Review Article

Breast Cancer: A Comprehensive Review of Epidemiology, Risk Factors, Diagnosis and Treatment

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ABSTRACT

Breast cancer is a prevalent and complex disease globally, with various subtypes and treatment options. Early detection and treatment are crucial to reducing mortality rates. This article discusses the epidemiology, risk factors, diagnosis, and treatment of breast cancer, including surgery, radiation, chemotherapy, immunotherapy, and genetic testing. It highlights the importance of understanding breast cancer genetics and molecular subtypes, such as Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC), to develop effective treatment strategies. The article also explores the role of digital mammography, ultrasound, and magnetic resonance imaging in breast cancer diagnosis and the potential benefits of immunotherapy and targeted therapies. Overall, it emphasizes the need for a multidisciplinary approach to breast cancer management, considering individual patient characteristics, tumor biology, and genetic profiles.

Keywords: Breast cancer, chemotherapy, immunotherapy, Tumor Cell Vaccine, surgery.

INTRODUCTION

Breast cancer is the second most common cancer diagnosed in women, after nonmelanoma skin cancer, and the leading cause of cancer-related deaths among women globally. In the United States, yearly, about 316,000 patients are diagnosed with breast cancer, making it the second most common cause of cancer-related deaths among women, after lung cancer [1]. It is anticipated that both in industrialized and emerging nations, the incidence and prevalence of cancer will continue to increase as the population ages. An estimated $1.16 trillion was spent on cancer each year. almost 2% of the world's gross domestic product in 2010, and it is still growing at an exponential rate. Breast cancer is still the most common cause of cancer in women, and the continued treatment of breast cancer patients is thought to be one of the key factors driving up the cost of cancer care [2].

The most common disease in the UK and worldwide, breast cancer refers to a variety of cancers that develop in the mammary glands (world Health Organization, 2021). To identify, evaluate, and refer patients with probable breast cancer, clinicians need to be competent and self-assured [3]. Digital mammography (DM), digital breast tomosynthesis (DBT), ultrasound (US), magnetic resonance imaging (MRI), or a mix of these are frequently used for breast imaging. In DM, a digital X-ray detector gathers X-rays that are sent through the breast to provide a two-dimensional (2D) picture of the breast. It is a quick and simple method. Nevertheless, it has the tissue superposition problem [4].

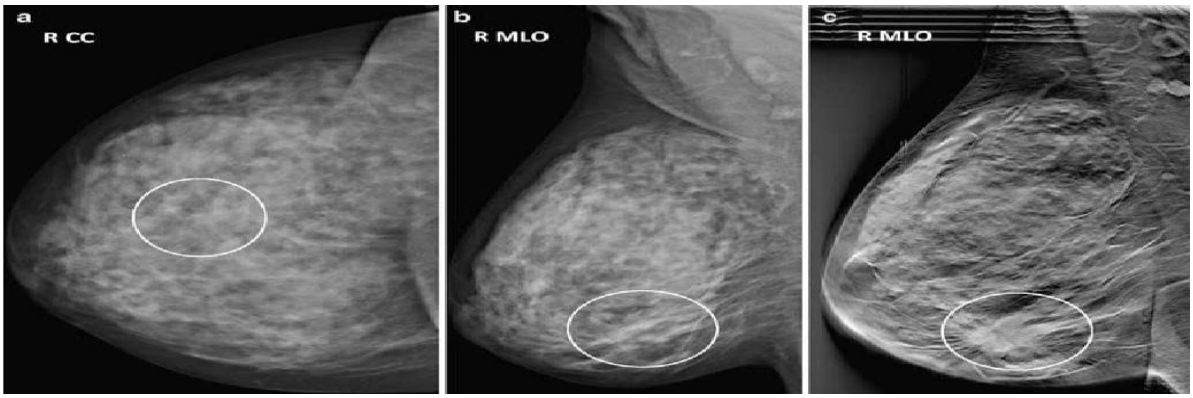

Figure 1: Digital monography, ultrasound and magnetic resonance scans of a 45 years old women with an infiltrating ductal carcinoma in the breast [4].

One of the most prevalent malignant tumor is breast cancer. Breast cancer is the most prevalent malignant tumor among Chinese women, and its incidence rate is rising annually, according to the Chinese Women's Survey. The key to reducing the mortality of breast cancer is early detection and Treatment. At today, mammography is the most extensively used approach to detect breast cancer [5]. Human development and the incidence of breast cancer are closely connected. Income alone is not as valuable as the human development index, which is a composite measure of wealth, education, and life expectancy. Breast cancer incidence is higher in nations with the highest levels of

human development [6]. Women with mammographically dense breast tissue may benefit from such a customized screening program. In 2022, the European Society of Breast Imaging (EUSOBI) declared that it would now recommend screening breast MRIs every two to four years for women aged 50 to 70 with extremely dense breast tissue [7]. Over the past few decades, international research efforts have brought attention to the benefits and drawbacks of different immunotherapeutic strategies. In breast cancer, immune checkpoint inhibitors (ICIs) have been studied both alone and in conjunction with chemotherapy and targeted treatments such cyclin-dependent kinase (CDK) 4/6 inhibitors, antibody-drug conjugates, monoclonal antibodies, and others [8]. Genetics of breast cancer (BC) has emerged as a key component of BC treatment. It affects guidelines for screening, follow-up, prevention, and treatment in women who carry a germinal BC susceptibility gene. Finding patient subgroups with a distinct prognosis or responsiveness to therapy is also beneficial [9]. Invasive ductal carcinoma, invasive lobular carcinoma, and mixed ductal-lobular carcinomas are the three primary histological subtypes of breast cancer. Receptors such HER2 protein receptors, triple-negative (no molecular receptors mentioned above), and oestrogen or progesterone receptors (hormonal receptors) are found on the surface of cancer cells or are overexpressed. A patient's prognosis and course of treatment are significantly impacted by the fact that they are found in cancer cells but not in healthy ones[10].

1. Nipple Abnormalities [11]

IBC may be characterized by nipple changes, such as crusting of the nipple/areolar complex, nipple inversion, or nipple fattening. However, further diagnostic criteria are needed to diagnose IBC since nipple anomalies might be explained by a variety of other benign or malignant etiologies. Fig. provides examples of these clinical criteria.

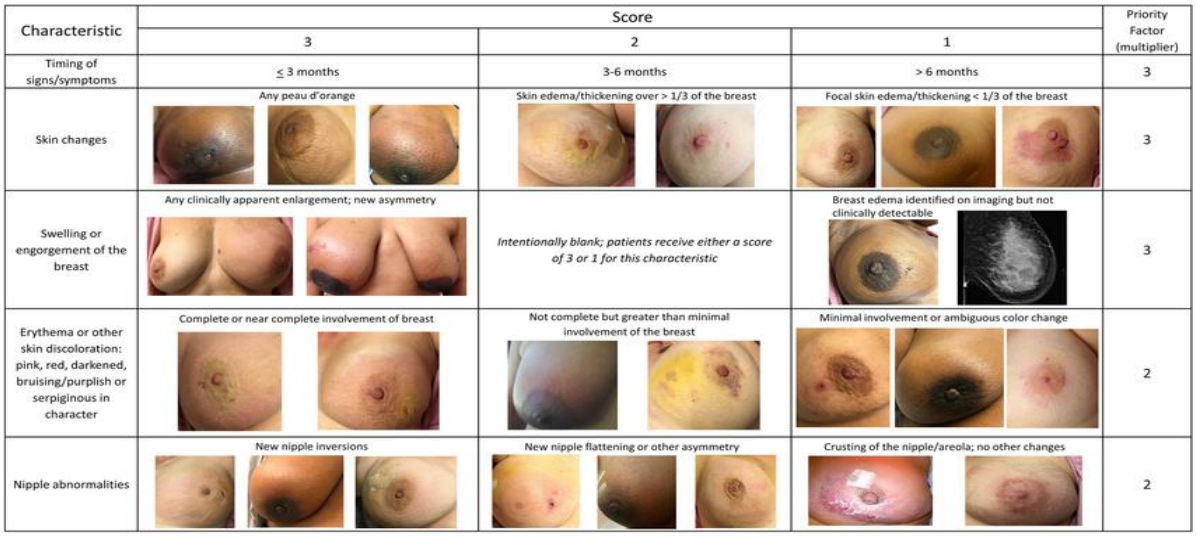

Figure 2: Clinical characteristic of inflammatory breast cancer.

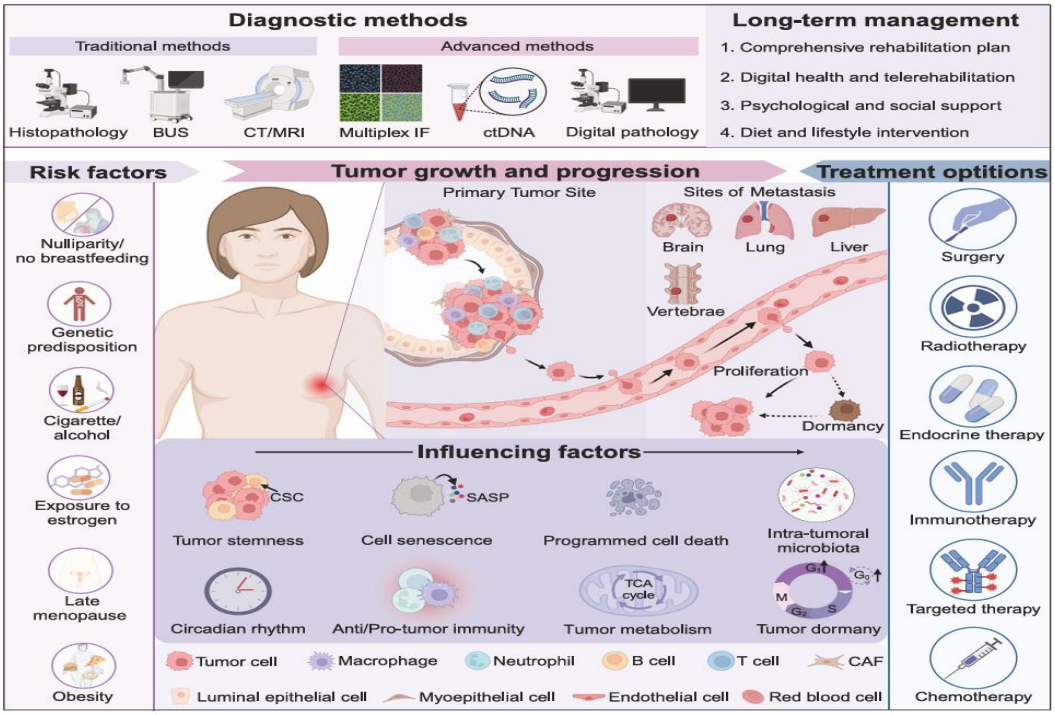

Figure 3: Comprehensive overview of breast cancer pathogenesis and treatment.

2. Epidemiology and risk factors of breast cancer [12]

There are several subtypes of breast cancer, each with its own epidemiological characteristics, making it a diverse disease. Around 15% of all cases identified worldwide are fatal, and breast cancer makes up around one-third of all female cancers. The global distribution of breast cancer is influenced by a complex interaction of lifestyle, environmental, and hereditary variables.

3. Multidisciplinary considerations in the treatment of young adults with breast cancer [13]

Although adjuvant radiation with tumor bed boost should be administered after breast-conserving surgery to promote local control, young age alone is not a contraindication. Young women's systemic medicine choices, like those for older women, are based on patient and tumor characteristics, including genetic risk profile where applicable, which predicts recurrence risk and probable response to treatment.

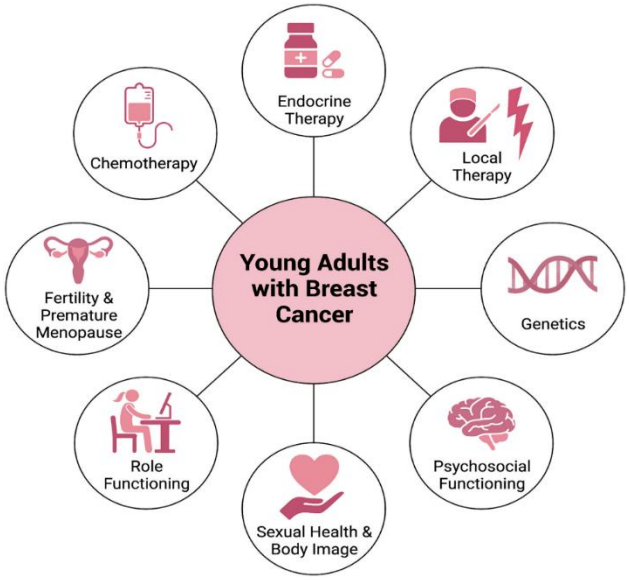

Figure 4: Multidiciplinary concideration in the treatment of young adults with breast cancer.

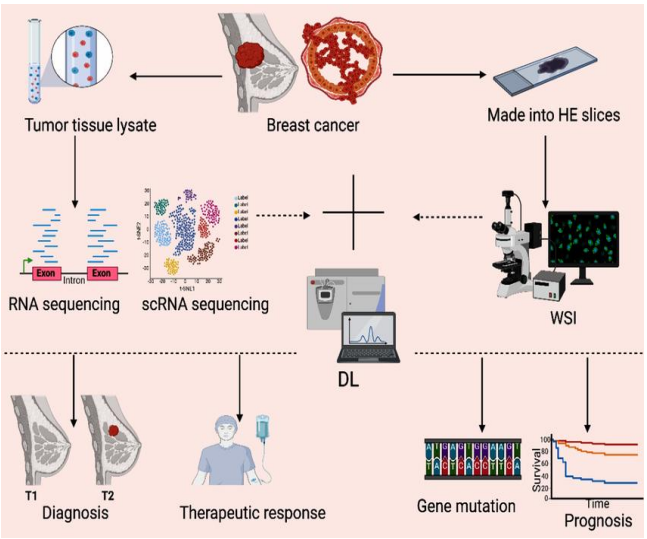

Figure 5: Specific application of DL in breast cancer

4. Application of dl in molecular typing of breast cancer[14]

To better direct therapy and forecast prognosis, breast cancer is classified into many subtypes using molecular markers and gene expression patterns. This process is known as molecular typing of breast cancer. Triple-negative (TNBC), HER2-positive, and hormone receptor-positive (HR+) breast tumors are included in the primary molecular type. The pathophysiology, biological behavior, and therapeutic response of each subtype vary greatly.

5. Types of cancer treatment[15]

1) Local Treatment

a. Surgery

b. Radiation

2) Systemic Treatment

a. Chemotherapy

b. Immunotherapy

5.1 Local Treatment

5.1.1 Surgery:

Any stage of pregnancy is a safe time to have breast cancer surgery. Standard concentrations of currently used anesthetics are recognized to have no teratogenic effects. The degree of ionization, molecular mass, protein binding, and lipophilicity all affect how well anesthetic drugs pass through the placenta. Preferences, gestational age, and tumor and patient characteristics should all be taken into consideration when deciding whether to do surgery [16]. For individuals with early-stage breast cancer, BCS is the best surgical choice. When necessary, oncoplastic procedures may be employed to provide favorable cosmetic results. For patients who cannot obtain negative margins and who are contraindicated for radiation (RT), BCS is contradicted. If R0 resection is verified, BCS may also be a possibility for individuals with a multifocal and multicentric disease [17].

5.1.2 Radiation:

Post-operative radiation treatment (RT) has the same indications as for older patients, but there is more evidence of the advantages of PMRT (Perinatal Mortality Review Tool) for young women. Following implant-based breast reconstruction, PMRT is linked to an increased incidence of capsular contracture (>30%) and reconstructive failure (>15%). Reconstructive failure is more frequent with PMRT with tissue expanders, although capsular contracture rates are lower [18]. Patients with breast cancer are often treated with radiation therapy. Patient's outcomes may be enhanced by looking into the underlying mechanisms of radiation resistance in breast cancer [19].

Table 1: Stages of breast cancer treatment [1]

Breast Cancer Treatment	Classification	Surgery	Radiation
0	In situ	Lumpectomy or mastectomy with sentinel lymph node biopsy	Yes, if lumpectomy
I and II	Early invasive	Commonly lumpectomy puls sentinel lymph node biopsy; mastectomy may be needed for larger tumors or because of patient choice	Yes, if lumpectomy or high-risk, node-positive diasease with mastectomy
III	Locally advanced	Commonly mastectomy puls axillary lymph node dissection	Yes, if lumpectomy or high-risk, node-positive diasease with mastectomy
IV	Metastatic	Mastectomy or lumpectomy may be appropriate when tumor burden impact quality of life	Radiation may be appropriate when tumor burden impacts quality of life.

5.2 Systemic Treatment:

Over the previous 50 years, significant progress has been achieved in the development of systemic treatments for breast cancer. The management of breast cancer has changed from primarily local therapies to a combination of local and systemic treatments with the introduction of new chemotherapeutic drugs, endocrine therapy, and targeted medicines for the human epidermal growth factor receptor (HER2/neu) [20].

5.2.1 Chemotherapy:

One of the primary treatment approaches for breast cancer is chemotherapy. One of the biggest challenges in treating breast cancer is chemoresistance. It would be easier to create new targets and coping mechanisms if one understood the process of chemoresistance. In breast cancer, CircRNAs contribute to the regulation of chemoresistance [19]. Several chemotherapy drugs, including gemcitabine, paclitaxel, carboplatin, and cisplatin, had been suggested for a phase I clinical study using PARPi. The ABCB1 gene is commonly demonstrated to be elevated following chemotherapy due to chromosomal translocations in ovarian and breast malignancies. Elizabeth and associates found that in recurrent breast cancer, numerous transcriptional fusions of ABCB1 increase substrate chemotherapeutic sensitivity [21].

5.2.2 Immunotherapy:

In recent years, immune checkpoint inhibitors (ICIs) have emerged as the gold standard for treating a wide range of cancers, including Hodgkin's lymphoma, lung cancer, urological tumors, and melanoma. The enrichment of TILs provides justification for immunotherapy studies in TNBC. Furthermore, it is very common for the immune cells that penetrate the tumor to express PD-L1 [22].

6. Different Subtypes of Breast Cancer

Investigating breast cancer at the molecular level is essential to properly addressing the disease's rising burden. Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC) are the four molecular subtypes of breast cancer. The amount of Ki67 and the positivity of the estrogen, progesterone, and HER2 receptors serve as the basis for this categorization. Every subtype has unique treatment strategies, prevalence trends, and risk factors [23].

Luminal A: These cancers are human epidermal growth factor receptor negative (−ve HER2), but they are estrogen-receptor and/or progesterone-receptor positive (+ve ER and/or +ve PR) [24].

Luminal B: Tumors in this category have high levels of the protein Ki-67 and are positive for ER and HER2, but negative for PR. The prognosis for luminal B BCs is somewhat poorer than that of luminal A BCs, and they mostly develop more quickly [24].

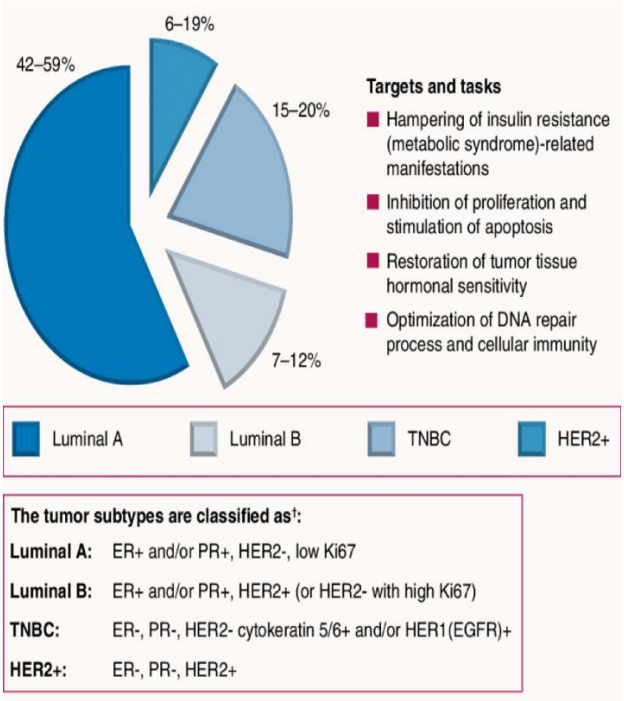

Figure 6: Representation for different breast cancer subtype [24].

7. Vaccine types for breast cancer [25].

1. The Peptide Vaccine
2. Vaccine Based on Proteins
3. Vaccine for Carbohydrate Antigen
4. Tumor Cell Vaccine
5. Vaccine Based on DNA
6. Vaccine Based on DC
7. Vaccine for DC-Tumor Cell Fusion

8. Mechanism of resistance in breast cancer [26]

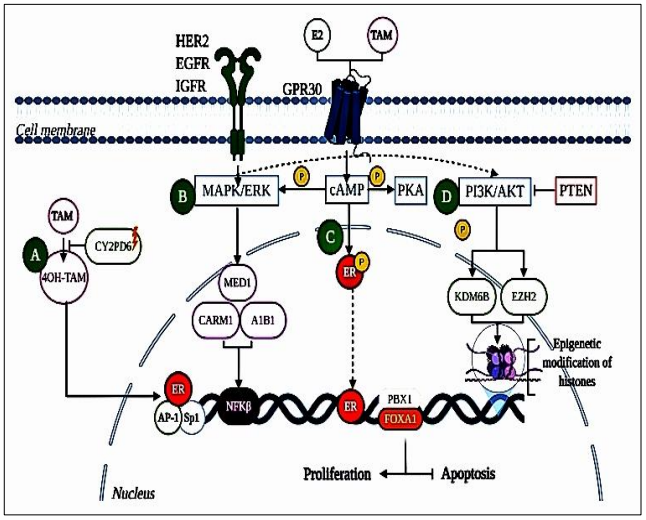

Figure 7: Mechanisms of endocrine resistance in breast cancer.

The standard treatment for ER+ breast cancer is thought to be endocrine therapy. ER modulators including tamoxifen, selective ER down regulators (FUL), and aromatase inhibitors (AIs) are used in the treatment. Tamoxifen is often not effective in treating patients with ER cancers. This process happens when cancer cells that were previously sensitive to hormone therapies, such as aromatase inhibitors or tamoxifen, change and create defenses against the drugs inhibitory effects. Endocrine-resistant breast cancer arises as a result of the complex interaction of signaling pathways, genetic alterations, and microenvironmental variables.

9. Breast cancer genetic testing [27]

The expression levels of the hormone receptors (HRs), progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor-2 (HER-2), are now used to categorize breast cancer into several subtypes. Drug sensitivity and biological characteristics vary throughout the molecular subtypes of breast cancer. Despite recommendations recommending specialized treatments for various subtypes of breast cancer, precision medicine has yet to achieve its full potential.

Despite their frequent interchangeability, genetics and genomics differ significantly in a few key ways. While genomics is the study of genes, their functions, and associated methods, genetics is the study of heredity. Genetics and genomics vary primarily in those genetics assesses the content and function of a single gene [28].

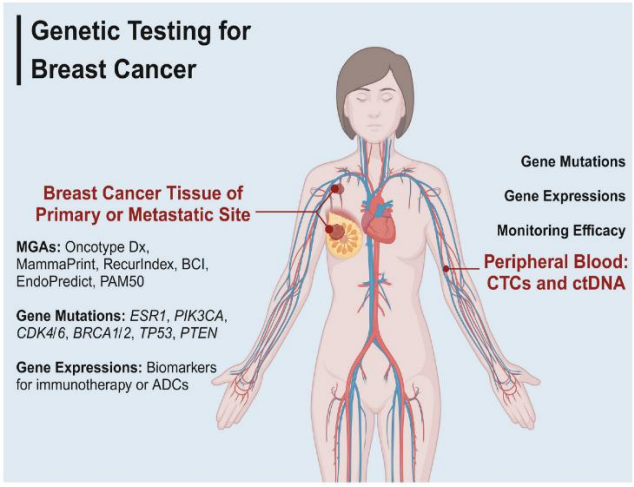

Figure 8: Genetic testing for breast cancer.

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