Fact sheet **31**

CANCER GENETICS OVERVIEW

This fact sheet talks about when some cancers can occur in a family because of a genetic factor. It provides an overview of how all cancer develops and describes when cancer is considered to be an inherited condition (also known as a 'familial condition').

IN SUMMARY

- Cancer is very common in the community and mostly occurs just by chance
- Sometimes cancer occurs in families because of a shared environment such as high sun exposure or cigarette smoke
- A small proportion of families have an inherited susceptibility to developing some cancers.

WHAT IS CANCER?

Cancer occurs when cells in the body continue to divide uncontrollably. This can happen in any tissue or organ in the body. Cancerous cells have the potential to spread to other parts of the body.

CELLS, DNA AND GENES

Our bodies are made up of billions of cells. Each cell contains a complete copy of our genetic information or DNA. Our DNA contains the instructions for growth and development and is packaged into chromosomes that contain all our genes. Genes provide a code for the proteins our body needs to function.

We all have two copies of every gene, one that is inherited from the mother, and one from the father. As we age and grow, our cells are continually dividing to form new cells by the process of cell division. This means our DNA is copied over and over again.

CANCER PROTECTION GENES

Some genes work together to instruct each cell how to copy its genes properly, and how to divide and grow in a controlled and orderly manner. These are called '**cancer protection**' genes. We all have many different cancer protection genes.

There are different types of 'cancer protection' genes:

- **Tumour suppressor genes** are genes that act as the 'brakes' on uncontrolled cell growth. Cancer may occur when both copies of a tumour suppressor gene (both 'brakes') fail to work properly
- **Oncogenes** are the accelerators of cell division (they increase the rate of cell division). Cancer may occur when these genes are switched on inappropriately (too much 'accelerator')
- **Mismatch repair genes** help find and repair mistakes in the genetic information that can occur during cell division. The mismatch repair genes act like 'spell checkers' on the computer. Cancer may occur when variations in these genes result in failure to repair mistakes in the DNA.

Another way of thinking about how these genes work in the cells is to imagine that the genetic control of cell division is a car that is working well (see *Figure 31.1*).

For the car to work, what makes the car move (the 'accelerator' or oncogenes) and stop (the 'brakes' or tumour suppressor genes) must be in balance. Also the mismatch repair genes are like the mechanic who keeps the car running smoothly.

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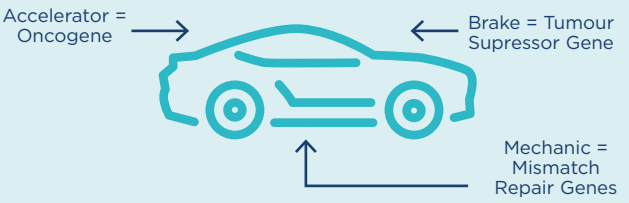
Figure 31.1:
The balance of cell growth and division is maintained by the 'cancer protection' genes just like a well-maintained car.



WHAT IS A PATHOGENIC VARIANT?

We all have thousands of variations in our genes, but some of these can affect how our bodies work. Generally, DNA variations that have no impact on our health are called **benign variants** or **polymorphisms**. These variants are the most common type. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a higher chance of a health condition is called a **pathogenic variant** or **mutation**.

HOW DOES CANCER DEVELOP?

Pathogenic variants in the 'cancer protection' genes may cause cells to grow and divide abnormally. For a cell to become cancerous, multiple variants have to occur in a number of different 'cancer protection' genes within the cell, over time.

It can take many years for a cancer to develop, and this is the reason why the risk of cancer increases with age, and most cancers occur in older people.

The reasons why these variants happen is thought to be a combination of genetic factors, environmental factors and the process of ageing.

HOW DO PATHOGENIC VARIANTS HAPPEN?

Pathogenic variants can occur in a number of ways in a person. They can come about in the body over time (**acquired**), they can be **inherited** from one or both parents, or they can occur for the first time in a person for no apparent reason (**sporadic**).

Acquired Variants

Acquired variants can come about due to things we experience during our lives, for example radiation produced by the sun, certain chemicals, or other environmental factors. Acquired variants may also occur as our cells are copied to enable us to grow or repair damaged cells throughout life as we age.

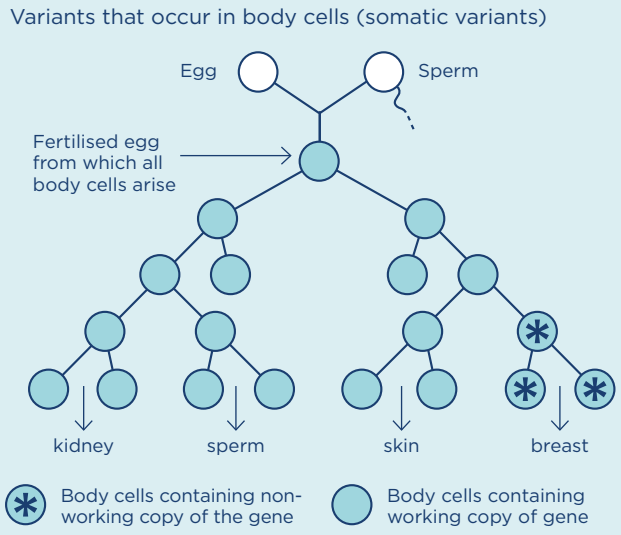
Although the body has an efficient system to repair these variants in the genes as they occur, sometimes there is a breakdown in the cell's repair system.

If a variant occurs and is not repaired, it will be copied into all the cells arising from that cell.

Body cells (not the egg or sperm) are called 'somatic cells' and therefore a variant that occurs in a somatic cell is called a **somatic variant**.

A somatic variant will only affect the part of the body in that particular individual (*Figure 31.2*). Somatic cells are therefore not passed down to children or inherited.

Figure 31.2:
Acquired variants in 'cancer protection' genes that occur in the body cells (somatic variants) during life such as in the breast cells are confined only to the breast tissue. The cancer protection genes in the person's egg or sperm cells are working and therefore they will not pass on the gene variant



Inherited (also known as 'Familial') Variants

Everyone is born with several pathogenic gene variants in their over 20,000 gene pairs. These are usually passed down in the father's sperm or the mother's egg.

Once that child has the variant, they will have it for life and can also pass it on to their future children. This is an **inherited variant**.

Inherited variants can be passed down by only the father, only the mother or by both parents. The way in which the variant(s) will affect the child will depend on other factors as well as the variant(s) themselves.

Sperm and egg cells are called 'germ cells' and therefore variants that are present in the genes of the egg or sperm are called germ cell or **germ-line variants**.

Sporadic Variants

When a health condition is caused by a variant that appears for the first time in a family, it is said to be **sporadic**. Sporadic genetic conditions come about when a spontaneous variant occurs in the egg or sperm that went on to become that person.

If a sporadic gene variant occurs at the time of fertilisation but is not inherited from one of your parents, you can still pass it on to your future children. Your sperm or eggs will now contain this variant.

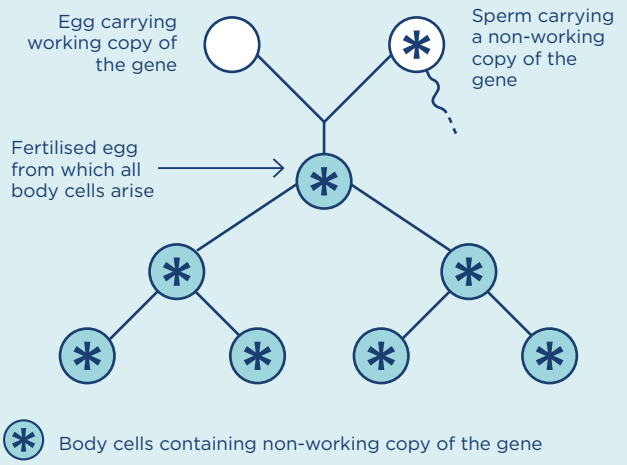
INHERITED SUSCEPTIBILITY TO CANCER

In a small number of cancer cases (about 5%), a pathogenic variant in a 'cancer protection' gene is present in all the cells of a person from birth. This is due to an inherited or sporadic pathogenic variant.

As shown in *Figure 31.3*, if a pathogenic variant in a 'cancer protection' gene is in the egg or sperm (**germ cell variant**), it will then be present in all the cells of the body of the individual arising from the fertilised egg.

When variants in 'cancer protection' genes are present in the germ cells, the variant can be passed on to a child.

Figure 31.3:
Inheritance of a pathogenic variant in a 'cancer protection' gene. The egg (from the mother) has a working copy of the gene. The sperm (from the father) has a non-working copy of the gene. Their offspring will have both a working copy and a non-working copy of the 'cancer protection' gene in all the cells of their body. This may also occur in the reverse situation, where the pathogenic variant has come from the sperm (from the father).

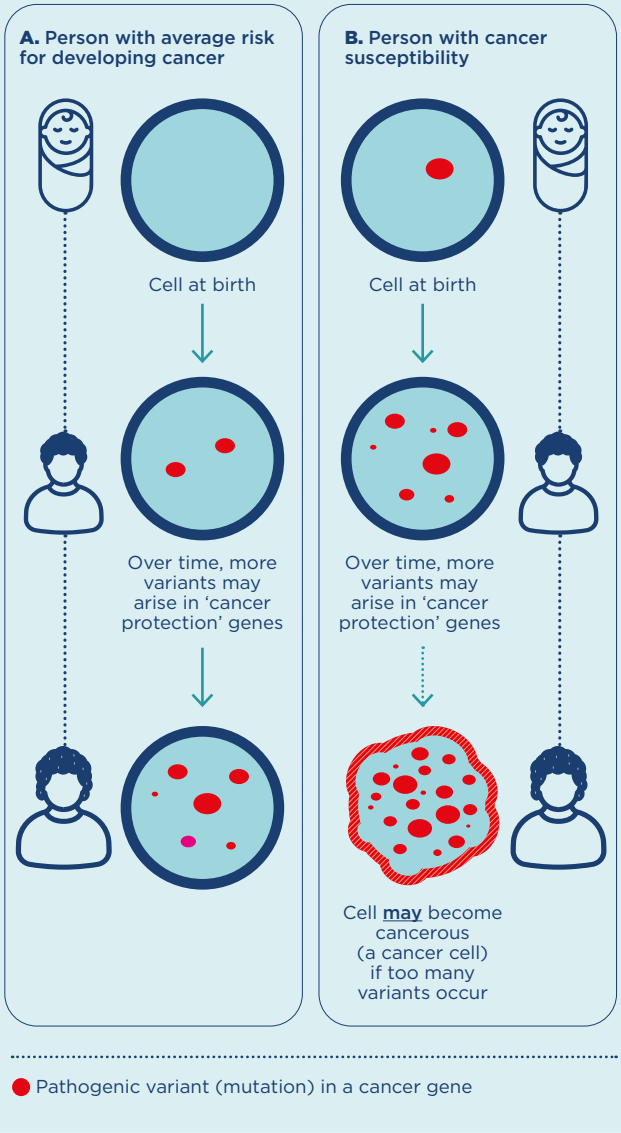


Most people are born having two working copies of each of the different 'cancer protection' genes in their cells. So that means that most people have not inherited a genetic susceptibility to developing cancer. A small number of people inherit a variant in one of the copies of their 'cancer protection' genes from a parent.

If a child is born with a pathogenic variant in one copy of a 'cancer protection' gene, the child has a higher than average risk of developing cancer in their lifetime. A cancer will not develop, however, unless other cancer protection genes in the cells also acquire variants during a person's lifetime.

Figure 31.4 shows a stylised image of a cell from a person with an average risk of developing cancer (left hand side) and the cell of someone with an inherited pathogenic variant at birth (right hand side).

Figure 31.4:
Increased chance of cancer cell development in those born with an inherited cancer susceptibility compared with the average person



Over time, as we age, we accumulate variants in genes that may increase the 'burden' or risk for developing cancer. If enough of these variants arise over time, the cell becomes cancerous (a 'cancer cell'). The person with the inherited pathogenic variant is more likely to have a cancer develop in their lifetime because their cells started with a pathogenic variant already present at birth. This means that fewer variations need to happen to the cells' protective genes for a cancer to develop.

A FAMILY HISTORY OF CANCER

Some families have a number of blood relatives who have been affected by cancer. A family history of cancer can be due to:

- Chance, because cancer is common
- Common environmental influences among family members
- An inherited pathogenic variant in a cancer protection gene.

WHAT IF YOU HAVE A FAMILY HISTORY OF CANCER?

Compile a family health history

Documenting the health history of family members (blood relatives) over several generations is important in determining if a condition is running in the family. Ask about the family history of cancer on both your mother's and father's side of the family. It is important to note:

- How the individual is related to you
- The type of cancer they have or had
- The age of the individual when they were first diagnosed or when they died from the cancer.

Discuss your family history with your doctor

Many cancers can be cured if picked up at the earliest stage. Discuss your personal and family history of cancer with your GP.

Genetic counselling and risk management

Some people with a strong family history may request referral by family doctor (GP) to their local genetic counselling service or family cancer clinic. In some instances other medical specialists such as oncologists may order testing covered by Medicare. The risk of developing cancer, based on a person's family history, can be estimated and discussed in more detail. National guidelines for health care professionals exist at the Cancer Institute NSW eviQ website.

The genetic counselling team may be able to:

- Work out their chance of developing cancer based on family history
- Answer questions they have about their family history of cancer
- Talk about what medical check-ups are appropriate
- Talk about the limitations, potential benefits, disadvantages and appropriateness of genetic testing
- In some cases, preventive surgery is considered. Research is continuing to investigate cancer prevention with drug therapy.

Genetic testing for pathogenic variants in the 'cancer protection' genes is complex and involves:

First, identifying the gene variant via a blood sample in a family member who has or had cancer (a **variant** search). A **variant search** is often performed on a group of selected genes (known as a panel) related to the types of cancer present in the family.

Second, and only if a pathogenic variant is found, testing may be arranged in other family members to work out if they have inherited the same variant (**predictive genetic testing**).

In some instances genetic testing may be covered by Medicare and guidelines for medical specialists ordering cancer genetic testing are available.

Lifestyle may help

Most cancers occur due to a combination of genetic factors, environmental factors and the process of ageing. Research is currently being undertaken to better understand the impact of specific gene variants.

Maintaining a balanced diet high in fibre and low in fat, no smoking and living a healthy lifestyle can reduce the risk of many cancers. Following community screening guidelines or following a personalised screening program given to you by your doctor is also very useful in preventing and picking up cancers early.