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ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF BREAST CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Breast cancer is the most common cancer in females in the United States and throughout the world. A positive prognosis for all cancer types depends on early detection and efficient treatment. Patients diagnosed with small tumors have a greater survival rate and a lower risk of the cancer being fatal. Therefore many medical techniques are now being developed for early detection of cancerous tumors such as BC as well as distant metastases. Theranostics has surfaced as a novel approach to concurrently diagnose, image, and treat tumors. It has the potential to provide timely and improved patient care via personalized therapy. In nanotheranostics, cell-specific targeting moieties, imaging agents, and therapeutic agents can be embedded within a single formulation for effective treatment. In this review, we will highlight the overview of breast cancer, Types of breast cancer, Breast cancer risk factor, different diagnosis techniques and treatment strategies for breast cancer management. We will explore potential concepts for successful breast cancer therapy and describe current trends and technology in breast cancer diagnostics and treatment as documented in recent research publications and patents.

INTRODUCTION

Breast cancer is one of the leading causes of cancer-related morbidity and mortality in women worldwide. **(Testa *et al.*, 2020)**. Due to the varied nature of BC, which determines the therapeutic alternatives, is one of the main challenges to therapy. As per the American Cancer Society, 281,550 women are expected to get a breast cancer diagnosis in 2021, and 43,600 women are expected to die from BC. The earliest recorded case of breast cancer dates back more than 3500 years, to around 1500 B.C., when the ancient Egyptians first identified it **(Sung *et al.*, 2021)**.

Early detection of the disease is essential for successful treatment and a good prognosis. In addition, individuals with small tumor at the time of diagnosis have a much lower risk of death and a greater survival rate. **(Ginsburg *et al.*, 2020)**. Currently, early detection of breast cancer and prompt treatment after diagnosis are the two main pillars that must be addressed in order to control the disease effectively and preserve lives.

Wide-spectrum tumours that exhibit variety in their clinical presentation, behaviour, and morphology are included in invasive breast cancer, therefor BC cud be classified into four molecular subtypes (Luminal A, Luminal B, HER2-enriched, and basal-like) based on the levels of mRNA gene expression **(Bhushan *et al*., 2021)**. For the identification, diagnosis, and clinical management of malignancies as well as the evaluation of the integrity of breast implants, imaging of the breast is almost solely used. In this review article, we focused on in female BC specifically because, as mentioned above, it currently constitutes the most common cancer in females.

Breast cancer risk factor

Aging

Ageing is one of the main risk factors for breast cancer, other than sex, because the age is a major factor in the incidence of breast cancer, In America, women over the ages of 40 and 60 accounted for 99.3% and 71.2%, respectively, of all breast cancer-related fatalities in 2016 **(Siegel *et al*., 2018)**. Thus, for women 40 years of age or older, a mammography screening must be scheduled in advance.

Estrogen

The risk of breast cancer is correlated with both endogenous and exogenous estrogens. Because the ovary produces endogenous estrogen in premenopausal women, having an ovariectomy can reduce the risk of breast cancer **(Łukasiewicz *et al*., 2021)**. Hormone replacement treatment (HRT) and oral contraceptives are the primary sources of exogenous estrogen. Since the 1960s, oral contraceptives have been used extensively, and their formulations have been improved to minimize side effects. For Iranian and African American women, the OR is still greater than 1.5 **(Soroush *et al*., 2016)**. However, women who discontinue using oral contraceptives for more than ten years do not have a higher risk of breast cancer. As part of hormone replacement therapy, menopausal or postmenopausal women receive exogenous estrogen or other hormones (HRT). The use of HRT has been linked to an increased risk of breast cancer, according to several studies. Between those who currently use HRT and those who have never used it, there is a 1.66 relative risk (RR), according to the UK's Million Women Study. HRs of 1.48 and 1.95 were found in a cohort study of 22,929 Asian women following HRT use for 4 and 8 years, respectively **(Liu *et al*., 2016)**. However, it has been demonstrated that stopping HRT for two years significantly reduces the risk of breast cancer. Breast cancer survivors who take hormone replacement therapy (HRT) have a high recurrence rate as well; the HR for a new breast tumor is 3.6. Since the adverse effects of hormone replacement therapy (HRT) were made public in 2003 based on the Women's Health Initiative randomized regulated trial, the incidence rate of breast cancer in the United States has decreased by approximately 7% due to a decrease in the percentage of people using HRT. **(Youn *et al*., 2020)**.

Lifestyle

Among today's lifestyle factors that increase the risk of breast cancer are over drinking and eating an excessive amount of fat. Drinking alcohol can stimulate the pathways connected to the estrogen receptor and raise the amounts of estrogen-related hormones in the blood. An intake of 35–44 grams of alcohol per day can increase the risk of breast cancer by 32%, according to a meta-analysis based on 53 epidemiological studies. The RR increases by 7.1% for every 10 grams of alcohol consumed above this threshold **(Jung *et al*., 2016)**. The modern western diet is excessively high in fat, particularly saturated fat, which is linked to mortality (RR=1.3) and a dismal prognosis for patients with breast cancer. While the link between smoking and the risk of breast cancer is still uncertain, non-lactating women's breast fluid has been found to contain cigarette smoke mutagens. Women who both smoke and drink have a higher risk of

developing breast cancer. (1.54 RR) **(Knight *et al.*, 2017)** Currently, an increasing number of research suggests that smoking raises the risk of developing breast cancer, especially if one starts smoking early in life. **(Kispert *et al.*, 2017)**.

Family history

A family history of breast cancer is linked to nearly 25% of cases. Breast cancer is more common in women whose mother or sister has the disease. According to a UK cohort study involving over 113,000 women, women who have a single first-degree relative who has breast cancer are 1.75 times more likely to get the disease than women who do not have any affected relatives. Furthermore, women who have two or more first-degree relatives who have breast cancer have a 2.5-fold increased risk **(Liu *et al.*, 2021)**. Hereditary susceptibility to breast cancer is partially caused by mutations in genes associated with the disease, such as BRCA1 and BRCA2.

Reproductive factors

Breast cancer risk can be raised by reproductive factors such as low parity, late menopause, early menarche, and late age at first pregnancy. A one-year delay in menopause causes a three percent increase in the risk of breast cancer. The chance of breast cancer drops by 5% or 10% for each year that menarche is delayed or for every extra birth, respectively. **(Dall *et al.*, 2017)**. The hazard ratio (HR) between late (≥35 years) and early (<20 years) age at first birth is 1.54, according to a recent Norwegian cohort study. Reproductive factors are highly correlated with the ER status, with differences in the odds ratios (OR) for parity (OR: 0.7 vs. 0.9 for ≥3 births vs. nulliparae) and age at first birth (OR: 1.6 vs. 1.2 for age ≥30 vs. <25 years) between ER+ and ER- breast cancer **(Xie *et al.*, 2022)**.

Race and ethnicity

When compared to other racial or ethnic groups, black women have the highest breast cancer death rate. Compared to White, Asian, and Pacific Islander women, women who identify as Black, Hispanic, American Indian, or Alaska Native are more likely to have breast cancer that has spread (metastasized) at the time of diagnosis **(Ozsoy *et al.*, 2017)**.

Excessive alcohol consumption

There is no doubt that drinking alcohol increases the risk of breast cancer, and the risk increase that results from this factor is proportional to the amount of alcohol drank. For instance, women who consume two to three drinks daily are about 20% more likely to develop breast cancer than women who do not consume alcohol. There is very little increase in risk for women who consume only one alcoholic beverage per day **(Sun *et al.*, 2017).**

Diagnosis

The key to effective breast cancer treatment is early detection. T3 tumors, which are largely the result of delayed diagnosis, have a 10-year survival rate of less than 60% while T1 tumors with a diameter of less than 2 cm had an about 85% 10-year survival rate **(Krishnaveni *et al.*, 2021)**. To identify, diagnose, treat, and monitor malignancies, as well as to evaluate the integrity of breast implants, imaging of the breast is mainly used. For many years, ultrasonography has been an essential instrument in the identification of breast cancer, image-guided biopsies, and lymph node diagnosis. Other frequently used imaging modalities include mammography, ultrasound, magnetic resonance imaging (MRI), scintimammography, single photon emission computed tomography (SPECT), and positron emission tomography (PET) **(Rainu *et al.*, 2023)**. The need for systemic therapy in breast cancer is determined based on the extent and severity of the disease. For the treatment of breast cancer, targeted medicines with few off-target adverse effects are

required. Since breast cancer affects people worldwide, there is a need to diminish inequalities in access to diagnosis, multimodal therapy, and innovative medications.

Mammography

Digital mammography offers a high-quality imagine with a low radiation dosage and can identify breast cancer in its early stages, improving patient survival **(Morgan *et al*., 2021)**.

Mammography has long been advised for the identification of breast cancer, and most American women over 40 take advantage of this recommendation **(Gordon et al 2022)**. There was a significant 48% reduction in breast cancer mortality in women aged 40–49 years in those who had screening, compared to none in those not exposed, according to recent research on 210,000 women in Sweden. X-rays are used to generate images in both screen-film mammography and digital mammography **(Procz *et al*., 2020)**.

Mammography Imaging Modality is First-line tool for breast screening, its Principle based on Low-dose ionizing x-ray creates detailed images of the breast **(Bhushan *et al*., 2022)**. The Advantages of Mammography are most cost-effective, good response with high specificity (90–95%) and sensitivity (75–90%), and Spatial Resolution: 50 _m, while the Limitations are useing ionizing radiation. Sensitivity decreases with increasing breast density. Accuracy is low in young women. High false-positive results in young women due to dense breasts. Poor contrast compared to MRI **(Korhonen *et al*., 2021)**.

Magnetic Resonance Imaging

Breast MRI is a safe and non-invasive diagnostic imaging technique that uses low-energy radio frequency waves and a magnetic field to produce detailed images of breast structures **(Willemink *et al*., 2020)**. It is utilized to assess cancer size and detect metastasized tumors in women with a history of breast cancer diagnosis (**Bhushan 2021**).

Contrast-enhanced breast magnetic resonance imaging (MRI) was quickly evaluated as an additional screening technique following the discovery that it had an extremely high sensitivity for the identification of breast cancer. the high sensitivity is based on the fact that no breast cancer can grow larger than 2 mm without forming new blood vessels that supply the required nutrition for the tumor to expand,. **(Lobbes *et al*., 2021)**.

The Advantages of MRI is the Ability to detect breast malignancies that often escape from clinical, mammograms, and ultrasound detection with Sensitivity: 75–100%, Specificity: 83–98.4% and Spatial Resolution: 25–100 _m, while the limitation are Expensive, inability to standardize the test. Unnecessary breast biopsies due to inability to distinguish between malignant and benign lesions. **(Wallyn *et al*., 2019)**.

Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is employed to gain insights into the chemical composition of breast lesions. The data obtained can be applied in various clinical scenarios, including tracking responses to cancer treatments and enhancing the accuracy of lesion diagnoses. Initial studies using MRS for breast cancer have yielded encouraging findings, leading to a growing number of research teams integrating this technique into breast MRI protocols. **(Sharma and Jagannathan, 2022)**.

Principle of MRS based on Employing magnetic field on body fluids and tissue samples to obtain chemical information of that region. The advantages of MRS are to overcome the limitations of mammography, Radiation-free imaging technology, Excellent sensitivity, Excellent spatial resolution, All imaging planes are possible with Sensitivity: 93% Spatial Resolution: up to 0.25 cm3. While the limitation of MRS are expensive and time-consuming, Low specificity 70%. Not portable, False-positive results in some benign tumors **(Alam *et al*., 2011)**.

Ultrasound

Due to the limitations of mammography technique regarding dense breasts, additional screening technique is required. An additional tool called ultrasound can be used to examine worrisome regions not seen on a mammogram and certain changes in the breasts in women with dense breast tissue **(Vourtsis 2019)**. This approach has the advantages of being widely available and not exposing patients to radiation. On the other hand, it is constrained by several elements. Most notably, it might not pick up on microcalcifications and might overlook some early warning indicators of cancer. Due to this drawback, this method is only utilized in certain circumstances and is not employed as a breast cancer screening tool. The fusion of ultrasound with other modalities Such as ultrasound imaging techniques and ultrasound-guided biopsy, provides important tools for the management of breast cancer patients. Principle of MRS based on Employs sound waves to image breast tissues **(Wallyn *et al*., 2019)**. The advantages of ultrasound are accessible, real-time lesion visualization, cost-effective, patient compliant. While the limitation is Failure to detect microcalcifications, possibility of false-positives.

Molecular Image-Guided Sentinel Node Biopsy

A technique called sentinel lymph node biopsy (SLNB) can detect metastases in individuals with early-stage breast cancer. To determine the best course of treatment, SLNB is often carried out based on the nodal metastatic status **(Lyman *et al*., 2017)**. The SLNB procedure is well renowned for having a far lower rate of post-operative complications than traditional axillary lymph node dissection. Due to this, SLNB management is essential to a good diagnosis and course of therapy for breast cancer. Principle of MRS based on Surgical procedure to detect spreading of cancer in lymphatic system. The advantage of SLNB is significantly reduces post-operative complications While the limitation Not useful for patients with locally advanced cancers and inflammatory breast cancer **(Rosenberger *et al*., 2019)**.

Types of breast cancer

1. Non-Invasive Breast Cancer

It divided into two types, ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). It is a diverse disease characterized by malignant epithelial cells that arise from the terminal ductal lobular and do not pass the basement membrane. Ninety percent of non-invasive breast cancer cases are ductal carcinoma in situ (DCIS). While, lobular carcinoma in situ (LCIS) is a less common type of breast cancer that is thought to be a risk factor for the disease **(Tagima *et al*., 2019)**. DCIS is the second most common subtype of male breast cancer, accounting for 5% of all occurrences. Because of the high probability of coexistence with invasive cancer, pure DCIS is uncommon. Palpable lumps and/or bloody nipple discharge are frequently found during physical examinations. In mammography, DCIS is seen as pleomorphic microcalcifications, which reflect in situ components of tumor cells. Yet parenchymal opacity or distortion could also be observed in the event that invasive carcinoma coexists **(Tagima *et al*., 2019)**.

2. Invasive Breast Cancer

Cells break through the duct and lobular walls and penetrate the breast's fatty and connective tissues. Cancer can spread to lymph nodes or other organs but not become metastatic **(Effiong *et al.*, 2022)**. Invasive ductal carcinomas are the most frequent type of breast cancer in women, accounting for roughly 70-80% of all diagnosis. These lesions are visible on physical examination as a hard, painless, palpable mass with subsequent characteristics such as nipple retraction, skin thickening, and palpable axillary. The latter one accompanies IDC in 50% of the cases. When there is a suspicion of malignancy, bilateral mammography is advised because underlying risk factors may contribute to the development of contralateral breast malignancy. IDC is seen on mammography as irregular, radiodense retroareolar masses with margins that are spiculated, lobulated, or microlobulated **(Udayasiri *et al.*, 2023)**.

Invasive lobular carcinomas (ILC) are the second most frequent histological type of breast cancer, accounting for 10-15% of all cases. Classical ILC is distinguished by the production of a single row of discohesive cells that infiltrate the breast stroma without creating desmoplastic stroma (**Tasli *et al.*, 2022**).

3. Papillary carcinoma

Presenting as a palpable subareolar mass, it accounts for 2.5-5% of male breast cancers and is more prevalent in men than women. (2:1). Mammographic findings include circumscribed, oval, lobulated, or irregular masses, as well as a subareolar tumor. A complex heterogeneous mass made up of solid and cystic components is the typical sonographic appearance. Other potential findings include pure solid mass or solid mural nodule in complex mass. **(Onder *et al.*, 2020)**.

4. Invasive mucinous carcinoma IMC

Is a histological form of breast cancer distinguished by the presence of extracellular mucus around neoplastic cells. Physical examination findings include a non-specific palpable hard subareolar lump. Furthermore, the typical mammographic finding is a round, well-defined opacity. **(Ginter *et al.*, 2020)**.

There are five major intrinsic or molecular subtypes of breast cancer based on gene upregulation **(Bhushan *et al.*, 2021)**:

Luminal A is a low-grade breast cancer is HER2- and HR+ (estrogen- and/or progesterone receptor positive), with low levels of the protein Ki-67, which controls how quickly cancer cells multiply.

Luminal B breast cancer is a molecular subtype in which tumors are HR+ (progesterone-receptor and/or estrogen-receptor positive) and have increased levels of the protein Ki-67 while being HER2- or HER2+.

HER2-enriched breast cancer is a molecular subtype of breast cancer in which tumors are HER2+ and HR- (i.e., estrogen- and progesterone-receptor negative) **(Liu *et al.*, 2020)**.

Normal-like breast cancer is identical to luminal A cancer as it is HER2–, HR+ (estrogen- and/or progesterone-receptor positive) with reduced levels of the Ki-67 protein.

- **Triple-negative breast cancer (TNBC)**

It is defined as a lack of expression of hormone receptors (estrogen receptor (ER) and progesterone receptor (PR)) and amplification of human epidermal growth factor receptor 2 (HER-2). It accounts for 15-20% of all breast cancers (**Nazmy *et al.*, 2021**).

Breast cancer treatment

For non-metastatic breast cancer, the primary goals of treatment are to remove the tumor from the breast and regional lymph nodes and to avoid metastatic recurrence. Local therapy for non-metastatic breast cancer consists of surgical resection and sampling or removal of axillary lymph nodes, with consideration of postoperative radiation. Systemic therapy may be preoperative (neo adjuvant), postoperative (adjuvant), or both **(Waks *et al*., 2019)**. The conventional systemic therapy for breast cancer is guided by the subtype, which includes endocrine therapy for all HR+ cancers (with some patients also requiring chemotherapy), Trastuzumab-based ERBB2-directed antibody therapy in combination with chemotherapy for all ERBB2+ cancers (with endocrine therapy added if concomitant HR positive), and chemotherapy alone for triple-negative breast cancer. The therapeutic goals for metastatic breast cancer are life extension and symptom relief. Currently, almost all patients with metastatic breast cancer are incurable. In metastatic breast cancer, the same broad types of systemic therapy are used as in the approaches mentioned above. Only in the case of metastatic disease are local therapeutic techniques (surgery and radiation) often employed for palliation **(Tong *et al*., 2018)**.

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