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Breast Cancer in the Modern Era: A Comprehensive Review on Advances in Understanding and Managing Breast Cancer

Wafa Khizar[1], Shahzad Hussain[2], Humayun Riaz[3], Laraib Kaleem[2], Hajra Zaheer[4], Ranaz Latif[4], Abdul Ghaffar[5], Brian Godman[6], Ahmed Ali[4]

[1]Faculty of Eastern Medicine, Hamdard University, Islamabad Campus, Pakistan
[2]Hamdard University, Islamabad Campus, Pakistan.
[3]Rashid Latif Institute of Pharmaceutical Sciences, Pakistan
[4]Department of Biosciences, COMSATS University Islamabad (CUI), Islamabad, Pakistan
[5]Drug Regulatory Authority of Pakistan
[6]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden Institute for Pharmacological Research 'Mario Negri', Milan, Italy Prescribing Research Group, University of Liverpool Management School, UK

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Correspondence to: Wafa Khizar,
Faculty of Eastern Medicine, Hamdard University, Islamabad Campus, Pakistan.
Email: wafa.khizar@hamdard.edu.pk

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ABSTRACT

Even with advances in screening and prevention methods, breast cancer is more often diagnosed in women than any other malignancy. An increased knowledge of genetics made it possible for researchers to sort breast cancer into four types: luminal A, luminal B, HER2-enriched, and triple-negative, all marked by specific biomarkers and estimations for the outcome. High-throughput genomic classifiers such as the Breast Cancer Classifier (BCC) have allowed doctors to more accurately choose the best medicine for HER2-low tumors. Now, liquid biopsies and multiplex immunofluorescence tests are being used, in addition to imaging and samples taken from tissue, to help recognize minimal amounts of disease at an early stage. Among hormone receptor-positive and BRCA-mutant patients, CDK4/6 inhibitors, antibody–drug conjugates, and PARP inhibitors have improved progression-free survival. Tools powered by artificial intelligence are regularly being included in the work of many health professionals, helping them detect diseases more accurately and measure a patient's probability of illness. However, because some cancer treatments can cause serious side effects in young people and early menopause, efforts are being made to trial new therapies that focus clearly on how these patients feel after surviving cancer. There is a need to explore how neoadjuvant therapy can be improved, use different kinds of data for assessing treatment needs, and ensure that all patients receive the best treatment available. The current review aimed to investigate advances in understanding and managing breast cancer.

INTRODUCTION

Breast cancer is one of the most prevalent and significant health concerns globally, particularly among women [1]. It is characterized by the uncontrolled growth of abnormal cells in the breast tissue. Breast cancer affects millions of individuals worldwide each year. According to the World Health Organization (WHO), it is the most common cancer among women, both in developed and developing countries [2]. It is estimated that approximately 2.3 million new cases of breast cancer were diagnosed globally in 2020. Breast cancer is a leading cause of cancer-related mortality among women. While mortality rates have decreased in some regions due to advancements in early detection and treatment, it remains a significant public health challenge [3].

Late-stage diagnosis and limited access to quality healthcare contribute to higher mortality rates, particularly in low- and middle-income countries [4]. Beyond the physical toll, breast cancer has profound emotional, social, and economic impacts on individuals, families, and communities. The disease can disrupt daily life, strain relationships, and impose financial burdens due to healthcare costs and loss of productivity [5]. Increasing awareness about breast cancer risk factors, symptoms, and the importance of early detection through regular screening mammograms and clinical breast exams is crucial for improving outcomes. The current review aimed to investigate advances in understanding and managing breast cancer.

Importance of Early Detection, Diagnosis, and Personalized Treatment Approaches

Early detection, diagnosis, and personalized treatment approaches play crucial roles in improving outcomes for individuals with breast cancer. Early detection increases the likelihood of successful treatment and improves survival rates [6]. Detecting breast cancer at an early stage often allows for less aggressive treatment options and better preservation of quality of life. Regular screening mammograms and clinical breast exams can identify breast cancer in its early stages, sometimes before symptoms are noticeable [7]. Prompt diagnosis following the detection of abnormalities on screening tests is essential for initiating timely treatment. Diagnosis involves confirming the presence of cancer, determining the type and subtype of breast cancer, assessing the extent of disease spread (staging), and evaluating tumor characteristics [8]. Accurate diagnosis guides treatment decisions and helps tailor interventions to the individual's specific needs. Breast cancer is a heterogeneous disease with various subtypes, each with distinct biological characteristics and responses to treatment [9]. Personalized treatment approaches consider factors such as tumor biology, hormone receptor status, HER2/neu expression, genetic mutations, and individual patient preferences [10]. Personalized medicine approaches, such as genomic testing and molecular profiling, help identify optimal treatment strategies and minimize the risk of overtreatment or undertreatment [11].

Global Incidence and Prevalence Rates of Breast Cancer

Breast cancer is the most common cancer among women globally, with millions of new cases diagnosed each year. According to the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), the incidence of breast cancer has been steadily increasing over the past few decades, partly due to population growth, aging, and lifestyle changes. In the GLOBOCAN 2022 fact sheet, 2296840 breast cancer cases have been reported worldwide, constituting 11.5 % of all cancers. Breast cancer incidence rates are generally higher in high-income countries, There has been a notable rise in incidence rates in low- and middle-income countries, partly due to changing reproductive patterns, urbanization, and adoption of Western lifestyles [12]. The prevalence of breast cancer reflects the total number of individuals living with breast cancer at a specific point in time. As breast cancer survival rates improve due to advances in early detection and treatment, the prevalence of breast cancer survivors is also increasing globally [13]. The prevalence of breast cancer survivors varies by region and is influenced by factors such as healthcare infrastructure, access to screening and treatment services, and socioeconomic disparities. There are significant disparities in breast cancer incidence and prevalence rates between regions and countries [14]. High-income countries typically have higher breast cancer incidence rates compared to low- and middle-income countries, partly due to differences in screening practices, healthcare infrastructure, and access to treatment [15]. Molecular subtypes of breast cancer and corresponding first-line targeted therapies are shown in Table 1, and Table 2 shows recent and emerging targeted agents in breast cancer management.

Table 1

Molecular Subtypes of Breast Cancer and First-Line Targeted Therapies

Subtype	Key Biomarkers	Clinical Features & Prognosis	First-Line Targeted Therapy	References
Luminal A	ER^+, PR^+, $HER2^-$, low Ki-67	Slow growth, low grade, best prognosis (5-year survival ≈ 90 %)	Endocrine therapy (e.g., letrozole, tamoxifen)	[16]
Luminal B	ER^+, PR^-/low, $HER2^-$ or $HER2^+$, high Ki-67	Faster growth, intermediate prognosis (5-year survival ≈ 75 %)	Endocrine therapy + CDK4/6 inhibitor (e.g., palbociclib)	[17]
HER2-enriched	ER^-, PR^-, $HER2^+$	Aggressive but responsive to HER2 blockade; improved outcomes with anti-HER2 agents	Anti-HER2 therapy (e.g., trastuzumab + pertuzumab; ado-trastuzumab emtansine)	[18]
Triple-negative (Basal-like)	ER^-, PR^-, $HER2^-$	Most aggressive, highest recurrence, poorer prognosis (5-year survival ≈ 65 %)	Chemotherapy; emerging: PARP inhibitors (e.g., olaparib), ADCs (e.g., sacituzumab govitecan)	[19]

Table 2

Recent and Emerging Targeted Agents in Breast Cancer Management

Agent	Target/Subtype	Mechanism of Action	FDA Approval	Key Trial(s)	References
Palbociclib	HR^+/$HER2^-$	CDK4/6 inhibitor—blocks cell-cycle G1 to S transition by preventing Rb phosphorylation	2015	PALOMA-2, PALOMA-3	[20]
Ribociclib & Abemaciclib	HR^+/$HER2^-$	CDK4/6 inhibitors—similar mechanism to palbociclib; add-on to endocrine therapy	2017, 2017	MONALEESA-2, MONARCH-3	[21]
Ado-trastuzumab emtansine (T-DM1)	$HER2^+$	ADC: trastuzumab linked to DM1 (microtubule inhibitor)	2013	EMILIA, KATHERINE	[22]
Trastuzumab deruxtecan (Enhertu)	$HER2^+$	ADC: trastuzumab associated to topoisomerase I inhibitor deruxtecan	2019	DESTINY-Breast01, DESTINY-Breast03	[23]
Sacituzumab govitecan (Trodelvy)	TNBC	ADC: anti-Trop-2 antibody associated to topoisomerase I inhibitor	2020	IMMU-132-01, ASCENT	[24]
Olaparib, Talazoparib	BRCA-mutant (TNBC, HR^+/$HER2^-$)	PARP inhibitors—trap PARP on DNA, bringing synthetic lethality in BRCA-deficient cells	2018, 2018	OlympiAD (olaparib), EMBRACA (talazoparib)	[25]

Genetic and Environmental Factors Contributing to Breast Cancer Development

A combination of genetic and environmental factors influences breast cancer development [26]. Inherited mutations in the BRCA1 and BRCA2 genes significantly increase the risk of developing breast and ovarian cancers. These genes play critical roles in repairing damaged DNA and maintaining genomic stability. Women with BRCA1 or BRCA2 mutations have a much higher lifetime risk of breast cancer compared to the general population [27]. BRCA1 and BRCA2 mutations are the most well-known genetic risk factors for breast cancer; other genetic mutations and variants also contribute to breast cancer susceptibility. These include mutations in genes such as TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), ATM, CHEK2, PALB2, and others [28]. A family history of breast cancer, particularly in first-degree relatives (such as a mother, sister, or daughter), increases an individual's risk of developing the disease. However, the majority of breast cancer cases occur in individuals with no family history, suggesting the involvement of additional genetic and environmental factors [29]. Certain reproductive factors can influence breast cancer risk [30]. Prolonged exposure to estrogen and progesterone due to menstrual cycles and hormone replacement therapy may also increase risk. Obesity, particularly postmenopausal obesity, is associated with an increased risk of breast cancer [31]. Adipose tissue produces estrogen, which can promote the growth of hormone receptor-positive breast cancers [32]. Alcohol consumption, even in moderate amounts, has been linked to an increased risk of breast cancer. Alcohol can influence hormone levels and metabolism, potentially contributing to breast cancer development [33]. High-dose ionizing radiation exposure, such as radiation therapy for other cancers or diagnostic imaging procedures, increases the risk of developing breast cancer later in life. [34]. Understanding the interplay between genetic and environmental factors is essential for identifying individuals at increased risk of breast cancer and implementing preventive strategies, early detection efforts, and personalized treatment approaches [35].

Role of Hormone Receptors (Estrogen, Progesterone, Her2/Neu) in Breast Cancer Pathogenesis

Hormone receptors, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu), play crucial roles in breast cancer pathogenesis by influencing tumor growth, progression, and response to therapy [36]. Estrogen receptor-positive (ER+) breast cancers account for approximately 75% of all breast cancer cases. In ER+ breast cancers, estrogen signaling promotes tumor cell proliferation, survival, and progression. Hormone therapy, such as selective estrogen receptor modulators or aromatase inhibitors, is commonly used to target ER signaling and inhibit tumor growth in ER+ breast cancers. Progesterone receptor-positive (PR+) breast cancers often co-exist with ER+ tumors, as PR expression is regulated by estrogen signaling. PR expression in breast cancer is associated with a better prognosis and response to hormone therapy. PR status is commonly assessed alongside ER status to guide treatment decisions in hormone receptor-positive breast cancers [37]. HER2/neu is a cell surface receptor involved in signaling pathways that regulate cell growth and proliferation. HER2/neu overexpression or amplification occurs in approximately 15-20% of breast cancers and is associated with aggressive tumor behavior and poorer prognosis. HER2-positive (HER2+) breast cancers are typically more aggressive and may have a higher risk of recurrence [38]. Targeted therapies such as HER2-targeted monoclonal antibodies (e.g., trastuzumab, pertuzumab), tyrosine kinase inhibitors (lapatinib), and antibody-drug conjugates (ado-trastuzumab emtansine) have significantly improved outcomes for patients with HER2+ breast cancer by inhibiting HER2 signaling and inducing tumor cell death [39]. Hormone receptor testing, along with other molecular and pathological assessments, helps oncologists tailor personalized treatment plans for patients with breast cancer, optimizing outcomes and minimizing treatment-related toxicities.

Genetic Predisposition (BRCA1/BRCA2 Mutations, Familial History)

Genetic predisposition to breast cancer, particularly through mutations in the BRCA1 and BRCA2 genes, significantly increases an individual's risk of developing the disease [27]. Inherited mutations in the BRCA1 or BRCA2 genes significantly increase the risk of breast and ovarian cancers, as well as other cancers such as pancreatic and prostate cancers. Women with BRCA1 mutations have an estimated lifetime risk of up to 70-80% of developing breast cancer, while those with BRCA2 mutations have a lifetime risk of approximately 40-70% [40]. BRCA mutations are more commonly found in individuals of Ashkenazi Jewish descent, but can occur in individuals of any ethnic background. Men with BRCA mutations also have an increased risk of developing breast cancer, although the risk is lower compared to women [41].

A family history of breast cancer, particularly among first-degree relatives (such as a mother, sister, or daughter), is a significant risk factor for developing the disease. Individuals with one first-degree relative diagnosed with breast cancer have approximately twice the risk of developing breast cancer compared to individuals with no family history [42]. The risk increases further with multiple affected relatives, particularly if the relatives were diagnosed at a young age or if the cancer was bilateral (affecting both breasts). In addition to BRCA1/BRCA2 mutations, other genetic syndromes associated with an increased risk of breast cancer include Li-Fraumeni syndrome (TP53 mutations), Cowden syndrome (PTEN mutations), and hereditary diffuse gastric cancer syndrome (CDH1 mutations), among others [43]. Genetic testing and counseling may be recommended for individuals with a strong familial history of breast cancer or other related cancers to assess their genetic risk and guide preventive measures and screening strategies. Understanding the genetic predisposition to breast cancer, including the presence of BRCA1/BRCA2 mutations and familial history, is crucial for identifying individuals at increased risk and implementing appropriate risk-

reduction strategies, such as increased surveillance, preventive surgery, and targeted therapies [44].

Hormonal Factors (Early Menarche, Late Menopause, Hormone Replacement Therapy)

Hormonal factors play a significant role in the development of breast cancer, with reproductive factors such as early menarche, late menopause, and the use of hormone replacement therapy (HRT) influencing an individual's risk of developing the disease. Early age at first menstruation (menarche) is associated with an increased risk of breast cancer [45]. Women who experience menarche at a younger age are exposed to higher levels of estrogen and progesterone over their lifetime, as menstrual cycles begin earlier and continue for a longer duration. Increased exposure to estrogen during periods of breast development may contribute to the initiation and promotion of breast cancer cells. Late age at menopause, the cessation of menstrual cycles, is also linked to an elevated risk of breast cancer [46]. Women who undergo menopause at a later age have prolonged exposure to endogenous estrogen and progesterone due to the continuation of hormonal activity. The sustained presence of estrogen and progesterone during postmenopausal years may contribute to the growth and progression of breast cancer cells [47].

Hormone replacement therapy (HRT), also known as menopausal hormone therapy, is prescribed to alleviate symptoms of menopause, such as hot flashes, vaginal dryness, and mood swings. HRT typically involves the use of estrogen alone (estrogen therapy) or a combination of estrogen and progesterone (combined hormone therapy) [48]. Estrogen-only therapy may also elevate breast cancer risk if used for an extended duration, particularly in women who have undergone hysterectomy and do not require progesterone supplementation [49].

Lifestyle Factors (Obesity, Alcohol Consumption, Physical Inactivity)

Lifestyle factors, including obesity, alcohol consumption, and physical inactivity, play significant roles in influencing an individual's risk of developing breast cancer. Obesity, particularly excess body weight after menopause, is associated with an increased risk of postmenopausal breast cancer [31]. Alcohol can influence breast cancer risk through various mechanisms, including its effects on estrogen metabolism, DNA damage, oxidative stress, and hormonal signaling pathways [50]. Women who consume alcohol should be aware of its potential impact on breast cancer risk and consider limiting their intake to reduce their risk. Regular physical activity has been shown to reduce breast cancer risk by influencing multiple biological pathways, including hormone metabolism, insulin sensitivity, inflammation, and immune function [51]. Exercise helps maintain a healthy body weight, reduces circulating estrogen levels, improves insulin sensitivity, and enhances overall immune surveillance, all of which may contribute to lower breast cancer risk. Engaging in regular moderate to vigorous physical activity, such as brisk walking, jogging, cycling, or swimming, is recommended for reducing breast cancer risk and promoting overall health [52].

Environmental Exposures (Radiation, Certain Chemicals)

Environmental exposures to radiation and certain chemicals have been implicated as risk factors for breast cancer development.[53]. Radiation exposure at a young age, particularly during periods of breast development, is more strongly associated with increased breast cancer risk than exposure later in life. High-dose radiation therapy for the treatment of other cancers, such as Hodgkin lymphoma or childhood cancers, may increase the risk of developing secondary breast cancer later in life [54]. Endocrine-disrupting chemicals (EDCs) are environmental pollutants that interfere with the body's endocrine system, which regulates hormone production and signaling [55]. Some EDCs, such as bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), and organochlorine pesticides, have been linked to an increased risk of breast cancer. These chemicals may mimic or interfere with the action of estrogen in the body, disrupt hormone signaling pathways, and promote abnormal cell growth and proliferation in breast tissue [56]. EDCs can be found in various sources, including plastics, food packaging, personal care products, pesticides, industrial pollutants, and contaminated water supplies. Minimizing exposure to EDCs through lifestyle choices and advocating for regulatory policies to limit environmental pollution are important strategies for reducing breast cancer risk [57].

Clinical Presentation

Common signs and symptoms of breast cancer can vary among individuals. The most common symptom of breast cancer is the presence of a lump or mass in the breast tissue or underarm area [58]. Breast cancer may cause changes in breast size or shape, including asymmetry between the two breasts. Changes in the appearance or texture of the nipple, such as inversion (pulling inward), flattening, or retraction (turning inward), may be signs of breast cancer. Discharge from the nipple, especially if bloody or clear, should be evaluated by a healthcare provider. Breast pain is more commonly associated with benign breast conditions. Persistent or unexplained breast pain or discomfort may warrant further evaluation, especially if accompanied by other symptoms [59]. Changes in the texture of the breast tissue, such as areas that feel unusually thickened or hard, may be indicative of breast cancer. These changes may be noticeable during breast self-exams or clinical breast exams [60]. However, any persistent or concerning signs or symptoms should be promptly evaluated by a healthcare professional for further assessment and appropriate diagnostic testing, such as mammography, ultrasound, or biopsy [61]. Regular breast self-exams (BSE), clinical breast exams by a healthcare provider, and adherence to recommended breast cancer screening guidelines are essential for early detection and prompt treatment of breast cancer, leading to better outcomes and survival rates.

Diagnosis of Breast Cancer

Imaging modalities play a crucial role in the diagnosis, staging, and monitoring of breast cancer. Mammography is the primary screening tool for breast cancer detection in asymptomatic women. It involves taking X-ray images of the breast tissue to identify any suspicious abnormalities,

such as masses, calcifications, or architectural distortions [62]. Mammography is highly sensitive for detecting early-stage breast cancer and has been shown to reduce breast cancer mortality through early detection. [63]. Ultrasound-guided breast biopsies can be performed to obtain tissue samples for pathological analysis, particularly for lesions that are not visible on mammography or palpable during physical examination [64]. Breast MRI is a highly sensitive imaging modality that can detect small breast lesions and evaluate the extent of disease, particularly in high-risk patients or those with dense breast tissue. Breast MRI is commonly used for screening in women with a high risk of breast cancer (such as those with BRCA mutations or a strong family history) and for preoperative staging in certain cases (e.g., determining the extent of disease in newly diagnosed breast cancer or assessing response to neoadjuvant chemotherapy) [65]. While breast MRI is highly sensitive, it may also have a higher false-positive rate compared to mammography, leading to additional diagnostic tests and procedures. A multimodal approach combining mammography, ultrasound, and MRI can provide comprehensive breast cancer assessment and improve diagnostic accuracy [66]. Core needle biopsy is the most common and preferred method for diagnosing breast cancer. CNB provides an accurate diagnosis, allows for histological evaluation of tissue architecture, and enables immunohistochemical staining for hormone receptors (estrogen and progesterone receptors) and HER2 status [67]. Fine-needle aspiration involves using a thin needle to withdraw a small sample of cells from the breast lump or suspicious area. FNA is primarily used for evaluating palpable breast masses or cysts. FNA is less invasive than core needle biopsy but may provide less tissue for histological evaluation and may not yield enough material for comprehensive molecular testing or subtyping of breast cancer [68]. Surgical biopsy, also known as excisional biopsy or open biopsy, provides a larger tissue sample for histological evaluation and molecular testing. It is more invasive and associated with higher risks of complications, scarring, and longer recovery times, Core needle biopsy is typically the preferred method for diagnosing breast cancer due to its accuracy, safety, and ability to provide sufficient tissue samples for comprehensive evaluation and molecular testing. Fine-needle aspiration may be used in certain situations, such as for evaluating palpable masses or cysts, while surgical biopsy is reserved for cases where additional tissue is needed or when core needle biopsy is not feasible or conclusive [69]. Close collaboration between radiologists, pathologists, surgeons, and oncologists is essential for selecting the most appropriate biopsy technique and ensuring accurate diagnosis and optimal management of breast cancer patients.

Treatment Modalities

Lumpectomy, also known as breast-conserving surgery or partial mastectomy, involves the surgical removal of the cancerous tumor along with a surrounding margin of normal breast tissue [70]. Mastectomy involves the surgical removal of the entire breast tissue, including the nipple-areolar complex [71]. Mastectomy may be recommended for larger tumors, multifocal disease, certain tumor locations, patient preference, or when lumpectomy is not feasible [72]. Sentinel Lymph Node Biopsy (SLNB) is a less invasive alternative to axillary lymph node dissection, in which only the first few lymph nodes draining the breast (sentinel nodes) are removed and examined for cancer spread. Lymph node status is an important prognostic factor in breast cancer and helps guide adjuvant treatment decisions [73]. The choice of surgical procedure depends on factors such as tumor size, stage, location, patient preferences, and the presence of genetic mutations [74]. A multidisciplinary approach involving surgeons, oncologists, radiation oncologists, and other healthcare professionals is essential for individualized treatment planning and comprehensive breast cancer care.

Adjuvant Therapies (Chemotherapy, Radiation Therapy, Hormone Therapy, Targeted Therapy)

Chemotherapy involves the use of cytotoxic drugs to kill cancer cells or prevent their growth and spread. Adjuvant chemotherapy is typically recommended for breast cancer patients at high risk of recurrence, including those with large tumors, lymph node involvement, or aggressive tumor characteristics [75]. Chemotherapy may be administered before (neoadjuvant) or after (adjuvant) surgery, depending on the specific treatment plan and tumor characteristics. Commonly used chemotherapy drugs for breast cancer include anthracyclines, taxanes, and other agents such as cyclophosphamide, fluorouracil, and platinum compounds. Radiation therapy involves the use of high-energy beams to target and destroy cancer cells in the breast or chest wall. Adjuvant radiation therapy is typically recommended after breast-conserving surgery (lumpectomy) to reduce the risk of local recurrence. It may also be used after mastectomy in patients with certain high-risk features, such as large tumors, positive margins, or extensive lymph node involvement [76]. Hormone therapy, also known as endocrine therapy, targets hormone receptor-positive (HR+) breast cancers, which express estrogen receptor (ER) and/or progesterone receptor (PR). Adjuvant hormone therapy is recommended for HR+ breast cancer patients to reduce the risk of recurrence and improve long-term survival [77]. Targeted therapy specifically targets molecular pathways involved in cancer growth and progression, often with fewer side effects than traditional chemotherapy. Adjuvant targeted therapy may be recommended for breast cancer patients with specific molecular alterations, such as HER2-positive (HER2+) tumors or tumors with other targetable mutations [78]. HER2-targeted therapies, such as trastuzumab, pertuzumab, ado-trastuzumab emtansine (T-DM1), and newer agents like neratinib and tucatinib, are used to block HER2 signaling and improve outcomes in HER2+ breast cancer. Other targeted therapies, such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (Palbociclib, ribociclib, abemaciclib), may be used in combination with hormone therapy for HR+/HER2- metastatic breast cancer [79]. Adjuvant therapies are tailored to each patient based on tumor characteristics, stage of disease, molecular subtype, and individual risk factors. [80].

Chemoprevention Strategies (Selective Estrogen Receptor Modulators, Aromatase Inhibitors)

SERMs are medications that act as estrogen receptor agonists or antagonists, depending on the target tissue. They exert their effects by binding to estrogen receptors in breast tissue, thereby blocking the effects of estrogen and reducing the risk of estrogen-driven breast cancer [81]. Tamoxifen is the most widely studied and commonly used SERM for breast cancer chemoprevention. Tamoxifen has been shown to significantly reduce the risk of both invasive and non-invasive breast cancer in women at high risk of the disease. It is typically recommended for premenopausal and postmenopausal women with a high risk of breast cancer, including those with a strong family history of the disease, prior breast abnormalities, or certain genetic mutations (e.g., BRCA1/BRCA2) [82]. Other SERMs, such as raloxifene and toremifene, have also been evaluated for breast cancer chemoprevention, with similar efficacy to tamoxifen in reducing breast cancer risk. Aromatase inhibitors are medications that block the enzyme aromatase, which converts androgens into estrogens in postmenopausal women. By reducing estrogen levels in the body, AIs inhibit the growth of estrogen-sensitive breast cancer cells and may help prevent the development of hormone receptor-positive breast cancer. AIs are primarily used as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer to reduce the risk of recurrence [83].

Screening Guidelines and Risk Assessment Tools for Early Detection

The American Cancer Society (ACS) recommends annual screening mammograms for women aged 40 and older, with the option to begin screening at age 45 and transition to biennial screening at age 55 [84]. The United States Preventive Services Task Force (USPSTF) recommends biennial screening mammograms for women aged 50 to 74, with the option for individualized screening decisions for women aged 40 to 49. Clinical breast examinations (CBE) by healthcare providers may be performed along with mammography, but are not recommended as a standalone screening method. Breast self-examination (BSE) is not recommended as a routine screening method due to limited evidence of effectiveness in reducing mortality and potential for increased anxiety and unnecessary biopsies [85]. The Gail model is a commonly used tool for estimating breast cancer risk based on factors such as age, race/ethnicity, family history of breast cancer, age at menarche, age at first live birth, and history of prior breast biopsies. The Tyrer-Cuzick model (IBIS Breast Cancer Risk Evaluation Tool) incorporates additional risk factors such as body mass index (BMI), hormone replacement therapy (HRT) use, and breast density to estimate breast cancer risk [86]. The Breast Cancer Risk Assessment Tool (BCRAT), also known as the "CARE" model, developed by the National Cancer Institute (NCI), estimates a woman's risk of developing invasive breast cancer over the next 5 years and up to age 90 based on age, race/ethnicity, family history of breast cancer, history of prior breast biopsies, and age at menarche and first live birth. The Breast Cancer Surveillance Consortium (BCSC) Risk Calculator incorporates data from the BCSC registry, including breast density, to estimate a woman's risk of developing invasive breast cancer over the next 5 years and up to age 90 [87].

Molecular Mechanisms Underlying Breast Cancer Progression and Metastasis

Genetic mutations in oncogenes drive aberrant cell proliferation, survival, and invasion in breast cancer. Dysregulation of DNA repair mechanisms and genomic instability contribute to the accumulation of genetic mutations and genomic alterations, promoting tumor heterogeneity and evolution [88]. Amplifications and deletions of specific genomic regions, including amplification of HER2 (ERBB2) and loss of heterozygosity (LOH) at tumor suppressor loci, are common genetic events in breast cancer progression. Activation of the PI3K/AKT/mTOR signaling pathway promotes cell growth, survival, and metabolism in breast cancer, contributing to tumor progression and resistance to therapy. Dysregulation of the MAPK/ERK signaling pathway, often through mutations in RAS or RAF genes, enhances cell proliferation, migration, and invasion in breast cancer cells [89]. Notch signaling regulates cell fate determination, stem cell maintenance, and epithelial-mesenchymal transition (EMT), promoting invasive and metastatic behavior in breast cancer cells. EMT is a cellular process by which epithelial cells lose their epithelial characteristics and acquire mesenchymal properties, facilitating invasion, migration, and metastasis [90]. Downregulation of epithelial markers (e.g., E-cadherin) and upregulation of mesenchymal markers (e.g., N-cadherin, vimentin) promote the acquisition of invasive and migratory phenotypes in breast cancer cells. EMT is regulated by transcription factors such as Snail, Slug, Twist, and Zeb, which repress epithelial genes and activate mesenchymal genes [91]. The tumor microenvironment, composed of stromal cells, immune cells, extracellular matrix (ECM), and soluble factors, plays a critical role in breast cancer progression and metastasis. Tumor-associated fibroblasts (CAFs) promote tumor growth, invasion, and angiogenesis through ECM remodeling and paracrine signaling [92]. The metastatic cascade involves a series of sequential steps, including local invasion, intravasation into blood or lymphatic vessels, survival in the circulation, extravasation at distant sites, and colonization of secondary organs. Tumor cells undergo phenotypic changes and adapt to survive in the hostile microenvironments of the bloodstream and distant organs, ultimately forming metastatic lesions at secondary sites [93]. Understanding the molecular mechanisms underlying breast cancer progression and metastasis is essential for identifying novel therapeutic targets, developing targeted therapies, and improving outcomes for patients with advanced disease.

Targeted Therapies and Personalized Medicine Approaches

Targeted therapies and personalized medicine approaches have revolutionized the treatment landscape for breast cancer, allowing for more precise and tailored interventions based on individual tumor characteristics, molecular profiles, and patient-specific factors [94].

Approximately 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2), which is associated with aggressive tumor behavior and poor prognosis. HER2-targeted therapies, such as monoclonal antibodies and antibody-drug conjugates, specifically inhibit HER2 signaling and have significantly improved outcomes for HER2-positive breast cancer patients [95]. Trastuzumab (Herceptin), pertuzumab, ado-trastuzumab emtansine (T-DM1), and newer agents like neratinib and tucatinib are used alone or in combination with chemotherapy to target HER2-positive breast cancer cells. Most breast cancers express hormone receptors, including estrogen receptor (ER) and progesterone receptor (PR), which drive tumor growth in response to estrogen stimulation. Hormone receptor-targeted therapies, such as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and selective estrogen receptor degraders (SERDs), disrupt estrogen signaling and inhibit tumor proliferation in hormone receptor-positive breast cancer [96]. Poly (ADP-ribose) polymerase (PARP) inhibitors exploit synthetic lethality in breast cancers with deficiencies in DNA repair pathways, such as those harboring BRCA1/BRCA2 mutations [97]. PARP inhibitors, such as olaparib and talazoparib, block PARP enzyme activity and impair DNA repair mechanisms, leading to synthetic lethality and cell death in BRCA-mutated breast cancer cells. PARP inhibitors are approved for the treatment of HER2-negative, hormone receptor-positive breast cancer with germline BRCA mutations and HER2-negative metastatic breast cancer with germline or somatic BRCA mutations [98]. Immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 antibodies, enhance the anti-tumor immune response by blocking inhibitory signaling pathways in T cells. While immune checkpoint inhibitors have shown limited efficacy as monotherapy in breast cancer, they may be effective in combination with chemotherapy or targeted therapies, particularly in triple-negative breast cancer (TNBC) and PD-L1-positive tumors [99].

Next-generation sequencing (NGS) technologies and multi-gene panel testing enable comprehensive genomic profiling of breast tumors to identify targetable mutations, copy number alterations, and gene expression patterns [100]. Liquid biopsies and circulating tumor DNA (ctDNA) analysis offer non-invasive methods for real-time monitoring of tumor dynamics, treatment response, and resistance mechanisms [101]. Detection of ctDNA mutations, copy number alterations, and gene expression profiles in blood samples provides valuable insights into tumor heterogeneity, clonal evolution, and treatment resistance, guiding treatment decisions and therapeutic strategies. Overall, targeted therapies and personalized medicine approaches have transformed breast cancer treatment paradigms, improving patient outcomes and survival rates with specific molecular subtypes and biomarker profiles [102]. Integration of genomic profiling, biomarker testing, and liquid biopsy technologies into clinical practice enables precision oncology and personalized treatment strategies tailored to the individual needs of breast cancer patients.

Innovations in Imaging Technology, Biomarker Discovery, and Liquid Biopsy Techniques

Innovations in imaging technology, biomarker discovery, and liquid biopsy techniques have significantly advanced breast cancer detection, diagnosis, treatment monitoring, and personalized management [103]. Digital Breast Tomosynthesis (DBT), also known as 3D mammography, improves breast cancer detection by capturing multiple images of the breast from different angles, allowing for clearer visualization of breast tissue and better identification of abnormalities. Contrast-enhanced mammography (CEM) combines mammography with the administration of contrast agents to enhance the visualization of breast lesions and improve the detection of invasive cancers, particularly in dense breast tissue [104]. Advances in breast ultrasound and magnetic resonance imaging (MRI) technology, including high-resolution imaging, advanced software algorithms, and functional imaging techniques, have improved the sensitivity and specificity of breast cancer detection, characterization, and staging [105]. Liquid biopsy techniques, such as circulating tumor DNA (ctDNA) analysis, circulating tumor cells (CTCs) enumeration, and extracellular vesicle (EV) profiling, offer non-invasive methods for real-time monitoring of tumor dynamics, treatment response, and emergence of resistance mutations [106]. Circulating Tumor DNA (ctDNA) analysis detects tumor-derived DNA fragments circulating in the bloodstream, providing insights into tumor heterogeneity, clonal evolution, treatment resistance, and minimal residual disease (MRD) monitoring [107]. Extracellular Vehicles (EVs), including exosomes and microvesicles, contain cargo molecules derived from tumor cells and reflect the tumor microenvironment, making them promising biomarkers for breast cancer diagnosis, prognosis, and therapeutic monitoring [108].

CONCLUSION

Breast cancer remains a significant public health challenge, but advances in research and clinical practice have improved patient outcomes. Mammography remains the gold standard for breast cancer screening, but innovations in imaging technology, such as digital breast tomosynthesis and contrast-enhanced mammography, hold promise for improving early detection rates. Future research should focus on optimizing screening strategies, identifying biomarkers for early detection, and developing non-invasive imaging modalities with higher sensitivity and specificity for early-stage breast cancer. Personalized medicine approaches, including genomic profiling, biomarker testing, and liquid biopsy techniques, enable tailored treatment strategies based on individual tumor characteristics, molecular profiles, and patient-specific factors. Clinical trials investigating novel targeted therapies, immunotherapies, and combination regimens are essential for identifying effective treatments for specific breast cancer subtypes, overcoming resistance mechanisms, and improving outcomes for advanced or metastatic disease. Advances in molecular biology, tumor microenvironment, and metastasis research deepen our understanding of breast cancer biology, heterogeneity,

and clonal evolution. Future research should focus on deciphering the molecular mechanisms underlying breast cancer progression, metastasis, and treatment resistance, as well as identifying novel therapeutic targets and biomarkers for predicting metastatic risk and guiding treatment decisions.

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