

REVIEW ARTICLE

Breast cancer: A review of risk factors, prognostic markers, diagnostics, and treatment approaches

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Abstract

Breast cancer remains a major global health challenge and was responsible for approximately 670000 deaths worldwide in 2022. Despite advances in screening, diagnosis, and treatment, it continues to be one of the leading causes of cancer-related mortality among women. This review provides a comprehensive overview of the major risk factors associated with breast cancer development and progression, emphasizing their relevance to prevention and early detection strategies. It further examines current diagnostic approaches, including imaging modalities and molecular characterization, as well as key prognostic biomarkers used for disease classification and clinical decision-making. Particular attention is given to estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, highlighting their roles in tumor biology, prognosis, and therapeutic response. The review also discusses contemporary treatment strategies, including surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapies, and immunotherapy, and considers their clinical benefits, limitations, and associated adverse effects. In addition, the growing role of biomarker-driven personalized medicine is explored, demonstrating how molecular profiling can guide treatment selection and improve patient outcomes. By integrating current knowledge on risk factors, diagnostic methods, prognostic biomarkers, and therapeutic interventions, this review provides a comprehensive perspective on breast cancer management and future directions in precision oncology.

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1. Introduction

1.1. Overview of breast cancer

Breast cancer caused 670,000 mortalities globally in 2022 and was the most common cancer in women, prevalent in 157 out of 185 nations in 2022.¹ A great number of cases occurred in transitioned nations in spite of having almost opposite mortality rates. The

burden of breast cancer predicted for the future is a rise of about 3 million additional cases and about 1 million mortalities in 2040.² Deaths due to breast cancer in women are high in many countries, accounting for a total of 684,996 deaths in the year 2020 alone, with Barbados being at the top of the list.² Between 1990 and 2021, the global burden of breast cancer among women of reproductive age rose substantially, with new cases, prevalence, and disability-adjusted life years increasing by 118.7%, 121.3%, and 66.8%, respectively.³ The steepest rises occurred in regions with low or low-middle sociodemographic index values.³ By 2050, new cases and deaths are projected to rise by 38% and 68%, respectively, with the greatest impact falling on low-Human Development Index countries. To reduce these disparities and effectively track progress toward cancer control targets, countries with low and medium Human Development Index scores require high-quality cancer and vital status data, along with sustained improvements in early diagnosis and access to treatment.⁴

The topic of breast cancer risk factors, biomarkers, and treatment strategies has been extensively studied. However, the novelty of the present review lies in its integrative and translational perspective. Specifically, this manuscript does not address these components in isolation; rather, it systematically links risk factors, prognostic biomarkers, and therapeutic strategies within a single, coherent framework. By doing so, it highlights the continuum from disease development to biomarker-driven treatment selection, which is less commonly synthesized in existing literature. In addition, the review incorporates both established biomarkers (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]) and emerging factors, such as circulating circular RNAs and tumor-associated macrophages, and discusses their combined relevance in disease progression, prognosis, and treatment responsiveness.

Moreover, with a focus on how prognostic markers influence individualized treatment choices, this narrative review aims to provide an integrated, therapeutically focused synthesis of breast cancer risk factors, prognostic biomarkers, diagnostic advances, and treatment approaches. This work integrates biomarker biology with practical clinical decision-making, in contrast to past reviews that concentrate on discrete domains such as molecular subtypes, diagnostic imaging, or therapy modalities. This review also fills a significant gap in the literature by connecting prognostic markers to treatment choices, side effects, and new diagnostic tools. This also illustrates the increasing trend toward precision oncology in the treatment of breast cancer.

1.2. Prevalence in Pakistan

Pakistan bears one of the highest breast cancer incidence rates among Asian countries, with breast cancer accounting for approximately 28.7% of all newly diagnosed cancers and 11.7% of cancer-related deaths nationwide.^{5,6} The elevated disease burden arises from a combination of genetic susceptibility, consanguineous marriages, delayed clinical presentation, limited screening programs, and inadequate awareness of early detection practices such as breast self-examination (BSE).^{7,8} Lifestyle transitions, including increasing obesity, reduced physical activity, declining breastfeeding rates, and changing reproductive patterns, further contribute to breast cancer risk through hormonal and metabolic pathways.^{7,9} These factors collectively highlight the need for population-specific prevention strategies and strengthened diagnostic infrastructure in Pakistan.

1.3. The anatomy of the breast

The human breast is composed of approximately 15–20 lobes arranged radially around the nipple, each containing lobules responsible for milk production (Figure 1).¹⁰

The breast, positioned on the front of the chest, consists of skin, fat, and glandular tissue, mainly overlying the pectoralis major muscle, with parts above the serratus anterior and oblique muscles. Surgical procedures such as mastectomies require the removal of all relevant tissue effectively, contained within fascial layers. Its anatomical limits are defined from the second to the sixth rib, stretching from the sternum to the midaxillary line, and may include the axillary tail of Spence.

Its blood supply is divided among three main arteries, with the majority coming from the anterior perforating intercostal arteries (from the internal thoracic artery), a significant portion from the lateral thoracic and thoracoacromial arteries, and the remainder from the posterior intercostal arteries. This circulation system, essential for tissue health, is supported by a corresponding venous drainage pattern.

Sensory innervation primarily arises from the second to sixth intercostal nerves, with the intercostobrachial nerve particularly important for sensation in the inner upper arm, a consideration in axillary surgeries. The integrity of the long thoracic nerve is also crucial to avoid impairing the latissimus dorsi muscle and to prevent the potential complication of a “winged scapula” from surgical damage.¹¹

Breast cancer most commonly originates from the epithelial lining of the ducts or lobules. Pre-invasive lesions,

such as ductal carcinoma *in situ*, remain confined to the ductal structures, whereas invasive carcinomas breach the basement membrane, infiltrate surrounding tissues, and gain access to lymphatic and vascular pathways, thereby enabling metastasis.¹¹ Schematic representations that compare normal breast architecture with pre-invasive and invasive disease states can facilitate understanding of disease progression.

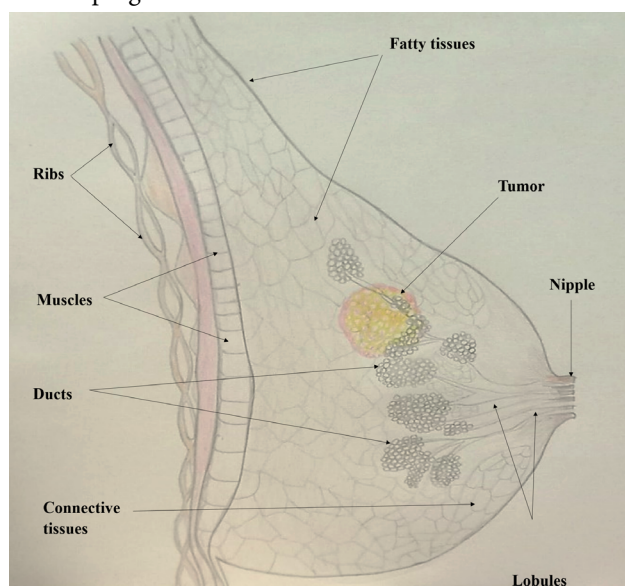


Figure 1. Anatomy of the breast with ductal carcinoma *in situ* (DCIS). DCIS pertains to the malignant transformation of breast ductal epithelial cells. The neoplastic cells remain localized within the ductal structures.

1.4. The development and progression of breast cancer

Breast cancer is the uncontrolled growth of abnormal cells within the breast that leads to the formation of tumors. Without intervention, these tumors have the potential to metastasize and spread to other parts of the body, ultimately resulting in fatality.¹² Breast cancer first develops inside breast cells. A cancerous tumor, a collection of cancer cells, can invade and destroy surrounding tissue.¹³ Breast cancer originates within the breast from the milk ducts or milk-producing lobules. The initial stage, termed “*in situ*,” poses no immediate threat to life and can be identified early. However, cancer cells may infiltrate the breast’s surrounding tissue, leading to invasive cancer. Invasive cancers have the potential to spread to nearby lymph nodes or other organs by a process known as metastasis, which can be fatal.¹⁴

Breast cancer arises due to pathological changes or carcinogenesis that affect one or both breasts, potentially occurring in any cell, tissue, or organ. Factors such as increased cell division, heightened angiogenesis, self-stimulated growth signals, hormonal influences, diminished apoptosis, and resistance to growth-suppressing signals contribute to the advancement of cancerous tumors. The growth and proliferation of breast cancer tumors can significantly vary, with some of the tumors taking years to reach a size substantial enough to cause noticeable symptoms (Figure 2).¹⁵

Molecular Progression of Normal Cell to Cancer

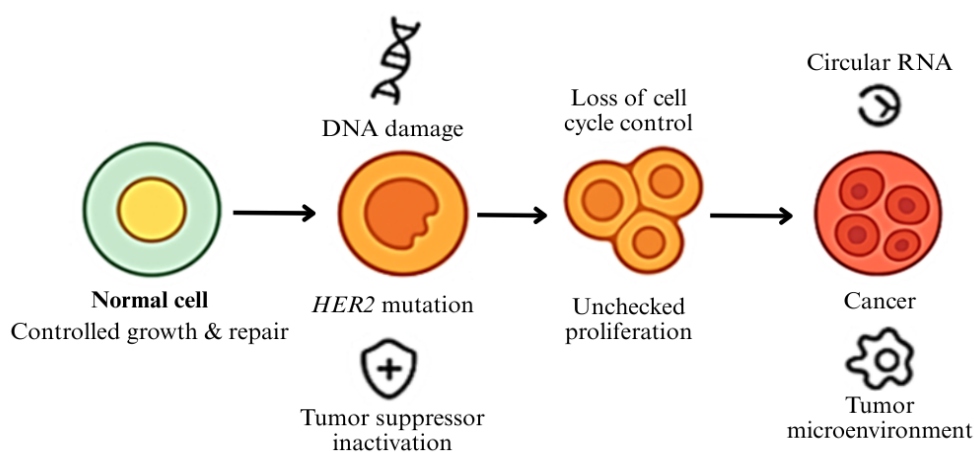


Figure 2. The diagram illustrates the process of cancer development, highlighting key factors such as genetic mutations, *HER2* mutations, and inactivation of tumor suppressor genes. These factors lead to the formation of defective cells, which proliferate and give rise to cancer cells. The diagram provides a concise overview of the complex molecular mechanisms underlying carcinogenesis.

Breast carcinogenesis is a multistep process driven by genetic mutations, epigenetic alterations, dysregulated hormone signaling, increased angiogenesis, immune evasion, and resistance to apoptosis.^{12,15} Tumor growth rates and metastatic potential vary widely across molecular subtypes, forming the biological basis for prognostic stratification and individualized treatment approaches.

2. Risk factors of breast cancer

The predominant breast cancer risk factor is being female, with approximately 99% of cases diagnosed in women, while 0.5–1% affect men. In men, management of breast cancer is the same as that of breast cancer in women.¹⁴

Certain risk factors that increase breast cancer incidence and progression include increasing age¹⁵, breast cancer history in first-degree relatives¹⁶, obesity¹⁷, tobacco use¹⁸, harmful use of alcohol¹⁹, history of radiation exposure²⁰, reproductive history (early menarche or late menopause)²¹, age at first pregnancy²², and hormonal replacement therapy after menopause.²³

Almost 50% of breast cancer cases occur in those women who lack any identifiable risk factors of breast cancer apart from being female and above the age of 40 years. Although having a breast cancer family history raises the breast cancer risk, most females with a breast cancer diagnosis do not have such a history (Table 1).

Table 1. Risk factors for breast cancer

Risk factors	Description	References
Age	Breast cancer incidence is highly related to increasing age. In 2016, approximately 99.3% and 71.2% of all breast cancer-related deaths in America were reported in women over the age of 40 and 60, respectively	24
Family history	Women with two or more first-degree relatives with breast cancer have a risk of 2.5-fold or higher	16
Obesity	Breast cancer patients who are obese manifest a distinguishable patient demographic, being at an increased probability of cancer development	17
Early menarche & late menopause	Each 1-year delay in menopause increases 3% risk of breast cancer and each 1-year delay in menarche reduces breast cancer risk by 5%, whereas each additional birth reduces risk by 10%	25
History of chronic inflammation	Chronic inflammation might contribute to the onset and progression of breast cancer, even though various persistent inflammatory processes occurring in breast tissue may develop into breast carcinogenesis	26
History of hormonal replacement therapy	As per the National Cancer Institute, estrogen-only hormonal replacement therapy may increase the breast cancer risk, and ceasing the therapy does not reduce the breast cancer risk	27
Late childbirth	Women having a term pregnancy before 20 years of age have a lower breast cancer risk than those having a pregnancy after 35 years of age	28
Lack of breastfeeding	For every 12 months of breastfeeding, the breast cancer risk reduces by 4.3%, and a 7% reduced risk for each birth is observed	9

3. Prognostic biomarkers

3.1. Estrogen receptor

Luminal A and B breast cancers are hormone-dependent subtypes that express the ER and are observed in about 70% of individuals with breast cancer.²⁹ Estrogens are the primary signals in these tumors, and they are crucial for the growth and spread of tumor cells. The nuclear ER (α , β) and the membrane G protein-coupled ER (GPER, also known as GPR30) are the main mechanisms via which estrogen acts in cells. The receptor thought to play the most important role in the development of breast cancer is ER α .³⁰

Since estrogen-induced ER α activation is responsible for about two-thirds of breast cancer cell growth, hormone therapy is the preferred treatment. By denying the tumor

estrogen, it inhibits the action of ER α , preventing breast cancer from returning and improving patient survival. The selective ER modulator family's ER α antagonists, including tamoxifen, are the most widely used and best described.³¹

By binding to ER α , tamoxifen (in contrast to estrogen) stimulates the recruitment of inhibitors, which in turn inhibit breast cancer cell development.³² For more than 20 years, tamoxifen has been the sole treatment available for advanced breast cancer. The first-line treatment for premenopausal and postmenopausal women is a 5-year course of tamoxifen. However, the introduction of aromatase inhibitors significantly changed first- and second-line treatments in the late 1990s. The therapeutically effective active ingredients (letrozole, anastrozole, or exemestane) inhibit the aromatase enzyme, thereby preventing the conversion of androgens to estrogens.³³

3.2. Progesterone receptor

Biologically different processes with particular biological behaviors and pathological traits are included in the diverse categories of breast cancer. PR-positive breast cancer cells mainly depend on progesterone signaling for growth. For individuals to benefit from endocrine treatment targeting estrogen activity, such as ER downregulators (fulvestrant), aromatase inhibitors (letrozole, anastrozole, exemestane), and selective ER modulators (tamoxifen), estrogen and progesterone expression are crucial determinants.

For patients with hormone-positive breast cancer, endocrine treatment is a simple alternative and frequently a well-tolerated treatment. Adjuvant endocrine treatment is often administered for five to ten years and can begin either before or after surgery. This treatment aims to prevent cancer from coming back. The endocrine treatment response is remarkable, as it can be impacted by the innate aggressiveness of cancer and the covert progression of the disease. Breast cancer that is both ER-positive and PR-positive is prevalent, and ER upregulates PR expression. In a study with 666,852 hormone receptor-positive breast cancer patients, 82.9% of patients were ER-positive/PR-positive, 15.0% of patients were ER-positive/PR-negative, and 2.0% of patients were ER-negative/PR-positive.³⁴

3.3. Human epidermal growth factor receptor 2

Human epidermal growth factor receptor 2 overexpression correlates with tumor size and type.³⁵ Peak *HER2* copy number, *HER2/CEP17* ratio, and *ERBB2* mRNA levels predict worse recurrence-free survival vs. intermediate levels. A subpopulation treatment effect pattern plot analysis of the APHINITY trial showed that lymph node-positive patients with extreme *HER2* copy number levels derived reduced benefit from pertuzumab-trastuzumab treatment.³⁶ *HER2* testing involves immunohistochemistry (IHC) or fluorescence *in situ* hybridization. *HER2*-positive tumors (IHC 3+ or fluorescence *in situ* hybridization-amplified) are treated with *HER2*-targeted therapies such as trastuzumab, pertuzumab, or lapatinib.³⁵ *HER2* status guides combination therapy with chemotherapy or hormone therapy.^{35,36} Despite aggressive disease, *HER2*-targeted therapies improve outcomes in *HER2*-positive patients.³⁵

3.4. Circulating circular RNA

Early detection is essential for enhancing the prediction of breast cancer in suspected cases; yet, there are currently no circulating indicators that illustrate good sensitivity and precision.³⁷ Circular RNAs, a novel category of noncoding RNAs, have emerged as vital regulators of cancer initiation

and advancement, functioning as either oncogenes or suppressors. Particularly in breast cancer, circular RNAs play important roles in tumor progression, recurrence, and resistance to multiple drugs through diverse mechanisms. Consequently, circular RNAs represent potential targets for therapeutic interventions targeted at managing breast cancer.³⁸ Because of their closely connected structure, circular RNAs are extremely stable and, in body fluids, can easily be detected, making circular RNAs the ideal candidates to be used as non-invasive biomarkers.³⁹

3.5. Tumor-associated macrophages

Tumor-associated macrophages in breast cancer are correlated with a worse prognosis.⁴⁰ Within the microenvironment of breast tumors, the most dominant immune cells are the tumor-associated macrophages, influencing the course of breast cancer. Throughout the initiation and progression of breast cancer, these macrophages aid tumor growth by promoting processes such as angiogenesis, metabolic regulation, metastasis, and immunosuppression. These macrophages exhibit considerable adaptability, with the potential to shift from supporting tumor growth to promoting tumor regression by repolarizing into M1 macrophages. These are viable targets for therapeutic interventions in breast cancer management (Figure 3).⁴¹

4. Diagnostic procedures

It is demonstrated that almost 80% of primary breast cancer might be treated if diagnosed at an early stage. Still, metastatic breast cancer remains challenging to treat despite therapeutic advances (Figure 4).⁴²

4.1. Breast self-examination

For years, women have been taught BSE methods, and it is recommended that they practice BSE regularly.⁴³ Women who practice BSE are most likely to find their breast tumor on their own, that the tumor tends to be smaller, and that these women have an increased survival.⁴⁴

4.2. Mammography

Mammography is the most reliable and preferred method for identifying early-stage breast cancer, especially ductal carcinoma, even before the manifestation of clinical indications. The use of mammography has reduced mortality rates by around 25–30%.⁴⁵ Diagnostic mammography uses low levels of radiation to produce an image of the breasts, typically employed to investigate any irregularities detected during a clinical breast examination or screening mammograms. Additionally, it can be used in conjunction with a biopsy to pinpoint anomalous regions.⁴⁶

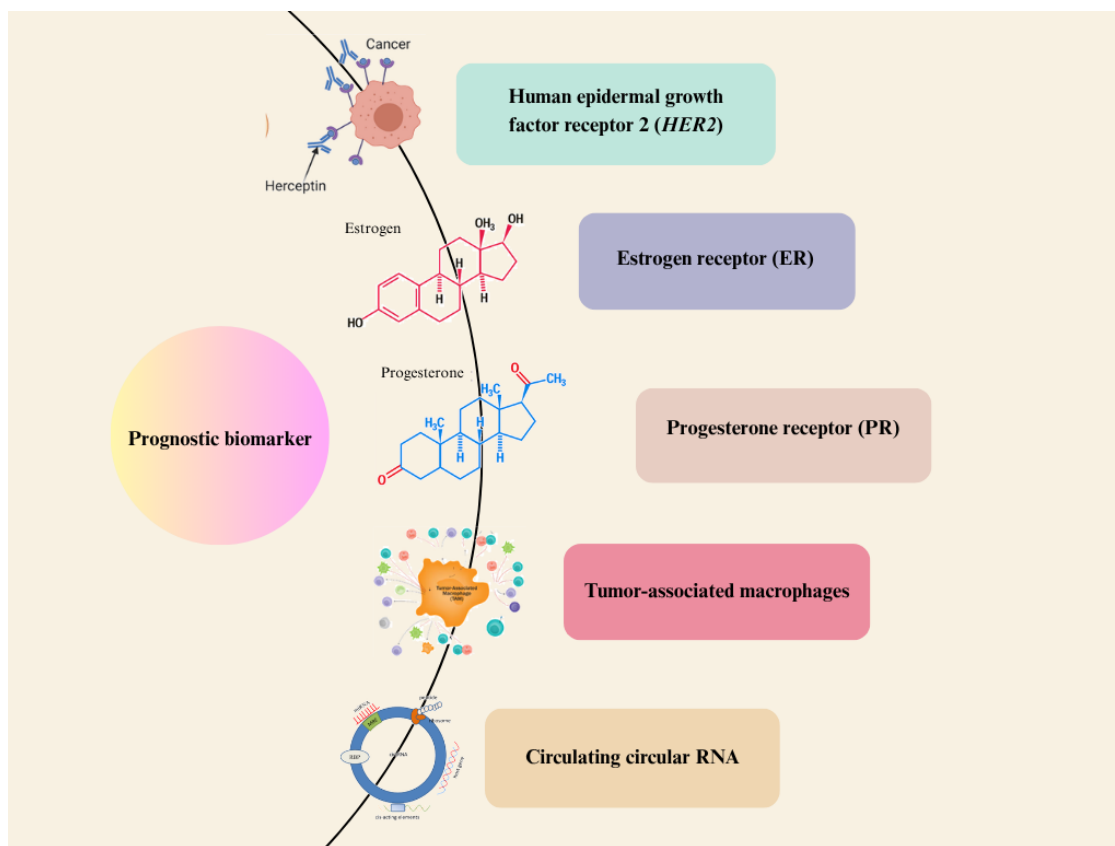


Figure 3. Key prognostic biomarkers in breast cancer progression

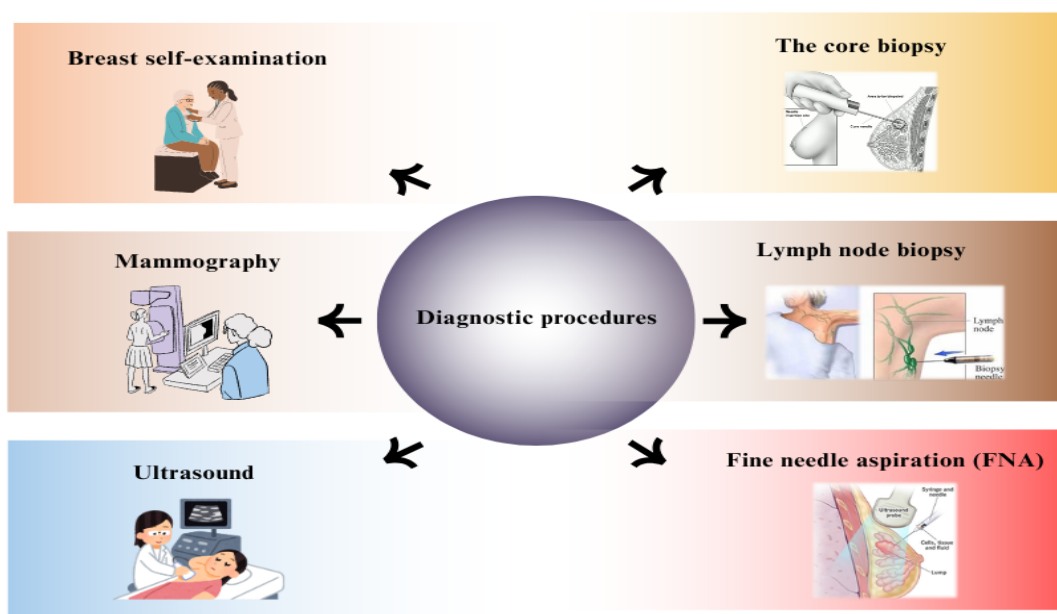


Figure 4. Diagnostic procedures for breast cancer

4.3. Ultrasound

Ultrasound imaging uses high-frequency sound waves to generate images of various body structures. Its primary application involves distinguishing between solid tumors and cysts within the breast. Moreover, medical practitioners utilize ultrasound to guide them to the precise location of the biopsy. In cases of advanced breast cancer, ultrasound scans may also assess the presence of liver metastasis.⁴⁷

4.4. Biopsy specimens

The definitive diagnosis of breast cancer relies on conducting a biopsy, which involves extracting cells or tissues from the affected part of the patient's body to be analyzed in a testing center or laboratory. The findings from the pathologist's examination determine whether cancerous cells are present in the sample. The selection of biopsy method hinges on whether the lump is palpable (detectable by touch) or non-palpable (not detectable by touch). To pinpoint the precise area for sampling, doctors may employ ultrasound or mammography. Typically, biopsies are performed in a hospital setting, and once the procedure is complete, patients are usually discharged to return home.⁴⁸

4.4.1. The core biopsy

Doctors utilize a specialized hollow needle to extract tissue from the body, particularly from areas in the breast deemed suspicious. This procedure may involve obtaining multiple samples from the targeted region. In certain cases, doctors employ a specialized vacuum to extract additional tissue through the hollow needle. This technique is known as vacuum-assisted core biopsy.⁴⁹

4.4.2. Lymph node biopsy

A lymph node biopsy involves a surgical intervention wherein lymph nodes are extracted for microscopic scrutiny to ascertain the presence of cancer cells. Breast cancer cells can break away from the primary tumor and travel via the lymphatic circulation, often targeting the lymphatic nodules in the armpit (below the arm) as their initial destination. Counting the number of affected lymph nodes aids doctors in determining the stage of breast cancer.⁵⁰

4.5. Fine needle aspiration

Fine needle aspiration (FNA) involves extracting a small tissue sample from a lump using an injector and a fine needle, helping physicians determine whether the lump is a cyst or a solid tumor. However, FNA cannot ascertain whether a cancer is non-penetrating (non-invasive) or penetrating (invasive).⁵¹

In an FNA, a physician uses an extremely fine, hollow needle connected to a syringe to extract fluid or a small sample of breast tissue from the area of concern. This procedure is commonly performed when the suspicious area is likely to contain fluid, such as an abscess or cyst. By draining the fluid, FNA can often alleviate discomfort caused by the cyst. If the area being biopsied is palpable, the needle can be inserted into it while the doctor palpates it. In situations where the lump is not easily detected, the doctor may monitor the needle's movement on an ultrasound screen as it approaches and enters the area. This procedure is known as ultrasound-guided FNA. When FNA is used to examine a suspicious area of the breast, the sample is subsequently examined for carcinogens. One limitation of FNA is that it retrieves only a small amount of tissue and cells, requiring a quick microscopic examination of the sample to determine whether further samples are needed.⁵²

4.6. Nanoscale diagnostic tools and cellular elasticity as emerging biomarkers

In addition to established diagnostic modalities such as imaging and histopathology, recent advances in nanoscale analytical technologies have created new opportunities for highly sensitive detection and characterization of breast cancer biomarkers. Nanomaterial-based platforms and probe-scale tools enable molecular and subcellular-level analysis, improving detection limits for circulating and tissue-based biomarkers and supporting earlier and more precise disease assessment.⁵³ Alongside biochemical markers, the biochemical properties of breast cancer cells are increasingly recognized as diagnostically relevant. Techniques such as atomic force microscopy allow nanoscale measurement of cellular stiffness and elasticity, revealing characteristic alterations in malignant cells that correlate with tumor progression and metastatic potential. These mechanical signatures may serve as complementary, label-free biomarkers that enhance current diagnostic frameworks when integrated with molecular and imaging approaches.⁵⁴

5. Prevention strategies for breast cancer

Protective interventions that reduce breast cancer risk for females are breastfeeding, early pregnancy, mastectomy for reducing risk, oophorectomy for reducing risk, use of estrogen after hysterectomy, ovarian ablation, selective ER modulators, aromatase deactivators or inhibitors, and regular exercise.⁵⁵⁻⁵⁷ Interventions such as lifestyle modification, preventative strategies, and advanced screening programs are essential factors contributing toward a possible reduction of breast cancer incidence rate and thus the execution of early treatment. Currently, the Breast Health Global Initiative program has taken

the responsibility of preparing suitable approaches and instructions to provide the most satisfactory breast cancer control interventions.⁵⁸

6. Lifestyle modification strategies

Lifestyle modification strategies for reducing breast cancer risk include maintaining a healthy weight, engaging in at least 30 minutes of physical activity daily to improve energy levels and mood, consuming a diet rich in fruits and vegetables, limiting alcohol intake, and avoiding or quitting smoking. may also help reduce risk. Women, particularly those older than 35 years who smoke, should avoid or limit the use of oral contraceptive pills. Hormone replacement therapy for menopausal symptoms should also be avoided or used cautiously when appropriate. High-risk women may benefit from preventive medications such as tamoxifen or raloxifene, but these should only be taken under a physician's prescription and supervision. Women with a strong family history should use preventive strategies to reduce the risk of disease. Mammogram

screening is important; however, it does not prevent breast cancer occurrence but can detect it at an early stage, where it is at the most treatable stage, which increases the survival rate to maximum.⁵⁹

7. Treatment strategies

Nuclear medicine screening facilities have enhanced diagnosis, classification, regular check-ups, and response examinations. Increasing progress in the therapeutic management of breast cancer has now been achieved with advanced tools and techniques, and the use of genomic studies and their comparisons has improved diagnostic procedures. Moreover, newer techniques are being discovered every day with improved approaches both for diagnostic and therapeutic interventions (Table 2).⁶⁰

7.1. Surgery

There are two primary surgical approaches for removing cancerous tissue from the breast: mastectomy and breast-conserving surgery (BCS). Breast-conserving surgery, often

Table 2. Clinical use and adverse effects of treatment strategies for breast cancer

Treatment strategies	Definition and mechanism	Clinical use and recent advances	Notable adverse outcomes
Surgery	Removal of tumor via mastectomy, lumpectomy, ± axillary node dissection	Oncoplastic/robotic techniques; improve aesthetics; standard for localized disease	Scarring; altered breast appearance; infection; pyrexia; recurrence; lymphedema risk ~20–30% post-axillary dissection; reduced with sentinel biopsy
Chemotherapy	Systemic cytotoxic drugs (e.g., anthracyclines, taxanes)	Neoadjuvant or adjuvant use; combined with immuno-/targeted agents	Bone marrow suppression; gastrointestinal toxicity; peripheral neuropathy (~30–40%); early menopause/infertility; increased risk of secondary leukemia/myelodysplasia (~1%)
Personalized medicine	Molecular profiling (e.g., ctDNA, <i>PIK3CA</i> , <i>BRCA</i> , MammaPrint) guiding therapy	Guides de-escalation (e.g., sparing chemo), treatment intensification, dynamic circulating tumor DNA monitoring	Minimal direct toxicity; though treatment decisions may risk undertreatment or misclassification errors
Radiation therapy	High-energy beams (X-ray/proton) targeting residual microscopic disease	Used post-surgery for local control (IMRT, APBI, proton)	Fibrosis; induration; edema; telangiectasia; cardiac toxicity risk (10–30%); lung fibrosis; <i>secondary malignancies</i> years later
Endocrine Therapy	Hormone manipulations (tamoxifen, AIs, GnRH agonists) for ER+/PR+ tumors	Long-term adjuvant; combined with CDK4/6 inhibitors in hormone receptor-positive patients with high risk	Hot flashes; arthralgia (20–30%); fatigue; mood issues; bone loss and fracture risk (~10–20% after 5 years); vascular effects: thrombosis, endometrial cancer, diabetes
Targeted/Biological therapy	HER2 monoclonal antibodies (trastuzumab, pertuzumab), ADCs, CDK inhibitors, PARP inhibitors	HER2+ regimens enhance survival; ADCs and PARPi for <i>BRCA</i> -mutated cases	Cardiotoxicity (~3–7% LVEF decline, <1–1.5% symptomatic HF); rash, diarrhea, hematologic toxicity
Immunotherapy/ACTs	Checkpoint inhibitors, CAR-T strategies	Emerging in TNBREAST CANCER and refractory HER2+ & luminal breast cancers	Immune-related adverse events: rash, colitis, pneumonitis, endocrinopathy; flu-like symptoms, fatigue

Abbreviations: ACTs: Adoptive cell therapies; ADCs: Antibody–drug conjugates; AIs: Aromatase inhibitors; APBI: Accelerated partial breast irradiation; CAR T: Chimeric antigen receptor T-cell; CDK: Cyclin-dependent kinase; ER: Estrogen receptor; GnRH: Gonadotropin-releasing hormone; HER2: Human epidermal growth factor receptor 2; HF: Heart failure; IMRT: Intensity-modulated radiation therapy; LVEF: Left ventricular ejection fraction; PARPi: Poly(ADP-ribose) polymerase inhibitors; *PIK3CA*: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR: Progesterone receptor; TNBC: Triple-negative breast cancer.

followed by radiation therapy, is preferred when the tumor can be completely excised while maintaining a satisfactory cosmetic outcome.⁶¹ Also referred to as lumpectomy, partial mastectomy, segmental mastectomy, quadrantectomy, or wide local excision, this procedure involves removing the tumor and a margin of surrounding tissue while preserving as much healthy breast tissue as possible. Modern techniques frequently incorporate reconstructive approaches, collectively known as oncoplastic surgery, to improve both functional and aesthetic outcomes.

Mastectomy, on the other hand, entails the entire excision of the breast, usually followed by immediate reconstruction. The procedure for removing affected lymphatic nodes includes axillary lymph node dissection and sentinel lymph node biopsy. Although breast-conserving surgery is generally considered more beneficial for patients, there remains a possibility that some individuals may subsequently require a mastectomy because of recurrence, incomplete tumor excision, or disease progression. Nevertheless, breast-conserving surgery is associated with superior cosmetic outcomes, reduced psychological distress, and fewer postoperative complications compared with mastectomy. Guidelines from the European Society for Medical Oncology⁶² for early breast cancer suggest that the choice of treatment should be based on tumor size, the practicality of surgery, clinical phenotype, and the patient's desire to conserve the breast. Surgical treatment may lead to persistent pain, scarring, sensory disturbance, and cosmetic changes. Axillary procedures increase the risk of lymphedema, reduced arm mobility, and shoulder stiffness, with additional psychosocial impact in mastectomy patients.⁶²

7.2. Chemotherapy

Recommended treatment choices in the United States, as well as other regions, incorporate chemotherapy (such as anthracycline, taxane, platinum, capecitabine), endocrine therapy (like tamoxifen, aromatase inhibitor, ovarian ablation/suppression), and bisphosphonates, anti-HER2 therapy (including trastuzumab, trastuzumab emtansine, pertuzumab, neratinib). Common toxicities include fatigue, myelosuppression, nausea, alopecia, and increased risk of infection. Long-term complications may involve peripheral neuropathy, cardiotoxicity (anthracyclines), cognitive effects, and premature menopause in younger women.⁶³

7.2.1. Neoadjuvant therapy

In the past, neoadjuvant therapy was developed for the treatment of locally advanced/progressive breast cancer, such as inflammatory breast cancer, as a systematic approach before definitive surgery.⁶⁴ The association

between polymerase chain reaction and positive outcomes was consistent.⁶⁵

7.2.2. Adjuvant therapy

Adjuvant chemotherapy is administered post-surgically to reduce the likelihood of cancer recurrence and to eliminate any residual carcinogens in the area. The agents employed in systemic therapy for adjuvant breast cancer encompass a variety of medications: Taxanes (such as docetaxel and paclitaxel), cyclophosphamide, anthracyclines (including doxorubicin), pertuzumab, ado-trastuzumab emtansine, trastuzumab, neratinib, cyclin-dependent kinase inhibitors (such as palbociclib, abemaciclib, and ribociclib), tamoxifen, aromatase inhibitors (such as anastrozole, exemestane, and letrozole), and pembrolizumab.⁶⁶

7.3. Personalized medicine

The primary objective of personalized therapy is to develop effective, targeted drugs for patients with different subphenotypes. This approach has gained widespread application in cancer treatment due to the discovery of genetic mutations that drive cancer growth, paving the way for the development of molecularly targeted drugs. These personalized anti-cancer drugs encompass a variety of treatments, including tyrosine kinase inhibitors, small-molecule inhibitors, vaccines, antibodies, and monoclonal antibodies. Notably, many of these drugs have been identified through drug repositioning efforts, uncovering new therapeutic opportunities for existing medications. Among the Food and Drug Administration-approved drugs used for personalized treatment through drug repositioning are pembrolizumab, nivolumab, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, gefitinib, erlotinib, afatinib, osimertinib, olaparib, rucaparib, trastuzumab deruxtecan, tucatinib, vemurafenib, larotrectinib, and ibrutinib. Although personalized medicine reduces unnecessary exposure, adverse effects still reflect the toxicity profiles of the guided therapies used. Additional challenges include rare pathway-specific toxicities, uncertain genomic results, and psychological burdens associated with genetic findings.⁶⁷

7.4. Radiation therapy

Radiation therapy is generally painless, though it may cause gradual skin discomfort. In the treatment of initial-stage breast cancer, radiotherapy is commonly administered following surgery. Surgery is performed to remove the cancer, while radiation is employed to eradicate any residual cancer cells post-surgery, thus lowering the risk of cancer recurrence.

Radiotherapy can also be utilized in cases such as unresectable metastatic breast cancer, where surgery is

not feasible. This typically refers to breast cancer that has spread to further parts of the body, including the bones, lungs, brain, or liver. Several types of radiation therapy are available, including beam radiation, intraoperative radiation therapy, external brachytherapy or internal radiation, and proton therapy. Radiation therapy can cause acute skin reactions, edema, and fatigue, with possible late effects such as fibrosis and cosmetic changes. In left-sided irradiation, a small but relevant risk of cardiopulmonary toxicity persists despite modern dose-sparing techniques.⁶⁸

7.5. Endocrine (hormonal) therapy

Endocrine therapy, also called anti-estrogen therapy or hormone therapy, plays a vital role in managing hormone receptor-positive breast cancer across all stages. This type of cancer is characterized by the presence of estrogen, progesterone, or both ERs and PRs on cancer cells, which foster their growth and proliferation when activated by these hormones. About two-thirds of breast cancer cases are hormone receptor-positive, as stated by the American Cancer Society.⁶⁹

The basic goal of hormonal therapy is to either block estrogen production in the body or inhibit estrogen's effects on breast cancer cells, efficiently obstructing the growth of hormone receptor-positive tumors. This form of therapy is not suitable for treating hormone receptor-negative breast cancer.

Endocrine therapy is distinct from hormone replacement therapy, which some women use to alleviate menopausal symptoms like mood swings and hot flashes. Conversely, whereas hormone replacement therapy increases estrogen levels after menopause, hormonal therapy for breast cancer is designed to reduce estrogen production or block its effects in the body. Tamoxifen may cause vasomotor symptoms, weight gain, and thromboembolic events, while aromatase inhibitors are associated with arthralgia, bone loss, and fracture risk. Long-term toxicity may affect adherence and requires ongoing monitoring.⁷⁰

7.6. Biological therapy

To combat cancer, biological or targeted therapy utilizes the body's immune (defense) mechanism by employing body-produced or lab-synthesized substances to boost the immune system's ability to detect and attack cancer-specific molecules. Unlike broader treatments such as chemotherapy or radiation, which can affect healthy cells, targeted therapies target cancer cells' unique receptors or molecules, sparing normal cells. This method is exemplified in treatments like HER2-targeted therapies for breast cancer, which only attack cells with the HER2 protein.⁷¹⁻⁷³ Usual approaches include monoclonal antibodies, poly(ADP-

ribose) polymerase inhibitors, kinase inhibitors, antibody-drug conjugates, cyclin-dependent kinase 4/6 inhibitors, and phosphoinositide 3-kinase inhibitors, addressing various breast cancer subtypes, including HER2-positive, hormone receptor-positive, triple-positive, triple-negative, and *BRCA*-mutated. Targeted agents generally exhibit pathway-specific toxicities; HER2-directed therapies may cause cardiac dysfunction, while poly(ADP-ribose) polymerase inhibitors and antibody-drug conjugates can cause fatigue, hematologic effects, and gastrointestinal symptoms, necessitating individualized risk assessment.⁷⁴

8. Conclusion

The review article emphasizes the significant impact of breast cancer worldwide. It highlights key risk factors, including genetic predisposition, hormonal influences, lifestyle factors, and environmental exposures, stressing the importance of understanding these factors for early detection and prevention, the most critical elements in reducing both mortality and treatment burden. Moreover, it discussed the role of prognostic markers, such as hormone receptors, in guiding treatment decisions and improving patient outcomes. Future research should prioritize the development of novel targeted agents, strategies to overcome therapy resistance, improved access to innovative treatments, and the integration of real-world evidence and artificial intelligence-driven clinical tools to further optimize patient-centered breast cancer care.

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Conflict of interest

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