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Important points

- The most important factors that can influence an individual's chance of developing bowel cancer are getting older and having a family history of bowel cancer
- A family history of bowel cancer can occur just by chance, because cancer is common; because family members are exposed to the same environmental factors; and rarely (in 5%-10% of all cases), because a predisposition to bowel cancer is running in the family
- Inherited predisposition to bowel cancer is due to inheriting from **either parent** a faulty copy of just one of the genes that usually prevents bowel cancer from developing (a faulty 'cancer protection' gene)
- There are at least two types of conditions that lead to bowel cancer known to be caused by the inheritance of a faulty 'cancer protection' gene: Familial Adenomatous Polyposis (FAP) and Hereditary Non Polyposis Colorectal Cancer (HNPCC, also called Lynch syndrome)
 - The genes involved are called *APC* and *MMR* respectively and we usually all have working copies of these genes in our cells
 - A person (man or woman) who has a faulty *APC* or *MMR* gene copy and a working copy of these genes is a carrier of a faulty bowel cancer gene and is predisposed to bowel cancer
 - The chance of developing bowel cancer is higher than average if an individual inherits either a faulty *APC* or *MMR* gene copy, but unless further changes occur over time in both copies of a number of additional other 'cancer protection' genes in bowel cells, those cells will never become cancerous. The individual will not develop bowel cancer
 - An individual who has not inherited the faulty 'cancer protection' gene(s) will not develop FAP or HNPCC but they still have the same risk for developing bowel cancer as the average man or woman in the Australian population
- There is 1 chance in 2 (or 50%) in every pregnancy that a parent who is a carrier of an *APC* or *MMR* faulty gene will pass the faulty gene on to their child
- Guidelines have been developed for doctors to identify from their family history those at potentially high risk for bowel cancer and some other cancers, due to an inherited predisposition
 - For these families, genetic counselling is available to clarify an individual's risk and discuss their options for genetic testing, its limitations, advantages and disadvantages and available prevention and early detection strategies
- Genetic testing for mutations in the *APC* and *MMR* genes is complex and involves
 - First identifying the mutation in a family member who has or had polyposis or bowel cancer (**mutation search**) and may take considerable time
 - Second, and only if a mutation is found, testing other family members without cancer to determine if they have inherited the faulty gene (**predictive genetic testing**)

In a small number of families in the community, an increased risk for developing cancer is running in the family (inherited predisposition to cancer). The cancers include

- Breast and ovarian cancer (see Genetics Fact Sheet 48)
- Melanoma (see Genetics Fact Sheet 50)
- Prostate cancer (see Genetics Fact Sheet 51)

This Fact Sheet discusses inherited predisposition (susceptibility) to bowel cancer.

What is bowel cancer?

Bowel cancer generally refers to cancer of the large bowel (which is made up of the colon and rectum). Bowel cancer is therefore also known as colorectal cancer. It is the second most common cause of death due to cancer in Australia.

Although bowel cancer mainly affects people over the age of 50 years, it can occur at any age.

The lifetime risk for developing bowel cancer in the general population (to age 75) is

- 1 in 17 for men
- 1 in 26 for women

Each year there are about 12,600 new cases of bowel cancer diagnosed and 4,700 deaths from the condition.

What causes bowel cancer?

There is no single cause. There are a number of factors (*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
- 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 had, bowel cancer. These relatives could be on **either the father's or the mother's side** of the family.

Close blood relatives (not relatives by marriage) are

- Parents, siblings or children (first-degree relatives - 10)
- Aunts, uncles, nephews, nieces or grandparents (second-degree relatives - 20)

Approximately 15%-20% of people with bowel cancer have a first-degree relative affected by the disease.

A family history of cancer can occur

- Just by chance, because cancer is common
- Because family members have environmental influences in common (eg some aspects of their diet)
- Because a predisposition to bowel cancer is running in the family, though this is rare

Many people may 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 been affected with bowel cancer.

- Most of these people may have a moderately increased chance of developing bowel cancer
- A few will have a potentially high chance of developing bowel cancer because a predisposition to this cancer is running in their family

Inherited predisposition to the development of bowel cancer

The majority of bowel cancer cases are not due to an inherited predisposition to develop the condition.

A small number of the cases of bowel cancer (about 5%-10%) in Australia involve an inherited predisposition to develop the cancer. In these cases, an individual has inherited a copy of a faulty bowel 'cancer protection' gene (see Genetics Fact Sheet 47 for further information about 'cancer protection' genes and inherited predisposition to cancer generally).

Cancer is a result of uncontrolled cell division and growth in cells in a particular part of the body, eg. in the cells of the bowel: if the cells divide and grow out of control, they accumulate to form a polyp, which may develop into a cancer.

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.

All cancers can be considered genetic in origin because they arise from changes in the normal 'cancer protection' genes.

A change (mutation) in the information in a 'cancer protection' gene makes the gene faulty and stops it doing its usual job in the cell. What causes these genes to become faulty is unknown, but may be due to a combination of genetic factors, environmental factors, and the process of ageing. The environmental factors may include exposure to various toxins, radiation, lifestyle and diet. Further research is being undertaken to more fully understand the cause of specific genetic mutations in the bowel cells.

The development of bowel cancer is not a quick or simple process. It is a progression involving a build-up of changes in a number of different 'cancer protection' genes in the cells of the

bowel **over a person's lifetime** (see Genetics Fact Sheet 47). This is why the development of bowel cancer can take many, many years, and is often seen in older people.

Most people are born having two working copies of each of the different 'cancer protection' genes in their cells. So that means that most people have not inherited a genetic predisposition to developing cancer and have an average chance of developing cancer.

Between 5% and 10% of all bowel cancers are believed to be due to having inherited a faulty **copy of one** of the 'cancer protection' genes that usually control cell division and growth in the bowel (see *Figure 49.1*).

- From birth, the division and growth of cells in these individual's bowel tissue is not very tightly controlled as it is in other individuals
- Although these cells would be on the first step on the staircase towards becoming cancerous, the other copy of that 'cancer protection' gene, and additional 'cancer protection' genes in the cells, are still working properly so the process of cell division and growth in the bowel tissue are still largely normal. See *Figures 47.2 and 47.3* in Genetics Fact Sheet 47 for more information about the progression to cancer
- The chance of developing bowel cancer is higher in people carrying a faulty gene than average but unless further changes occur over time in a number of other 'cancer protection' genes in bowel cells, a cancer will not occur
- It is thought that not just one but many gene changes are associated with the development of bowel cancer

It is important to remember that the bowel cancer itself is not inherited, although cancer that arises from an inherited faulty 'cancer protection' gene is sometimes called hereditary cancer.

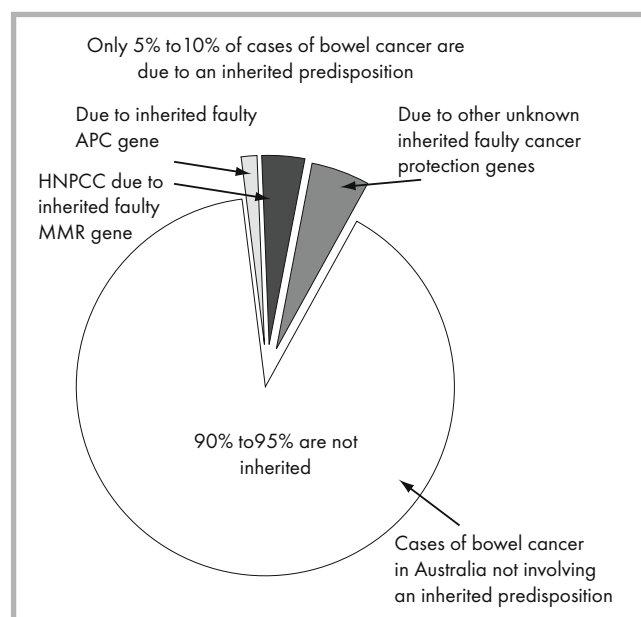


Figure 49.1. Proportion of cases of bowel cancer that do and do not involve an inherited predisposition (susceptibility).

Bowel cancer due to an inherited faulty ‘cancer protection’ gene

There are at least two types of conditions that lead to bowel cancer known to be caused by the inheritance of a faulty ‘cancer protection’ gene. These are described below:

1. Familial Adenomatous Polyposis (FAP)
2. Hereditary Non Polyposis Colorectal Cancer (HNPCC)

1. Familial Adenomatous Polyposis (FAP)

Familial adenomatous polyposis (FAP)

- Is a rare condition that accounts for less than 1% of all bowel cancer (Figure 49.1)
- Is an inherited condition in which an individual develops many growths called polyps (also called *adenomas*) in their bowel (usually more than 100), generally by their late teens. Without treatment, some of these adenomas will develop into cancer over time. The risk of cancer is so high that the bowel needs to be surgically removed (*colectomy*) to prevent cancer
- Results in bowel cancer often by the time the person is aged in their 20s, 30s or 40s and sometimes even earlier
 - May also cause problems outside the large bowel, such as cancer in the upper part of the gastro-intestinal tract (especially of the duodenum), desmoid tumours (fibrous tissue tumour) and osteomas (bony tumour)
- Involves an inherited mutation in a copy of a gene called the adenomatous polyposis coli (*APC*) gene
 - This gene appears to function as a **tumour suppressor** gene and is located on the long (‘q’) arm of chromosome 5
 - The *APC* gene can be thought of as a ‘cancer protection’ gene. For more information about tumour suppressor genes, see Genetics Fact Sheet 47

Everyone is born with two copies of an *APC* gene. Most people are born with two working copies of their *APC* gene; a few people are born with a working copy and a faulty copy of their *APC* gene.

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 (for example, they may have died of some other cause before FAP appeared)
- The mutation occurred spontaneously in one copy of the *APC* gene in either the egg or sperm at the time of conception. This is called a new mutation. The parent who passed on the mutation in the egg or sperm does not have FAP since the body cells (including those of the colon) are unlikely to have the faulty gene

Whether the faulty (mutated) *APC* gene copy is inherited from an affected parent, or whether it is due to a new mutation, further mutations in additional other ‘cancer protection’ genes in the cells of the bowel are necessary for bowel cancer to develop. For more information about how mutations build up in cells and cause cancer, see Genetics Fact Sheet 47.

2. Hereditary Non Polyposis Colorectal Cancer (HNPCC) – Lynch Syndrome

Hereditary Non Polyposis Colorectal Cancer (HNPCC)

- Is a rare condition that accounts for between 1% and 4% of all bowel cancers (Figure 49.1)
- Is an inherited form of bowel cancer and is also known as ‘Lynch syndrome’
- Is characterised by the early onset of bowel cancer, usually before the age of 50 years. People who are affected by HNPCC often have one or more polyps (*adenomas*) in the bowel but do not have the large numbers of polyps occurring in people with FAP
 - Bowel cancer risk can be reduced by regular colonoscopy to remove polyps
- Cancers occurring outside the large bowel may also be a feature of HNPCC. The most common of these is endometrial cancer (cancer of the lining of the uterus), but the syndrome also includes cancers of the ovary, stomach, small bowel, renal tract, brain and biliary tract.
- Relys on the accurate recording of a strong family history of cancer for its diagnosis
- Is associated with an inherited mutation in a copy of one of a group of genes known as DNA 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. For more information about mismatch repair genes, see Genetics Fact Sheet 47.

Everyone is born with two copies of the *MMR* genes. Most people are born with two working copies of each of their *MMR* genes; a few people are born with a working copy and a faulty copy of one of their *MMR* genes.

What is the pattern of inheritance in families with a faulty *APC* or *MMR* gene?

Two factors influence the pattern of inheritance of the faulty *APC* or *MMR* genes in families.

1. The *APC* and *MMR* genes are located on autosomes (one of the numbered chromosomes)
2. The effects of changes in the *APC* and *MMR* genes are ‘dominant’ over the information in the working copy of the genes on the partner chromosomes (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty genes causing predisposition to bowel cancer is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

In Figure 49.2 the autosomal dominant faulty gene causing predisposition to bowel cancer is represented by ‘D’; the working copy by ‘d’.

Where one of the parents has or had bowel cancer involving a faulty *APC* or *MMR* gene, or has been identified as a carrier of a faulty *APC* or *MMR* gene, **in every pregnancy**, each of their children has

- 1 chance in 2 (50% chance) of inheriting the faulty gene from the affected parent

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

Some important things to note:

- The 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
- Children who have not inherited the faulty gene are not at increased risk of developing polyposis or bowel cancer over their lifetime and cannot pass the faulty gene on to their own children
 - They still, however, have the same risk for developing bowel cancer as the average man or woman in the Australian population
- While *Figure 49.2* shows the father as the parent carrying the faulty APC or MMR gene, the same situation would arise if it was the mother
 - **A faulty APC or MMR gene can be inherited from either the mother or the father**
- The environmental factors that cause the mutations in the APC or MMR gene(s) are still largely unknown. The identification of these factors and preventing their action paves the way for the prevention of many cancers. This is the subject of intense research
- The identification of the environmental factors that cause the mutations in additional other 'cancer protection' genes over the individual's lifetime that eventually lead to bowel cancer are also unknown

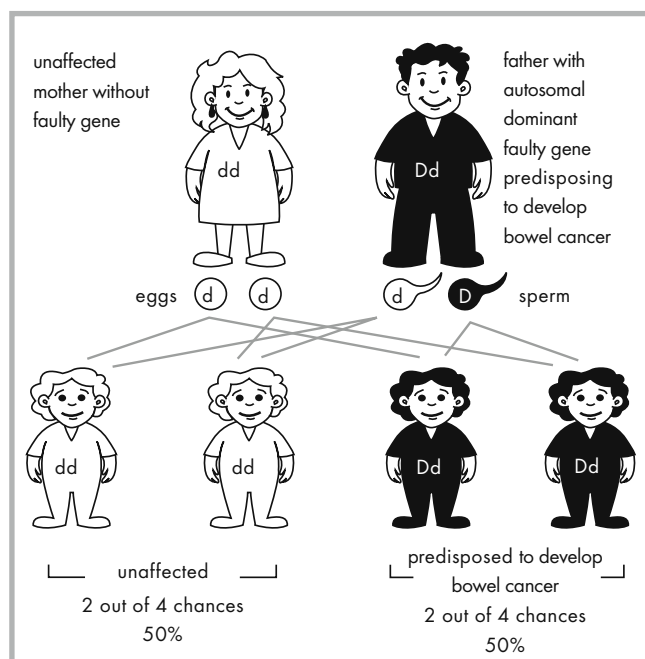


Figure 49.2: Autosomal dominant inheritance when one parent has a faulty APC or MMR gene copy. The faulty gene is represented by 'D'; the working copy by 'd'.

What are the clues in a family history of bowel cancer that suggest that family members are at potentially high risk?

The Australian Cancer Network (2006) has produced a guide for doctors on assessing the family health history to see if the bowel cancer in the family could potentially be due to an inherited faulty gene.

Based on the number of relatives with bowel cancer, the family relationship and the age of diagnosis, individuals are categorised into risk groups for developing bowel cancer. The family relationship is classified as

- **First-degree relatives (1°):** parents, siblings or children
- **Second-degree relatives (2°):** aunts, uncles, nephews, nieces or grandparents

Risk for developing bowel cancer based on family history

The guidelines for doctors categorise an individual's risks for developing bowel cancer based on their family history of cancer into 3 groups (Table 49.1):

- Category 1. At or slightly above average risk
- Category 2. Moderately increased risk
- Category 3: Potentially high risk

It should be noted that not all individuals with the Category 3 family history will have a genetic susceptibility to bowel cancer (FAP or HNPCC).

- Without treatment, those with proven FAP have a lifetime risk of bowel cancer of almost 100%. The risk is reduced by surgery to remove the bowel
- For those with a mutation in an MMR gene, the lifetime risk is less, but may be up to 80% in some families. The risk is reduced by regular screening
- For family members shown **not** to have the mutation in the APC or MMR gene causing cancer in the family, their risk for polyps and bowel cancer is the same as that of the general population

Can an individual determine if they have inherited a faulty APC or MMR gene?

Individuals with a strong family history like that described for Category 3 can seek advice from a specialist family cancer service (if available) or their local genetic counselling service. They will need a referral. Their risk of developing polyps or bowel cancer, based on their family history, can be estimated and discussed in more detail (see Genetics Fact Sheet 3).

The genetic counselling team may be able to:

- Clarify their chance of developing polyps or bowel cancer based on their family history
- Answer any questions they have about their family history of cancer
- Discuss what medical check-ups are appropriate
- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing (see Genetics Fact Sheet 21)

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

Table 49.1: Risks for developing bowel cancer based on a family history of cancer (1° = first degree relative ie parents, siblings, 2° = second degree relative ie uncles, aunts)

Category 1: At or slightly above average risk	Category 2: Moderately increased risk	Category 3: Potentially high risk
More than 98% of people in the population are in this 'risk group'.	Around 1-2% of people in the population are in this 'risk group'. Their lifetime risk is 3-6 times the population average.	Less than 1% of people in the population are in this 'risk group'. Their lifetime risk is 3-6 times the population average.
<p>Average risk No personal history of bowel cancer, colorectal adenomas or chronic inflammatory bowel disease and No confirmed close family history of bowel cancer. <i>Their risk is related to their age.</i></p> <p>Slightly above average risk One 1° or 2° relative with bowel cancer diagnosed at age 55 or older. Two relatives diagnosed with bowel cancer at age 55 or older but on different sides of the family <i>Their lifetime risk is up to 2 times the population average risk based on their age. People with affected relatives may have up to double the average risk, but most of this additional risk is expressed after the age of 60.</i></p>	<p>One 1° relative with bowel cancer diagnosed before the age of 55 years (without potentially high risk features as in category 3).</p> <p>Two 1° relatives or one 1° and one 2° relative/s on the same side of the family with bowel cancer diagnosed at any age (without potentially high risk features as in Category 3).</p>	<p>Three or more 1° relatives or a combination of 1° and 2° relatives on the same side of the family diagnosed with bowel cancer.</p> <p>Two or more 1° or 2° relatives on the same side of the family diagnosed with bowel cancer, plus any of the following high risk features: multiple bowel cancers in a family member; bowel cancer before the age of 50; a family member who has/had an HNPCC-related cancer (endometrial, ovarian, stomach, small bowel, renal pelvis or ureter, biliary tract, brain cancer).</p> <p>At least one 1° or 2° relative with a large number of adenomas throughout the large bowel (suspected FAP).</p> <p>Member of a family in which a gene mutation that confers a high risk of bowel cancer has been identified.</p>

- **First**, identifying the mutation in a family member who has or had bowel cancer due to FAP or HNPCC. This is called a **mutation search** and may take considerable time
- **Second**, and only if a mutation is found, testing other family members without cancer to determine if they have inherited the faulty gene and are therefore at increased risk of developing cancer. This is called **predictive genetic testing** (see Genetics Fact Sheet 21)

What can be done if an individual has inherited a faulty gene causing FAP or HNPCC and predisposition to bowel cancer?

More than 90% of bowel cancer can be cured if picked up at the earliest stage.

FAP

- Individuals who **have inherited** a faulty APC gene copy need regular bowel checkups (called sigmoidoscopy or colonoscopy) from their early teenage years and eventually an operation to remove the bowel and prevent bowel cancer
- Individuals who **have not inherited** a faulty APC gene copy will not develop FAP. They still, however, have the same

chance of developing bowel cancer as others in the general population.

HNPCC

- It is strongly recommended that people **who have inherited** a faulty MMR gene copy have regular checkups (including a bowel test called colonoscopy) and possibly surgery
- People **who have not inherited** a faulty MMR gene copy will not develop HNPCC but they still have the same chance of developing cancer as others in the general population

The progression to bowel cancer requires further mutations to build up in a number of the 'cancer protection' genes in the bowel cells over time. If the environmental factors could be identified that cause these mutations, preventive strategies could be implemented. As yet, there is limited understanding of these factors, although a 'best bet' may include a healthy diet high in fibre and low in fat, no smoking and a healthy lifestyle.

Hereditary Bowel Cancer Registers assist doctors to identify, treat, support and follow-up individuals with or at-risk of developing bowel cancer due to inherited bowel conditions.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 21, 47, 48, 50, 51

Information in this Fact Sheet is sourced from:

Australian Cancer Network (2006). *Familial Aspects of Bowel Cancer: a guide for health professionals* [online]. Available from <http://www.cancer.org.au> [Accessed June 2007]

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Author/s: A/Prof Kristine Barlow-Stewart, A/Prof Judy Kirk and Dr Kathy Tucker

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