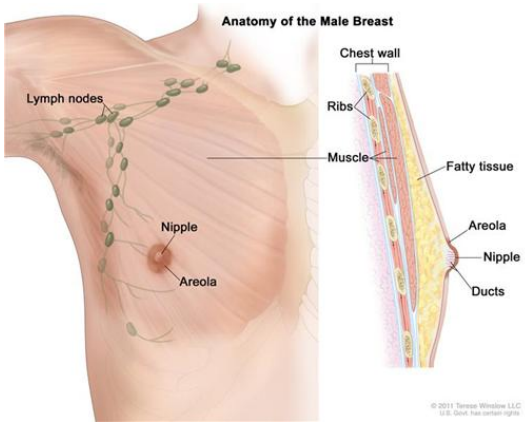
Cancer Association of South Africa (CANSA)

CANSA Fact Sheet
on
Breast Cancer in Men

Introduction

The exterior of both male and female chests are basically the same, however, the size, shape, and function of breasts vary significantly between the sexes.



[Picture Credit: Male Breast]

The male breast also has a nipple and an areola (the darker pigmented circle around the nipple), but men lack the mammary glands and ducts necessary to produce milk.

Unlike women, a typical male does not have extensive fat deposits on his chest - in a woman, these protect the mammary glands. Instead, the shape of a man's chest is determined by the muscles underneath the skin. Although atypical, men can develop large mammary glands that result in breast enlargement. This condition is known as gynaecomastia. It is more common is adolescent boys but typically disappears after puberty.

Bhardwaj., P.V, Gupta, S., Elyash, A. & Teplinsky, E. 2024.

Purpose of review: Male breast cancer is a relatively uncommon and rare disease that is often managed based on evidence adopted from trials pertaining to female breast cancer due to low accrual rates or exclusion of males. This is despite the known differences in the biology and epidemiology of this condition. This review provides an update regarding the management and surveillance of male breast cancer.

Recent findings: Men with breast cancer tend to undergo more extensive surgery in the breast and axilla. The outcomes of male breast cancer compared to a similar subtype of female breast cancer appear worse when matched for stage. Systemic therapies remain predominantly based on recommendations for female breast cancer, although tamoxifen is the more optimal endocrine therapy for men than women. Surveillance with mammograms is recommended for patients harboring a breast cancer susceptibility gene but is otherwise not advised for men who have undergone a mastectomy. Notably, the role of other imaging modalities, including ultrasound and magnetic resonance imaging, is minimal. Although the focus on survivorship care among men is low, it is abundantly clear that this is a stigmatizing diagnosis for men, and they suffer from long-term

physical and psychological sequelae following a diagnosis and treatment of breast cancer. In summary, providing more gender-inclusive care and advocating for increased representation of men in prospective breast cancer studies and clinical trials may help improve outcomes and provide enhanced support for this population.

Ye, M., Qiu, L., Jin, Y. & Huang, Y. 2024.
Background: The experiences, physical and mental health and needs of women with breast cancer have been studied in some detail, but there is a lack of discussion of the experiences of stakeholder groups such as men with breast cancer, partners and carers and healthcare professionals. The aim of this study was to explore and understand the experiences and perceptions of male breast cancer stakeholders from diagnosis through to survivorship.
Methods: We conducted a thematic review of qualitative studies included in a large published scoping review on male breast cancer (reported under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews extension). To be included in a qualitative evidence review, studies had to use qualitative methods for data collection and analysis to capture the perspectives of men with breast cancer, partners or caregivers, and healthcare workers. Key characteristics and findings were extracted and a conceptual coding framework was summarized using thematic analysis.
Results: Out of a total of 310 studies in the research literature (published research articles and gray literature), 15 studies met the inclusion criteria. These studies reported on the experiences of men with breast cancer, partners or caregivers, and healthcare workers, with participant numbers ranging from 2 to 31. A total of 17 descriptive themes (study outcomes) were identified. From these, four high-level analytic themes emerged: (1) Predicament; (2) Emotion; (3) Support; (4) Coping.
Conclusions: The gender stigma that exists at the patient, healthcare system, and family-society levels largely influences the experiences of the male breast cancer stakeholder population. To address gender inequalities in breast cancer care, healthcare organizations and society at large should remain equally attentive to the needs of male and female breast cancer patients. These needs include reducing healthcare and social stigma, providing gender-specific information and emotional support, and access to support groups.

Parpex, G., Ottaviani, M., Lorphelin, H., Mezzadri, M., Marchand, E., Cahen-Doidy, L., Benifla, J.L., Huchon, C. & Mimoun, C. 2024.
Background: Sentinel lymph node biopsy (SLNB) is commonly used in the surgical management of male breast cancer. Contrary to female breast cancer, limited data exist about its performance in male breast cancer. The objective of this systematic review and meta-analysis was to evaluate the SLNB accuracy in male breast cancer.
Methods: MEDLINE, EMBASE, Web of Science and The Cochrane Library were searched from January 1995 to April 2023 for studies evaluating the SLNB identification rate and false-negative rate in male breast cancer with negative preoperative axillary evaluation and primary surgery. For SLNB false-negative rate, the gold standard was the histology of axillary lymph node dissection (ALDN). Methodological quality was assessed by using the QUADAS-2 tool. Pooled estimates of the SLNB identification rate and false-negative rate were calculated. Heterogeneity of the pooled studies was evaluated using I^2 index.
Results: A total of 12 retrospective studies were included. The 12 studies that reported the SLNB identification rate gathered a total of 164 patients; the 5 studies that reported the SLNB false-negative rate gathered a total of 50 patients with a systematic ALND. The pooled estimate of the SLNB identification rate was 99.0%. The SLNB false-negative rates were 0% in the 5 included studies and consequently so as the pooled estimate of the false-negative rate with no heterogeneity.

Conclusion: SLNB for male breast cancer, following negative preoperative axillary assessment and primary surgery, appears feasible, consistent, and effective. Our research supports conducting immediate SLNB histological evaluation to facilitate prompt ALND in case of positive results.

Tumour Grade and Tumour Stage

Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope. Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

What are the cancer stages?

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers. Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.
The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

The International Classification of Diseases 10th version (ICD-10)
The International Classification of Diseases (ICD) is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics. This includes providing a format for reporting causes of death on the death certificate.

ICD serves a broad range of uses globally and provides critical knowledge on the extent, causes and consequences of human disease and death worldwide via data that is reported and coded with the ICD. Clinical terms coded with ICD are the main basis for health recording and statistics on disease in primary, secondary and tertiary care, as well as on cause of death certificates. These data and statistics support payment systems, service planning, administration of quality and safety, and health services research. Diagnostic guidance linked to categories of ICD also standardizes data collection and enables large scale research.

For more than a century, the International Classification of Diseases (ICD) has been the basis for comparable statistics on causes of mortality and morbidity between places and over time. Originating in the 19th century, the latest version of the ICD, ICD-11, was adopted by the 72nd World Health Assembly in 2019 and came into effect on 1st January 2022.

The ICD-10 Code for Malignant neoplasm of breast of unspecified site is C50. 92.

Incidence of Breast Cancer in Men in South Africa

According to the latest edition of the National Cancer Registry (2022) the following cases of Breast Cancer in Men was histologically diagnosed in 2022. Histologically diagnosed means that a sample of tissue (biopsy) was forwarded to an approved laboratory where a specially trained pathologist confirmed a diagnosis of cancer:

Group 2022	Actual Number of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	207	1:930	0,49%
Asian males	9	1:693	0,85%
Black males	123	1:1 015	0,83%
Coloured males	20	1:1 075	0,40%
White males	55	1:713	0,24%

Frequency of Histologically Diagnosed Cases of Breast Cancer in Men

According to the National Cancer Registry (2022), the frequency of histologically diagnosed cases of Breast Cancer in Men in South Africa is as follows:

Group 2022	0 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	80 + Years
All males	0	1	13	34	39	56	47	17
Asian males	0	0	2	0	2	3	2	0
Black males	0	1	10	23	25	34	23	7
Coloured males	0	0	1	4	3	7	3	2
White males	0	0	0	7	9	12	19	8

According to the Breast Health Foundation (South Africa) it is estimated that South Africa has one of the highest incidences of male breast cancer in the world with 1-3% of breast cancer cases diagnosed in South Africa occurring in men. It is estimated that up to 400 cases of male breast cancer cases were diagnosed in South Africa during 2018.

Risk Factors for Breast Cancer in Men

Men diagnosed with male breast cancer at an early stage have a good chance for a cure. However, many men delay seeing a doctor when they notice unusual signs or symptoms, such as a breast lump. For this reason, many male breast cancers are diagnosed when the disease is more advanced.

Factors that increase the risk of male breast cancer include:

- Older age. Breast cancer is most common in men ages 40 to 80. About 1 in 5 men with breast cancer (20%) have a close relative who has also had breast cancer.
- The genes store the biological information inherited from parents. The genes most commonly linked to an increased risk of breast cancer in families are BRCA1 and BRCA2. Men in families with

the BRCA2 gene are more likely to develop breast cancer than men in BRCA1 families. It is thought that the BRCA2 gene may cause up to 1 in 10 of breast cancers in men (10%).

- Exposure to oestrogen. If one takes oestrogen-related drugs, such as those used as part of sex reassignment surgery, the risk of breast cancer is increased. Oestrogen drugs may also be used in hormone therapy for prostate cancer. Although all men have oestrogen in their bodies, obesity, cirrhosis (liver disease) and Klinefelter's syndrome (a genetic disorder) increase oestrogen levels.
- Family history of breast cancer. If one has a close family member with breast cancer, there is a greater chance of developing the disease. If a first-degree relative—their mother, father, brother, sister, children—has breast cancer, men are also at slightly higher risk to develop the disease themselves. Men who have a BRCA mutation (a mutation or change in a gene that predisposes them to breast cancer) are at a greater risk. Although their chance of developing breast cancer is still low (only about 5% to 6%), men with a mutation in BRCA2 have a 100-fold greater risk of developing breast cancer than men in the general population.

  There may be a breast cancer gene in a family if:
  - a man in the family has breast cancer
  - there are three close relatives on the same side of the family who developed breast cancer at any age
  - there are two close relatives on the same side of the family who developed breast cancer under the age of 50
  - there is one close relative who developed breast cancer under the age of 40
  - there is a close relative with breast cancer in both breasts
  - there is a close relative with breast cancer and another relative on the same side of the family with ovarian cancer

  Close relatives, sometimes called one's first degree relatives, are parents, children, sisters and brothers.

- Klinefelter's syndrome. This genetic syndrome occurs when a boy is born with more than one copy of the X chromosome. Klinefelter's syndrome causes abnormal development of the testicles. As a result, men with this syndrome produce lower levels of certain male hormones (androgens) and more female hormones (oestrogens).
- being a heavy user of alcohol, which can limit the liver's ability to regulate blood oestrogen levels.
- Liver disease. If one has liver disease, such as cirrhosis of the liver, the male hormones may be reduced and female hormones may be increased. This can increase the risk of breast cancer.
- Obesity. Obesity may be a risk factor for breast cancer in men because it increases the number of fat cells in the body. Fat cells convert androgens into oestrogen, which may increase the amount of oestrogen in the body and, therefore, the increased risk of breast cancer.
- Radiation exposure. If one has received radiation treatments to the chest, such as those used to treat cancers in the chest, one is more likely to develop breast cancer later in life.

The Role of BRCA Gene Mutation

BRCA is an abbreviation originating from **Br**(east) **Ca**(ncer) and are tumour suppressor genes. Every cell in a human body contains them. There are two types: BRCA1 and BRCA2. Their main function in the body is to repair DNA, keep other genes healthy, and prevent cancerous changes. These genes can become mutated.

A mutation is a change in the gene which makes the gene stop doing its main function, therefore, no longer keeping abnormal cell growth in check. These changes (mutations) can be inherited or passed on from parents, grandparents, and great grandparents.

If someone has a gene mutation, their risk of cancer increases.

Anyone can have a BRCA gene mutation. Though, they are more commonly found in certain ethnic groups, including Ashkenazi Jews, Afrikaners, French Canadians, and people of Icelandic backgrounds. The most common cancers that can result from BRCA gene mutations are breast cancer, ovarian cancer, and prostate cancer. The full list includes.

WOMEN	**MEN**
BRCA1	**BRCA1**
Breast cancer	Breast cancer
Ovarian cancer	Prostate cancer
Pancreatic cancer	Pancreatic cancer
BRCA2	**BRCA2**
Breast cancer	Breast cancer
Ovarian cancer	Prostate cancer
Pancreatic cancer	Melanoma
Melanoma	Pancreatic cancer

If someone has a BRCA mutation, they may pass the mutation to their children. Each child has a 50% chance of inheriting their parents' BRCA gene mutation. One's siblings may also have inherited the BRCA gene mutation.

Symptoms and Signs of Breast Cancer in Men

Symptoms of breast cancer in men are similar to those seen in women. Most male breast cancers are diagnosed when a man discovers a lump in his breast. But unlike women, men tend to delay going to the doctor until they have more severe symptoms, like bleeding from the nipple. At that point the cancer may have already spread.

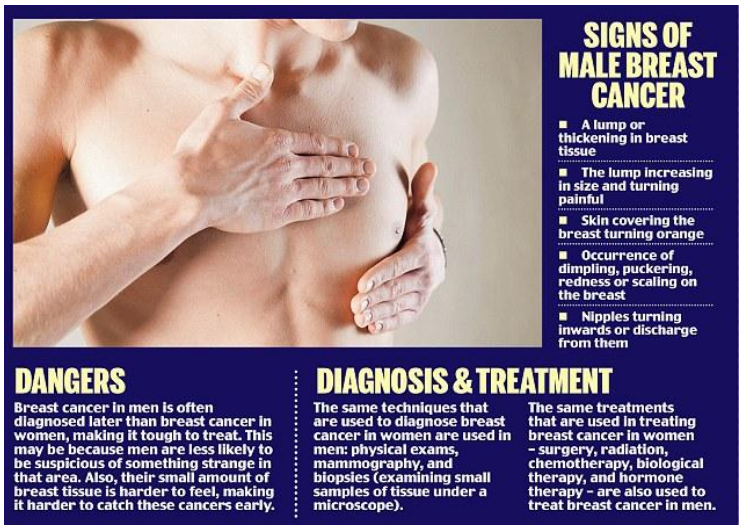
The most common sign of breast cancer in men is a firm, non-painful mass located just below the nipple. There may not be other associated symptoms.

The cancer may cause skin changes in the area of the nipple. These changes can include:

- ulceration of the skin
- puckering or dimpling
- redness or scaling of the nipple
- retraction (turning inward) of the nipple
- bloody or opaque discharge from the nipple may also occur

Less than 1% of cases are bilateral (occurring on both sides).

Breast cancer that has spread (metastasised) to the bones may also produce bone pain at the sites of metastases. Advanced breast cancer can also produce symptoms typical of many cancers, including malaise, weakness, and weight loss. Breast cancer in men can spread to many other organs and cause other symptoms as well.



Male Breast Self-Examination
How to do a Male Breast Self-Examination (MBSE).

<u>Look at the breasts in a mirror</u>

- Look at the size and shape of each breast and nipple.
- Check for swelling, lumps, dimpling, scaly skin, or other skin changes.
- Look for nipple changes, such as a nipple that is painful or beginning to pull inward.
- Gently squeeze both nipples and check to see if fluid comes out of them.
- Check the breasts while sitting or standing in the following 3 positions:

Hang the arms down at your sides
Raise the hands and join them behind your head
Put firm pressure with the hands on the hips. Bend slightly forward while looking at the breasts in the mirror

<u>Lie down and feel the breasts</u>
When lying down, the breast tissue spreads out evenly over the chest. This makes it easier for to feel for lumps and anything that may not be normal for your breasts.

- Place a small pillow or towel under the left shoulder. Put the left arm behind the head.
- Use the 3 middle fingers of the right hand. Use the fingertip pads, on the top of the fingers.

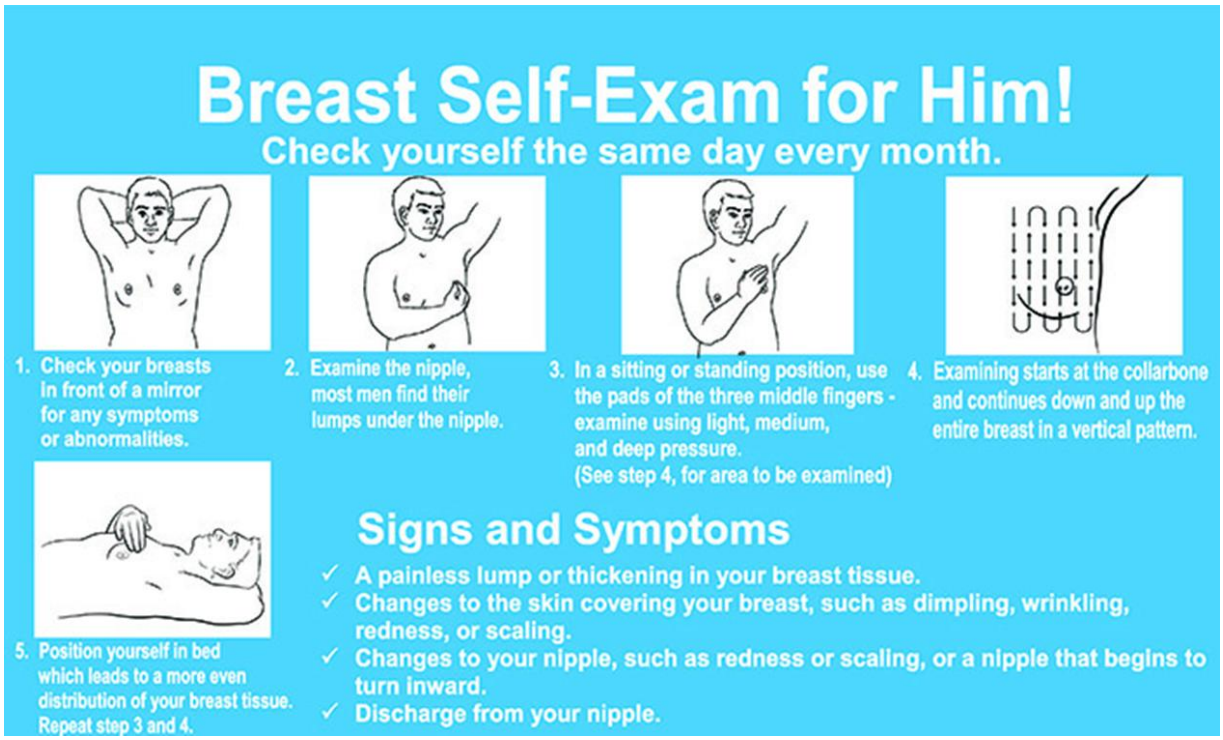
- The fingertip pad is the most sensitive part of the finger.
- Use small circles to feel the breast tissue.
- Use the fingertip pads to make overlapping circles on the breast and armpits.
- First, press lightly. Second, press with medium pressure to feel a little deeper into the breast. Last, use firm pressure to feel deep within the breast.

<u>Examine the entire breast area</u>

- Examine the breast area from above the breast to below the breast where you feel only ribs.
- Make small circles with the fingertips, starting in the middle of the armpit.
- Make circles going up and down the breast area. Continue toward the breast and all the way across it.
- Examine the area from the armpit all the way over to the middle of the chest (breastbone). Stop at the middle of the chest.
- Move the pillow or towel to the right shoulder and put the right arm behind the head.
- Use the 3 fingertip pads of the left hand.

Repeat the above steps to examine the right breast.

Male Breast Self-Examination at a Glance



Diagnosis of Breast Cancer in Men
The same techniques that are used to diagnose breast cancer in women are used in men:

- Physical examination
- Mammography
- biopsies (examining small samples of tissue under a microscope)

[Picture Credit: Male Mammography]

Genetic Counselling is a Must for Men
All men with breast cancer should be referred for genetic counselling.

This is different from women who are not automatically referred to a genetic counsellor for genetic testing, such as for mutations in BRCA-1 or 2. These "tumour suppressor genes" allow breast and other types of cancer to develop when they fail to function normally. Only women with a significant family history or certain other characteristics, such as being young or having triple-negative breast cancer (which lacks oestrogen, progesterone, and HER2 receptors), are recommended to have genetic testing.

Men should tell their health care provider if any man in their family has had breast cancer. Even if one's grandfather is deceased, if he had breast cancer, that is important. Because male breast cancer is so rare, seeing even one man in a family lineage raises concerns about hereditary breast cancer.

Types of Breast Cancer in Men
The most common type of male breast cancer is infiltrating ductal carcinoma, which is also a common type of breast cancer in women. Ductal carcinoma refers to cancers with origins in the ducts (tubular structures) of the breast, and the term infiltrating means that the cancer cells have spread beyond the ducts into the surrounding tissue. On the other hand, lobular cancers (cancers of the milk glands), common in women, are extremely rare in men since male breast tissue does not normally contain lobules.

Other uncommon types of cancers of the breast that have been reported in men include ductal carcinoma *in situ* (cancer in the ducts that has not spread beyond the ducts themselves), cystosarcoma phyllodes (a type of cancer of the connective tissue surrounding the ducts), and Paget's Disease of the breast (a cancer involving the skin of the nipple). Some other types of breast cancer that occur in men are named for their growth patterns and microscopic appearance of the cancer cells, including papillary carcinoma, inflammatory carcinoma, and medullary carcinoma.

About 85% of breast cancers in men have oestrogen receptors on their cell membranes. Oestrogen receptors on the cell membranes allow oestrogen molecules to bind to the cancer cells. Oestrogen binding to the cancer cells can stimulate cell growth and multiplication.

Special Tests
The following tests and investigations may be ordered:

Breast ultrasound - ultrasound, also known as *sonography*, uses high-frequency sound waves to outline a part of the body.

Magnetic resonance imaging (MRI) of the breast - MRI scans use radio waves and strong magnets instead of X-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body.

Nipple discharge examination - fluid leaking from the nipple is called *nipple discharge*. If a patient has a nipple discharge, he should have it checked by his doctor. If there is blood in this fluid, the patient might need more tests. One test collects some of the fluid to look at under a microscope to see if cancer cells are present.

Biopsy - a biopsy removes a body tissue sample to be looked at under a microscope. A biopsy is the only way to tell if a breast abnormality is cancerous. Unless the doctor is sure the lump is not cancer, this should always be done. There are several types of biopsies. One's doctor will choose the type of biopsy based on the situation.

- Fine needle aspiration biopsy: Fine needle aspiration (FNA) biopsy is the easiest and quickest biopsy technique. The doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from a suspicious area.
- Core needle biopsy: For a core biopsy, the doctor removes a small cylinder of tissue from a breast abnormality to be looked at under a microscope. The needle used in this technique is larger than that used for FNA. The biopsy is done with local anaesthesia and can be done in a clinic or doctor's office.

Treatment Options for Breast Cancer in Men
The same treatments that are used in treating breast cancer in women are also used to treat breast cancer in men, and may include:

[Picture Credit: Mastectomy]

Surgery - Surgery is usually the first treatment if the breast abnormality is found to be a cancer. Surgery helps get complete information about the cancer and it is a critical step in treatment. The most common surgery in men is called a modified radical mastectomy. This means that the nipple, areola (dark, round area around the nipple), and all of the breast tissue are removed. The muscles on the chest are left alone. Lymph nodes are also removed.

Radiation therapy - Radiation therapy is a highly targeted, highly effective way to destroy cancer cells that may linger after surgery. This reduces the risk of recurrence (the cancer coming back).

Chemotherapy - Chemotherapy refers to special medicines that work to kill cancer cells. The doctor may recommend chemotherapy if a patient is at risk of having the cancer spreading beyond the breast or if it already has spread. Chemotherapy is not used for cancers with a low risk of spreading to other parts of the body.

Targeted therapy - Medications that specifically target an abnormality within the cancer cells may be able to offer extra benefits and few side effects.

Hormone therapy - Medicines that target hormone receptors in breast cancer cells are called hormonal therapies. This form of treatment can be very effective against hormone-receptor-positive breast cancer - having either oestrogen or progesterone receptors present in the cancer. Most breast cancers in men are hormone-receptor-positive.

Follow-up Care and Treatment for Breast Cancer in Men

After treatment for breast cancer ends, the patient should talk to his treating physician about developing a follow-up care plan. This plan may include regular physical examinations and/or medical tests to monitor recovery for the coming months and years. This could also include regular physical examinations to help keep track of the breast cancer treatment received and develop a survivorship care plan once treatment is completed. In some instances, patients may be seen at survivorship clinics that specialise in the post-treatment needs of people with cancer.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: https://pactr.samrc.ac.za/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific condition or situation. Readers of this document should seek appropriate medical advice prior to taking or refraining from taking any action resulting from the contents of this Fact Sheet. As far as permissible by South African law, the

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References and Sources Consulted or Utilised

Ali, A., Xie, Z., Stanko, L., De Leo, E., Hong, Y.R., Bian, J. & Daily, K.C. 2022. Endocrine adherence in male versus female breast cancer: a seer-medicare review. *Breast Cancer Res Treat*. 2022 Apr;192(3):491-499.

Al-Thamiree Mezban, S. & Fox, S.W. 2023. Genistein and coumestrol reduce MCF-7 breast cancer cell viability and inhibit markers of preferential metastasis, bone matrix attachment and tumor-induced osteoclastogenesis. *Arch Biochem Biophys*. 2023 May 15;740:109583.

American Cancer Society
http://www.cancer.org/cancer/breastcancerinmen/detailedguide/breast-cancer-in-men-diagnosis

Amrino, M.A., GAucalp, A., Leithner, D., Keating, D., AVendano, D., Bernard-Davila, B., Morris, E.A., Pinker, K. & Jochelson, MS. 2019. Mammographic screening in male patients at high risk for breast cancer: is it worth it? *Breast Cancer Res Treat*. 2019. 2019 Oct;177(3):705-711. doi: 10.1007/s10549-019-05338-1. Epub 2019 Jul 6.

Bhardwaj., P.V, Gupta, S., Elyash, A. & Teplinsky, E. 2024. Male Breast Cancer: a Review on Diagnosis, Treatment, and Survivorship. *Curr Oncol Rep*. 2024 Jan;26(1):34-45.

Benassai, G., Miletti, A., Calemma, F., Furino, E., De Palma, G.D. & Quarto, G. 2020. Male breast cancer: an update. *Ann Ital Chir*. 2020;91:359-365.

BRCA Gene Mutation
https://www.buddiesforlife.co.za/frequently-asked-questions-brca-gene-mutations/

Breast Health Foundation
https://www.mybreast.org.za/

Breastcancer.org
http://www.breastcancer.org/symptoms/types/male_bc/risk
http://www.breastcancer.org/symptoms/types/male_bc/symptoms
http://www.breastcancer.org/symptoms/types/male_bc/treatment/surgery
http://www.breastcancer.org/symptoms/types/male_bc/treatment/lymph_nodes
http://www.breastcancer.org/symptoms/types/male_bc/treatment/radiation
http://www.breastcancer.org/symptoms/types/male_bc/treatment/chemo
http://www.breastcancer.org/symptoms/types/male_bc/treatment/hormonal
http://www.breastcancer.org/symptoms/types/male_bc/treatment/targeted

Bucalo, A., Conti, G., Valentini, V., Capalbo, C., Bruselles, A., Tartaglia, M., Bonanni, B., Calistri, D., Coppa, A., Cortesi, L., Giannini, G., Gismondi, V., Manoukian, S., Manzella, L., Montagna, M., Peterlongo, P., Radice, P., Russo, A., Tibiletti, M.G., Turchetti, D., Viel, A., Zanna, I., Palli, D., Silvestri, V. & Ottini, L. 2023. Male breast cancer risk associated with pathogenic variants in genes other than BRCA1/2: an Italian case-control study. *Eur J Cancer*. 2023 Jul;188:183-191.

Cancer.Net
http://www.cancer.net/cancer-types/breast-cancer-male/after-treatment

Cancer Therapy Advisor
http://www.cancertherapyadvisor.com/fact-sheets/early-stage-breast-cancer-diagnostic-test-treatment/article/273260/2/

De La Cruz, L.M., Thiruchelvam, P.T.R., Shivani, J., Trina, J., Blankenship, S.A. & Fisher, C.S. 2019. Saving the Male Breast: A Systematic Literature Review of Breast-Conservation Surgery for Male Breast Cancer. *Ann Surg Oncol*. 2019 Nov;26(12):3939-3944. doi: 10.1245/s10434-019-07588-1. Epub 2019 Jun 27.

Deldar, R., Sayyed, A.A., Towfighi, P., Aminpour, N., Sogunro, O., Son, J.D., Fan, K.L. & Song, D.H. 2022. Postmastectomy Reconstruction in Male Breast Cancer. *Breast J.* 2022 Mar 29;2022:5482261.

Deng, G., Davatgarzadeh, A., Yeung, S. & Cassileth, B. 2010. Phytoestrogens: science, evidence, and advice for breast cancer patients. *Soc Integr Oncol*. 2010 Winter;8(1):20-30.

Duso, B.A., Trapani, D., Marra, A., D'Amico, P., Guerini Rocco, E., Fusco, N., Mazzarella, L., Criscitiello, C., Esposito, A. & Curigliano, G. 2020. Pharmacological management of male breast cancer. *Expert Opin Pharmacother*. 2020 Aug;21(12):1493-1504.

Eggemann, H., Bernreiter, A.L., Reinisch, M., Loibl, S., Taran, F.A., Costa, S.D. & Ignatov, A. 2019. Tamoxifen treatment for male breast cancer and risk of thromboembolism: prospective cohort analysis. *Br J Cancer*. 2019 Jan 17. doi: 10.1038/s41416-018-0369-2. [Epub ahead of print]

Elbachiri, M., Fatima, S., Bouchbika, Z., Benchekroun, N., Jouhadi, H., Tawfig, N., Sahraoui, S. & Benider, A. 2017. Breast cancer in men: about 40 cases and literature review. *Pan Afr Med J*. 2017 Dec 4;28:287. doi: 10.11604/pamj.2017.28.287.13527. eCollection 2017.

Farhat, E.K., Sher, E.K., Džidić-Krivić, A., Banjari, I. & Sher, F. 2023. Functional biotransformation of phytoestrogens by gut microbiota with impact on cancer treatment. *J Nutr Biochem*. 2023 Aug;118:109368.

Freitas, A.C., Opinião, A., Fragoso, S., Nunes, H., Santos, M., Clara, A., Bento, S., Luis, A., Silva, J., Moura, C., Filipe, B., Machado, P., Santos, S., André, S., Rodrigues, P., Parreira, J. Vaz, F. 2018. Men seeking counselling in a Breast Cancer Risk Evaluation Clinic. *Ecancermedicalscience*. 2018 Jan 30;12:804. doi: 10.3332/ecancer.2018.804. eCollection 2018. PMID: 29456621.

Gao, Y., Agoldberg, J.E., Young, T.K., Babb, J.S., Moy, L. & Heller, S.L. 2019. Breast cancer screening in high-risk men: a 12-year longtitudinal observational study of male breast imaging utilization and outcomes. Published Online**:** Sep 17 2019. https://doi.org/10.1148/radiol.2019190971

Gucalp, A., Traina, T.A., Eisner, J.R., Parker, J.S., Selitsky, S.R., Park, B.H., Elias, A.D., Baskin-Bey, E.S. & Cardoso,F. 2018. Male breast cancer: a disease distinct from female breast cancer. *Breast Cancer Res Treat.* 2018 Sep 28. doi: 10.1007/s10549-018-4921-9. [Epub ahead of print]

Hansra, D., Jackson, S., Sequeira, J., Vazirani, R. & Alvares, R. 2020. Male patient with metastatic stage IV breast cancer achieves complete remission on second line Abemaciclib, Fulvestrant and Leuprolide: a case report. *Mol Clin Oncol*. 2020 Feb;12(2):120-125. doi: 10.3892/mco.2019.1955. Epub 2019 Nov 29.

Hassett, M.J., Somerfield, M.R., Baker, E.R., Cardoso, F., Kansal, K.J., Kwait, D.C., Plichta, J.K., Ricker, C., Roshal, A., Ruddy, K.J., Safer, J.D., Van Poznak, C., Yung, R.L. & Giordano, S.H. 2020. Management of male breast cancer: ASCO Guideline. *J Clin Oncol*. 2020 Jun 1;38(16):1849-1863.

Healthline
http://www.healthline.com/human-body-maps/chest

Ibrahim, M., Yadav, S., Ogunleye, F. & Zakalik, D. 2018. Male BRCA mutation carriers: clinical characeristics and cancer spectrum. *BMC Cancer*. 2018 Feb 13;18(1):179. doi: 10.1186/s12885-018-4098-y. PMID: 29433453.

International Classification of Diseases
https://www.google.com/search?q=ICD-10+coding+system&rlz=1C1GCEA_enZA1014ZA1014&ei=u47PY7TLO4KA8gKii7-YDg&ved=0ahUKEwj0lM-d3d_8AhUCgFwKHaLFD-MQ4dUDCA8&uact=5&oq=ICD-10+coding+system&gs_lcp=Cgxnd3Mtd2l6LXNlcnAQAzIFCAAQgAQyBggAEBYQHjIGCAAQFhAeMgYIABAWEB4yBggAEBYQHjI

GCAAQFhAeMgYIABAWEB4yBggAEBYQHjIGCAAQFhAeMggIABAWEB4QCjoKCAAQRxDWBBCwAzoECAAQQzoFCAAQkQI6BQguEIAEOgkIABAWEB4Q8QRKBAhBGABKBAhGGABQywpY6W5giYoBaAJwAHgBgAHYBYgBniKSAQwyLTExLjEuMC4xLjGYAQCgAQHIAQjAAQE&sclient=gws-wiz-serp
https://www.who.int/standards/classifications/classification-of-diseases
https://www.health.gov.za/wp-content/uploads/2021/02/icd-10_technical_mzuserguide.pdf

Khattab, A., Kashyap, S. & Monga, D.K. 2022. Male breast cancer. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2022 Jun 27.

Kwok, H.T., Van, M., Fan, K.S. & Chan, J. 2022. Top 100 cited articles in male breast cancer: A bibliometric analysis. *Breast Dis*. 2022;41(1):15-20.

Leone, J.P., Freedman, R.A., Leone, J., Tolaney, S.M., Vallejo, C.T., Leone, B.A., Winer, E.P., Lin, N.U., & Hassett, M.J. 2023. Survival in male breast cancer over the past 3 decades. *J Natl Cancer Inst.* 2023 Apr 11;115(4):421-428.

Lin, A.P., Huang, T-W. & Tam, K-W. 2021. Treatment of male breast cancer: meta-analysis of real-world evidence. *Br J Surg*. 2021 Sep 27;108(9):1034-1042.

Makdissi, F.B.A., Santos, S.S., Bitencourt, A. & Campos, F.A.B. 2022. An introduction to male breast cancer for urologists: epidemiology, diagnosis, principles of treatment, and special situations. *Int Braz J Urol*. 2022 Sep-Oct;48(5):760-770.

Male Breast
https://www.google.co.za/search?q=human+male+breast&source=lnms&tbm=isch&sa=X&ei=5szhU-PMNNHb7Aaj7YDIDg&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=1C4tI2ypCvGeVM%253A%3BBnDfbXdVdEHbCM%3Bhttp%253A%252F%252Fwww.cancer.gov%252Fimages%252Fcdr%252Flive%252FCDR694414-750.jpg%3Bhttp%253A%252F%252Fwww.cancer.gov%252Fcancertopics%252Fpdq%252Ftreatment%252Fmalebreast%252FPatient%252Fpage1%3B750%3B593

Male Breast Cancer
http://www.dailymail.co.uk/indiahome/indianews/article-3840009/Indian-men-face-increasing-risk-Male-Breast-Cancer-faulty-genes-alcoholism.html

Male Mammography
https://www.thesun.co.uk/living/2796328/men-breast-cancer-symptoms/

MacMillan Cancer Support
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Breastmale/Aboutbreastcancerinmen/Causes.aspx

Male breast cancer treatment (PDQ®): health professional version. PDQ Adult Treatment Editorial Board. 2018. PDQ **Cancer** Information Summaries [Internet]. Bethesda (MD): National **Cancer** Institute (US); 2002-. 2018 Feb 8. PMID: 26389234.

Massarweh, S.A. & Choi, G.L. 2016. Special considerations in the evaluation and management of breast cancer in men. Curr Probl *Cancer*. 2016 Mar - Aug;40(2-4):163-171. doi: 10.1016/j.currproblcancer. 2016.09.003. Epub 2016 Sep 17.

Mastectomy
http://blog.thebreastcancersite.com/cs-chest-cancer/

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/male-breast-cancer/basics/risk-factors/con-20025972

MedicineNet.com
http://www.medicinenet.com/male_breast_cancer/page3.htm#what_are_the_different_types_of_male_breast_cancer

National Cancer Institute
http://www.cancer.gov/cancertopics/factsheet/clinicaltrials/clinical-trials

Nelles, J.L., Hu, W-y. & Prins, G.S. 2011. Estrogen action and prostate cancer. *Expert Rev Endocrinol Metab*. 2011. May 6(3):437-451.

Nofal, M.N. & Yousef, A.J. 2019. The diagnosis of male breast cancer. *Neth J Med*. 2019 Dec; 77(10):356-359.

Parpex, G., Ottaviani, M., Lorphelin, H., Mezzadri, M., Marchand, E., Cahen-Doidy, L., Benifla, J.L., Huchon, C. & Mimoun, C. 2024. Accuracy of sentinel lymph node biopsy in male breast cancer: Systematic review and meta-analysis. *Breast*. 2024 Mar 5:75:103703.

Pensabene, M., Von Arx, C. 7, De Laurentiis, M. 2022. Male Breast Cancer: From Molecular Genetics to Clinical Management. *Cancers (Basel).* 2022 Apr 15;14(8):2006.

Reger, M.K., Zollinger, T.W., Liu, Z., Jones, T. & Zhang, J. 2016. Urinary phytoestrogens and cancer, cardiovascular, and all-cause mortality in the continuous National Health and Nutrition Examination Survey. *Eur J Nutr*. April 2016; 55(3):1029-1040.

Sharma, S., Fischer, A., Hatch, P. & Sharma, S. 2023. A case of bilateral male breast cancer – what does it teach us? *Radiol Case Rep*. 2023 Feb 11;18(4):1592-1595.

Shin, K., Martaindale, S. & Whitman, G.J. 2018. Male breast magnetic resonance imaging: when is it helful? Our experience over the last decade. *Curr Probl Diagn Radiol*. 2018 Jan 10. pii: S0363-0188(17)30307-9. doi: 10.1067/ j.cpradiol.2018.01.002. [Epub ahead of print] Review.

Sakhiri, S., Jaidane, O., Bouhani,M., Adouni, O., Kammoun, S., Chargui, R. & Rahal, K. 2019. Pure ductal carcinoma in situ in the male breast: a rare entiry. *Eur J Breast Health*. 2019 Dec 5;16(1):77-80. doi: 10.5152/ejbh.2019.4928. eCollection 2020 Jan.

Shimamura, N., Miyase, K., Warashina, T. & Fuji, S. 2006. Phytoestrogens from *Aspalathus linearis*. *Biol Pharm Bull*. 2006 June 29(6)1271-4.

Soni, A., Verma, Y., Chauhan, A., Kaur, P., Kaushal, V. & Paul, D. 2023. Male breast cancer: a 30 year retrospective analysis from a tertiary cancer care centre. *Ecancermedicalscience*. 2023 May 18;17:1551.

Srour, M.K., Amersi, F., Mirocha, J., Giuliano, A.E. & Chung, A. 2020. Male breast cancer: 13-year single institution experience. *Am Surg*. 2020 Oct;86(10):1345-1350.

Tumour Grade and Tumour Stage
https://www.medicinenet.com/cancer_101_pictures_slideshow/article.htm

US Food and Drug Administration
https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm402937.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery
https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm402937.htm

Wang, Y., Chen, K., Yng, Y., Tan, L., Chen, L., Zhu, L., Su, F., Liu, X. & Li, S. 2019. Incidence and survival outcomes of early male breast cancer: a population-based comparison with early female breast cancer. *Ann Transl Med*. 2019 Oct;7(20):536. doi: 10.21037/atm.2019.10.04.

WebMD
http://www.webmd.com/breast-cancer/guide/breast-cancer-men

Ye, M., Qiu, L., Jin, Y. & Huang, Y. 2024. Stakeholders' experiences and perceptions of male breast cancer: A qualitative evidence synthesis. *Breast*. 2024 Feb 20:74:103694.

Yetkin, G., Celayir, M.F., Tanik, C., Citgez, B., Uludag, M. & Mihmanli, M. 209. Male breast cancer: a 10 year retrospective case series in aa tertiary care hospital. *J Pak Med Assoc*. 2019 Aug;69(8):1209-1212.