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BREAST CANCER: IT'S JUST A THING

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ABSTRACT

Breast cancer is the most common cancer affecting women worldwide. Breast cancer is the most common cause of cancer-related deaths in women and occurs most frequently in postmenopausal women over the age of 50.Breast cancer arises from cells in the breast that have grown abnormally and multiplied to form a lump or tumour. The earliest stage of breast cancer is non-invasive disease (Stage 0), which is contained within the ducts or lobules of the breast and has not spread into the healthy breast tissue (also called in situ carcinoma). Breast cancer also occurs in men but is very rare, making up around 1% of all breast cancer cases. It's important to understand that most breast lumps are only benign and but not malignant. They are not life threatening, but some types of benign breast lumps can increase a woman's risk of getting breast cancer. With the advancement in the medical field, there are so many techniques have been developed that helps to treat this serious disease and also helps to detect it even at the earlier stages which is useful to treat the respective growth with suitable treatment and medications.

INTRODUCTION

The Breast is a highly complex part of the human body. It goes through many changes over a lifetime – from birth, puberty, pregnancy and breastfeeding, right through to menopause.

Breast tissue extends from the collarbone, to lower ribs, sternum (breastbone) and armpit.[1] Each breast contains 15-20 sections called lobes and each lobe has many smaller sacs, or lobules (glands). It is these lobules that produce milk in breastfeeding women. The lobes and lobules are connected to the nipple by tubes called ducts, which carry milk to the nipple. The nipple is located at the center of the areola, the dark area of skin surrounding the nipple.

The breast and armpit contain lymph nodes that belong to the lymphatic system- a network of nodes and tubes that drain fluid (lymph) and transport white blood cells (immune cells involved in fighting against infections). The remainder of the breast consists of fatty and connective (or fibrous) tissue.[2,3]

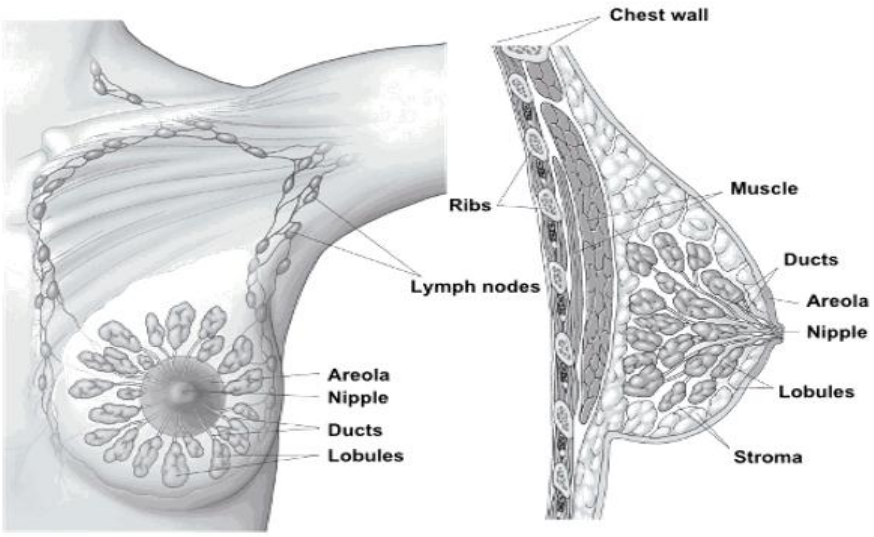

Fig 1: Normal Breast Tissue.[4]

Beginning Of Cancer In The Breast: Healthy cells are the basic building blocks of all tissues in the body. Normal cells are programmed to grow and divide in an orderly and controlled manner. However, sometimes, cells become damaged. They may develop (or have inherited) abnormalities (also called 'mutations'[6;7]) in their genes, which are the cell's instructions for how to behave. Accumulating these abnormalities can lead to abnormal cell growth. Breast cancer occurs when the cells in the breast divide and grow out of control. Breast cancer usually begins in the ducts that carry milk to the nipple (called ductal carcinoma), or within the lobules (called lobular carcinoma).[8] In rare cases, other cancer types can also occur in the breast, such as lymphomas (cancer of the lymphatic system) or sarcomas (cancer of the soft tissues). Although a lump in the breast is a common symptom of breast cancer, not all breast cancers have obvious symptoms. For example, some lumps may be too small to be felt, but can be detected with a screening mammogram or other tests.[9,10] There are also some benign (non-cancerous) conditions that can cause lumps in the breast, such as cysts. Hormones seem to play a role in many cases of breast cancer.

Inherited versus acquired DNA mutations: Normal breast cells become cancer because of changes (mutations) in DNA. DNA is the chemical in our cells that makes up our genes. Genes have the instructions for how our cells function. Some mutations can greatly increase the risk of certain cancers. They cause many of the cancers that run in some families and often cause cancer when people are younger.

But most DNA mutations linked to breast cancer are acquired. This means the change takes place in breast cells during a person's life rather than having been inherited or born with them. Acquired DNA mutations[11] take place over time and are only in the breast cancer cells.

Mutated DNA can lead to mutated genes. Some genes control when our cells grow, divide into new cells, and die. Changes in these genes can cause the cells to lose normal control and are linked to cancer.

Proto-oncogenes: Proto-oncogenes are genes that help cells grow normally. When a proto-oncogene mutates (changes) or there are too many copies of it, it becomes a "bad" gene that can stay turned on or activated when it's not supposed to be. When this happens, the cell grows out of control and makes more cells that grow out of control. This can lead to cancer. This bad gene is called an ***oncogene.***[12]

SPREADING OF CANCER BEYOND THE BREAST

Breast cancer can spread through nearby tissue, or through the body via the lymphatic system and blood.

Tissue: the cancer spreads from the original site and grows into nearby areas (often referred to as "invasive").[13]

Lymphatic system: breast cancer cells can enter nearby lymph tubes (vessels), grow in nearby lymph nodes or travel through lymph vessels to other parts of the body.[14]

Blood: breast cancer cells can enter and travel through nearby blood vessels to other parts of the body.[15]

Usually, a surgical procedure to remove one or more nearby lymph nodes is needed to determine how far cancer has spread.

TYPES OF BREAST CANCER

Breast cancer can be categorised by whether it is non-invasive or invasive:

Non-invasive breast cancer (in situ): Ductal carcinoma in situ (DCIS) is a pre-malignant lesion – it is not yet cancer, but can progress to become an invasive form of breast cancer. In this type of cancer, the cancer cells are in the ducts of the breast but have not spread into the healthy breast tissue. Lobular neoplasia[17] (previously called lobular carcinoma in situ) is when there are changes in the cells lining the lobules, which indicate that there is an increased risk of developing breast cancer in the future. Lobular neoplasia is not actually breast cancer, and although women with lobular neoplasia will have regular check-ups, most will not develop breast cancer.

Invasive breast cancer: Invasive breast cancer[18] is the name given to a cancer that has spread outside the ducts (invasive ductal breast cancer) or lobules (invasive lobular breast cancer). These can be further classified by their histology; for example, tubular, mucinous, medullary and papillary breast tumours are rarer subtypes of breast cancer.

Breast cancer is also categorised by how advanced the disease is Early breast cancer[19]**:** Breast cancer is described as early if the tumour has not spread beyond the breast or axillary lymph nodes (also known as Stage 0- IIA breast cancer). These cancers are usually operable and the primary treatment is often surgery to remove the cancer, although many patients also have preoperative neo-adjuvant systemic therapy.

Locally-advanced breast cancer[20]: Breast cancer is locally-advanced if it has spread from the breast to nearby tissue or lymph nodes (Stage II B-III). In the vast majority of patients, treatment for locally-advanced breast cancer starts with systemic therapies. Depending on how far the cancer has spread, locally-advanced tumours may be either operable or inoperable (in which case surgery may still be performed if the tumour shrinks after systemic treatment).

Metastatic breast cancer[21]: Breast cancer is described as metastatic when it has spread to other parts of the

body, such as the bones, liver or lungs (also called Stage IV). Tumours at distant sites are called metastases. Metastatic breast cancer is not curable but is treatable.

Advanced breast cancer[22]: Advanced breast cancer is a term used to describe both locally-advanced inoperable breast cancer and metastatic breast cancer.

STAGES OF BREAST CANCER

STAGES	DESCRIPTION
Stage-0	• Abnormal cells in the lining of the ducts(or) sections of the breast. • Results in increased risk of developing cancer in both breasts.
Stage-1	• Invasive breast cancer , the cancerous cells are breaking through to or invading surrounding normal tissue.
Stage-2a 2b	• No tumour but there are cancerous cells in the lymph nodes , or there is a tumour that has grown. • Cancerous cells in the lymph nodes and/or tumour has grown.
Stage-3	• Cancer has spread to lymph nodes near breastbone and chest wall.
Stage-4	• Cancer has spread to other parts

Fig 2: Different stages of Breast Cancer with description.[21-24]

Subtypes based on hormone receptor status and HER2 gene expression[25,26]

- The growth of some tumours is stimulated by the hormones oestrogen and progesterone. It is important to find out whether a tumour is oestrogen receptor (ER) or progesterone receptor (PgR) positive or negative, as tumours with a high level of hormone receptors can be treated with drugs that reduce the supply of hormone to the tumour.
- HER2 is also a receptor that is involved in the growth of cells and is present in about 20% of breast cancers. Tumours that have a high level of HER2 can be treated with anti-HER2 drugs.
- Tumours that don't have ER, PgR or high levels of HER2 are described as triple-negative tumours. Tumours can be classified into subtypes based on hormonal and HER2 receptor status as follows[27-28]

- Luminal A-like (ER and PgR positive, HER2 negative tumours),
- Luminal B-like (ER and/or PgR positive, HER2 positive or negative tumours),
- HER2 overexpressing (ER and PgR negative, HER2 positive tumours) and
- Basal-like (triple-negative tumours).

SYMPTOMS OF BREAST CANCER

Symptoms of breast cancer include[29]

- ✓ A lump in the breast
- ✓ Change in the size or shape of the breast
- ✓ Dimpling of the skin or thickening in the breast tissue
- ✓ An inverted nipple
- ✓ Rash on the nipple
- ✓ Discharge from the nipple
- ✓ Swelling or a lump in the armpit
- ✓ Pain or discomfort in the breast that doesn't go away
- ✓ Skin redness
- ✓ Skin thickening

However, it is important to remember that these symptoms may also be caused by other conditions. Certain symptoms may indicate the presence of metastases – for example, a lump or swelling under the armpit, in the breast bone or collar bone area may be a symptom of lymph node metastases. Pain in a bone or a bone prone to fracture might suggest bone metastases, and lung metastases may cause symptoms of ongoing chest infections, persistent cough and breathlessness. It's important not to be alarmed by these symptoms as they don't necessarily mean that you have metastases; however, a consultation with the doctor is necessary to determine what does the appeared symptoms mean.

RISK FACTORS AND RISK PREDICTION

There are various factors that have been associated with an increased risk for the development of female breast cancer.

1. ***Age*:** The risk of developing breast cancer increases with age. By using the Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman in the United states developing breast cancer is a lifetime risk of 1 in 8; 1 in 202 from birth to age 39 years of age, 1 in 26 from 40-59 years, and 1 in 28 from 60-69 years.[30]

2. ***Personal history*:** A personal history of breast cancer is also a significant risk factor for the development of a breast cancer.[31] Factors associated with an increased risk of a second breast cancer include an initial diagnosis of DCIS, stage IIB, hormone receptor negative cancers, and young age.[32]

3. ***Breast pathology***: Proliferative breast disease is associated with an increased risk of breast cancer. Proliferative breast lesions without atypia, including usual ductal hyperplasia, confer only a small increased risk of breast cancer development, approximately 1.5-2 times that of the general population.[9] Atypical hyperplasia including both ductal and lobular, usually incidentally found on screening mammography, confers a substantial increased risk of breast cancer. Women with atypia have an approximately 4.3 times greater risk of developing cancer compared to the general population.[32,33]

4. ***Family history***: A woman's risk of breast cancer is increased if she has a family history of the disease. In the Nurses' Health Study follow-up, the highest risk is associated with increasing number of first degree relatives diagnosed with breast cancer at a young age (under age 50). Compared with women who had no affected relative, women who had one, two or three or more affected first degree relatives had risk ratios of 1.80, 2.93 and 3.90, respectively.[34]

5. ***Genetic predisposition***: Approximately 20%-25% of breast cancer patients have a positive family history but only 5%-10% of breast cancer cases demonstrate an autosomal dominant inheritance.[34,35] Genetic predisposition alleles have been described in terms of clinical significance.[36] High-risk predisposition alleles conferring a 40%-85% lifetime risk of developing breast cancer. Half of the breast cancer predisposition syndromes are associated with mutations. Women with BRCA1 or BRCA2 deleterious mutations have a significantly higher risk of developing breast cancer. Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2.[37-39] Numerous lowrisk common alleles have been identified largely through genome-wide association studies[35] and the clinical application in the presence of these mutations is yet to be determined.

6. ***Endogenous hormone exposure and reproductive factors***: The cycles of endogenous estrogen levels throughout a woman's lifetime have implications for the development of or the protection against breast cancer.
   - ❖ Early menarche
   - ❖ Parity and age at first full term pregnancy
   - ❖ Breast feeding
   - ❖ Testosterone
   - ❖ Age at menopause

7. ***Exogenous hormone exposure***: Evidence suggests a relationship between the use of hormone replacement therapy (HRT) and breast cancer risk. Breast cancers related to HRT use are usually hormone receptor positive. When compared with patients who do not use HRT, breast cancer risk is higher in HRT users.[40] Data from the Nurses' Health Study, however, suggest that women who use unopposed postmenopausal estrogen increase their risk of breast cancer by 23% at age 70.[41]

8. ***Lifestyle factors*:** Modifiable risk factors including the excessive use of alcohol, obesity and physical inactivity account for 21% of all breast cancer deaths worldwide.[40]
   - ❖ Alcohol consumption
   - ❖ Physical activity
   - ❖ Obesity
   - ❖ Radiation

Diagnosis of Breast Cancer

History: The clinical history is directed at assessing cancer risk and establishing the presence or absence of symptoms indicative of breast disease. It should include age at menarche, menopausal status, previous pregnancies and use of oral contraceptives or post-menopausal hormone replacements. A personal history of breast cancer and age at diagnosis, as well as a history of other cancers treated with radiation. In addition, a family history of breast cancer and/or ovarian cancer in a first- degree relative should be established. Any significant prior breast history should be elucidated including previous breast biopsies.[42]

***Physical examination*:** Physical examination should include a careful visual inspection with the patient sitting upright. Nipple changes, asymmetry and obvious masses should be noted. The skin must be inspected for changes such as; dimpling, erythema, peaud' orange (associated with local advanced or inflammatory breast cancer).[43]

Diagnostic imaging: The initial choice of imaging should be individualized to each patient based on the age and characteristics of the lesions. Diagnostic imaging and image-guided needle biopsies play a central role in the diagnosis, treatment planning, and staging of patients with breast cancer. It includes:[44]

- ✓ ***Mammography*:** Mammography remains the mainstay in breast cancer detection.[45] Diagnostic mammograms are performed in women who have a palpable mass or other symptom of breast disease, a history of breast cancer within the preceding 5 years, or have been recalled for additional imaging from an abnormal screening mammogram. The breast imaging reporting and database system (BI-RADS) is the standardized method for reporting of mammographic findings.[46]

- ✓ ***MRI (Magnetic resonance imaging)*:** Breast MRI has become an integral part of breast cancer diagnosis and management in selected patients. Current indications for breast MRI include evaluation of patients in whom mammographic evaluation is limited by augmentation, determining the extent of disease at the time of initial diagnosis of breast cancer.
- ✓ ***Ultrasound*:** There are several studies supporting the use of adjunctive screening ultrasound in high risk patients with dense breast tissue, which imparts a substantial but accepted number of false positives.[47]

TREATMENT FOR THE BREAST CANCER

The treatment depends upon the size, location and number of tumours and the pathology (subtype, grade and presence of biomarkers[48-49]) of the tumour, as well as age and general health. The choice and combination of treatments are selected on these basis and performed on the patients.

A) SURGERY METHOD: Most women with breast cancer have some type of surgery as part of their treatment. There are different types of breast surgery, and it may be done for different reasons, depending on the situation. For example, surgery may be done to:

- Remove as much of the cancer as possible (breast-conserving surgery or mastectomy).
- Find out whether the cancer has spread to the lymph nodes under the arm (sentinel lymph node biopsy or axillary lymph node dissection)
- Restore the breast's shape after the cancer is removed (breast reconstruction)
- Relieve symptoms of advanced cancer

There are two main types of surgery to remove breast cancer

- ***Breast-conserving surgery*[50-52]** (also called a lumpectomy, quadrantectomy, partial mastectomy, or segmental mastectomy) is a surgery in which only the part of the breast containing the cancer is removed. The goal is to remove the cancer as well as some surrounding normal tissue. How much breast is removed depends on where and how big the tumor is, as well as other factors.
- ***Mastectomy*** is a surgery in which the entire breast is removed, including all of the breast tissue and sometimes other nearby tissues. There are several different types of mastectomies. Some women may also get a double mastectomy, in which both breasts are removed.

B) Radiation Therapy[53-54]: It is treatment with high-energy rays (or particles) that destroy cancer cells. Some women with breast cancer will need radiation, in addition to other treatments. Radiation therapy is used in several situations:

- After breast-conserving surgery (BCS), to help lower the chance that the cancer will come back in the same breast or nearby lymph nodes.
- After a mastectomy, especially if the cancer was larger than 5 cm (about 2 inches), if cancer is found in many lymph nodes, or if certain surgical margins have cancer such as the skin or muscle.
- If cancer has spread to other parts of the body, such as the bones or brain.

The main types of radiation therapy that can be used to treat breast cancer are external beam radiation therapy (EBRT) and brachytherapy.

Fig. 3: Various treatments to cure Breast Cancer.[55]

1) ***External beam radiation*:** This is the most common type of radiation therapy for women with breast cancer. A machine outside the body focuses the radiation on the area affected by the cancer.
- Whole breast radiation
- Accelerated partial breast irradiation
- Chest wall radiation
- Lymph node radiation

2) Brachytherapy: It also known as internal radiation[56], is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, a device containing radioactive seeds or pellets is placed into the breast tissue for a short time in the area where the cancer had been removed(tumor bed).

C) CHEMOTHERAPY: Chemotherapy[57-58] (chemo) uses anti-cancer drugs that may be given intravenously (injected into your vein) or by mouth. The drugs travel through the bloodstream to reach cancer cells in most parts of the body. Occasionally, chemo may be given directly into the spinal fluid which surrounds the brain and spinal cord.

Not all women with breast cancer will need chemo, but there are several situations in which chemo may be recommended:
After surgery (adjuvant chemotherapy[59]): Adjuvant chemo might be given to try to kill any cancer cells that might have been left behind or have spread but can't be seen, even on imaging tests.

Before surgery (neoadjuvant chemotherapy[60]): Neoadjuvant chemo might be given to try to shrink the tumor so it can be removed with less extensive surgery. Because of this, neoadjuvant chemo is often used to treat cancers that are too big to be removed by surgery when first diagnosed (called **locally advanced cancers**).

For advanced breast cancer: Chemo can be used as the main treatment for women whose cancer has spread outside the breast and underarm area, either when it is diagnosed or after initial treatments.

Adjuvant and neoadjuvant drugs[59-62]
- Anthracyclines, such as doxorubicin (Adriamycin) and epirubicin (Ellence)
- Taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere)
- 5-fluorouracil (5-FU) or capecitabine
- Cyclophosphamide (Cytoxan)

Drugs for breast cancer that has spread (advanced breast cancer)[63]
- Taxanes, such as paclitaxel (Taxol), docetaxel (Taxotere), and albumin-bound paclitaxel (Abraxane)
- Anthracyclines (Doxorubicin, pegylated liposomal doxorubicin, and Epirubicin)
- Platinum agents (cisplatin, carboplatin)
- Vinorelbine (Navelbine)
- Capecitabine (Xeloda)
- Gemcitabine (Gemzar)

D) HORMONE THERAPY: Some types of breast cancer are affected by hormones, like estrogen and progesterone. The breast cancer cells have receptors (proteins) that attach to estrogen and progesterone, which helps them grow. Treatments that stop these hormones from attaching to these receptors are called **hormone or endocrine therapy.[64-65]**

About 2 out of 3 breast cancers are hormone receptor-positive. Their cells have receptors (proteins) for the hormones estrogen (ER-positive cancers) and/or progesterone (PR-positive cancers) which help the cancer cells grow and spread.There are several types of hormone therapy for breast cancer. Most types of hormone therapy either lower estrogen levels or stop estrogen from acting on breast cancer cells.

Drugs that block estrogen receptors[65]
These drugs work by stopping estrogen from fueling breast cancer cells to grow.
- Tamoxifen
- Fulvestrant (Faslodex)

Treatments that lower estrogen levels[66]
1) Aromatase inhibitors:
- Letrozole (Femara)
- Anastrozole (Arimidex)
- Exemestane (Aromasin)

Less common types of hormone therapy[67]
Some other types of hormone therapy that were used more often in the past, but are rarely given now include:
- Megestrol acetate (Megace), a progesterone-like drug
- Androgens (male hormones)
- High doses of estrogen

E) TARGETED THERAPY
As researchers learn more about changes in cells that cause cancer, they've been able to develop new types of drugs that specifically target these changes. Targeted drugs work differently from chemotherapy (chemo) drugs. Like chemotherapy, these drugs enter the bloodstream and reach almost all areas of the body, which makes them useful against cancers that have spread to distant parts of the body. Targeted drugs sometimes work even when chemo drugs do not. Some targeted drugs can help other types of treatment work better.[68]

a) Targeted therapy for HER2-positive breast cancer[69]
In about 1 in 5 women with breast cancer, the cancer cells have too much of a growth-promoting protein known as HER2 on their surface. These cancers, known

as HER2-positive breast cancer, tend to grow and spread more aggressively. Different types of drugs have been developed that target the HER2 protein.

Monoclonal antibodies
- Trastuzumab
- Pertuzumab (Perjeta)

Antibody-drug conjugates
- Ado-trastuzumab emtansine (Kadcyla or TDM-1)
- Fam-trastuzumab deruxtecan (Enhertu)

Kinase inhibitors
- Lapatinib (Tykerb)
- Neratinib (Nerlynx)
- Tucatinib (Tukysa)

b) Targeted therapy for hormone receptor-positive breast cancer[70]

CDK4/6 inhibitors
- Palbociclib (Ibrance)
- Ribociclib (Kisqali)
- Abemaciclib (Verzenio)

mTOR inhibitor
- Everolimus (Afinitor)

c) Targeted therapy for women with *BRCA* gene mutations[71]
- Olaparib (Lynparza)
- Talazoparib (Talzenna)

CONCLUSION

Breast cancer is the most frequently diagnosed cancer in women across 140 countries.[1] Approximately 1 in 8 women worldwide have a lifetime risk of developing breast cancer.[72] Breast cancer develops through a multistep process, and the pathogenesis of this disease has not yet been elucidated. In the last decade, the tumor microenvironment and breast CSCs have been identified as contributors to breast tumorigenesis.[10,11] Breast cancer is also influenced by genetic and environmental factors. In summary, breast cancer is preventable. Reducing risk factors and taking chemoprevention are two main measures to prevent breast cancer. However, there's a long way to go in creating public breast cancer awareness. With improvements in sequencing technology, individual genome sequencing may be a powerful method to evaluate the risk of breast cancer. Better medicines with less adverse effects and a favorable risk-benefit ratio need to be developed in the future.

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