

AMPATHCHAT

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Breast cancer

The current facts

- Breast cancer is the most common potentially fatal invasive cancer in women.
- It is more than 100 times more common in women than in men. Males tend to have poorer outcomes.
- It is correlated with age.

The incidence is higher in first world countries. Western lifestyle changes such as high fat/alcohol intake, smoking, oral contraceptives and changing childbearing patterns in developing countries have significantly increased its world-wide incidence.

Prognosis and survival rates depend on the type of cancer and staging. With early diagnosis and treatment, the five-year overall survival rate is 85%:

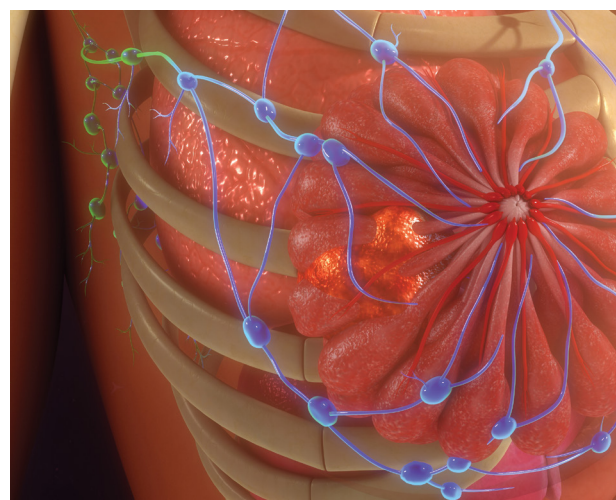
- Stage 0: 99–100%
- Stage I: 95–100%
- Stage II: 86%
- Stage III: 57%
- Stage IV: 20%

Risk factors

- **Age:** The risk is low under the age of 30, but increases with age. Early-onset cancers tend to be more aggressive than later-onset cancers.
- **Exposure to oestrogen:** Early menarche (under 12 years) and the late onset of menopause (under 55 years).
- **Nulliparity:** Non-child bearing and non-breast feeding.
- **Diet:** High fat intake, high alcohol consumption.
- **Obesity:** Those with a normal body mass index at 20 years of age, gaining weight over time have almost double the risk.
- **Smoking:** Active and passive smoking increase risk of breast cancer. The risk increases from 15% to 40% as a result of

factors such as early commencement, longer duration, increase in number of cigarettes per day.

- **Early exposure to radiation**
- **Certain breast changes:** According to many studies, patients with proliferative breast disease may have an elevated lifetime risk for breast cancers; often one may find atypical ductal hyperplasia, in situ ductal carcinoma or in situ lobular neoplasia in patients with fibrocystic disease or proliferative breast disease with ductal hyperplasia or the varying forms of adenosis.
- **Prior history:** Regardless of the type of cancer, the patient with a prior history of breast cancer is at an increased risk of developing cancer in the second breast.
- **Family history:** The risk is higher if an immediate family member (mother, sister or daughter) has been diagnosed with breast cancer. The risk is especially significant if at least two close relatives have had breast or ovarian cancer, especially premenopausally.
- **Carriers of BRCA risk mutations:** These have a high lifetime risk for breast and ovarian cancer, depending on the type of mutation.



http://www.medicinenet.com/breast_cancer_pictures_slideshow/article.htm

Important information pertaining to BRCA

- All individuals with a positive family history of breast or ovarian cancer are not equally at risk. The likelihood that BRCA testing will be informative should be assessed prior to testing.
- The test limitations and possible implications of positive or equivocal results should be fully discussed during pre-test counselling sessions.
- Post-test counselling is necessary to inform patients about the risks associated with specific mutations identified and how to deal with BRCA genetic variants with as yet unknown effects.
- Experience and training in these aspects are required, and qualified genetic counsellors can assist clinicians.
- Specimens for BRCA mutation testing are accepted by all major South African laboratories and, in some instances, referred to local laboratories that focus on these tests. The clinician should, however, confirm whether only "hot spots" in the gene are tested, and whether "negative" results can be followed up by full sequencing of the gene and determination of the status of the gene promoter that controls gene activity. This is important, as selective testing for the most common areas in the gene where mutations occur ("hot spots") may miss other less frequent, yet crucial changes within the gene or its control mechanisms.
- It is the patient's right to be fully informed about the costs of the various testing levels and the limitations of the tests.
- BRCA testing deals with only one aspect of cancer-associated gene changes. Negative testing is not a reason to abolish regular routine screening approaches such as self-examination and mammography.
- It is important to note that not all familial breast cancers are the result of BRCA 1 or BRCA 2 gene mutations. Other mutated genes may include p53 and PTEN. One can also test for mutations in these genes by using next-generation sequencing technology.

Signs and symptoms

Breast cancer develops in the terminal duct-lobular complex, and may differentiate along either ductal or lobular phenotypes along a spectrum of morphological patterns.

- The presence of a lump or thickening in the breast (not all lumps are malignant)
- Swelling, dimpling, redness or soreness of the skin
- Change in shape or appearance of the nipple (see Figure 2)
- Nipple discharge

All new symptoms should always be taken seriously, because of the possibility of an underlying malignancy. Breast lumps are not always palpable, and early breast cancer is best detected by a mammogram (see Figure 1).

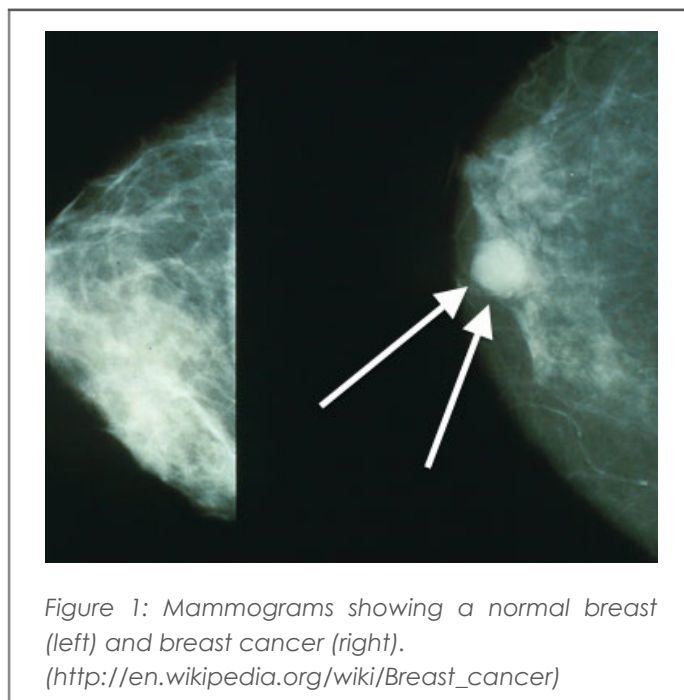


Figure 1: Mammograms showing a normal breast (left) and breast cancer (right).

(http://en.wikipedia.org/wiki/Breast_cancer)

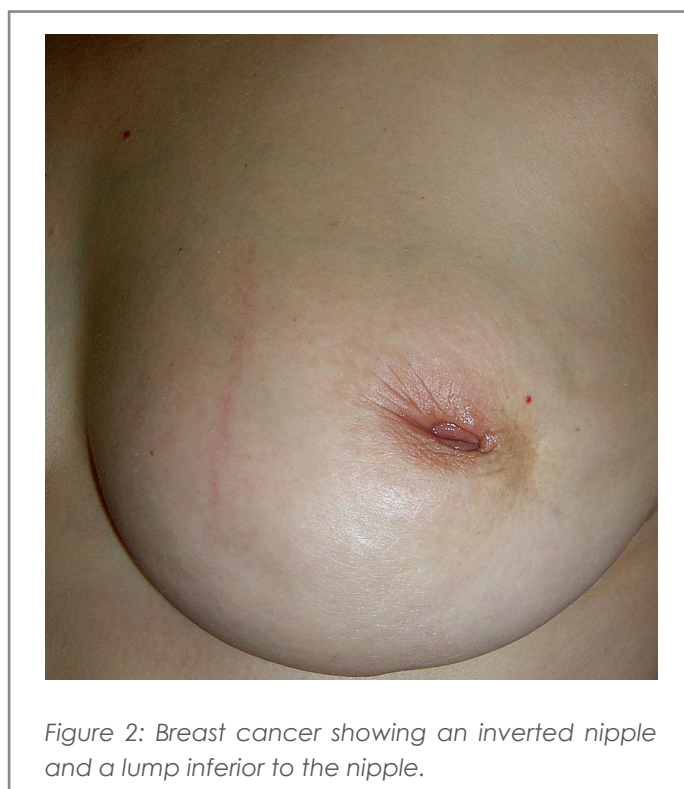


Figure 2: Breast cancer showing an inverted nipple and a lump inferior to the nipple.

Prevention

Women may be able to reduce their risk as follows:

- Increasing physical activity, maintaining a healthy weight and avoiding obesity
- Reducing alcohol intake
- Breastfeeding their infants
- Considering a prophylactic bilateral mastectomy in patients with certain BRCA1 and BRCA2 mutations.

Screening, detection and diagnosis

Self examination, clinical examination and mammography are the major screening tools that should be used regularly after the age of 40 years. Other tools include the following:

- Ultrasound
- Breast MRI
- PET scan

In women at high risk, such as those with a strong family history of cancer, mammography screening is recommended at an earlier age. Additional testing may include genetic screening tests for the BRCA genes.

Pathology studies for diagnosis require the following:

- Fine needle aspiration (FNA)
- Core needle biopsy
- Sentinel lymph node biopsy (2011 NCCN guidelines state that this is preferred over axillary lymph node dissection for staging)

The role of the pathology laboratory in breast cancer

- **Histopathology.** Most breast cancers are classified by their histological appearance as either ductal or lobular, or as one of the many other morphological variants of these tumours. Carcinoma in situ is the growth of neoplastic cells within the ductal or lobular system without invasion of the surrounding tissue; as opposed to an invasive carcinoma that extends through the ductal basement membrane and infiltrates into the surrounding connective tissue compartment.
- **Grade.** Cancer cells are disorganised and cell division is uncontrolled. Cell nuclei are less uniform. Tumour cells may be described as well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3). They progressively lose the features seen in normal cells. Poorly differentiated cancers have a worse prognosis.
- **Stage.** Breast cancer staging is done using the TNM system, which is based on tumour size (T), lymph node involvement (N) and metastasis to other parts of the body (M).
 - Stage 0 is a precancerous or marker condition: either ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS).
 - Stages 1 to 3 are within the breast or regional lymph nodes.
 - Stage 4 is "metastatic" cancer (bone or brain)
- **Receptor status.** Cell receptors (ER and PR and HER-2) guide treatment options and determine prognosis.

ER positive (ER+) cancer cells (see Figure 3) can be treated with drugs that block the effects of oestrogen (for example, tamoxifen). HER2+ breast cancer cells (see Figure 4) respond to the addition of drugs such as trastuzumab as part of chemotherapy. Cells lacking these receptors are classified as basal-like or triple negative.

- **Serum tumour markers in breast cancer.** The most widely used serum-based tumour marker is CA 15-3, which is increased in 50% to 90% of patients with metastatic breast cancer.

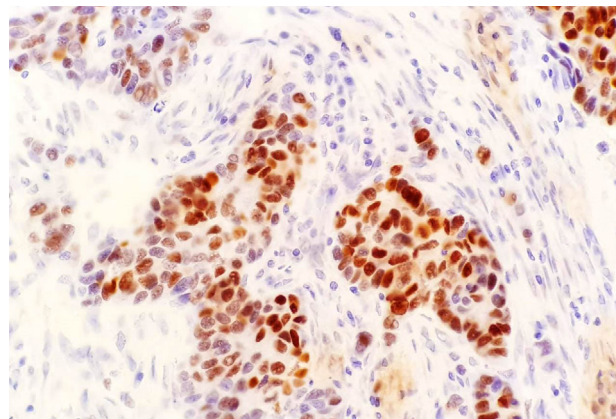


Figure 3: ER positive cells showing distinct nuclear staining

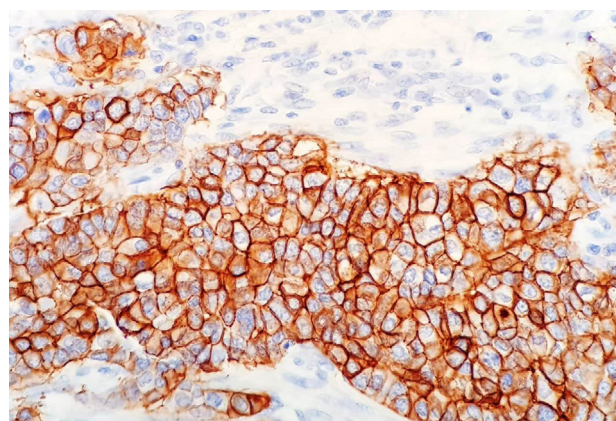


Figure 4: HER-2 positive cells showing a strong, complete membranous stain (the "lace-like" membranous pattern at the membrane is very characteristic of HER-2)

Uses

- Pre-operative levels in newly diagnosed patients are combined with existing prognostic factors for predicting outcomes.
- Monitoring response to therapy in patients with advanced metastatic breast cancer that is less easily detectable by clinical and radiological means.
- As an indicator of the progression or recurrence of the cancer, it can guide decisions regarding initiating or changing therapy.

DNA microarrays- Where do we stand in South Africa?

DNA microarrays show differences in the expression of many genes in breast cancer cells. Commercially marketed DNA microarray tests, particularly the OncotypeDx and MammaPrint assays, analyse clusters of genes and may help decide on the best treatment options. They are used in North America and Europe.

Although there is considerable evidence that these tests can refine treatment decisions in a meaningful proportion of breast cancers, they are costly. In South Africa, the MammaPrint Gene panel is available at the University of Stellenbosch's Department of Pathology (please contact the laboratory to enquire about the cost of this test). This is used as a prognostic test for women under the age of 61 years with either oestrogen receptor-positive or receptor-negative, lymph node-negative breast cancer.

This test requires freshly prepared tissue collected into an RNA preservative solution. The 70 genes that comprise the MammaPrint assay are focused primarily on proliferation with additional genes associated with invasion, metastasis, stromal integrity and angiogenesis. The optimal use of these molecular assays remains a challenge to the practicing oncologist.

Additional laboratory investigations

The following laboratory tests are also recommended for asymptomatic women with early-stage breast cancer:

- Full blood cell (FBC) count with differential
- Liver function tests (LFT) (metastases and staging)
- Renal function tests
- Serum calcium (hypercalcaemia)

Genetic testing

Genetic testing for BRCA1 and BRCA2 can be requested in selected high-risk patients with a strong family history of breast or ovarian carcinoma. Genetic counselling and a discussion of management and treatment options should be performed before testing.

Treatment

Individualised treatment for each patient is based on the following:

- Location of the tumor and how far it has spread
- Tumour size
- Whether the tumor is hormone receptor-positive or receptor-negative
- The presence or absence of HER-2 receptors

Options include the following:

- **Surgery:** This includes a lumpectomy, mastectomy, or an axillary lymph node dissection. In selected, well-differentiated tumours of small size, the surgical removal of the tumour provides the single-largest benefit and may be sufficient. Chemotherapy regimens are combined with surgery to increase the likelihood of long-term disease-free survival. Radiation can be added to eradicate cancer cells in the breast that may have been missed by the surgery, which may extend the patient's survival.
- **Hormone therapy:** This includes selective oestrogen receptor modulators (SERMs) such as tamoxifen, and aromatase inhibitors, such as exemestane (aromasin).
- **Immunotherapy:** Monoclonal antibody therapy includes Herceptin® (trastuzumab), where HER-2 +ve receptors are present.

Does hormone replacement therapy cause breast cancer?

Few studies show that post-menopausal hormone replacement therapy (HRT) may be implicated in an increased risk of developing breast cancer. The actual impact of HRT on the risk of breast cancer is currently under investigation. The current consensus is that HRT should be prescribed on an individualised basis based on the presence or absence of risk factors.

References and further reading

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- http://www.asco.org/ASCOV2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=84331
(*Journal of Clinical Oncology* 29: 2011 (suppl; abstr e11124)
Predictors and prevalence of germ-line BRCA1 and BRCA2 mutations in high-risk patients screened at a community hospital.)