Fact sheet **35**

PROSTATE CANCER & INHERITED SUSCEPTIBILITY

This fact sheet talks about when prostate cancer is considered to be a hereditary or familial condition. A small number of families have an increased chance of developing cancer because they have inherited a DNA change in a cancer protection gene.

IN SUMMARY

- Cancer is very common in the community and mostly occurs by chance
- A small proportion of families have an inherited susceptibility to developing some cancers
- Having an inherited non-working copy of the *BRCA1* or *BRCA2* gene increases the likelihood of developing prostate cancer and some other cancers.

WHAT IS PROSTATE CANCER?

The prostate, a small gland found only in men, is located at the base of the bladder. As men grow older, especially over the age of 50, the prostate normally gets bigger. This enlargement can block the passage of urine, causing problems. While this is commonly due to a non-cancerous enlargement, prostate cancer may also cause these problems.

Prostate cancer is a common disease in the community. About 1 in 19 (5.3%) Australian men will develop prostate cancer before the age of 70 years. Prostate cancer is the most common cancer for men over 55 years of age, but rarely occurs before the age of 50.

WHAT CAUSES PROSTATE CANCER?

There is no single cause for prostate cancer. There are however, several risk factors which can influence someone's chance of developing prostate cancer. The most important are:

- Being a man
- Getting older. More than two-thirds (70%) of men newly diagnosed with prostate cancer are over the age of 65
- Having a strong/significant family history of prostate cancer and/or breast cancer and/or ovarian cancer.

WHAT IS MEANT BY A FAMILY HISTORY OF PROSTATE CANCER?

A family history of prostate cancer means having one or more close blood relatives who have, or have had, prostate cancer.

Relatives could be on **either the father's or the mother's side** of the family, but not usually added together.

The closest male blood relatives (not relatives by marriage) are fathers, brothers and sons and are called first-degree relatives. Uncles, nephews and grandfathers 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 shared genetic factors such as a non-working 'cancer protection' gene in the family.

Many men have a few relatives who have or had prostate cancer just because prostate cancer is common. Such men may be only slightly above the average risk. Some men have a '*stronger*' family history where a number of their close male blood relatives have or had prostate cancer. Depending on the strength of the family history, the man may be at moderate or potentially high risk of developing prostate cancer.

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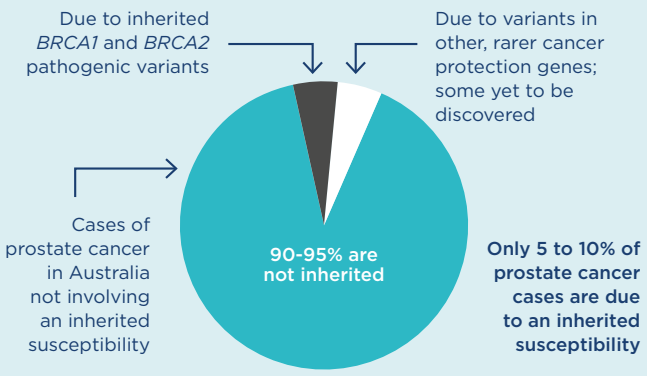
Figure 35.1:
Proportion of cases of prostate cancer that involve an inherited predisposition (susceptibility).



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.

INHERITED SUSCEPTIBILITY TO PROSTATE CANCER

Most prostate cancer is not inherited, however, a small number of cases in Australia (around 5-10%) involve an inherited susceptibility to develop the cancer (*Figure 35.2*). In these cases, a person has inherited a non-working copy of a gene which usually protects against cancer (called a '**cancer protection**' gene). A spelling mistake in the gene that stops it working properly is called a **pathogenic variant** or **mutation**.

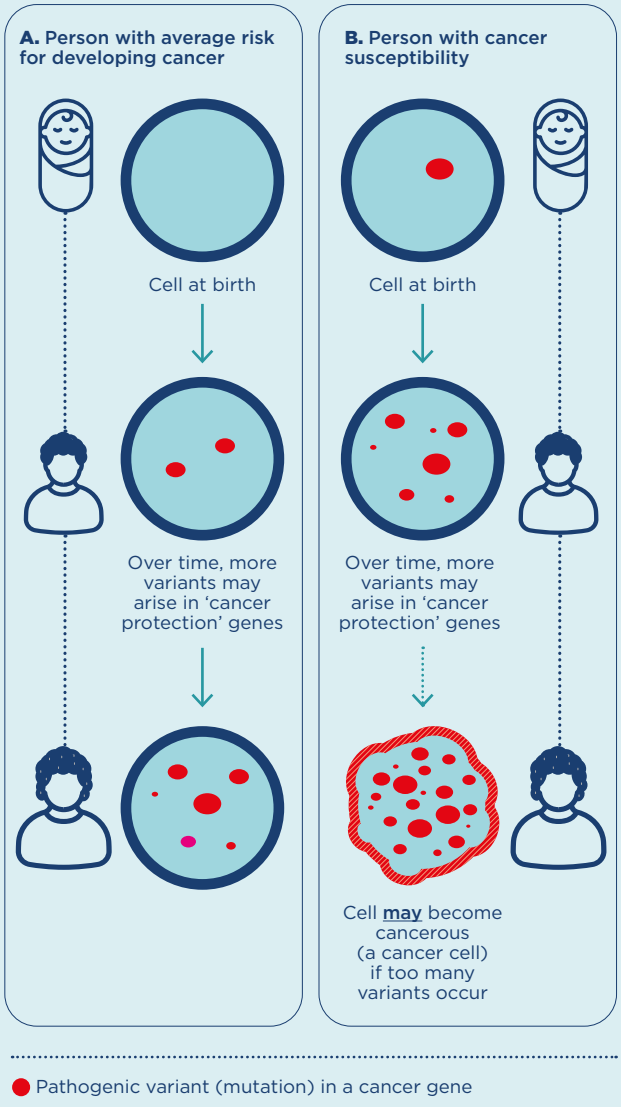
We all have many different '**cancer protection**' **genes** which control the growth and division of our cells throughout life.

Pathogenic variants in these cancer protection genes may cause cells to grow and divide in an uncontrolled way. For a cell to become cancerous, multiple variants have to build up in a number of different 'cancer protection' genes within a 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 reason why these variants occur is thought to be a combination of genetic factors, environmental factors and the process of ageing.

Figure 35.2 shows a stylised image of a cell from a person with average risk of developing cancer (left hand side) and the cell of someone with an inherited *BRCA1* or *BRCA2* pathogenic variant at birth (right hand side). 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.

Figure 35.2:
Increased chance of cancer cell development in those born with a cancer susceptibility compared with the average person



WHAT IS A 'STRONGER' FAMILY HISTORY THAT SUGGESTS AN INHERITED SUSCEPTIBILITY?

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

Characteristics of a family that may suggest an inherited pathogenic variant include:

- A family member diagnosed with prostate cancer at a younger age, usually before the age of 60
- Two or more male relatives on the same side of the family with prostate cancer, particularly a father and brother
- Having one or more relatives with ovarian cancer or multiple relatives with breast cancer and/or young ages of diagnosis may indicate a *BRCA1* or *BRCA2* variant.

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

WHAT ARE THE 'CANCER PROTECTION' GENES THAT CAUSE AN INCREASED RISK OF PROSTATE CANCER WHEN NOT WORKING?

There has been no single gene found that is associated with most prostate cancers. Research is continuing to understand why prostate cancer is so common.

However, there are a number of 'cancer protection' genes in which inherited pathogenic variants can increase the risk of prostate cancer developing in men.

Two genes that have been identified are:

- **B**reast **Ca**ncer **1** gene (*BRCA1*)
- **B**reast **Ca**ncer **2** gene (*BRCA2*)The *BRCA1* and *BRCA2* 'cancer protection' genes are known more specifically as **tumour suppressor genes** because their role is to act as the 'brakes' on uncontrolled cell growth.

Pathogenic variants in the *BRCA1* and *BRCA2* genes are also well known to be involved in increasing the risk of breast and ovarian cancer.

Other genes linked with prostate and other types of cancer are described further at the Cancer Institute NSW eviQ website.

Both men and women, have *BRCA1* and *BRCA2* genes in their cells.

HOW IS A *BRCA1* OR *BRCA2* GENE VARIANT INHERITED?

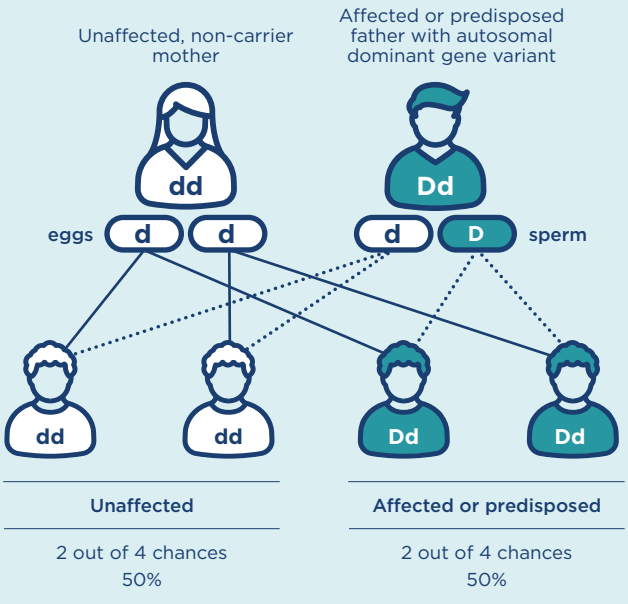
BRCA1 and *BRCA2* gene variants are inherited in an autosomal dominant pattern (*Figure 35.3*).

1. Every person carries two copies each of the *BRCA1* and the *BRCA2* genes, one inherited from their mother, one inherited from their father.
2. The effects of the pathogenic variants in the *BRCA1* and *BRCA2* genes are **dominant** over the information in the working copy of the genes.

Where one parent has a *BRCA1* or *BRCA2* gene variant, in every pregnancy each of their children has a:

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

Figure 35.3:
Autosomal dominant inheritance when one parent has a non-working gene copy. The non-working gene copy is represented by 'D'; the working copy by 'd'.



A *BRCA1* or *BRCA2* gene variant 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 the pathogenic variant are *not* at increased risk of cancer and cannot pass it on to their children. However, they still have the same risk for developing cancer as the average person in the Australian population.

GENETIC COUNSELLING AND TESTING

People with a strong family history can be referred by their doctor to a specialist or to a family cancer clinic. When meeting certain criteria for testing, genetic testing may be covered by Medicare or by the hospital.

The genetic counselling team may be able to:

- Work out the chance of developing prostate cancer based on a person's family history
- Work out whether genetic testing is likely to be helpful
- Talk about the limitations, potential benefits and disadvantages of genetic testing
- Talk about cancer screening and ways of reducing the chance of developing cancer.

Genetic testing for pathogenic variants in the *BRCA1* and *BRCA2* genes is complex and involves:

- First identifying the gene variant via a blood sample in a family member who has or had prostate cancer (a **variant search**). A **variant search** is often performed on a group of selected genes (known as a panel). This group may include several different genes depending on the cancer types present in the family.

  Results can show:

  1. The pathogenic variant was found
  2. No pathogenic variant was found
  3. A variant of uncertain significance (VUS) was found. This is an unclear result. Further information to understand different types of results is available at www.genetics.edu.au.

Table 35.1:
Chance of developing prostate cancer or other cancers for people with a *BRCA1* or *BRCA2* pathogenic variant. Information extracted from eviQ Risk Management Guidelines.

Gene variant	Chance (risk) for men developing prostate cancer up until age 75 years or breast cancer up until age 70 years	Chance (risk) for women developing breast or ovarian cancer up until age 80 years	Chance (risks) over a lifetime of developing pancreatic cancer in men and women
BRCA1	About 21% for prostate cancer About 1% risk for breast cancer	About 72% for breast cancer About 44% for ovarian or fallopian tube cancer	unknown but likely increased (strongly associated with smoking)
BRCA2	About 27% for prostate cancer About 7% for breast cancer	About 69% for breast cancer About 17% for ovarian or fallopian tube cancer	Unknown but increased
Risk for the general population	About 5% for prostate cancer Much less than 1% for breast cancer	About 12% for breast cancer About 1% for ovarian or fallopian tube cancer	About 1% risk for pancreatic cancer

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

WHAT ARE THE CHANCES OF DEVELOPING CANCER FOR SOMEONE WHO CARRIES A PATHOGENIC VARIANT IN *BRCA1* OR *BRCA2*?

People with a pathogenic variant in *BRCA1* or *BRCA2* have an increased chance of developing prostate cancer and some other cancers including breast and ovarian cancer (*Table 35.1*).

WHAT CAN BE DONE TO MANAGE AN INCREASED RISK OF PROSTATE CANCER DUE TO A *BRCA1* OR *BRCA2* PATHOGENIC VARIANT?

Genetic counselling and risk management

It is recommended that people with a *BRCA1* or *BRCA2* gene variant and their relatives, seek management advice from a family cancer clinic or medical specialist. National guidelines for practitioners exist at the Cancer Institute NSW eviQ website.

Screening

Men with a *BRCA1* or *BRCA2* pathogenic variant are encouraged to increase awareness of their chest area and discuss regular chest palpation with their doctor. This is to check for the increased chance of breast cancer happening. They should also consider with their doctor an annual PSA test with or without digital rectal exam starting from their early 40s.

Lifestyle may help

Most cancers occur due to a combination of genetic factors, environmental factors and the process of ageing.

Maintaining a balanced diet high in fibre and low in fat, not smoking and living a healthy lifestyle can reduce the risk of many cancers.

Planning a pregnancy

Testing may be available for inherited cancer during a pregnancy. Genetic testing in a pregnancy for genetic causes of cancer is optional and should be talked about in full with your doctor, midwife or genetic counsellor. It may also be possible to have pre-implantation genetic diagnosis (PGD) to look for inherited causes in an embryo made using in vitro fertilisation (IVF). Some people also investigate egg, sperm or embryo donation. Others choose to have a natural pregnancy with no testing.

Reproductive genetic carrier screening for a range of genetic conditions that follow a recessive pattern of inheritance is also available for couples who are planning pregnancy, or are in early pregnancy.

When planning a family, options for testing are best talked about and considered before pregnancy.

More support and information is available for individuals and families through support organisations including the Cancer Council, Prostate Cancer Foundation of Australia & Genetic Alliance Australia.