

Important points

- The most important factors that can influence a chance of developing breast and/or ovarian cancer are
 - Being female
 - Getting older
 - Having a family history of breast and/or ovarian cancer
 - Having Ashkenazi Jewish ancestry
- A family history of these cancers 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 breast and ovarian cancer is running in the family
- Inherited predisposition is due to inheriting from **either parent** a faulty copy of just one of the genes that usually prevents breast and ovarian cancer from developing (a faulty 'cancer protection' gene)
- Inherited variations (mutations) which make two genes called *BRCA1* and *BRCA2* faulty are known to cause a predisposition to breast and ovarian cancer. Mutations in other genes may also be involved.
- We all usually have two working copies of each of the *BRCA1* and *BRCA2* genes in our cells
- An individual (man or woman) who has a faulty *BRCA1* or *BRCA2* gene copy and a working copy of these genes is a carrier of a faulty *BRCA1* or *BRCA2* gene(s) and is predisposed to breast and other cancers
- A woman's chance of developing breast and/or ovarian cancer is higher than average if she inherits a faulty *BRCA1* or *BRCA2* gene copy but unless further changes occur over time in both copies of a number of additional other 'cancer protection' genes in breast and/or ovarian cells, those cells will never become cancerous. The woman will not develop breast and/or ovarian cancer.
- A woman who has not inherited a faulty *BRCA1* or *BRCA2* gene copy will still have the same risk for developing breast and/or ovarian cancer as the average woman in the Australian population
- A man's chance of developing breast cancer or prostate cancer is slightly higher than average if he inherits a faulty *BRCA1* or *BRCA2* gene copy but unless further changes occur over time in both copies of a number of additional other 'cancer protection' genes in prostate cells, those cells will never become cancerous
- There is 1 chance in 2 (or 50%) in every pregnancy that a parent who is a carrier of a faulty *BRCA1* or *BRCA2* 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 breast and ovarian cancer and some other cancers due to inherited predisposition
 - For these families, genetic counselling is available to clarify an individual's risk and discuss options for genetic testing, its limitations, advantages and disadvantages and available prevention and early detection strategies
- Genetic testing for mutations in the *BRCA1* and *BRCA2* genes is complex and involves
 - **First**, identifying the gene mutation in a family member who has or had breast and/or ovarian 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 faulty gene (**predictive genetic testing**)

Breast cancer and ovarian cancer in Australia

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

- Bowel cancer (see Genetics Fact Sheet 49)
- Melanoma (see Genetics Fact Sheet 50)
- Prostate cancer (see Genetics Fact Sheet 51)

This Fact Sheet discusses inherited predisposition (susceptibility) to breast and ovarian cancer.

Breast cancer

- Affects about 1 in 11 women before the age of 75
- Is the most common cause of cancer deaths in women
- Also occurs in men, but it is rare

Ovarian cancer

- Affects about 1 in 100 women before the age of 75
- Is the leading cause of death from gynaecological cancers

What causes breast and ovarian cancer?

There is no single cause. There are a number of factors (*risk factors*) which can influence an individual's chance of developing breast and/or ovarian cancer. The most important are:

- Being a woman
- Getting older. Most women who develop breast and/or ovarian cancer are over the age of 50
- Having a family history of breast and/or ovarian cancer
- The presence of Ashkenazi Jewish ancestry. Women with this background are more likely to carry specific types of faulty genes causing breast and/or ovarian cancer

What is meant by a family history of breast and/or ovarian cancer?

A family history of cancer can occur:

- Just by chance, because cancer is common
- Because family members are exposed to the same environmental factors
- Because a predisposition to cancer is running in the family, though this is rare

A family history of breast and/or ovarian cancer means having one or more close blood relatives who have, or have had, breast and/or ovarian 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)

Many women have a few relatives who have or had breast cancer and/or ovarian cancer just because breast cancer is common in women, though ovarian cancer less so. Such women may be only slightly above the average risk.

Some women have a 'stronger' family history where a number of their close blood relatives have or had breast and/or ovarian cancer. Most of these women may have a moderately increased chance of developing breast cancer. A few will have a potentially high chance of developing breast and/or ovarian cancer because a predisposition to breast and/or ovarian cancer is running in their family.

Inherited predisposition to the development of breast and/ or ovarian cancer

The majority of breast and/or ovarian cancer cases are not due to an inherited predisposition to develop the condition.

A small number of the cases of breast and/or ovarian cancer (about 5%-10%) in Australia involve an inherited predisposition to develop the cancer. In these cases, the women have inherited a faulty copy of a breast and/or ovarian '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 colon: if the cells divide and grow out of control, they accumulate into a tumour.

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. Although not all cancers are caused by an inherited change all cancers can be considered genetic in origin because they arise from changes in the normal 'cancer protection' genes that we all have.

A variation in the information in a 'cancer protection' gene that makes the gene faulty (a mutation) stops it doing its usual job in the cell. The reason why these variations occur 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 breast and/or ovarian cells.

The development of breast and/or ovarian cancer is not a quick or simple process. It is a progression involving a build-up of variations in a number of different 'cancer protection' genes in the cells of the breast and/or ovaries **over a woman's lifetime** (see Genetics Fact Sheet 47). This is why the development of breast and/or ovarian cancer can take many, many years and is often seen in older women. Men who carry such changes may have a small increase in risk for developing cancer during their lifetime and these are discussed later in more detail.

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

Between 5% and 10% of all breast and ovarian 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 cells in the breast and ovarian tissue (see *Figure 48.1*).

- From birth, the division and growth of cells in these women's breast and ovarian cells is not as very tightly controlled as in other women in the population
- Although these cells may 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 cells in the breast and ovarian tissue is still largely normal. See *Figures 47.2 and 47.3* in Genetics Fact Sheet 47 for more information about the progression to cancer
- Their chance of developing breast and/or ovarian cancer is higher than average but unless further mutations occur over time in a number of other 'cancer protection' genes in breast or ovarian cells, those cells will never become cancerous
- It is thought that not just one but many gene changes are associated with the development of breast and ovarian cancer

What are the inherited faulty 'cancer protection' genes involved in predisposition to breast and/or ovarian cancer?

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

Around 5% of cases of breast and 10% of cases of ovarian cancers can be explained by the woman having inherited a faulty copy of just one of the 'cancer protection' genes that usually control cell division and growth in breast and ovarian tissue (see *Figures 48.2 and 48.3*).

- Their chance of developing these cancers is higher than average but unless further mutations occur over time in a number of other 'cancer protection' genes in breast and/or ovarian cells, those cells will never become cancerous.

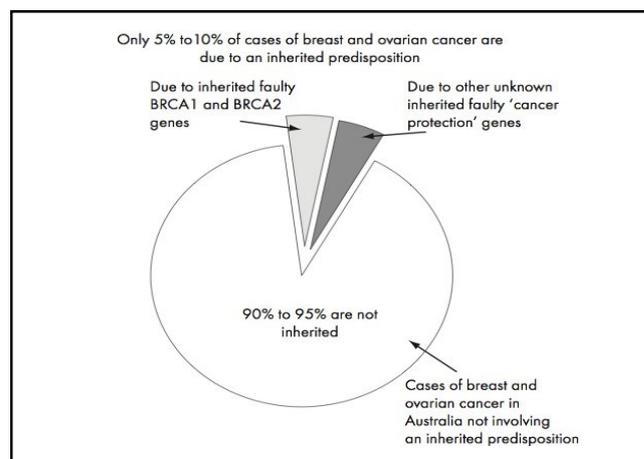


Figure 48.1: Proportion of cases of breast and ovarian cancers that do and do not involve an inherited predisposition (susceptibility).

There are a number of 'cancer protection' genes in which inherited changes that make the genes faulty (mutations) can contribute to the development of breast and/or ovarian cancer.

Two of these genes that have been identified are called:

- the **Breast Cancer 1 gene** (*BRCA1*)
- the **Breast Cancer 2 gene** (*BRCA2*)

The *BRCA1* and *BRCA2* 'cancer protection' genes are known as **tumour suppressor genes** and their role is to act as the 'brakes' on uncontrolled cell growth (see Genetics Fact Sheet 47).

Men and women, have the *BRCA1* and *BRCA2* genes in their cells and their role in the cell is to protect against cancer.

There are also a number of families where it is clear from the family history that members are at potentially high risk for having an inherited predisposition to breast and ovarian cancer, but where mutations in these two genes are not identified. It is likely that there are a number of as yet unidentified genes in which mutations predispose to breast and ovarian cancer. Research is continuing to try to identify these genes and their function.

What is the pattern of inheritance in families with a faulty *BRCA1* or *BRCA2* gene?

Two factors influence the pattern of inheritance of the faulty *BRCA1* or *BRCA2* gene(s) in families.

1. The *BRCA1* and *BRCA2* genes are located on chromosomes 17 and 13 respectively. Both of these chromosomes are autosomes (one of the numbered chromosomes)
2. The effects of changes in the *BRCA1* and *BRCA2* genes are 'dominant' over the information in the working copy of the genes on the partner chromosomes 17 and 13 (see Genetics Fact Sheets 1, 4 & 5)

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

In *Figure 48.4* the autosomal dominant faulty gene causing predisposition to breast and/or ovarian cancer is represented by 'D'; the working copy by 'd'.

Where one of the parents has or had breast and/or ovarian cancer involving a faulty *BRCA1* or *BRCA2* gene, or is a carrier of a faulty *BRCA1* or *BRCA2* 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:

- Cancer will not develop in a woman who is a carrier of a faulty *BRCA1* or *BRCA2* gene unless further mutations occur in additional other 'cancer protection' genes in the cells during her life
- Women who have not inherited a faulty gene are not at increased risk of developing breast and/or ovarian cancer over their lifetime and cannot pass the faulty gene on to their own children. However, they still have the same risk for developing breast and/or ovarian cancer as the average woman in the Australian population
- While *Figure 48.4* shows the father as the parent carrying the faulty *BRCA1* or *BRCA2* gene, the same situation would arise if it was the mother.



Figure 48.2: Chance of having breast cancer due to an inherited predisposition. Adopted from *Genetic Testing for breast and ovarian cancer risk: Hereditary Cancer Clinic, Prince of Wales Hospital Sydney, Australia, 2004.*

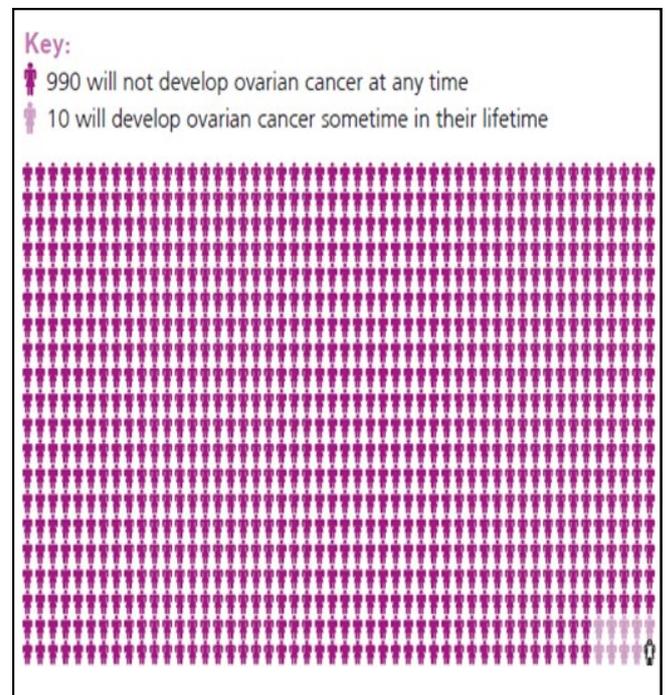


Figure 48.3: Chance of having ovarian cancer due to an inherited predisposition. Adopted from *Genetic Testing for breast and ovarian cancer risk: Hereditary Cancer Clinic, Prince of Wales Hospital 2004.*

A faulty *BRCA1* or *BRCA2* gene can be inherited from either the mother or the father

- Environmental factors causing mutations in the *BRCA1* or *BRCA2* 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 causing mutations in other 'cancer protection' genes over the woman's lifetime that eventually lead to breast and ovarian cancer are also unknown
- Women of Ashkenazi Jewish ancestry have a higher chance of being a carrier of a faulty *BRCA1* or *BRCA2* gene copy

What are the clues in a family history of breast and/or ovarian cancer that suggest that family members are at potentially high risk due to an inherited predisposition?

The National Breast Cancer Centre (2006) has produced a guide for professionals on assessing family health history to identify if the breast and/or ovarian cancer in the family could potentially be due to an inherited faulty gene.

Based on the number of relatives with breast and/or ovarian cancer, the family relationship and the age of diagnosis, women are categorised into separate risk groups for developing breast and/or ovarian cancer. The family relationship is classified as

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

The guidelines for doctors are used to categorise a woman's risks for developing breast cancer based on her family history of cancer into 3 groups (Table 48.1):

- Category 1: At or slightly above average risk
- Category 2: At moderately increased risk
- Category 3: At potentially high risk

The guidelines for doctors also categorise a woman's risks for developing ovarian cancer based on her family history of cancer into 2 groups (Table 48.2):

- Category 1 or Category 2: At average or moderately increased risk
- Category 3: At potentially high risk

Can a woman determine if she has inherited a faulty *BRCA1* or *BRCA2* gene?

Women with a strong family history like that described for Category 3 or where a faulty *BRCA1* or *BRCA2* gene has been identified in their family, can seek advice from a specialist family cancer service (if available) or their local genetic counselling service. Their risk of developing breast and/or ovarian 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 breast and/or ovarian cancer based on their family history
- Answer any questions they have about their family history of cancer
- Discuss what medical check-ups are appropriate

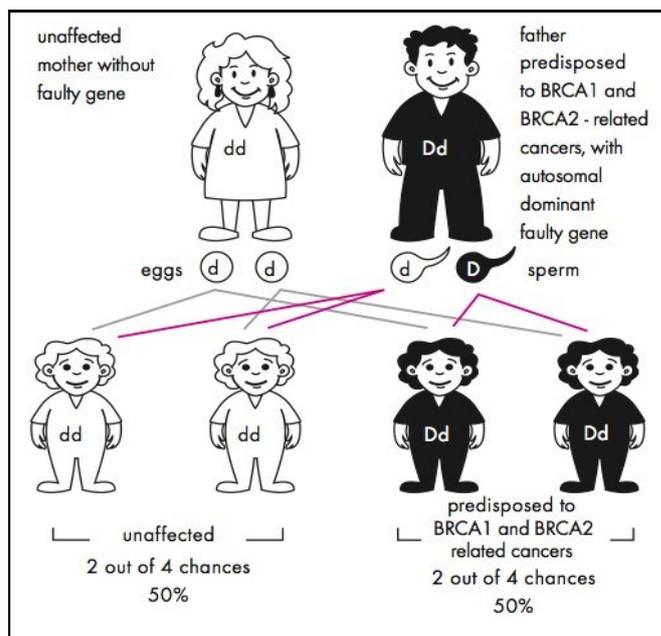


Figure 48.4: Autosomal dominant inheritance when one parent has a faulty *BRCA1* or *BRCA2* gene copy. The faulty gene is represented by 'D'; the working copy by 'd'.

- Discuss the limitations, potential benefits, disadvantages and appropriateness of genetic testing (see Genetics Fact Sheet 21)

Genetic testing for mutations in the *BRCA1* and *BRCA2* genes is complex and involves

- **First**, identifying the gene mutation in a family member who has or had breast and/or ovarian 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 faulty gene (**predictive genetic testing**).

Where appropriate, a mutation search genetic test can also be done to determine whether the breast and/or ovarian cancer that has developed is due to having inherited the faulty *BRCA1* or *BRCA2* gene copy. This is increasingly being used to guide treatment decisions

What does it mean if a man or a woman has inherited a faulty *BRCA1* or *BRCA2* gene?

For a woman the chance (*risk*) that breast and/or ovarian cancer will develop in her lifetime as a result of inheriting a faulty copy of the *BRCA1* or *BRCA2* gene is increased over the general population risk (Table 48.3). The chance (*risk*) is different for breast and ovarian cancer and other cancers depending on whether they have inherited a faulty copy of the *BRCA1* or *BRCA2* gene.

If a man has inherited a faulty copy of the *BRCA1* or *BRCA2* gene (Table 48.3), his risk for developing prostate cancer is increased.

If a man has inherited a faulty copy of the *BRCA2* gene (but not the *BRCA1* gene) he has a slightly increased risk of developing breast cancer.

Category 1: At or slightly above average risk for developing breast cancer	Category 2: Moderately increased risk	Category 3: Potentially high risk
More than 95% of women in the population are in this 'risk group'. Women in this group have a risk of breast cancer up to age 75 between 1 in 11 and 1 in 8. This risk is no more than 1.5 times the population average.	Less than 4% of women in the population are in this 'risk group'. Women in this group have a risk of breast cancer up to age 75 between 1 in 8 and 1 in 4. This risk is 1.5 to 3 times the population average.	Women in this group have a risk of breast cancer up to age 75 between 1 in 4 and 1 in 2. Risk may be more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known.
<p>No confirmed family history of breast cancer</p> <p>One 1^o relative diagnosed with breast cancer at age 50 or older</p> <p>One 2^o relative diagnosed with breast cancer at any age</p> <p>Two 2^o relatives on the same side of the family diagnosed with breast cancer at age 50 or older</p> <p>Two 1^o or 2^o relatives diagnosed with breast cancer, at age 50 or older, but on different sides of the family (i.e. one on each side of the family)</p>	<p>One 1^o relative diagnosed with breast cancer before the age of 50 (without the additional features of the potentially high-risk group (see Category 3)</p> <p>Two 1^o relatives, on the same side of the family, diagnosed with breast cancer (without the additional features of the potentially high-risk group - see Category 3)</p> <p>Two 2^o relatives, on the same side of the family, diagnosed with breast cancer, at least one before the age of 50, (without the additional features of the potentially high-risk group – see Category 3)</p>	<p>Includes women who are at potentially high risk of ovarian cancer (see 'Category 2' for familial ovarian cancer below)</p> <p>Breast cancer that is "basal like" or oestrogen, progesterone and HER2 receptor negative diagnosed < or at 40 years</p> <p>Bilateral breast cancer with first diagnosis under age 50 years</p> <p>Male breast cancer</p> <p>Breast or ovarian cancer diagnosis and Ashkenazi Jewish ethnicity</p> <p>Breast cancer diagnosed < 30 years</p> <p>Two 1^o or 2^o relatives diagnosed with breast cancer if one woman was diagnosed under age 40 years OR both women were diagnosed under age 50 years</p> <p>Two 1^o or 2^o relatives on one side of the family diagnosed with either breast and/or ovarian cancer plus one or more of the following features on the same side of the family:</p> <ul style="list-style-type: none"> • Additional relative(s) with breast or ovarian cancer • Breast and ovarian cancer in the same woman • Breast cancer diagnosed before the age of 40 years • Ashkenazi Jewish ancestry (Jews from Central and Eastern Europe) • Bilateral breast cancer • Breast cancer in a male relative • One 1^o or 2^o relative diagnosed with breast cancer at age 45 years or younger plus another 1^o or 2^o relative on the same side of the family with sarcoma (bone/soft tissue) at age 45 years or younger • Member of a family in which the presence of a high risk breast cancer gene mutation has been established.

Table 48.1: Risks for developing breast cancer based on a family history of cancer (1^o = first degree relatives ie parents, siblings, 2^o = second degree relatives ie uncles, aunts)

Category 1: At average risk or Category 2: At moderately increased risk	Category 3: Potentially high risk
More than 99% of women in the population are in this 'risk group'. Women in this group have a risk of ovarian cancer up to age 75 is between 1 in 100 and 1 in 30. This risk is no more than 3 times than the population average.	Less than 1% of women in the population are in this 'risk group'. Women in this group have a risk of ovarian cancer up to age 75 is between 1 in 30 and 1 in 2. This risk is more than 3 times the population average. Individual risk may be higher or lower if genetic test results are known
<p>No confirmed family history of epithelial ovarian cancer.</p> <p>One 1^o or 2^o relative diagnosed with ovarian cancer at any age (provided the family is not of Ashkenazi Jewish ancestry and does not have any additional cases of breast cancer).</p> <p>Two 1^o or 2^o relatives diagnosed with ovarian cancer, but on different sides of the family (ie one on each side of the family).</p>	<p>Includes women who are at potentially high risk of breast cancer (see 'Category 3' for familial breast cancer above).</p> <p>One 1^o or 2^o relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry.</p> <p>One 1^o or 2^o relative with ovarian cancer at any age, and another with breast cancer diagnosed before the age of 50 years, where the women are 1^o or 2^o relatives of each other.</p> <p>Two 1^o or 2^o relatives on the same side of the family diagnosed with epithelial ovarian cancer especially if one or more of the following features occurs on the same side of the family:</p> <ul style="list-style-type: none"> • additional relative(s) with breast or ovarian cancer • breast cancer diagnosed before the age of 40 • bilateral breast cancer • breast and ovarian cancer in the same woman • breast cancer in a male relative. <p>Three or more 1^o or 2^o degree relatives on the same side of the family diagnosed with a family history suggestive of Lynch Syndrome e.g. colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract (see 'Genetics Fact Sheet 49).</p>

Table 48.2: Risks for developing ovarian cancer based on a family history of cancer (1^o = first degree relative ie parents, siblings, 2^o = second degree relative ie uncles, aunts)

Gene	Risk for a woman developing breast and/or ovarian cancer up to age 75 yrs	Risk over a lifetime for developing other cancers in men and women
<i>BRCA1</i>	About 60% for breast cancer (between 40% and 70%) About 40% for ovarian cancer (between 30% and 50%)	Very slight increased risk for male breast cancer and prostate cancer.
<i>BRCA2</i>	About 50% for breast cancer (between 40% and 60%) About 20% for ovarian cancer (between 10% and 30%)	Slight increased risk for male breast cancer and prostate cancer. Risk may be slightly increased for pancreatic cancer and melanoma

Table 48.3: Lifetime risks for breast, ovarian, prostate and pancreatic cancers as a result of inheriting a faulty copy of the *BRCA1* or *BRCA2* genes.

What can be done if a woman has an inherited predisposition to breast and ovarian cancer?

Regular breast screening is important for women with an inherited predisposition to breast and ovarian cancer.

Risk reducing surgery should be discussed to reduce the risk of ovarian cancer (see Genetics Fact Sheet 49) for which there is no screening test available.

Risk reducing breast surgery may also be considered for some women.

Research is continuing to investigate cancer prevention with drug therapy.

The progression to breast and/or ovarian cancer requires mutations to build up in a number of the 'cancer protection' genes

in the breast and/or ovarian 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 and a healthy lifestyle.

The earlier a cancer is found, the more successful the outcome of treatment is likely to be. Therefore, all women should

- Be aware of changes in their breasts and visit their doctor promptly with any unusual changes
- Have a mammogram every two years from the age of 50. These are conducted free at BreastScreen. For an appointment ring 13 20 50 from anywhere in Australia.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 21, 47, 49, 50, 51