

INCIDENCE

Disorders of the breast constitute a common surgical problem and represent about 15-20% of new patient referrals to a general surgical outpatient department.

Breast cancer is predominantly a disease of western civilisation and differences in incidence are thought to be more likely environmental related rather than racial.

It is the second most common cause of cancer in females in the developed and developing world countries. The most common in developed being lung cancer and developing cervical cancer. In 10 women in the USA will develop breast cancer in their lifetime. The incidence in South African white women approximates this. The incidence is lower in mixed race women and even lower in black women.

Most deaths from breast cancer occur within the first 5 years of the diagnosis being made. For the survivors, the risk of recurrence and death remains for the rest of their lives. As a result, it has a massive psychosocial effect on not only patients but their partners and families.

AETIOLOGY

Risk factors for developing breast cancer

Age is probably the most important risk factor. The age-adjusted incidence of breast cancer continues to increase with advancing age of the female population. It is extremely rare before age 20 and in women younger than 30 constitute less than 2% of cases.

Identification of high risk

- Family history of:
 - Breast, ovarian cancer
 - Bilateral disease
 - Early age of onset
 - Several family members

Magnitude of risk:

- No family history (8%)
- Mother >age 50 (9-11%)
- Mother <age 50 (13-21%)
- Mother+sister <age 50 (35-48%)

GENETICS

Many studies have looked at the relationship of family history and risk for breast cancer. Results show:

- First-degree relatives (mothers, sisters and daughters) have a two to threefold excess risk
- Risk decreases quickly in women with distant relatives affected (cousins, aunts, grandmothers)
- Risk is much higher if affected first-degree relatives had premenopausal onset and bilateral breast cancer

Genetic factors are estimated to cause 5-10% of all breast cancer cases but may account for 25% of cases in women younger than 30 years.

In 1994, a cancer susceptibility gene on the long arm of chromosome 17(17q21) was discovered. The gene, BRCA1 accounts for 40% of familial cancer.

A year later, a second gene, BRCA2 was discovered. In addition to breast cancer, patients with either mutations also have an increased risk of developing ovarian cancer.

Due to the recognized high risks of developing breast cancer, genetic counselling can now be offered for women with strong family histories of early-onset breast cancers and close

surveillance from the age of 18 instituted.

Summary of risk factors for breast cancer

MAJOR	MINOR	CONTROVERSIAL
Female	Wide oestrogen window (early menarche, late menopause)	No lactation
Advancing age	Few / no children	Alcohol
Contra-lateral disease	Late birth of first child	Diet
Family history	HRT (Hormone replacement therapy)	
Irradiation	OCP (oral contraceptive pill)	
BRCA1	Smoking	
BRCA2		

CLINICAL FEATURES

Symptoms

The most common presenting symptom is that of a painless lump (80%), either noticed by the patient or a health worker.

Other less common symptoms are:

- change in breast appearance (13%)
- Nipple discharge (2%). of concern if bloody
- Eczematous change of nipple (Paget's)
- Extra-mammary metastasis

5% of patients are asymptomatic and found on mammographic screening.

Signs

The signs depend on the location and extent of spread of the disease. As the cancer progresses:

- Sub-clinical (mammographic) lesion / nipple discharge
- Thickened area/ill-defined, shelving mass

- Overlying skin dimpling/nipple retraction
- Visible mass / fixity to underlying muscle
- Skin oedema/palpable axillary nodes
- Skin fixity and ulceration/supraclavicular glands
- Symptomatic metastases

The differential diagnoses in the early stages are fibro-adenoma, cyst or fat necrosis. The later signs are rarely found in benign breast conditions other than a breast abscess with skin changes and lymphadenopathy.

DIAGNOSIS

The diagnosis is made by TRIPLE ASSESSMENT i.e. examination, radiological assessment and tissue confirmation.

History and Physical examination

This is a vital first step. At completion of the examination the doctor must have decided whether there is no abnormality (reassure the patient re physical aberration), whether its part of the benign breast spectrum or whether there are signs warranting further investigation.

Radiological investigations

Mammography

Is a special X-ray film of the breast which can suggest but not make a diagnosis. It is not routine in all women and does involve small doses of radiation. It is also not very useful in women < 30 years of age as the dense breast tissue makes interpretation difficult.

Features of malignancy on mammogram:

- Microcalcification (DCIS)
- Density with surrounding speculation
- Distortion of breast architecture

- Tethering

Indications for mammography:

- Proven cancer
 - to exclude multicentric/contralateral disease
 - to exclude DCIS
 - follow-up
- Clinical problems
 - discrete mass in women >30
 - vague thickening in women >30
 - single nipple discharge
 - focal mastalgia
 - unexplained nipple retraction
- Screening
 - Screening implies that the pt is well with no symptoms of breast disease.
 - positive family history (start 10 yrs before 1st degree relative acquired disease)
 - >55 yrs. 2 yearly (UK National Health)
 - currently no formal screening programme in SA

Ultrasonography

U/s detects whether palpable or mammographic lesions are solid or cystic. It is particularly useful in young women with dense breast tissue. However, it is not very sensitive in differentiating benign vs. malignant solid lesions. It is also useful as a biopsy tool for impalpable lesions.

Tissue Diagnosis

Cytology (FNAC/FNAB)

Fine needle aspiration cytology is essential in investigating breast masses.

Technique: A conventional 22 gauge needle attached to a syringe is used. Using an aseptic technique, several aspiration passes are done through the mass in different directions. The

material is then ejected and smeared onto slides for fixation and staining.

Under ideal circumstances, immediate processing and reporting are done, allowing a diagnosis to be made at the clinic. It allows for the interpretation of cells only though so is not adequate as a single investigation tool to diagnose breast cancer.

Trucut /Core Biopsy

Takes a core of tissue for histopathological assessment. It is important if clinical findings, mammogram and cytology are not all unequivocally positive. A good core biopsy can also yield useful information regarding tumour type, biology and hormone receptor status.

Excision Biopsy (with or without frozen section)

Not usually recommended as it is preferable to have a pre-operative diagnosis to allow for appropriate counselling, workup and treatment planning. Done in rare cases where doubt remains regarding malignancy but there is a high degree of suspicion.

PATHOLOGY

Primary breast cancer is divided into 3 broad categories: See Table below

- Non-invasive epithelial cancers (carcinoma in situ)
- Invasive epithelial cancers
- Mixed connective and epithelial (rare)

PATHOLOGICAL CLASSIFICATION OF PRIMARY BREAST CANCERS
1. Non-invasive Epithelial Cancers (carcinoma in situ)
Lobular carcinoma in situ Ductal carcinoma in situ or intraductal carcinoma <ul style="list-style-type: none"> Papillary, cribriform, solid and comedo types
2. Invasive Epithelial Cancers
Invasive lobular (IO- 15 /0) Invasive ductal carcinoma <ul style="list-style-type: none"> Infiltrating ductal carcinoma NOS (50-70%) Tubular carcinoma (2-3%) Mucinous or colloid carcinoma (2-3%) Medullary carcinoma (5%) Invasive cribriform carcinoma (1-3%) Invasive papillary carcinoma (1-2%) Adenoid cystic carcinoma (1%) Metaplastic carcinoma (1%)
3. Mixed Connective and Epithelial Cancers (rare)
Phylloides tumours, benign and malignant Carcinosarcoma Angiosarcoma

Infiltrating ductal carcinoma is the most common invasive breast cancer accounting for 50-70% of tumours. When these tumours take on differentiated features, they are named accordingly e.g. infiltrating cells secreting copious amounts of mucous would be mucinous tumours.

Pathologists also describe tumours according to their size, grade, blood vessel or lymphatic invasion and receptor status i.e. ER (oestrogen), PR (progesterone) and HER-2 surface receptors.

The presence of these factors affects prognosis and adjuvant therapy.

STAGING

The role of staging is to define the extent of tumour spread so that prognosis can be estimated and most

appropriate treatment planned.

Many staging systems exist but the simplest and most common one in routine use is the TNM system. This system uses clinical and investigative tools to grade local tumour size, regional lymph node spread and presence or absence of metastases (See Table below)

TNM staging of Breast Cancer		
TUMOUR SIZE	LYMPH NODE SPREAD	METASTASES
Tis - tumour in situ	N0 - no axillary lymph nodes	Mx – metastases suspected but not confirmed
Tx - tumour cannot be assessed	N1 - mobile axillary lymph nodes	M0 - no distant metastases
T0 - no tumour	N2 - fixed axillary lymph nodes	M1 - Metastases present
T1 - tumour is <2cm	N3 - ipsilateral internal mammary 1 nodes are involved	
T2 - tumour is 2-5cm		
T3 - tumour is >5cm		
T4 - extension of tumour to skin or chest wall		

Breast cancer can then be grouped into 4 stages (see Table below), which are used for treatment planning and prognostication.

Staging of Breast Cancer	
Stage	Description
0	Cancer in situ
1	T1 without nodes
2	T1 or 2 with nodes or T3 (with or without nodes)
3	Locally advanced in breast (T4) or Locally advanced nodes (N2-3)
4	Distant metastases

TREATMENT

Workup

Once the diagnosis of breast cancer is confirmed, the patient will need appropriate staging investigations, more information on the tumour biology and counselling prior to treatment being offered.

Metastatic Screening:

The more advanced the T and N stage, the more likely that the patient will have metastases.

- All patients
 - CXR
 - Liver function tests (LFTs)
- If LFTs are abnormal or >T3
 - Liver U/S
- >T3
 - Bone Scan (may have false positives in arthritis though)
- Selected cases
 - Bone X-rays/CT/MRI

Hormone Receptor Analysis:

Oestrogen (ER) and progesterone (PgR) receptor analysis is very helpful in treatment planning. ER+/PgR+ patients may respond to Endocrine manoeuvres such as Tamoxifen. The Her-2-neu receptor may also be over expressed. Positivity implies that the patient has a very aggressive tumour and she may have significant benefit from the biological modifier Trastuzumab (Herceptin).

Counselling:

This is a vital part of the workup in patients with breast cancer. The patient is faced with the staggering news of diagnosis. Prognosis, surgery, months of adjuvant therapy and illness, loss of a female sexual organ. etc. Breaking of the news should take place together with a family member so that they may adjust to the realisation of the diagnosis and fully understand the treatment options and implications. In some cultures the family group, senior family member or religious leader may be expected to make the treatment decision. Some patients may even refuse treatment because of cultural or religious beliefs, ignorance and/or fear. It is important to listen and acknowledge the patient's fears. ease them if you can, give them the opportunity to digest the news and discuss it with the rest of the family if necessary before coming to a mutual decision regarding treatment.

THERAPY OPTIONS

The various options are:

- Surgery
- Radiotherapy
- Chemotherapy
- Endocrine manipulation
- Biological treatments

These may be used alone or more frequently, in combination. Treatment selection depends upon the stage of the cancer, hormone receptor or her-2-neu positivity and on the patient's preference.

Surgical options for the breast are either a total Mastectomy or Breast Conserving Surgery (Wide Local Excision). WLE has the same survival rate as a mastectomy but does have a slightly higher local recurrence rate. It is also better for post operative body image for the patients but does lead to increased anxiety levels in some.

Patients are suitable for a wide local excision (WLE) if:

- Tumour size <5cm. single lesion
- Large breast (only 10% should be removed)
- Outer quadrants
- No family history
- No multifocal disease
- Willing to receive 6 weeks of adjuvant radiotherapy (essential with all WLEs)

Surgical options for the axilla are either an Axillary Nodal Clearance or a Sentinel Lymph Node Biopsy (SLNB).

Patients suitable for a SLNB are:

- T1/2 lesion
- No palpable lymph nodes
- No prior axillary surgery, irradiation or neo-adjuvant chemotherapy

Sentinel Lymph Node Biopsy

Lymphatic mapping with sampling of the first draining sentinel lymph node is a minimally invasive procedure which allows precise axillary staging by removal of the first draining 'sentinel' node. The patient has radio-isotope (technetium) injected peritumourally 24 hours prior to the operation. The SLN/s uptake is then detected with gamma rays. Intra-operatively, the patient has dye injected around the areola in the same quadrant as the cancer. The SLN is then detected with a sterile hand-held gamma probe and the visualization of the blue dye. The node is detected and sent for frozen section. If the node is positive for cancer, an ANC is undertaken. If negative, nothing further is done to the axilla.

Adjuvant therapy is the use of agents in addition to apparently curative surgery, whether mastectomy or WLE. The rationale for its use is that 1-4 of women relapse within 5 years of apparently curative surgery. This is thought to be due to undetected, subclinical metastases. Adjuvant therapy is directed against these

metastases. Most women will receive some form of adjuvant therapy. The only exceptions may be very small (<1cm) well-differentiated lesions.

Types of Adjuvant therapy:

- Radiotherapy
- Chemotherapy
Agents may be used singly or in combination. Combinations including Adriamycin are often used. The newer Taxanes are thought to be more effective but are more expensive.
- Endocrine manipulation
This involves altering the patient's hormonal environment in the hope of tumour regression. The cancer cells may express ER or PgR. If positive, the patient is more likely to respond to hormonal manoeuvres.
 - Premenopausal
 - Tamoxifen (ER receptor site competitor)
 - LHRH agonists (Zoladex). Down regulate the LHRH-LH-oestrogen pathway resulting in medical, reversible menopause.
 - Progesterones
 - Oophorectomy (effective but rarely used)
 - Postmenopausal:
 - Aromatase inhibitors. These stop the peripheral conversion of oestrogen precursors into oestrogen and hence decrease production.
 - Tamoxifen
 - Progesterones
- Biological Modifiers
Trastuzumab has a significant effect on her-2-neu positive patients but is very expensive and not readily available in government hospitals.

TREATMENT BY STAGE

STAGE 0

Breast cancer is thought to arise from the epithelium of the duct or lobule. In-situ disease does not invade the basement membrane and remains within the duct or lobule. It is often bilateral and multifocal. It may present as a mass or may be an incidental finding on a mammogram. The main mammographic features are that of pleomorphic microcalcifications ± a spiculated mass. Localised, focal lesions are suitable for a WLE. For multifocal disease without a mass, a mastectomy without an ANC is done.

STAGES 1&2

This is early disease confined to the breast and axilla, not invading the skin or chest wall. The current treatment options are:

- Total mastectomy and SLNB or WLE and SLNB if the nodes are impalpable (N0). If the nodes are palpable (N1) or the SLNB is positive, the patient will undergo an axillary nodal clearance. Plastic surgical reconstruction may be done at the time of the surgery or as a delayed procedure. The available options are tissue expanders, prosthesis or muscle flaps. Radiotherapy is recommended only in high risk patients or patients post WLE.
- Adjuvant therapy:
 - low risk (node negative, <2cm, low grade, ER+), nil or Tamoxifen.
 - Intermediate/high risk (everything else), hormonal treatment and/or tamoxifen

STAGE 3

Implies locally advanced disease but with no obvious metastases. Often a triple modality approach is used, i.e. chemotherapy, surgery (Mastectomy and ANC) and radiotherapy. Hormone therapy may be added if receptor

positive. Neoadjuvant (upfront/prior to surgery) chemotherapy is often used to downsize the tumour.

Shrinkage may then allow surgery in previously inoperable cases. This would be followed by radiotherapy and possibly hormonal therapy.

STAGE 4

These patients have incurable, metastatic disease (Bone, lungs, liver, and brain). All treatment options are aimed at palliation. Endocrine manipulation is especially useful for older women with hormone responsive disease and bone and soft tissue metastases. Younger, fit women with life-threatening, rapidly growing visceral metastases may benefit from Chemotherapy. Most women fit somewhere between these two and the oncologist will need to decide on appropriate treatment. Endocrine and chemotherapy can both be used but not simultaneously. Single brain metastases can be excised otherwise radiotherapy for symptomatic brain and bone metastases may be very useful.

SPECIAL CASES

Paget's Disease

Paget's disease of the nipple is intraductal carcinoma which invades the breast. It

presents as nipple erythema, itching, crusting and rawness. It often mimics eczema.

Paget's is differentiated from eczema as it always involves the nipple and then moves out to the areola. Tissue diagnosis is done via a punch biopsy. Mammogram may show an underlying invasive carcinoma. Patients are treated with a mastectomy with excellent survival rates if no invasive component.

Inflammatory Breast cancer

This is a locally advanced carcinoma which mimics a cellulitis / abscess.

Clinically the patients present with a red, hot, oedematous breast with a rapid course. There may be no palpable mass or mammographic features of malignancy. Tissue diagnosis can be made in the form of a punch, wedge or core biopsy. Histologically, dermal lymphatic invasion is characteristic. Aggressive treatment is needed starting with neoadjuvant chemotherapy followed by mastectomy if it becomes resectable.



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Male Breast Cancer

Accounts for about 1% of breast cancers. It is characterized by late presentation of disease and advanced stage. Men are treated the same as women. Mastectomy +/- ANC is performed if possible and adjuvant Tamoxifen given as most cancers are ER+. Radiotherapy is often required for the chest wall. Other endocrine therapies such as stilboestrol (oestrogen), orchidectomy and aromatase inhibitors may also be used.

Pregnancy and Lactation

< 1% of breast cancers. The treatment and prognosis, stage for stage, are the same as any other time. Diagnosis may however be difficult to make (hypervascular, engorged breasts with difficult palpation) and easily missed. Radiotherapy and certain drugs need to be avoided.

SURVIVAL

The most powerful factor influencing survival is the stage of the disease. Histological factors and receptor status also play a role. Gene microarrays are currently being investigated and may be more useful in determining prognosis in the future. 5 year survival rates for stage 0 and 1 are in the order of 100% and steadily decline to 20% for stage four.