

# Epidemiology, risk factors and genetics of breast cancer

**Breast cancer is the most common cancer in South African women.**

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## Epidemiology and risk factors

Breast cancer is the most commonly diagnosed cancer in South African women. The most recent figures are those from 1999 and they were published in 2005 by the South African National Cancer Registry. To look at trends, these have to be compared with the 1993 and 1995 figures.<sup>1</sup>

In South Africa, breast cancer accounted for 19.4% of all cancers seen in women (this compares with 10% worldwide). The overall incidence of breast cancer was 1:26 for South African women (compared with 1:9 in developed countries). The risk varies with ethnic origin, with white South African women having a lifetime risk of 1:12 while black women in South Africa have a smaller risk of 1:49. The ratio of black:white women has altered over the years. The ratio was 1:6 in 1993 and has risen to 1:4 in 1999, implying that breast cancer is becoming more common in the black population.<sup>2</sup>

There are many factors that may account for the difference in incidence between developed countries and South Africa and in racial differences within South Africa.

By looking at the incidence of breast cancer at different ages (Table I) and taking into account the fact that the average life expectancy of women in South Africa is 45 years, compared with 82 years in the developed world, much of the discrepancy can be accounted for. Other factors to be considered in explaining racial differences include late menarche, early first birth, multiparity, low HRT usage and a diet typically low in fat. The rise in incidence of breast cancer among the black population may mirror the adoption of a Western lifestyle.<sup>3</sup>

**Table I. Risk of breast cancer development by age<sup>3</sup>**

Age (years)	Risk of developing breast cancer
25	1 in 15 000
30	1 in 1 900
40	1 in 200
50	1 in 50
60	1 in 23
70	1 in 15
80	1 in 11
85	1 in 10
Lifetime risk (all ages)	1 in 9

The aetiology of breast cancer is multifactorial and includes age, genetic, environmental, medical and lifestyle factors (Tables I and II). The genetic contribution is confirmed by family history being one of the strongest known predictive risk factors for breast cancer and by the observation of families with multiple affected family members, many of which show an autosomal dominant pattern of inheritance.

Improved understanding of cancer genetics enables health care providers to identify at-risk individuals and families and to advance breast cancer prevention and management.

**Table II. Risk factors shown to affect breast cancer risk in the general population<sup>3</sup>**

Risk factor	Relative risk	High-risk group
Age	See Table I	Elderly
Family history	>2	Breast cancer in first-degree relative
Cancer in the contralateral breast	>4	
Age at menarche	>2	<11
Age at menopause	>2	>54
Age at first full-term pregnancy	3	First child in 40s
Hormone replacement therapy	1.3	Use for >5 years
Radiation exposure	3	Abnormal exposure in young females
Alcohol consumption	1.3	Excessive intake
Body weight	2	Body mass index >35 postmenopausal
Benign breast disease	4	Atypical hyperplasia

**Of the overall group of breast cancers, only 5 - 10% are likely to have a strong inherited genetic contribution.**

The genetic contribution to breast cancer is complex, involving both low-frequency, high-penetrance gene mutations that are associated with a high risk of developing cancer and gene mutations that occur more commonly but have a smaller effect. Of the overall group of breast cancers, only 5 - 10% are likely to have a strong inherited genetic contribution.<sup>4</sup>

Public awareness through the media and access to information on the Internet regarding familial breast cancer susceptibility and genetic testing are increasing. This may raise concern and lead to anxiety in individuals exposed to such information. In many instances, the evaluation of the family history would not show increased risk, and health care providers would be able to reassure patients. In a subset of patients evaluation of the family history may be more complex and suggestive of a significant genetic contribution. In these families, referral to cancer risk genetic counselling services could inform the client and family of risks, set up a management plan for dealing with such risks and possibly reduce distress through informed decision-making.

*Breast cancer genes*

Although the majority of families with clear autosomal dominant predisposition to breast and/or ovarian cancer are found to have germline mutations in the genes BRCA1 and BRCA2, the contribution of BRCA1 or BRCA2 mutations to breast cancer in the general population is small. The BRCA1 and BRCA2 protein products are classified as tumour suppressor genes and are involved in DNA repair, genomic stability, transcriptional regulation and cell cycle control.<sup>4</sup> Disruption of these genes predisposes particularly to breast and ovarian cancer but can be associated with a smaller risk of certain other cancers. The individual risk for developing breast and ovarian cancer depends on the gene implicated, the particular mutation and the family history, but typically ranges between 45% and 86% lifetime risk for breast cancer and 10 - 48% risk for ovarian cancer.<sup>5</sup>

**Penetrance** refers to the probability that a person who inherits a mutation will ever manifest signs of the associated condition.

**Expressivity** refers to the variable effects that can result from a mutation, e.g. the age of onset, breast cancer alone or breast and ovarian cancer.

**Characteristics of autosomal dominant inheritance of breast cancer**

- The cancer-predisposing mutation is transmitted from generation to generation through one side of the family (Fig. 1).
- Each child has a 50% risk of inheriting the predisposing mutation (not everyone with the mutation will develop cancer because of incomplete penetrance and gender-related expression).
- Both males and females can inherit and transmit an autosomal dominant cancer predisposing mutation. A male who inherits a mutation and shows no evidence of it can still pass the mutation on to his sons and daughters.

Other genes that predispose to breast cancer have been identified. These may be genes associated with other familial cancer syndromes or may largely be associated with increased breast cancer risk. For the majority of families who do not harbour BRCA1 or BRCA2 mutations, it is considered likely that a number of genetic factors, each with a small cumulative contribution, are responsible. This is supported by evidence that even in families with a strong family history known to carry BRCA1 or BRCA2 mutations, mutation-negative individuals retain a lifetime breast cancer risk that is higher than that in the general population.<sup>6</sup> There is insufficient evidence to aid accurate risk interpretation to make genetic testing

for these mutations clinically indicated at present.

*Identifying individuals and families at high risk for BRCA1 or BRCA2 mutations*

**Personal characteristics (usually in association with a positive family history)**

- Breast cancer diagnosed at an early age. (NB <30 years)
- Bilateral breast cancer.
- Breast and ovarian cancer.
- Male breast cancer.

**Family history characteristics**

- Four or more cases of breast cancer (or breast and ovarian cancer) diagnosed <60 years of age.
- Three cases of breast cancer diagnosed <50 years of age.
- Two cases of breast cancer and one ovarian cancer.
- Male breast cancer and any further family history.
- Ethnic group associated with high risk, e.g. Ashkenazi Jewish ancestry.

*Genetic counselling for familial breast cancer*

Genetic counselling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

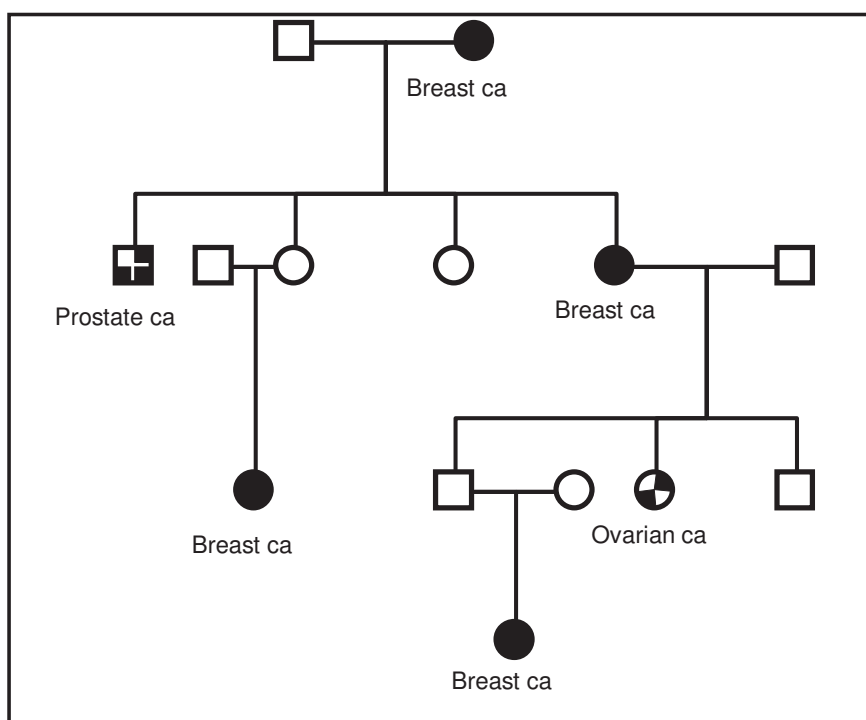


Fig. 1. A pedigree depicting a family with an autosomal dominant inheritance pattern of breast cancer.

## Epidemiology and genetics

This process integrates:

- interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- education about inheritance, testing, management, prevention, resources and research
- counselling to promote informed choices and adaptation to the risk or condition.<sup>7</sup>

Breast cancer genetic counselling services are best provided in a multidisciplinary setting including a variety of health care providers, such as genetic counsellors, medical geneticists, genetic nurses, oncologists, surgeons, gynaecologists and family practitioners.

The process of breast cancer genetic counselling would generally include:

- taking a three-generation family history (and drawing a pedigree)
- obtaining, confirming and assessing personal and family medical histories
- risk calculation using validated models:
  - risk of an individual developing breast cancer
  - likelihood of detecting a BRCA1 or BRCA2 mutation in the family
- communication of genetic information regarding cancer susceptibility
- consideration of appropriateness of genetic testing (including the benefits, risks and limitations of testing)
- testing strategy (including advantages of testing of an affected family member first)
- supportive counselling (to facilitate informed choices and adaptation to risk)
- information regarding management options
- informed consent for genetic testing
- laboratory selection
- test interpretation
- post-test counselling (including the implications of results for the individual and other family members and supportive counselling when needed).

### Ethical considerations in breast cancer genetic counselling

- Confidentiality
- Family dynamics and communication
- Presymptomatic testing of children (not recommended for individuals <18 years)
- Informed consent.

### Genetic testing for BRCA1 and BRCA2 mutations

Both BRCA1 and BRCA2 are large genes with large numbers of deleterious mutations

that have been identified. Comprehensive screening of the genes is limited by both cost and availability. For this reason a stepwise approach to testing is recommended (Fig. 2).

In the South African context it is important to consider whether a family is at an increased risk for breast cancer because of their ethnic population. Founder mutations have been established for the Ashkenazi Jewish and Afrikaner population groups, and this should be taken into consideration when deciding on a genetic testing strategy. Founder mutations refer to specific mutations that are very common in a certain ethnic population.

Genetic testing for the BRCA1 and BRCA2 genes is available in South Africa. However, different laboratories offer different testing options. The testing options include the Ashkenazi Jewish and Afrikaner founder mutations, limited testing of certain regions of genes, comprehensive testing (sequencing of both genes) and looking for large rearrangements (by using Multiplex ligation-dependent probe amplification (MLPA). Some laboratories perform

these different options of genetic testing themselves while others send samples to laboratories outside South Africa.

### Management options for high-risk women including those identified as BRCA1 or BRCA2 mutation carriers

It is best to individualise management in consultation with other health care practitioners.

#### Breast surveillance

- Breast awareness
- Clinical breast examination
- Mammography
- Magnetic resonance imaging
- Ultrasound

#### Ovarian surveillance (controversial)

- Clinical examination
- Ultrasound
- Tumour markers

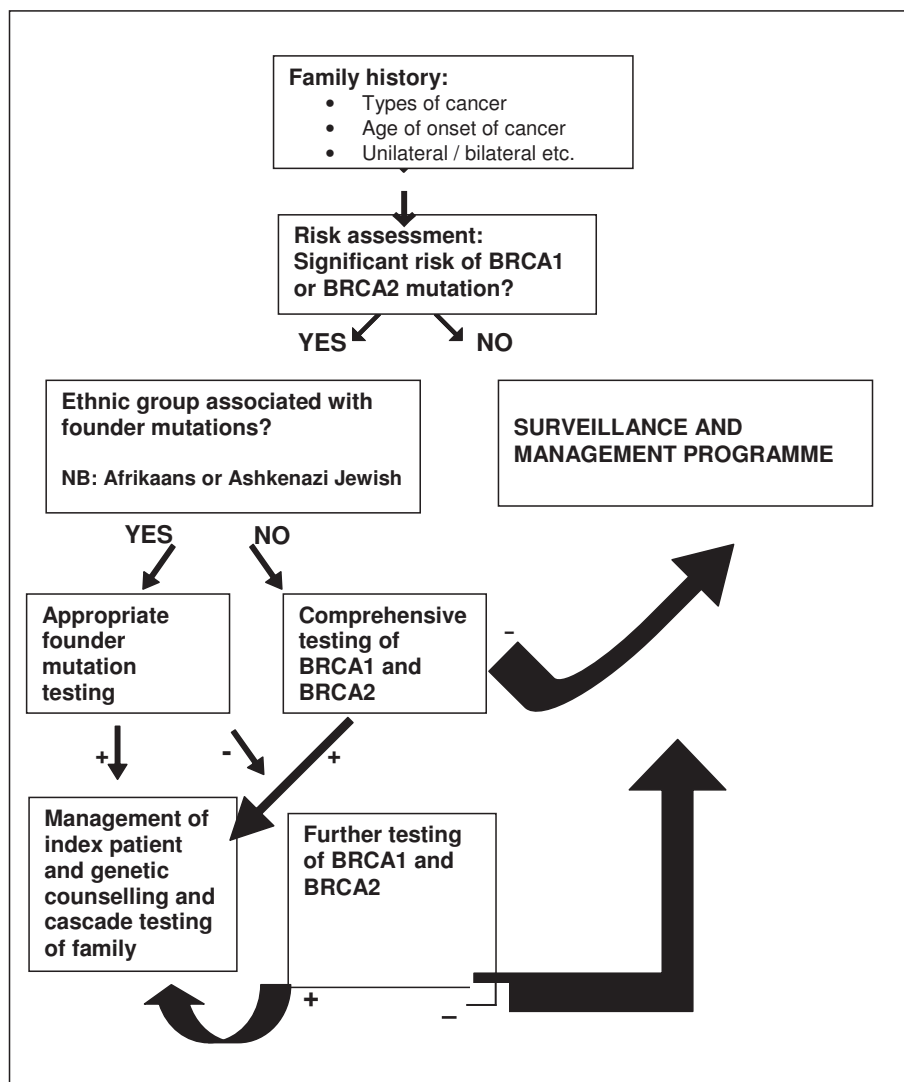


Fig. 2. Algorithm to represent a stepwise approach to genetic testing.

**Chemoprevention****Risk-reducing surgery**

- Risk-reducing mastectomy (lowers breast cancer risk by 90 - 95%)
- Risk-reducing salpingo-oophorectomy (may lower breast cancer risk by up to 50% and ovarian cancer risk by ~95%)

**References**

1. SA Cancer Registry 1998-1999.
2. Vorobiof D, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. *J Clin Oncol* 2001; 19 (18s): 125s -127s.
3. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: breast cancer – epidemiology, risk factors and genetics. *BMJ* 2000; 321: 624-628.
4. Goldberg JL, Borgen PI. Breast cancer susceptibility testing: past, present and future. *Expert Rev Anticancer Ther* 2006; 6(8): 1205-1214.
5. Genereviews:<http://www.geneclinics.org/servlet/access?db=geneclinics&site=gt&tid=888892&key=xYsHs0Engt6wW&gry=&fcn=y&fw=rWbC&filename=/profiles/brca1/index.html>
6. Smith A, Moran A, Boyd MC, *et al.* Phenocopies in BRCA1 and BRCA2 families: evidence for modifier genes and implications for screening. *J Med Genet* 2007; 44: 10-15.
7. National Society of Genetic Counselors, 2005.

**Further reading**

Genetics of Breast and Ovarian Cancer – National Cancer Institute: <http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian>

**CANCER GENETIC COUNSELLING SERVICES CONTACT INFORMATION****Cape Town**

UCT Division of Human Genetics, tel: 021 406 6304

Tygerberg Genetic Clinic, tel: 012 938 4217

Private practice:

Frieda Loubser, Registered Genetic Counsellor, tel: 083 225 4289 / 021 480 6252

**Johannesburg**

Wits Division of Human Genetics, tel: 011 489 9224

Private practice:

Sarah Walters, Registered Genetic Counsellor, tel: 082 772 3930

Julie Lampret, Registered Genetic Counsellor, tel: 082 445 9574

**Pretoria**

Private practice:

Julie Malan, Registered Genetic Counsellor, tel: 082 553 5891

Familial Cancer Clinic at Femina Hospital, tel: 021 328 2676

**Bloemfontein**

UFS Division of Human Genetics, tel: 051 405 3047

**Durban**

Genetic Clinic Inkosi Albert Luthuli Central Hospital, tel: 031 240 1000

*In a nutshell*

- Family history is an important risk factor for the development of breast cancer.
- Identification and referral of high-risk women and families can promote appropriate management and reduce the morbidity of breast cancer.
- Genetic testing is available for the major breast and ovarian cancer predisposing genes, BRCA1 and BRCA2.
- Identification of families appropriate for genetic testing, testing strategy and interpretation of results should be done in the context of genetic counselling.
- BRCA1 and BRCA2 mutations are inherited in an autosomal dominant manner. This means that both males and females have a 50% risk of passing the mutation on to children of both sexes.
- Genetic counselling can promote informed decision-making, adaptation to risk and a family-orientated approach to care.

**ERRATUM**

In the article on nutritional management of the burn patient, p. 432 of September *CME*, the NPE:N ratio is given as 100:1 in Table II, but is reversed in the nutshell. The values in the table are correct. We apologise for any inconvenience.