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Review Paper

A comprehensive review of breast cancer: epidemiology, symptoms, risk factors, histopathology, and treatment approaches

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ABSTRACT:
Mutations in genes controlling cell cycle, DNA replication, apoptosis, etc., are found associated with cancer development. Including this, exposure to carcinogens also enhances the risk of developing cancers. There are many risk factors linked with breast cancer such as age, female gender, lifestyle, hormone therapy, family or personal history, etc. Breast cancers are one of the most common cancers found in females around the world. But these are not exclusively observed in females. Some breast cancer cases are also observed in men. Breast cancers are also categorized into invasive ductal carcinoma and invasive lobular carcinoma. It is also found that some breast cancer cases are also associated with hereditary susceptibility. Some important mutations associated with breast cancers are mutations in BRCA 1, BRCA 2, and TP53, etc. This article provides a comprehensive overview of breast cancer, covering risk factors, symptoms, and histopathological studies. Understanding the multifaceted aspects of breast cancer is crucial for early detection, diagnosis, and effective treatment. This article addresses the overview of breast cancer epidemiology, risk factors, and classification with an emphasis on molecular types, prognostic biomarkers, as well as possible treatment modalities.

Keywords: Breast cancer; Epidemiology; Risk factors; Symptoms; Histopathology; Diagnosis; Treatment

INTRODUCTION:

It is well known that cancer is caused by uncontrolled cell division. At the molecular level, mutations in tumor suppressor genes (for example BRCA gene and p53gene), proto-oncogene (for example HER_2 gene), and DNA repair genes, etc (National Cancer Institute, 2024; Eldridge, 2023). There are multiple factors that are responsible for the development and progression of factors. Cancer can start anywhere in the body. Cancer can spread, invade, and enter into distant organs by a process called metastasis (National Cancer Institute, 2024). Including this, a large number of mutagenic agents like physical agents, chemical agents, UV radiation, and γ-radiation, such agents are commonly termed carcinogens. It is also observed that long-term use of tobacco has an increased risk of lung cancer (Basu, 2018). Cancer cells accumulate a large number of mutations and out of them, only a few are responsible for the progression of cancer. Such mutations are termed as termed driver mutations (Ostroverkhova et al., 2023). As germline mutations are considered key factors associated with heritable diseases, similarly somatic mutations are primarily responsible for cancer (Shendure and Akey, 2015). Furthermore, epigenetic changes are found linked with cancer (Eldridge, 2023).

Histologically, the breast comprises lobules, ducts, and connective tissues. Lobular structures are related to terminal duct lobular units (TDLU). Breast cancer depends on the types of cells in convert into cancer. Commonly breast cancers are developed in lobules or ducts. Later these spread outside the breast via a process of metastasis. The breast cancers are commonly categorized into invasive ductal carcinoma and invasive lobular carcinoma. Both types of breast cancer can spread to other parts of the body.

Invasive ductal carcinoma (IDC) is the most common type contributing about 70% to 80% of breast cancer cases. The cancer develops in ducts and spreads to other parts of the breast. Patients with IDC experience a lump in the breast or underarm. The small lump may be observed by a mammogram. Invasive lobular carcinoma (ILC) being the second most common type of breast cancer contributes about 10% to 15% of cases. This cancer develops in lobules and may spread to nearby breast tissues. ILC typically does not make a lump. Although, it appears as thickened connective tissue. Thus, it is difficult to visualize by mammogram. Furthermore, in comparison to IDC, the ILC is more

likely to develop in both breasts (CDC, Breast Cancer, 2024). Including these types, there are other types of breast cancers such as Inflammatory breast cancer, and Paget's disease of the breast.

Breast cancer is a heterogeneous clinical condition that has an association with genetic and environmental factors. Breast cancer stem cells play a key role in the development of different tumors, and including this, these cells are also posing the main challenge in cancer treatment. Breast cancer stem cells demonstrate unique growth abilities including differentiation potential, self-renewal, and resistance to many anti-cancer agents like chemotherapy and/or radiotherapy (Geng et al., 2014). It was found that differential genes in SIK2+ epithelial cells may work as key therapeutic targets for breast cancer. It was also suggested that SIK2 may be a potential prognostic and predictive biomarker for breast cancer and it may be an oncogenic messenger (Wu et al., 2023).

EPIDEMIOLOGY:

Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide with more than 2.3 million new cases in 2020. It has been analyzed that about 685000 deaths were associated with breast cancer in 2020 (Arnold et al., 2022). World Health Organization's fact sheet (Mar 2024) on breast cancer estimated about 670,000 deaths at the global level in 2022. Moreover, 2.3 million women were identified with breast cancer. Including this, it was also observed that about half of all breast cancers develop in women with no specific risk factors except sex and age. Breast cancer occurs in every country, and surprisingly about 0.5–1% of breast cancers are also reported in men (WHO, Breast Cancer, 2024). As per Cancer Research UK, breast cancer is the most common cancer in women UK. Furthermore, in the UK, one in seven women develop breast cancer during their lifetime. It was estimated that in the UK, every year around 390 men, and 56,400 women are diagnosed with breast cancer (Cancer Research UK, 2024).

World Health Organization also revealed significant breast cancer burden inequities according to the Human Development Index (HDI). For example, in countries with a very high HDI, 1 out of 12 women is expected to be diagnosed with breast cancer in their lifetime, and death of 1 out of 71 women. While, in countries with a low HDI, 1 out of 27 women is diagnosed with breast cancer in their lifetime, and death of 1 out of 48 women.

SYMPTOMS AND RISK FACTORS:

World Health Organization suggested breast cancer represents combinations of symptoms in the advanced stage. Although most breast lumps are not cancer. Some symptoms of breast cancer may be as follows (WHO, Breast Cancer, 2024);

1. Variation in size, shape, or appearance of the breast
2. Observation of breast lump or thickening, generally no pain
3. Dimpling, redness, pitting, or other changes in the skin
4. Change in nipple appearance or areola
5. Discharge of abnormal or bloody fluid from the nipple

Although, females are more prone (about 99%) to develop breast cancer however 0.5-1% of breast cancers also develop in men. Risk factors for breast cancer include a combination of factors such as age, ethnicity, mutations, dense breast, family history of breast or ovarian cancer, personal history of breast cancer, reproductive history, previous treatment using radiation therapy, and exposure to the drug diethylstilbestrol (DES). Some other factors are lifestyle, obesity, physical inactivity, hormone replacement therapy, use of contraceptive pills, smoking and alcohol consumption (CDC, Breast Cancer, 2024; Cancer Research UK, 2024). The incidence and death rates due to breast cancer have increased due to the change in risk factor profiles, better cancer registration, and cancer detection. It is suggested that about 5%-10% of cases in women are associated with hereditary susceptibility due to mutations in autosomal dominant genes (Sheikh et al., 2015).

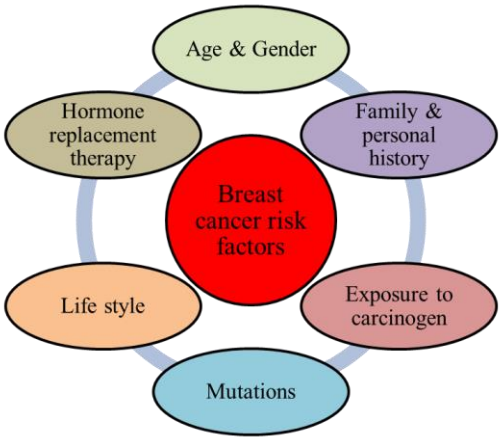

Fig. 1: Some examples of breast cancer risk factors

BRCA genes BRCA1 and BRCA2 are mainly associated with breast cancer development but other genes also play important roles, such as the PALAB2 gene, ATM gene, CHEK2 gene, Li-Fraumeni syndrome due to the TP53 gene, Peutz Jeghers Syndrome due to SKT11gene, PTEN Hamartoma tumor syndrome, etc (Cancer Research UK, 2024; Kleibl and Kristensen, 2016). These genes are also categorized as high penetrance, and moderate-penetrance breast cancer-susceptibility genes (Kleibl and Kristensen, 2016; Łukasiewicz et al., 2021). BRCA1 and BRCA2 genes are found associated with 20-60% risk of ovarian cancer in lifetime, and 85% risk of breast cancer in lifetime (Foretova et al., 2019).

Table 1: Some examples of genes associated with breast cancer development (Łukasiewicz et al., 2021)

S. No.	Gene	Associated cancers	Major Functions
1.	BRCA1, BRCA 2	Breast cancer Ovarian cancer	DNA repair Cell cycle control
2.	TP53	Breast cancer Colorectal cancer	DNA repair Cell cycle control Apoptosis, Senescence, Cellular metabolism
3.	PTEN	Breast cancer Prostate cancer	Proliferation, invasion, and metastasis
4.	STK11	Breast cancer Pancreatic cance	Cell cycle control Maintenance of energy homeostasis
5.	ATM	Breast cancer Lymphoma Ataxia-teleangiectasia	control cell growth and repair damaged DNA
6.	PALAB2	Breast Cancer, Pancreatic cancer Fanconi anemia	DNA Repair
7.	CHEK2	Breast cancer Li-Fraumeni syndrome Prostate cancer Osteosarcoma	Cell cycle control

DIAGNOSIS OF BREAST CANCER:

Early diagnosis plays a key role in disease management and treatment Following approaches are followed to perform diagnosis of breast cancer. According to the US Preventive Services Task Force, women of age group 40 to 74 years and are at average risk for breast cancer are recommended to be investigated by mammogram at the interval of every 2 years (CDC, Breast Cancer, 2024). There are many types of investigation recommended to check the presence of breast cancer (Canadian Cancer Society, Diagnosis of Breast Cancer, 2024). These are as follows;

Health history and physical exam:

This is a preliminary examination to learn about family history, personal history, history of other diseases, hormone replacement therapy, presence of other types of cancer, exposure to risk factors, etc.

Mammography and ultrasound:

Mammograms are low-dose X-rays used to diagnose breast cancer. These can be used to investigate abnormal areas during biopsy.

Ultrasound is used to rule out if the breast lump is a solid tumor or a cyst. Ultrasound may be used to guide to an area that needs to be examined during biopsy. Ultrasound is also used to check the spread of cancer to liver.

Biopsy:

Biopsy is considered as a definitive way for the diagnosis of breast cancer. Moreover, a mammography or ultrasound may be performed to find the area for biopsy. The type of biopsy will depend on the type of lump i.e. palpable or non-palpable.

Fine needle aspiration (FNA) is used to find out if the lump is a cyst but FNA is not able to distinguish whether the cancer is a non-invasive or invasive type. Other types of biopsy include core biopsy, vacuum-assisted core biopsy, stereotactic core biopsy (uses 3-

D, or stereotactic images to know the location of a suspected area), Wire localization biopsy (uses mammography), Surgical or open biopsy, and Punch biopsy. Lymph node biopsy is conducted to know the spread of the cancer to lymph nodes. This study also assists in determining the stage of cancer.

Other methods for the detection of breast cancer include breast MRI, scintimammography, and ductography.

As hormones estrogen and progesterone play a key role in the growth of breast cancer cells thus hormone receptor test is also conducted for progesterone receptors (PRs) and estrogen receptors (ERs) in the breast cancer cells. Including this, there are other tests for breast cancer diagnosis such as; human epidermal growth factor receptor 2 (HER2) status testing, complete blood count (CBC), Blood chemistry tests, Tumor marker tests {cancer antigen 15-3 (CA15-3), carcinoembryonic antigen (CEA)}, Bone scan, and Scintimammography, etc. (Canadian Cancer Society, Diagnosis of Breast Cancer, 2024).

ROLE OF MOLECULAR RECEPTORS:

The methodologies and techniques used for the detection of breast cancer provide the status of breast cancer and according to which treatment may be recommended. Mammograms, ultrasound, cancer markers, and biopsies are good approaches for the detection of the level of breast cancer. This information provides information about the onset of the disease so that efficient management may be planned.

Breast cancer is recognized as a heterogeneous disease concerning histology, dissemination patterns to distant sites, therapeutic response, and patient outcomes. Based on genomic studies, a Normal Breast-like group and five breast cancer intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, Claudin-low, and Basal-like) are established (Prat and Perou, 2010; Maggi and Weber, 2015).

Estrogen receptor (ER) is an important diagnostic determinant for breast cancer. The HER receptors are found for therapeutic and prognostic significance, and cytoplasmic tyrosine kinases like PTK6 (brk) influence their activity. PTK6 is recognized as a prognostic marker of metastases-free survival, and this is not dependent on the classical morphological and molecular markers of involvement of lymph node, size of the tumor, and status of HER2 (Aubele et al., 2007). BRK (non-receptor tyrosine kinase) is found overexpressed in about 85% of human invasive ductal breast cancers. Furthermore, BRK is also found as a prognostic marker for ER+ breast cancers (Miah et al., 2019).

Another study revealed that among the estrogen receptor ER+ breast cancer, the luminal subtype A has been shown to exhibit good clinical outcomes with endocrine therapy, while the luminal subtype B represented the more complicated type, diagnostically as well as therapeutically (Zhang et al., 2013).

Progesterone receptor (PR) is also found at the level of highly expressed (>50%) in patients with ER-positive while it was found very rarely in individuals with ER-negative breast cancer. The expression of PR is under the influence of ER (Hick and Lester, 2016).

HER2 overexpression is one of the earliest events during breast carcinogenesis. The overexpression of HER2 is found associated with approximately 15–30% of breast cancers. HER2 overexpression is also found associated with other cancers such as bladder, colon, endometrium, ovary, lung, and head and neck (Iqbal and Iqbal, 2014). It is also found that many ABCB1 and VEGFA gene polymorphisms have been found linked with the risk of breast cancer and clinical outcomes (Madrid-Paredes et al., 2020).

TREATMENT:

The treatments of breast cancer are based on multidisciplinary approaches and considering the tumor load, and study of molecular makers.

The treatment options are based on the stage of cancer and available options (Fig. 2). Some common approaches for cancer treatment are chemotherapy, radiation therapy, hormone therapy, and immunotherapy. Sometimes, chemotherapy or hormone therapies are recommended before the surgery. The surgical removal of affected tissue is performed accordingly. The basic types of surgical procedures for breast cancer are tumor excision, mastectomy, excision of the sentinel lymph node, and excision of the armpit lymph nodes. Breast amputation involves the removal of the entire breast and the entire skin covering the mammary gland. Radiation therapy is also performed after surgery to destroy the remaining cells and also reduces the chances of redevelopment of breast cancer (Mayo Clinic, Breast Cancer, 2024).

For early-stage breast cancer, surgery aiming for breast conservation with radiotherapy or mastectomy alone is considered the standard management approach. Further, the use of adjuvant systemic therapy is based on the hormone receptors, the status of lymph nodes, and HER-2. In the case of metastasis, the goal of treatments focuses mainly on prolonging survival and maintaining quality of life (Wang and Wu et al., 2023).

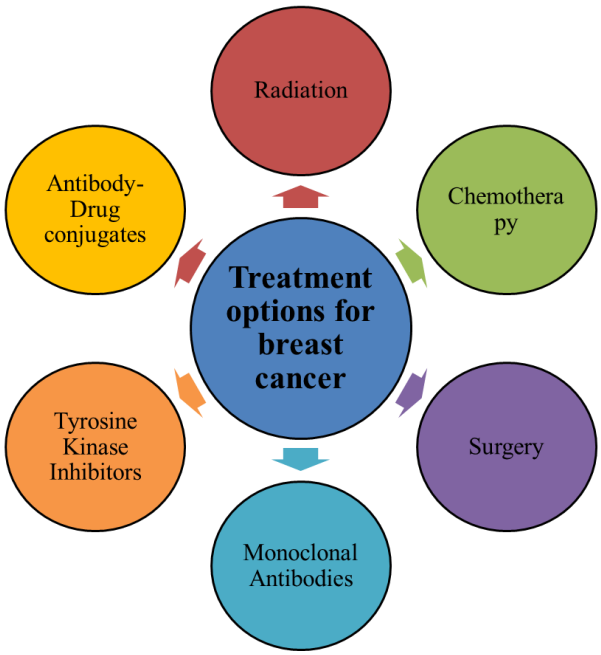

Fig. 2: Treatment options for breast cancer

Breast cancer treatments target receptors (endocrine and anti-HER2 therapies) as a personalized treatment. However, along with chemotherapy and radiotherapy, these treatments also exhibit adverse effects and there are possibilities to develop resistance against these agents. Further, standardized treatments are absent for triple-negative breast cancers (Burguin et al., 2021).

Other approaches:

New approaches have emerged for breast cancer treatment such as; monoclonal antibodies (immunotherapies), conjugated antibodies, and targeting other pathways (kinase inhibitors. Advanced therapies are also termed as targeted therapies.

Multiple therapeutic modalities have been developed for the treatment of HER2-positive breast cancer such as monoclonal antibodies, antibody-drug conjugates, and tyrosine kinase inhibitors (Swain et al., 2022). Some examples of monoclonal antibodies for HER2-positive breast cancer include Trastuzumab (Herceptin), trastuzumab and hyaluronidase injection (Herceptin Hylecta), Pertuzumab (Perjeta), Margetuximab (Margenza), Trastuzumab, pertuzumab, and hyaluronidase injection (Phesgo). Antibody-drug conjugates for HER2-positive breast cancer include Ado-trastuzumab emtansine (Kadcyla), and Fam-trastuzumab deruxtecan (Enhertu) are used for breast cancer treatment. The kinase inhibitors used for HER-2 positive breast cancers are Lapatinib (Tykerb), Neratinib (Nerlynx), and Tucatinib (Tukysa) (American Cancer Society, 2024). It is reported that for triple-negative breast cancer, combination therapy based on PD-1/PD-L1 immune checkpoint inhibitors with chemotherapy was found effective for both in advanced and early setting phase 3 clinical trials (Debein et al., 2023).

CONCLUSION:

Breast cancer is one of the most common cancers at the global level that has an impact on cancer deaths worldwide. Breast cancer is present in females in every country, at any age after puberty but rates are increasing with growing older. Breast cancer consists of a group of biologically and molecularly heterogeneous diseases originating from the breast. Early diagnosis and timely treatment are considered to be important in reducing the global burden of this disease. It is found that estrogen receptor-positive (ER+) breast cancer is the most prevalent subtype of invasive breast cancer (Geyer et al., 2012). There are many biomarkers used for breast cancer detection such as Estrogen receptor (ER), Progesterone receptor, and human epidermal growth factor receptor 2 (HER2) for breast cancers (Orrantia-Borunda et al., 2022). Including this, Wu et al., (2023) also suggested SIK2 as a prognostic and predictive biomarker for breast cancer. Further, it is suggested that detailed mutation detection by next-generation sequencing and more exploration of the mechanisms by which mutations cause breast cancer will assist further in diagnosis, prevention, and therapeutic options.

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