

This Fact Sheet describes when bowel cancer is considered to be a hereditary or familial condition. A small number of families have an increased chance of developing cancer because of an inherited faulty gene in the family. This is known as an inherited predisposition to cancer.

In summary

- **Cancer is very common in the community and mostly occurs just by chance**
- **Some rare families have an inherited faulty gene that can increase the likelihood of some individuals developing bowel cancer**
- **There are two main inherited bowel cancer syndromes**
 1. **Familial Adenomatous Polyposis (FAP)**
 2. **Lynch Syndrome also known as Hereditary Non Polyposis Colorectal Cancer (HNPCC).**

WHAT IS BOWEL CANCER?

Bowel cancer generally refers to cancer of the large bowel which is made up of the colon and rectum and therefore also known as colorectal cancer. Bowel cancer is a common disease in the community. About 1 in 15 women (6.6%) and 1 in 10 (10%) men will develop bowel cancer by the age of 85 years. It is the second most common cause of cancer deaths in Australia.

WHAT CAUSES BOWEL CANCER?

There is no single cause. There are a number of risk factors which can influence an individual's chance of developing bowel cancer. The most important are:

- Getting older. Most people who develop bowel cancer are over the age of 50, although it can occur at any age
- Having a family history of bowel cancer.

WHAT IS MEANT BY A FAMILY HISTORY OF BOWEL CANCER?

A family history of bowel cancer means having one or more close blood relatives who have, or have had, bowel cancer. Relatives could be on **either the father's or the mother's side** of the family, but not added together.

The closest blood relatives (not relatives by marriage) are parents, siblings and children and are called first-degree relatives. Aunts, uncles, nephews and nieces are second-degree relatives.

A family history of cancer can be due to:

- Chance, because cancer is common
- Common environmental and lifestyle influences among family members
- Having a faulty 'cancer protection' gene in the family.

Many people have a few relatives who have or had bowel cancer just because bowel cancer is common. Such people may be only slightly above the average risk. Some people have a 'stronger' family history where a number of their close blood relatives have or had bowel cancer.

Most of these people will have a moderately increased chance of developing bowel cancer. A small number will have a potentially high chance of developing bowel cancer because their family has an inherited a predisposition to this cancer.

INHERITED PREDISPOSITION TO BOWEL CANCER

Most bowel cancers are not due to an inherited predisposition.

However a small number of cases (about 5%-10%) in Australia involve an inherited predisposition to develop the cancer. In these cases, a person has inherited a faulty copy of a bowel 'cancer protection' gene (*Figure 33.1*).

Cancer occurs when cells in the body continue to divide uncontrollably. This can happen in any tissue or organ in the body. A group of cells that has resulted from uncontrolled cell division and growth is called a tumour.

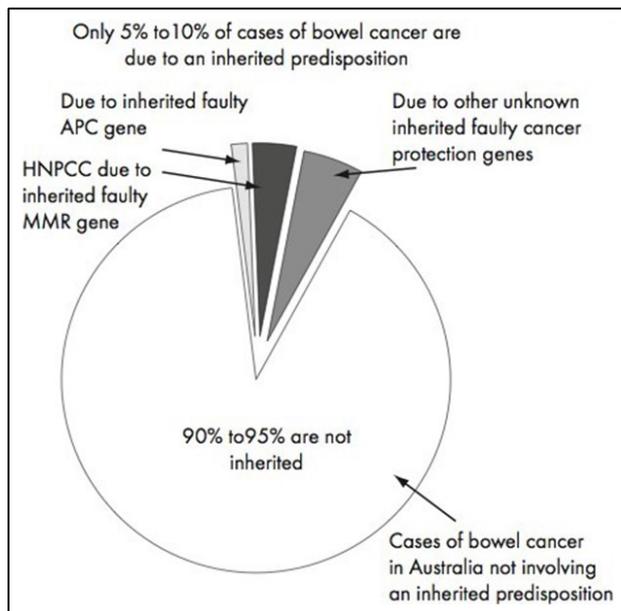


Figure 33.1: Chance of having bowel cancer due to an inherited predisposition.

We all have two copies of a number of different genes that normally control orderly growth and division of our cells throughout life. These genes can therefore be thought of normally acting as ‘cancer protection’ genes.

Variations to the information in one of these ‘cancer protection’ genes such as a breast or bowel cell may cause the process of cell division to be less well controlled and cells may grow and divide abnormally. A variation that makes the gene faulty is called a **mutation** or a **pathogenic variant**.

Mutations have to occur in a number of different ‘cancer protection’ genes in a cell, building up over time, before that cell becomes cancerous. This is why the development of bowel cancer can take many, many years and is often seen in older people.

The reason why these mutations occur is thought to be a combination of genetic factors, environmental factors and the process of ageing. Research is currently being undertaken to more fully understand the cause of specific gene mutations.

For the small number of people that have inherited a mutation in a ‘cancer protection’ gene the division and growth of bowel cells is not as tightly controlled as in other people in the population.

One way of representing this process is to think of the path to cancer as a staircase where the bottom of the staircase represents a normal cell and the top a cancerous cell (*Figure 33.2*).

The steps of the staircase represent a progression of changes to the information that may occur in one or both copies of a number of different ‘cancer protection’ genes in a cell. Some of these changes will be mutations.

So for a normal cell to become cancerous, both copies of a number of different ‘cancer protection’ genes in the cell of a tissue or organ must become faulty over time.

If a person is born with a mutation in one of the ‘cancer protection’ genes, they are already on the first step of the staircase (see *Figure 33.2*). Their chance of developing bowel cancer is higher than average but unless further mutations occur over time in a number of other ‘cancer protection’ genes, those cells will never become cancerous.

It is thought that not just one but many gene changes are associated with the development of bowel cancer.

WHAT ARE THE BOWEL CANCER SYNDROMES CAUSED BY AN INHERITED FAULTY ‘CANCER PROTECTION’ GENE?

It is important to remember that the bowel cancer itself is not inherited, although cancer caused by an inherited ‘cancer protection’ gene mutation is sometimes called hereditary cancer.

There are a number of conditions in which inherited gene mutations contribute to the development of bowel cancer.

Two of these conditions are:

1. Familial Adenomatous Polyposis (FAP)
2. Lynch Syndrome, also known as Hereditary Non Polyposis Colorectal Cancer (HNPCC).

1. Familial Adenomatous Polyposis (FAP)

FAP is a rare condition that accounts for less than 1% of all bowel cancer. (*Figure 33.1*). People with FAP develop many pre-cancerous growths called **polyps** (also called *adenomas*), usually more than 100, in their large bowel.

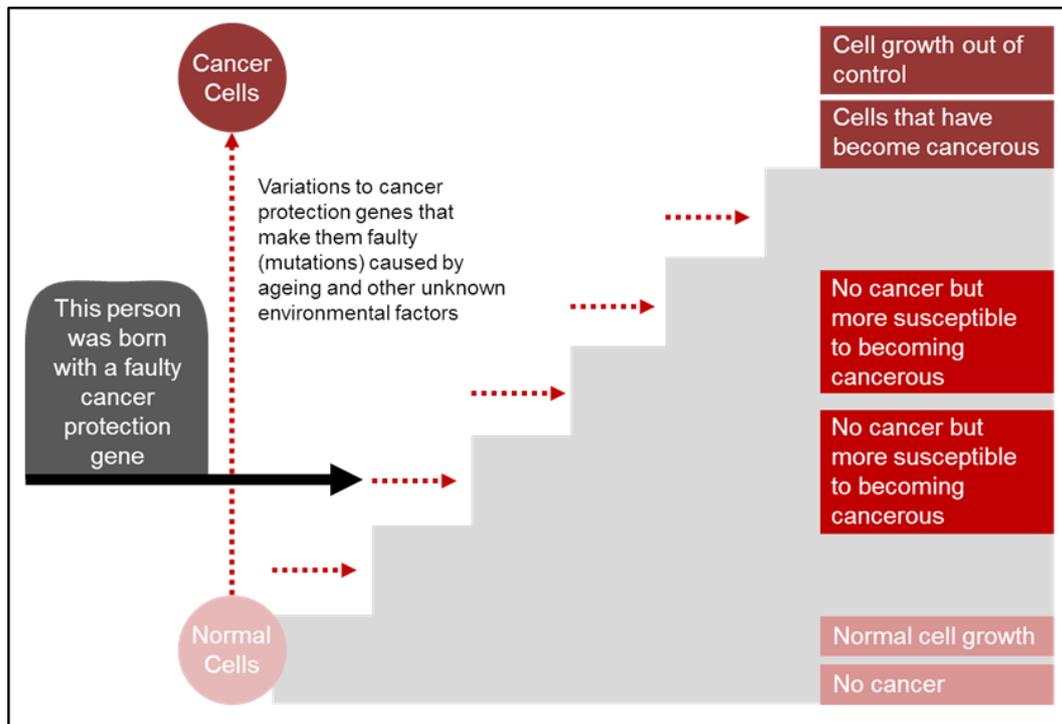


Figure 33.2: Changes build up in the different ‘cancer protection’ genes in the cells over time due to ageing and other environmental factors. Some of these changes make the ‘cancer protection’ genes faulty. Each step on the staircase to becoming cancerous cells represents a change in a copy of one of the many ‘cancer protection’ genes in the cells.

Most people with FAP develop bowel polyps during their late teens however they may start at any age, (but rarely before the age of 10 years). If left untreated, these polyps will eventually develop into bowel cancer over time. The chance of developing bowel cancer is high. People with FAP may also develop cancer in the upper part of the gastro- intestinal tract (especially of the duodenum, the first part of the intestine) and rare non-cancerous tumours such as desmoid tumours (fibrous tissue tumour).

FAP stands for:

- **Familial** because it runs in families (i.e. it is hereditary)
- **Adenomatous** because the polyps that develop in FAP are adenomas. Adenomatous polyps have the potential to develop into cancer
- **Polyposis** which means multiple polyps.

FAP develops as a result of an inherited mutation in the adenomatous polyposis coli (*APC*) gene. The *APC* ‘cancer protection’ gene is known as a tumour suppressor gene and its role is to act as ‘brakes’ on uncontrolled cell growth in the large bowel. Polyps form when cell growth is uncontrolled.

About one third of people with FAP have no known family history of the condition. There are two possible explanations for this: one of the parents had FAP but it was never recognised, or the mutation occurred spontaneously in one copy of the *APC* gene causing a new mutation at the time of conception. The parent who passed on the mutation in the egg or sperm does not have FAP.

There is a milder form of FAP, also caused by *APC* mutations, called **Attenuated FAP (AFAP)**. People with AFAP usually develop less polyps than people with FAP.

2. Lynch Syndrome also known as Hereditary Non Polyposis Colorectal Cancer (HNPCC)

Lynch syndrome is a rare condition that accounts for between 1% and 4% of all bowel cancers. (Figure 33.1)

People with Lynch syndrome develop bowel cancer at a younger age, usually before the age of 50 years. They often have one or more polyps (**adenomas**) in the bowel but do not have the large numbers of polyps occurring in people with FAP.

In addition, people with Lynch syndrome are at risk of developing a number of different cancers outside of the large bowel most commonly endometrial (cancer of the lining of the uterus) as well as other cancers (including ovary, stomach, small bowel, renal tract, and brain cancer).

Lynch syndrome develops as a result of an inherited mutation in mismatch repair (*MMR*) genes, specifically *MLH1*, *MSH2*, *MSH6* and *PMS2*. The different *MMR* genes are involved in the repair of mistakes that can occur when the genes are copied to make new cells and they are located on different chromosomes. The chance of developing cancer varies according to which of the *MMR* genes have a mutation.

WHAT IS THE PATTERN OF INHERITANCE IN FAMILIES WITH FAP AND LYNCH SYNDROME?

FAP and Lynch syndrome follow an autosomal dominant pattern of inheritance (Figure 33.3).

This is because:

1. The *APC* and *MMR* genes are located on the autosomes (numbered chromosomes)
2. The effects of the mutations in the *APC* and *MMR* genes are **dominant** over the information in the working copy of the genes.

Where one of the parents has an *APC* or *MMR* gene mutation, in every pregnancy each of their children has a:

- 1 chance in 2 (50% chance) of inheriting the gene mutation
- 1 chance in 2 (50% chance) of *not* inheriting the gene mutation and inheriting a working copy of the gene from both parents.

An *APC* or *MMR* gene mutation can be inherited from either the mother or the father and passed on to either a son or a daughter.

People who have not inherited a faulty gene are not at increased risk of developing bowel cancer over their lifetime and cannot pass the faulty gene on to their own children. However, they still have the same risk for developing bowel cancer as the average person in the Australian population.

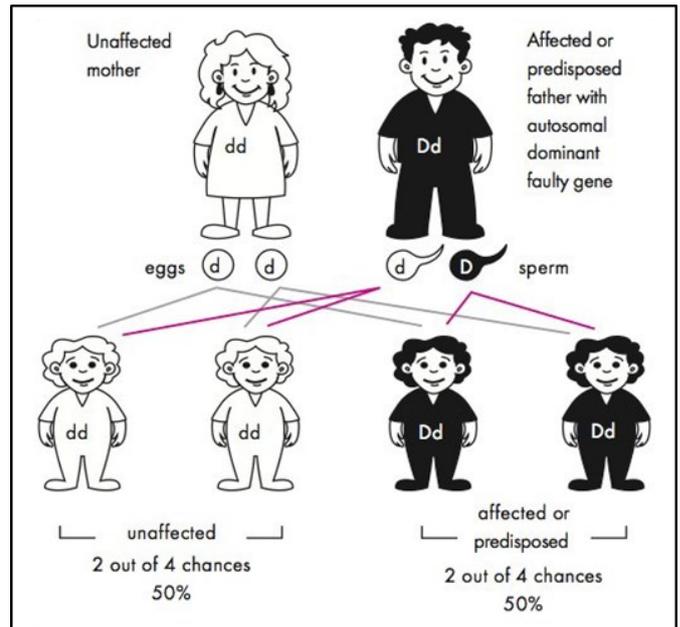


Figure 33.3: Autosomal dominant inheritance when one parent has a faulty gene copy. The faulty gene is represented by 'D'; the working copy by 'd'.

It is important to note that bowel cancer will not develop in a man or woman who is a carrier of a faulty *APC* or *MMR* gene unless further mutations occur in additional other 'cancer protection' genes in the cell during the individual's lifetime. Environmental factors that cause the mutations in the *APC* or *MMR* gene(s) are still largely unknown as are the factors that cause the mutations in additional other 'cancer protection' genes that eventually lead to bowel cancer.

People with Lynch syndrome usually have a strong family history of cancer.

WHAT ARE THE CLUES IN A FAMILY HISTORY?

Documenting the health history of family members over several generations helps determine if a person has a strong family history. It is important to record how the individual is related, the type of cancer they have or had and the age of the individual when cancer was first diagnosed.

A strong family history of bowel cancer may mean an inherited gene mutation is present in the family.

This usually includes one or more of the following:

- Two close relatives with bowel cancer diagnosed before the age of 50
- Three Lynch syndrome related cancers (e.g. bowel, endometrial, ovary, stomach, renal tract or brain cancer) in close relatives diagnosed at any age.

GENETIC COUNSELLING AND TESTING

People with a strong family history can be referred by their doctor to a specialist family cancer service or their local genetic counselling service.

The genetic counselling team may be able to:

- Clarify the chance of developing bowel cancer based on a person's family history
- Answer any questions about the family history of cancer
- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing
- Discuss cancer screening and risk reducing strategies.

Genetic testing for mutations in the *APC* and *MMR* genes is complex and involves

- First, identifying the gene mutation via a blood sample in a family member who has or had bowel cancer (a **mutation search**). This may take considerable time

- Second, and only if a mutation is found, testing other family members to determine if they have inherited the mutation (**predictive genetic testing**).

WHAT IS THE CHANCE OF DEVELOPING BOWEL CANCER AND OTHER CANCERS?

People with FAP and Lynch syndrome have an increased chance of developing bowel cancer and some other cancers (*Table 33.1.*). For people with Lynch syndrome, the chance of developing these cancers may also vary according to which of the *MMR* genes are involved.

MANAGING AN INCREASED CHANCE OF DEVELOPING BOWEL CANCER

Early diagnosis – talk to your family and your doctor

More than 90% of bowel cancer can be cured if picked up at the earliest stage. It is important that if you are aware of an inherited cancer in you or a close relative you let your doctor know as soon as possible

Genetic counselling and risk management

It is recommended that people with FAP or Lynch syndrome, seek management advice from a genetic service, a family cancer clinic or medical specialist.

Condition	Chance (risk) for women developing bowel cancer and other cancers up until age 70 years	Chance (risks) for men developing bowel cancer and other cancers up until age 70 years
<i>FAP</i>	Greater than 90% for bowel cancer Greater than 5% for duodenal cancers	Greater than 90% for bowel cancer Greater than 5% for duodenal cancers
<i>Lynch syndrome</i>	About 31% for bowel cancer About 33% for endometrial cancer (lining of the uterus) Slightly increased chance of developing cancer of the ovary, stomach, small bowel, renal tract, and brain	About 38% for bowel cancer Slightly increased chance of developing cancer of the stomach, small bowel, renal tract, and brain

Table 33.1: Chance of developing bowel and other cancers for people with FAP or Lynch syndrome

FAP

People who have an *APC* gene mutation need regular bowel check-ups (called sigmoidoscopy or **colonoscopy**) from their early teenage years and eventually an operation to remove the bowel and prevent bowel cancer.

People who do not have an *APC* gene mutation will not develop FAP, however they still have the same chance of developing bowel cancer as others in the general population.

Lynch syndrome

It is strongly recommended that people who have a *MMR* gene mutation have regular check-ups (including a bowel test called **colonoscopy**). Surgery may be recommended for some people.

People who do not have a *MMR* gene mutation will not develop Lynch syndrome however they still have the same chance of developing cancer as others in the general population.

It is recommended that people with FAP and Lynch syndrome are enrolled by their doctor on a local hereditary cancer registry for information and surveillance reminders. NSW Hereditary Cancer Registry information is available at www.cancerinstitute.org.au/data-and-statistics/cancer-registries/hereditary-cancer-registry.

Lifestyle may help

The progression to bowel cancer requires mutations to build up in a number of the 'cancer protection' genes in the bowel cells over time. The reason why these mutations occur is thought to be a combination of genetic factors, environmental factors and the process of ageing. Research is currently being undertaken to more fully understand the cause of specific gene mutations. However researchers do believe a balanced diet high in fibre and low in fat, no smoking and living a healthy lifestyle will reduce the chance of developing cancer.