



Brief Overview about Breast Cancer

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Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Breast cancer is a significant issue globally. It is the most commonly diagnosed cancer in women. BC accounts for 1 in 4 cases in women globally and contributes to 15% of mortality. As estimated by Global Cancer Observatory (GLOBOCAN) in December 2020, Breast cancer was the most prevalent cancer and the main cause of mortality in Egyptian females. Breast cancer is caused by genetic mutations and DNA damage, both of which are impacted by estrogen exposure. DNA flaws or cancer-causing genes like BRCA1 and BRCA2 may occasionally be inherited. So, having ovarian or breast cancer in the family raises the chance of developing breast cancer. In a healthy person, the immune system targets cells that have aberrant DNA or abnormal development. When this happens to people with breast cancer, tumors develop and spread. Based on which cell origin is involved, breast cancers can be divided into two broad classifications, carcinomas and sarcomas. Carcinomas are breast cancers arising from the epithelial component of the breast, which consists of the cells that line the lobules and terminal ducts. Sarcomas are a much rarer form of breast cancer (<1% of primary breast cancer) arising from myofibroblasts and blood vessel cells.

Keywords: Breast cancer

Introduction

Breast cancer is a significant issue globally. It is the most commonly diagnosed cancer in women. BC accounts for 1 in 4 cases in women globally and contributes to 15% of mortality. There is a large variation in BC survival rates around the world, with an estimated 5-year survival of 80% in high income countries to below 40% for low income countries. According to the World Health Organization, improving BC outcome and survival by early detection remains the cornerstone of breast cancer control. (1)

Epidemiology

Breast cancer is currently one of the most prevalently diagnosed cancers and the 5th cause of cancer-related deaths with an estimated number of 2.3 million new cases worldwide according to the GLOBOCAN 2020 data. In 2008, 8 million deaths were recorded as a result of malignant diseases, and this figure is estimated to reach 11 million by 2030 (2)

According to the WHO, malignant neoplasms are the greatest worldwide burden for women, estimated at 107.8 million Disability-Adjusted Life Years (DALYs), of which 19.6 million DALYs are due to breast cancer. (3)

In order to reduce the occurrence rate of BC and implement early treatment, a number of measures, such as preventative behaviors generally as well as screening programs, are essential. At the moment, the Breast Health Global Initiative (BHGI) is in charge of creating the necessary policies and strategies to provide the most effective BC control globally. (4,5)

Cancer Statistics in Egypt

As estimated by Global Cancer Observatory (GLOBOCAN) in December 2020, Breast cancer was the most prevalent cancer and the main cause of mortality in Egyptian females. (6)

The highest incidence number for specific cancers in Egyptian females was breast (22,038) with a total of (68090) for all cancers. The specific cancer distribution in females is shown in (Fig.).

Pathophysiology

Breast cancer is caused by genetic mutations and DNA damage, both of which are impacted by estrogen exposure. DNA flaws or cancer-causing genes like BRCA1 and BRCA2 may occasionally be inherited. So, having ovarian or breast cancer in the family raises the chance of developing breast cancer. In a healthy person, the immune system targets cells that have aberrant DNA or abnormal development. When this happens to people with breast cancer, tumors develop and spread. (6,7)

Pathogenesis

Breast tumors often begin as ductal hyperproliferation, and after being repeatedly stimulated by numerous carcinogenic stimuli, they progress to benign tumors or even metastatic carcinomas. In the development and spread of breast cancer, tumor microenvironments such stromal effects and macrophages are crucial. (8)

Cancer stem cells (CSCs), a new subclass of malignant cells within tumors, have recently been identified and linked to tumor initiation, escape, and recurrence. This small population of cells has the capacity for self-renewal and is resistant to traditional treatments like chemotherapy and radiotherapy. They may arise from stem cells or progenitor cells in healthy tissues. BCSCs are more likely to originate from luminal epithelial progenitors rather than from basal stem cells. However, further research is required to comprehend bCSCs and create fresh approaches to completely eradicate the bCSCs. The cancer stem cell hypothesis and the stochastic theory are two speculative explanations for the onset and spread of breast cancer. (9)

According to the transit-amplifying cell or stem cell (progenitor cell) hypothesis of cancer, all tumor subtypes are descended from the same stem cells. In stem cells or progenitor cells, acquired genetic and epigenetic alterations will result in various tumor phenotypes. According to the stochastic hypothesis, each tumor subtype develops from just one type of cell (stem cell, progenitor cell, or differentiated cell). Any breast cell can progressively acquire random mutations, and when enough mutations have accumulated, the breast cell can convert into a tumor cell. Despite the fact that both hypotheses are well supported by evidence, neither can fully account for the causes of human breast cancer. (9)

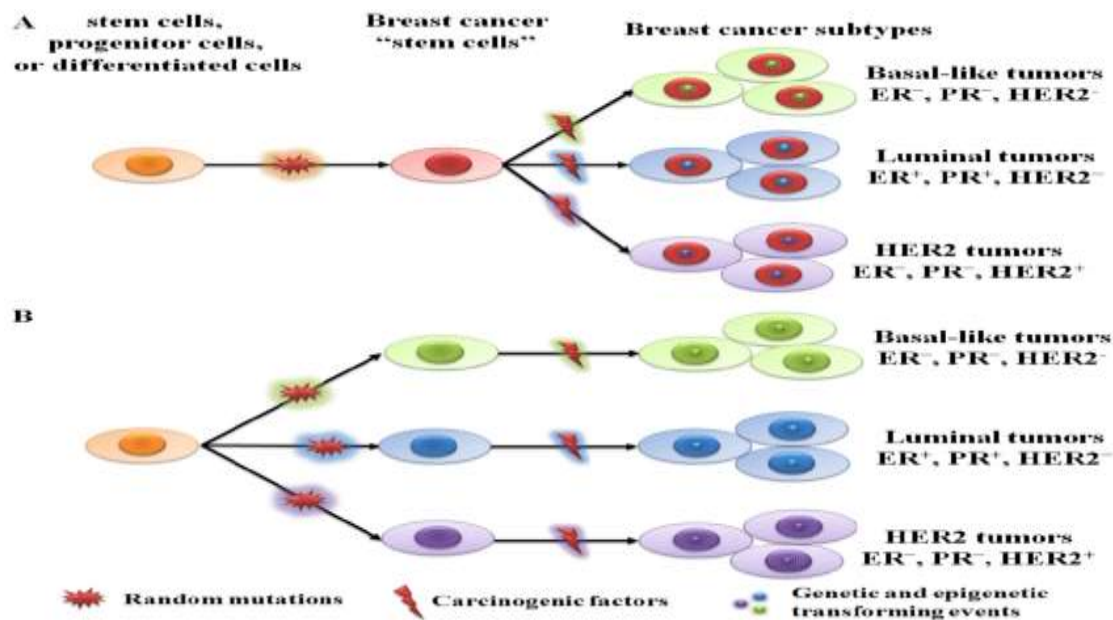


Figure 3. Two

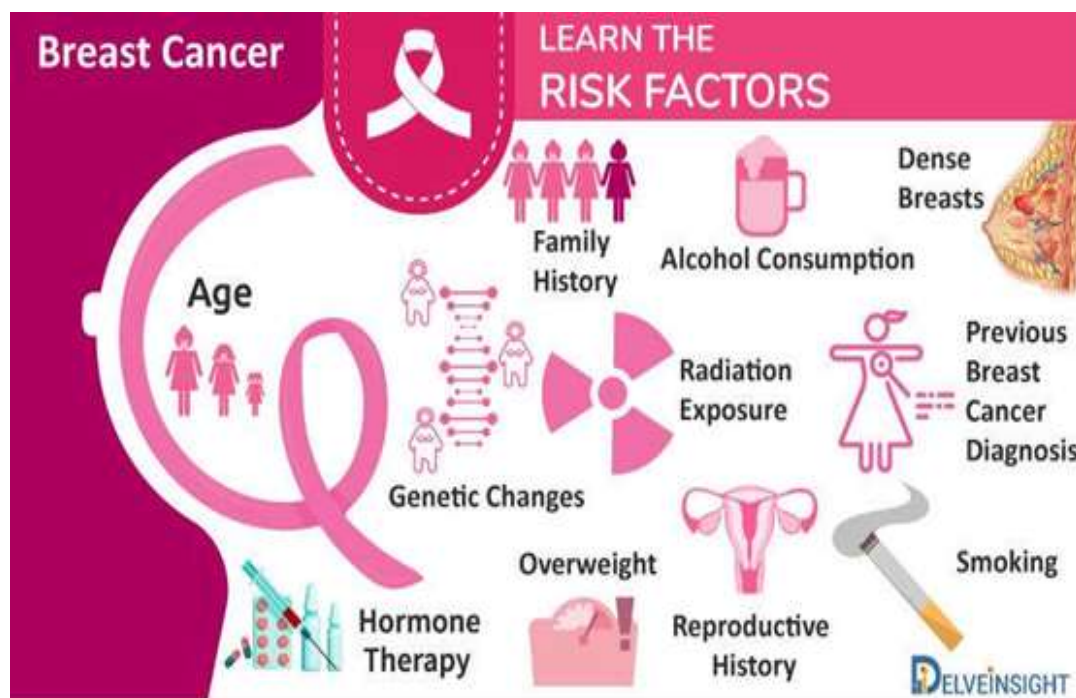
hypothetical theories of breast cancer initiation and progression. (A) All subtypes of tumor are derived from the same stem cells or progenitor cells. Different tumor phenotypes are then determined by subtype-specific transforming events. (B) Each tumor subtype is initiated from a single cell type (stem cell, progenitor cell, or differentiated cell). Random mutations can gradually accumulate in any breast cells, leading to their transformation into tumor cells when an adequate number of mutations have accumulated (9)

Risk factors of breast cancer

Breast cancer is a multifactorial disease, meaning that many different things can cause it. Despite the disease's global prevalence, there are significant regional differences in the disease's incidence, mortality, and survival rates, which may be caused by a variety of factors including population structure, way of life, genetics, and environment. (10)

Classification of women based on risk factors for breast cancer can be effective in improving risk-free methods and designing targeted breast cancer screening programs (11)

The number of risk factors of breast cancer is significant and includes both modifiable factors and non-modifiable factors.



Non-Modifiable Factors

Female Sex

Breast cancer is often a disease that is unique to women and is a rare malignancy in men, accounting for less than 1% of all cases of cancer and The average age of men at the diagnosis is about 67. (12)

Older Age

The second most significant known risk factor for breast cancer is age .When a woman reaches menopause, the incidence rate of breast cancer reaches a peak and then gradually declines or remains constant. (13)

It's interesting to note that there is a correlation between a patient's age and a particular molecular subtype of cancer; for example, aggressive resistant triple-negative breast cancer is most frequently diagnosed in populations under 40, while luminal breast cancer is diagnosed in patients over 70. (14)

Family History

The risk of breast cancer rises noticeably as the number of first-degree relatives affected rises; the risk may even be higher if the affected relatives are under 50. Regardless of age, all patients with a family history of breast cancer have significantly higher incidence rates. (14)

Genetic Mutations

There have been reports linking a number of genetic variants strongly to an elevated risk of breast cancer. BRCA1 (placed on chromosome 17) and BRCA2 (located on chromosome 13) are two important genes that exhibit substantial penetrance. They are mostly related to the development of breast cancer. Although spontaneous mutations are also often reported, autosomal dominant inheritance accounts for the majority of the mutations in the aforementioned genes. TP53, CDH1, PTEN, and STK11 are other genes with a high penetrance of breast cancer. (15)

Race/Ethnicity

In general, white non-Hispanic women continue to have the greatest incidence rate of breast cancer. Contrarily, black women have a considerably greater mortality risk from this cancer, and they also have the lowest survival rates of any group of women. (16)

Reproductive History

Numerous studies have established a clear link between endogenous hormone exposure (particularly progesterone and estrogen) and a heightened risk of breast cancer in females. Therefore, the occurrence of specific events like pregnancy, breastfeeding, the start of menstruation, and menopause, as well as their duration and any accompanying hormonal imbalance, are crucial in terms of a potential induction of the carcinogenic events in the breast microenvironment. (17)

Density of Breast Tissue

premenopausal and postmenopausal females both exhibit this trend, which is that a higher breast tissue density is associated with a higher risk of developing breast cancer. (13)

Breast tissue density testing has been suggested as a promising, quick, non-invasive method for enabling rational surveillance of females at higher risk of cancer (18)

Previous Radiation Therapy

Patients who get radiation therapy before the age of 30 have a higher chance of developing breast cancer, which is strongly related to an individual's age. In order to reduce the risk of secondary cancer, it is essential to choose the right radiation technology. (19)

Modifiable Factors

Chosen Drugs

According to several studies, women who take hormone replacement treatment (HRT) for more than 5 or 7 years are at an elevated risk of developing breast cancer. (20)

Physical Activity

Regular exercise has been proven to lower breast cancer risk in a dose-dependent way, with mild exercise providing a 2% reduction in risk and strenuous exercise conferring a 5% reduction in risk. (21)

Body Mass Index

Epidemiological data show a link between obesity and an increased risk of breast cancer. Obese postmenopausal females have a higher risk of developing estrogen-receptor-positive breast cancer, which intensifies this connection. Additionally, the researchers found a link between higher BMI and more aggressive biological characteristics of tumor's, such as a higher proportion of lymph node metastasis and larger size. (22)

Alcohol Intake

The main factor influencing the risk of cancer is not the kind of alcohol, but rather the amount of alcohol in alcoholic beverages. Increased estrogen levels brought on by alcohol use and resulting hormonal imbalance, which affects the risk of carcinogenesis in female organs, are the cause of this connection. (23)

Smoking

Women who have a history of breast cancer in their families are more likely to smoke for longer periods of time and before their first full-term pregnancy (23)

Insufficient Vitamin Supplementation

Most studies are currently focused on vitamin D supplementation confirming its potentially protective effects. High serum 25-hydroxyvitamin D levels are associated with a lower incidence rate of breast cancer in premenopausal and postmenopausal women (24)

Exposure to Artificial Light

Artificial light at night (ALAN) has been recently linked to increased breast cancer risk. The probable causation might be a disrupted melatonin rhythm and subsequent epigenetic alterations (24)

Intake of Processed Food/Diet

Ultra-processed food is rich in sodium, fat, and sugar which subsequently predisposes to obesity recognized as another factor of breast cancer risk . (24)

Exposure to Chemicals

Females chronically exposed to chemicals present significantly greater plausibility of breast cancer which is further positively associated with the duration of the exposure. The number of chemicals proposed to induce breast carcinogenesis is significant; so far, dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyl (PCB) are mostly investigated in terms of breast cancer since early exposure to those chemicals disrupts the development of mammary glands (25)

Types of breast cancer

Based on which cell origin is involved, breast cancers can be divided into two broad classifications, carcinomas and sarcomas. Carcinomas are breast cancers arising from the epithelial component of the breast, which consists of the cells that line the lobules and terminal ducts. Sarcomas are a much rarer form of breast cancer (<1% of primary breast cancer) arising from myofibroblasts and blood vessel cells. Based on pathological features and invasiveness, common breast cancers can be divided into three major groups: non-invasive (or in situ), invasive, and metastatic breast cancers. (26)

1-Non-invasive (or in situ) breast cancer

- **Ductal carcinoma in situ (DCIS):** It has high potential to become invasive, so early treatment is important.

2-invasive breast cancers are divided into:

- **Invasive Ductal Carcinoma (IDC):** IDC is the most common type of breast cancer and accounts for 80% of all breast cancers being constituted by invasive ductal carcinomas. It is classified into: tubular, medullary, mucinous, papillary, and cribriform carcinoma of the breast.
- **Invasive Lobular Carcinoma (ILC):** ILC is the second most common type of breast cancers and accounts for approximately 10–15% of all breast cancers. It is more common in older women.

3-Metastatic breast cancer

also known as stage IV or advanced breast cancers which have spread to other organs in the body. Metastases from breast cancers can be found in lymph nodes in the armpit, and/or in distant sites such as the lung, liver, bone and brain. (27)

Less common types of breast cancer

- **Inflammatory breast cancers:** it makes the skin red and warm.
- **Paget disease of the breast:** It starts in the breast ducts, spreads to the skin of the nipple and then expands to the areola.
- **Papillary carcinoma:** Most papillary carcinomas are invasive, and are treated in the same manner as IDCs.
- **Phyllodes tumor:** They develop in the stromal cells of the breast.
- **Angiosarcoma of the breast:** It originates from epithelial cells that line blood or lymph vessels. (28)

An alternative classification based on gene expression profiles identifies four molecular types: ER \square positive luminal \square like, basal \square like, ErbB2 \square positive and normal \square like. (29)

- **Diagnosis**

- 1) **Taking a family history**

- 2) **Clinical diagnosis**

- Most early breast cancer patients are asymptomatic and discovered during screening mammography.





- The most common symptom of breast cancer is a new lump or mass (although most breast lumps are not cancer). A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be also soft, round, tender, or even painful. **.(30)**

Other possible symptoms of breast cancer include:

- Swelling of all or part of a breast (even if no lump is felt)
- Skin dimpling (sometimes looking like an orange peel)
- Breast or nipple pain
- Nipple retraction (turning inward)
- Nipple or breast skin that is red, dry, flaking, or thickened
- Nipple discharge (other than breast milk)
- Swollen lymph nodes under the arm or near the collar bone (Sometimes this can be a sign of breast cancer spread even before the original tumor in the breast is large enough to be felt. **(30)**)

CLINICAL Staging

Staging is performed to group patients into risk categories that define prognosis and guide treatment recommendations for patients with a similar prognosis. Breast cancer is classified with the TNM classification system, which groups patients into 4 stage groupings based on the primary tumor size (T), the regional lymph nodes status (N), and if there is any distant metastasis (M). The most widely used system is that of the American Joint Committee on Cancer. **(31)**

Tumor size T	Tumor size < 2 cm  T1	Tumor size 2-5 cm  T2	Tumor size > 5 cm  T3	Tumor extends to skin or chest wall  T4
Lymph Nodes N	N0 No lymph node metastasis	N1 Metastasis to ipsilateral, movable, axillary LNs	N2 Metastasis to ipsilateral fixed axillary, or IM LNs	N3 Metastasis to infraclavicular/supraclavicular LN, or to axillary and IM LNs
Metastasis M	M0 No distant metastasis	M1 Distant metastasis	LNs= Lymph Nodes; IM= Internal Mammary	

Diagnostic Imaging

Mammography

Mammography is still the gold standard for detecting breast cancer. Diagnostic mammograms are conducted on women who have a palpable tumor or other breast illness symptom, a history of BC within the last 5 years, or who have been recalled for further imaging due to an abnormal screening mammography. Special views on diagnostic mammography include focused compression of one region of breast tissue or magnification pictures. **(32)**

MRI

Current indications for breast MRI include determining the extent of disease at the time of initial diagnosis of breast cancer, assessing response to neoadjuvant chemotherapy by imaging before, during, and/or after treatment and identifying residual illness in patients with positive margins following lumpectomy. (33)

Ultrasound

Current indications for breast ultrasonography include palpable findings (including as the initial imaging test for palpable findings in patients younger than 30 years, pregnant, or lactating), abnormalities or suspected abnormalities on mammography or MRI, problems with breast implants, suspected underlying mass in the setting of micro-calcifications or architectural distortion on mammography, and supplemental screening in women at high risk for breast cancer who are not currently screened. Ultrasonography may also provide real-time imaging, making it perfect for interventional operations. (34)

Fine-Needle and Core Biopsy:

The diagnostic usage of these procedures includes a morphological diagnosis along with the application of necessary ancillary techniques such as performing immunochemistry for estrogen and progesterone receptors in the malignant epithelial neoplasms. Both the procedures can be performed for palpable and nonpalpable lesions of the breast with or without the assistance of radiology. (34)

PROGNOSTIC INDICATORS

Estrogen receptor

Estrogen receptor (ER) expression is an essential diagnostic factor since it is seen in roughly 70-75% of invasive breast carcinomas. ER expression may be a predictive factor patients with high ER expression frequently have much better clinical outcomes (35)

progesterone receptor status

Both ER and PR are abundantly expressed in breast cancer cells and are thought to be diagnostic and prognostic indicators of breast cancer (particularly ER-positive ones). Greater PR expression is linked with improved overall survival, time to recurrence, and time to treatment failure or advancement, whereas lower PR levels are associated with a more aggressive course of the illness, as well as poorer recurrence and prognosis. (36)

Human Epidermal Growth Factor Receptor 2

The expression of human epidermal growth factor receptor 2 (HER2) accounts for approximately 15–25% of breast cancers and its status is primarily relevant in the choice of proper management with breast cancer patients; HER2 overexpression is one of the earliest events during breast carcinogenesis. HER2 amplification leads to further overactivation of the pro-oncogenic signaling pathways leading to uncontrolled growth of cancer cells which corresponds with poorer clinical outcomes in the case of HER2-positive cancers (37)

Treatment Strategies

Surgery

There are two major surgical methods for removing breast malignant tissues: (1) breast-conserving surgery (BCS) and (2) mastectomy. However, the use of BCS is typically associated with much better cosmetic outcomes, a lower psychological load of a patient, and a lower number of postoperative problems. The European Society for Medical Oncology (ESMO) guidelines for patients with early breast cancer base treatment decisions on tumor size, surgical feasibility, clinical phenotype, and the patient's wish to preserve the breast. (38)

2. Chemotherapy

Chemotherapy is a systemic cancer treatment that can be neoadjuvant or adjuvant. The best option is determined by the characteristics of the breast tumor; chemotherapy may also be used in secondary breast cancer. Neoadjuvant chemotherapy is used for locally advanced breast cancer, inflammatory breast cancers,

downstaging large tumors to allow BCS, or in small tumors with poor prognosis molecular subtypes (HER2 or TNBC) that can help identify prognostics and predictive factors of response and can be given intravenously or orally. (39)

3. Radiation Therapy

Radiotherapy is a type of local cancer treatment that is usually given after surgery and/or chemotherapy. It is done to guarantee that all of the malignant cells are killed, reducing the likelihood of a return of breast cancer. Furthermore, in the case of metastatic or unresectable breast cancer, radiation treatment is beneficial. (39)

4. Endocrinal (Hormonal) Therapy

Endocrinal therapy might be used either as a neoadjuvant or adjuvant therapy in patients with Luminal-molecular subtype of BC; it is effective in cases of breast cancer recurrence or metastasis. Since the expression of ERs, a very frequent phenomenon in breast cancer patients, its blockage via hormonal therapy is commonly used as one of the potential treatment modalities. Endocrinal therapy aims to lower the estrogen levels or prevents breast cancer cells to be stimulated by estrogen. Drugs that block ERs include SERMs (tamoxifen, toremifene) and SERDs (fulvestrant) while treatments that aim to lower the estrogen levels include AIs (letrozole, anastrozole, exemestane) (40)

5. Biological Therapy

Biological treatment (targeted therapy) can be given before or after surgery as neoadjuvant therapy. Trastuzumab, pertuzumab, trastuzumab deruxtecan, lapatinib, and neratinib are examples of key medications used in HER2-positive breast cancer patients. In the instance of Luminal, HER2-negative breast cancer, premenopausal women are more likely to get everolimus -TOR inhibitor with exemestane, whereas postmenopausal women are more likely to take CDK 4-6 inhibitor palbociclib or ribociclib concurrently with hormone treatment. Atezolizumab is approved in triple-negative breast cancer, while denosumab is approved in case of metastasis to the bones (41)

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