S Afr Gen Pract. 2024;5(1):33-35
https://doi.org/10.36303/SAGP.0396

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621

VANTAGE POINT

Hereditary breast ovarian cancer syndrome

J Malan

MSc Genetic Counselling
Genetic Counsellor Ampath Laboratory
Corresponding author, email: *geneticsclinic@ampath.co.za*

Introduction

In South Africa, breast cancer is the most frequently diagnosed cancer among women, with a lifetime risk of 1 in 27.[1] There are many known causes of breast cancer, such as lifestyle choices, genetic predisposition and environmental factors. The majority of breast cancers are sporadic and not caused by inherited mutations (as shown in Figure 1), and only 5% -10% of breast and 10%-15% of ovarian cancers are hereditary.[2] Hereditary cancer indicates that cancer may result from germline pathogenic variants (mutations) in specific genes, inherited from either parent. Familial cancers (15–20%) are those that appear to have a genetic component, affecting more family members than would be expected by chance alone; however, a single genetic cause or explanation is not known. Familial cancers may not be linked to a known gene mutation but may be due to a combination of factors shared by a family, including genetic and environmental factors.

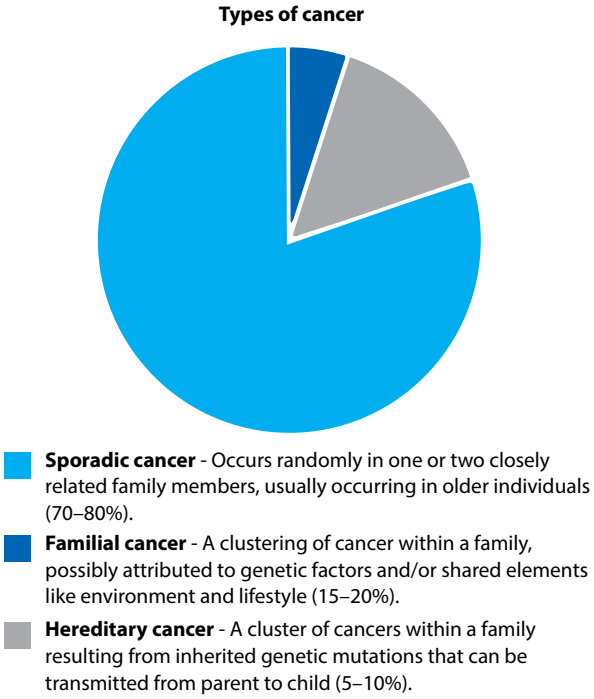

Figure 1: Causes of cancer

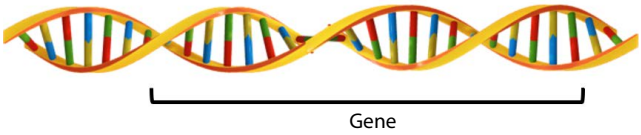

Figure 2: Gene

The genetics of cancer

Cancer arises from alterations in genes that regulate cell growth and division. Cells are the body's basic units and contain our entire genetic blueprint encoded in DNA. Genes are segments of DNA that provide instructions for protein production (Figure 2).

Numerous DNA changes and genetic variations (pathogenic variants) may lead to the development, proliferation, and metastasis of cancer. Pathogenic variants include sequence variants and structural variants.

Sequence variants involve minor alterations that influence a small number of nucleotides, including single nucleotide variants (SNV) and small insertions/deletions (INDELs). These alterations are particularly important when they interfere with

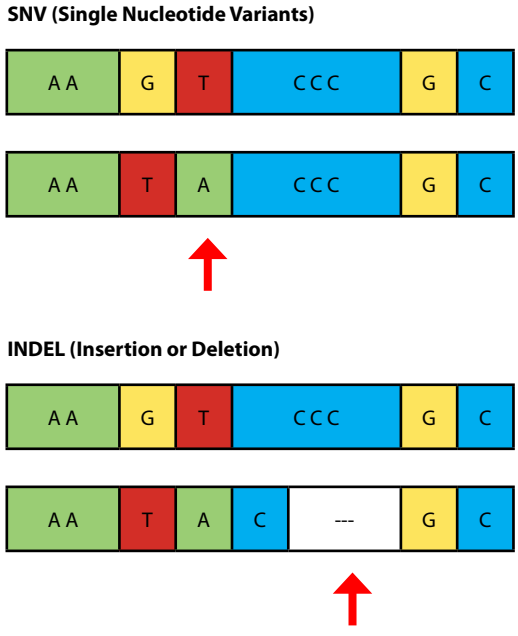

Figure 3: Sequence variants

gene coding sequences, potentially causing modifications in the amino acid sequence of proteins (Figure 3).

Structural variants (SVs) are significant genetic events (> 50 bp) involving the alteration of entire segments of genetic material. For instance, a deletion results in the removal of a complete DNA segment. These SVs can profoundly impact gene dosage within a cell by duplicating or deleting entire exons or genes simultaneously.

Hereditary cancer

With hereditary cancers in general, we may see an early age of cancer diagnosis (< 50 years of age), several generations of a family affected, individuals with more than one primary cancer, the occurrence in one family of cancers, which are known to be genetically related (such as breast and ovarian cancer, or colon and uterine cancer), the presence of physical signs which are known to be associated with hereditary cancer (such as moles and melanoma, or polyps and colon cancer), and certain rare types of cancer (such as breast cancer in males).

BRCA1 and *BRCA2* genes

The *BRCA1* and *BRCA2* genes are crucial in the battle against cancer, functioning as tumour suppressors. In their normal state, these genes play a vital role in regulating the growth and division of cells in the breasts, ovaries, and various other tissues. They produce proteins that help repair damaged DNA, thus preventing excessive and uncontrolled cell growth.

Individuals inheriting pathogenic variants in the *BRCA1* and *BRCA2* genes have an elevated risk of developing breast, ovarian, and other cancers at younger ages compared to the general population. The risk for developing breast cancer by the age of 70 years is as in Table I.[3]

Table I: Cancer risk implications for carriers of a *BRCA1* or *BRCA2* pathogenic variant

Type of cancer	Risk for developing cancer	
	BRCA1	***BRCA2***
Breast	55–72%	45–69%
Contralateral breast cancer	20–30% within 10 years	40–50% within 20 years
Ovarian	39–44%	11–17%
Male breast	1–2%	6–8%
Prostate	21–29%	27–60%
Pancreatic	1–3%	3–5%
Melanoma		Elevated risk

When should BRCA gene testing be considered?

- Women diagnosed with breast cancer at 45 years or younger.
- Women diagnosed at age 46–50 years with:
  - Unknown or limited family history.
  - A second primary breast cancer.
  - At least one close relative with breast cancer at any age.
  - One or more close relative with breast, ovarian, pancreatic, or prostate cancer at any age.
- Women diagnosed at age 60 years or younger with triple negative breast cancer.
- Women diagnosed at any age with:
  - At least one close relative with breast cancer diagnosed younger than 50 years.
  - At least two close relatives on the same side of the family with breast cancer at any age.
  - At least one close relative with ovarian cancer at any age.
  - At least two close relatives on the same side of the family with pancreatic and/or prostate cancer at any age.
  - At least one close male blood relative with breast cancer.
  - Ashkenazi Jewish or Afrikaner or other ethnic groups associated with founder mutations.
- Women with a personal history of ovarian cancer (including cancer of the fallopian tube or peritoneal cancer).
- A mutation identified in testing of tumour tissue that has clinical implications if it is also identified in the germline.[4]

How are the BRCA1 and BRCA2 genes inherited?

If an individual has a parent with a *BRCA* mutation, or a mutation in one of the other cancer susceptibility genes, he or she has a 50% chance of inheriting the same mutation. Both males and females have an equal chance of inheriting a *BRCA* mutation. This is called autosomal dominant inheritance (Figure 4).

Why refer a patient to a genetic counsellor for BRCA gene testing

- The genetic counsellor will review the medical and family history and determine whether the patient meets the criteria for a specific hereditary cancer syndrome. To prepare for the meeting, the patient needs to find out as much as possible about their family's cancer history – age of diagnosis and type of cancer.
- The genetic counsellor will explain the risks and benefits of genetic testing, the importance of these results for the patient and other family members, and answer all their questions.

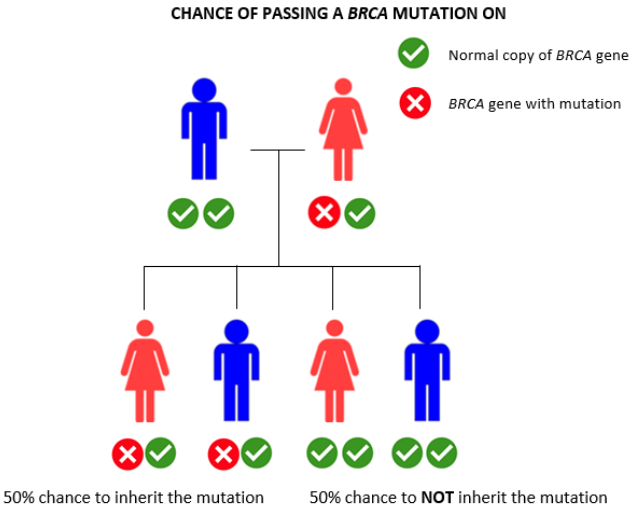

Figure 4: Autosomal dominant inheritance

- Taking the history into account, the counsellor will discuss possible cancer risks, genetic testing in general, and medical management that may be available if a specific mutation is identified in a cancer susceptibility gene.
- The most appropriate genetic test option, taking the family history into account, will be discussed.
- The genetic counsellor will coordinate the collection of a blood sample and will plan to discuss the results and the implications thereof with the patient.

BRCA testing available in South Africa

Testing in South Africa can be requested through Ampath Laboratory and the following options are available:

- Testing for a known pathogenic variant previously identified in a family member.
- Testing for the eight common pathogenic variants found in the Afrikaner and Ashkenazi Jewish population groups (Founder mutations).
- Full sequencing of the *BRCA1* and *BRCA2* genes.
- Full sequencing of a panel of nine cancer susceptibility genes, including the *BRCA1* and *BRCA2* genes, that increases the risk for breast and ovarian cancer.

Benefits of doing genetic testing

- A positive test result can help a patient to understand and make informed decisions about their current and/or future health. Screening as well as risk-reducing options are available to reduce certain cancer risks.
- For someone who has already been diagnosed with a cancer, the results of genetic testing may enable the oncologist to make decisions about treatment. Results will also enable further discussions around understanding risks for the development of other cancers.
- Genetic testing provides an opportunity for family members to learn more about their own cancer risks.
- A true negative result gives a person a sense of relief not only regarding their own cancer risk, but also knowing that their children are not at risk of inheriting the family's cancer susceptibility gene.

Conclusion

Genetic testing for families with inherited breast cancer is available in South Africa. Although most breast and ovarian cancers are not caused by inherited pathogenic variants in cancer susceptibility genes, offering testing to those families where there is a strong history of cancers, can offer life saving information to patients. If a pathogenic variant is identified in a patient, testing can be offered to family members to either relieve anxiety or help them make informed decisions with regards to improved screening or risk reduction options.

ORCID

J Malan https://orcid.org/0009-0002-4001-1612

References

1. National Cancer Registry. (2021). National Health Laboratory Services. Cancer in South Africa, 2019 full report. Republic of South Africa. Available from: https://www.nicd.ac.za/wp-content/uploads/2021/12/NCR_Path_2019_Full_Report_8dec2021.pdf.
2. Centers for Disease Control and Prevention. Hereditary breast cancer and BRCA genes. Available from: https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/index.htm.
3. Nancie Petrucelli, MS, Mary B Daly and Tuya Pal. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer (Genereviews). NCBI Bookshelf (nih.gov). 2023
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic. Version 2. 2021.