSH2* gene. When functioning normally, these genes work to suppress uncontrolled growth of cells (cancer). When we have inherited a change in either of these genes *MSH2* or *MLH1* from either parent, it makes us more susceptible to colorectal cancer and a person with one of these gene faults has a higher risk of developing cancer.

How Are These Faulty Genes Inherited In A Family?

We are all born with two copies of about 30,000 different genes, one copy of each gene from our mother and the other from our father. A person with HNPCC only has one functional copy of their control genes and they are thus at a higher risk of developing cancer than the general population who have two functioning copies.

- HNPCC is an autosomal dominant condition (Refer to fact sheet 9). This means that people with HNPCC have a 50% chance of passing the gene fault to each of their children.
- The gene fault can be passed on even if the parent has had his or her own colon removed following cancer growth.
- Individuals who do not inherit the gene mutation cannot pass it on to their own children.
- Some individuals with HNPCC do not have an affected parent. These individuals, who are the first in the family to have the condition are referred to as having a new mutation.
- An individual with a new mutation, however can pass the gene fault on to their children.

Genetic Testing And HNPCC

The Division of Human Genetics at UCT is currently doing research on families with HNPCC. Certain faults in the *MSH2* and *MLH1* gene have already been identified to occur in families with HNPCC. If one of these faults can be identified in an affected person (known as a diagnostic test), other blood relatives can be offered genetic testing (known as predictive testing) to see if they have the same mutation. Predictive test results usually take 4 weeks. This is only offered to adults over the age of 18. If, however, one of the specified mutations is not found in the affected member, then the DNA can remain in the research laboratory for further investigation into the genetic basis of the condition.

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What Are The Criteria For Diagnosing HNPCC?

Selection criteria for testing must include all of the following: at least three relatives with a HNPCC associated cancer (colorectal, endometrail, small bowel, ureter, renal or pelvis). One affected individual should be a first degree relative to the other two and at least two successive generations must be affected. At least one case of HNPCC associated cancer must have been diagnosed before the age of 45 and familial adenomatous polyposis (a different condition leading to colorectal cancer involving multiple colorectal polyps) must be excluded.

What Are The Important Concerns In Predictive Genetic Testing?

There are many important issues to consider before having predictive genetic testing, which a genetic counsellour will discuss with you prior to the testing, including:

- A positive result (you have the fault in *MSH2* or *MLH1* gene) means you have a 80-90% chance of developing HNPCC
- Finding out ones genetic risk of HNPCC can have important implications for other family members, who may find that they are at an increased risk
- Having the genetic test raises many issues for relatives who have not had cancer and for relatives who have had cancer
- A negative result does not guarantee that you will not get colorectal cancer. Your risk will still be the same as any person in the population.

What Can I do If I think I have A Strong Family History Of Colorectal Cancer?

a) Genetic Counselling

From your family history, the counsellor can estimate how likely it is that you have inherited an increased tendency to develop colorectal cancer. The colorectal unit at Groote Schuur Hospital, provides specialists who can give expert advice concerning this complex condition.

The counsellors can help to clarify your risk of colorectal cancer based on your family history, discuss the options for screening and reducing your risk, what medical check-ups are appropriate for you and discuss the advantages and disadvantages of genetic testing.

b) Surveillance

A colonoscopy and a sigmoidoscopy, examine the lining of the bowel to identify and remove polyps before a cancer occurs and are able to detect the earliest signs of cancer. Individuals with HNPCC are advised to have a colonoscopy every 2 years until they are 30 and thereafter have one every year.

These tests reduce the risk of colorectal cancer by more than 50%, prevent colorectal cancer deaths and decrease the overall mortality by 65% in HNPCC families.

Further Information On HNPCC Can Be Found At:

http://www.coloncancer.org
http://www.geneclinics.org/profiles
http://web.uct.ac.za/depts/genetics/

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