African Journal of
Medicine, Surgery and Public Health Research

ISSN: 1595-8000

Index: Harvard, Boston, Sydney University, Dimensions, Lens, ResearchGet Scilit, Semantic, Google Scholar, Base etc

https://doi.org/10.58578/AJMSPHR.v2i2.6068

Breast Cancer in the Modern Era: Molecular Strategies for Tumor Targeting and Diagnosis

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Article Info:

Submitted:	Revised:	Accepted:	Published:
Apr 15, 2025	May 25, 2025	May 27, 2025	Jun 1, 2025

Abstract

Breast cancer is a multifactorial and heterogeneous malignancy arising from the uncontrolled proliferation of breast tissue cells, primarily affecting women but also occurring in men. Among its various subtypes, invasive ductal carcinoma (IDC) accounts for 70% to 80% of cases, making it the most prevalent form. As one of the leading causes of cancer-related mortality among women globally, breast cancer remains a major public health concern, driving continuous research into its etiology, detection, and treatment. The disease is influenced by an interplay of genetic, hormonal, and environmental risk factors. While non-modifiable determinants such as age and sex are critical, modifiable lifestyle factors, such as physical activity, dietary habits, and alcohol consumption also contribute significantly to disease risk. Advances in screening technologies, including mammography and magnetic resonance imaging (MRI), have facilitated earlier detection, improving treatment outcomes. However, disparities in access to diagnostic and therapeutic resources persist, particularly in low-resource and marginalized populations, reinforcing existing health inequities. The treatment landscape has evolved markedly with the advent of personalized medicine and immunotherapeutic approaches, offering targeted interventions based on tumor biology.

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Nevertheless, ongoing challenges include treatment resistance, overdiagnosis, and the ethical dilemmas surrounding management of low-risk lesions. Furthermore, debates continue regarding optimal screening strategies, the role of genetic testing, and the balance between therapeutic benefit and potential harm. These complexities underscore the need for integrative, equity-focused approaches to breast cancer prevention, diagnosis, and care.

Keywords: Breast Cancer; Invasive Ductal Carcinoma; Early Detection; Personalized Medicine; Health Disparities; Screening Controversies

Types of Breast Cancer

Breast cancer is a heterogeneous disease with various subtypes that differ in their biological characteristics, treatment responses, and clinical outcomes. The classification of breast cancer can generally be divided into two main categories: invasive and non-invasive types.

Non-Invasive Breast Cancer

Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS) is a non-invasive form of breast cancer where abnormal cells are found in the lining of the breast milk ducts but have not spread to surrounding breast tissue[1][3]. Although considered non-invasive, DCIS can increase the risk of developing invasive breast cancer in the future. Early detection and treatment are crucial for improving outcomes[4].

Invasive Breast Cancer

Invasive Ductal Carcinoma (IDC)

Invasive ductal carcinoma (IDC) is the most common type of breast cancer, accounting for approximately 70% to 80% of all breast cancer cases[2][5]. It begins in the milk ducts and then invades the nearby breast tissue. IDC can metastasize to lymph nodes and other parts of the body, making early diagnosis and treatment essential[3][6].

Invasive Lobular Carcinoma (ILC)

Invasive lobular carcinoma is the second most common type, comprising about 10% to 15% of breast cancer cases[2]. ILC has distinct characteristics compared to IDC, including a different pattern of spread and unique imaging challenges[6]. It may be less detectable on

mammograms and is often diagnosed at later stages, which can lead to a greater likelihood of lymph node involvement[5].

Other Types of Invasive Breast Cancer

Additional subtypes of invasive breast cancer include inflammatory breast cancer and metastatic breast cancer[1][2]. Inflammatory breast cancer is a rare and aggressive form that often presents with swelling and redness of the breast, while metastatic breast cancer refers to cancer that has spread from the breast to other organs in the body[3].

Male Breast Cancer

While breast cancer is predominantly a female disease, males can also develop breast cancer, typically presenting as invasive ductal carcinoma[2]. Male breast cancer is rare, making up less than 1% of all breast cancer cases, but it requires similar treatment approaches to female breast cancer.

Risk Factors

Breast cancer risk factors can be categorized into those that are beyond an individual's control and those that can be modified through lifestyle changes. While factors such as being female and aging are unchangeable, other lifestyle-related risk factors can be altered to potentially reduce the risk of developing breast cancer.

Lifestyle-Related Risk Factors

Physical Activity

Regular physical activity has been shown to reduce the risk of breast cancer, particularly in women who are postmenopausal. Engaging in moderate to vigorous exercise may lower breast cancer risk through various mechanisms, including effects on body weight, inflammation, and hormone levels.[7][8] The American Cancer Society recommends adults engage in 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity activity each week.[8] Even a couple of hours of physical activity per week may provide some benefit, although more substantial benefits are associated with increased levels of activity.

Alcohol Consumption

Alcohol consumption is clearly linked to an increased risk of breast cancer. Research indicates that even small amounts of alcohol can elevate this risk, with women who consume one

alcoholic drink per day facing a 7% to 10% increased risk, while those who drink two to three drinks daily have about a 20% higher risk.[7][8] It is advisable for women to limit alcohol intake to no more than one drink per day to mitigate this risk.

Body Weight

Maintaining a healthy weight is another critical factor in breast cancer risk. Increased body weight and weight gain during adulthood are associated with a higher risk of breast cancer after menopause.[8] The American Cancer Society emphasizes the importance of balancing caloric intake with physical activity to avoid excess weight gain.

Reproductive Factors

Several reproductive choices influence breast cancer risk. Women who have not had children or who give birth for the first time after the age of 30 may have

a slightly elevated risk of breast cancer. Conversely, having multiple pregnancies and becoming pregnant at a younger age is associated with a reduced risk.[7][8] Additionally, breastfeeding for several months post-childbirth may also provide a protective effect against breast cancer.

Hormone Therapy

The use of hormone therapy following menopause can increase the risk of breast cancer. Women considering hormone therapy for menopausal symptoms should discuss non-hormonal alternatives with their healthcare providers to minimize this risk.[8]

Symptoms

Breast cancer symptoms can vary depending on the type and stage of the disease. Invasive breast cancer, which spreads beyond the original site, may present with different symptoms compared to non-invasive breast cancer, which remains localized[9].

Common Symptoms

The most common symptoms of breast cancer include:

1. **Lump in the Breast:** A palpable mass or lump in the breast is one of the most common early signs of breast cancer. This lump may feel different from the surrounding tissue and may be painless.
2. **Changes in Breast Shape or Size:** Unexplained changes in the shape or size of the breast can indicate the presence of cancer.

3. **Nipple Discharge**: Any discharge from the nipple that is not related to breastfeeding should be evaluated by a healthcare professional. This may include blood or other fluids.
4. **Skin Changes:** Dimpling, puckering, or changes in texture of the breast skin can be a symptom of breast cancer. The skin may appear red or inflamed.
5. **Nipple Changes:** Inverted or retracted nipples, or changes in the appearance of the nipple itself, can also be symptoms of breast cancer.

Other Symptoms

In addition to the above, some patients may experience additional symptoms, espe- cially in later stages of the disease:

1. **Pain or Tenderness:** Although breast cancer is often painless, some individuals may experience discomfort or tenderness in the breast area.
2. **Swelling:** Swelling in or near the breast or in the lymph nodes under the arm can indicate the spread of cancer.
3. **Weight Loss**: Unexplained weight loss may occur, particularly in advanced stages of the disease.

It is essential for individuals to be vigilant about changes in their breasts and to consult a healthcare professional if they notice any unusual symptoms. Early detection and diagnosis can significantly impact treatment outcomes and survival rates.

Diagnosis

Overview of Screening Methods

Breast cancer diagnosis typically begins with screening tests aimed at detecting signs of the disease in asymptomatic individuals. Early detection is crucial, as it increases the likelihood of successful treatment and favorable outcomes[10][11]. Common screening methods include mammography, clinical breast examinations, and, increasingly, magnetic resonance imaging (MRI) for certain populations.

Imaging Techniques

Mammography

Bilateral mammography is routinely performed at the time of breast cancer diagnosis to rule out synchronous disease. This is essential not only for identifying primary tumors but also for detecting any recurrence in patients who have undergone breast-conserving surgery[12].

MRI

The role of MRI in breast cancer diagnosis is evolving, especially in screening for contralateral breast disease. While MRI can increase the detection rate of mammographically occult lesions, it is recommended that positive MRI findings undergo pathological confirmation due to the high likelihood (75%) of false-positive results[- 12].

Biopsy Procedures

When suspicious abnormalities are detected via imaging, a biopsy is often performed to obtain tissue samples for definitive diagnosis. Typically, suspicious axillary nodes are also biopsied before the initiation of systemic therapy when indicated[12].

Sentinel Lymph Node Biopsy

Sentinel lymph node (SLN) biopsy has been the standard method for axillary staging in patients with clinically node-negative invasive breast cancer. However, recent randomized controlled trials, including the SOUND trial and the INSEMA trial, have suggested that SLN biopsy may be safely omitted in certain populations. For in- stance, the SOUND trial involved 1,493 women with tumors smaller than 2 cm and negative preoperative axillary ultrasonography, revealing no significant difference in disease-free survival between the no-surgery and SLN biopsy groups[12].

Pathological Staging

The Clinical Prognostic Stage, which utilizes TNM (Tumor, Node, Metastasis) classification based on clinical and pathological findings, is essential for staging invasive breast cancer in the United States. For patients treated initially with surgery, the Pathological Prognostic Stage incorporates detailed surgical and pathological data, while those who receive neoadjuvant therapy before surgery are not classified under this system[12].

Prognostic Factors

Several prognostic factors can influence diagnosis and treatment decisions. The absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expressions define triple-negative breast cancer (TNBC), which is particularly challenging due to its insensitivity to many effective therapies. Patients with TNBC often receive preoperative systemic therapy, with emerging evidence suggesting that adding carboplatin to chemotherapy regimens may improve treatment outcomes[12].

Treatment

The treatment of breast cancer (BC) involves a multifaceted approach that varies based on the type and stage of cancer, as well as the individual patient's characteristics. Recent advancements in personalized therapy have led to the development of a variety of treatment modalities that aim to optimize outcomes for patients with breast cancer.

Treatment Modalities

Current treatment strategies include small molecule targeted drugs, peptide drugs, antibody drugs, cell therapy, and gene therapy, among others.[13][14] A significant area of focus is immunotherapy, which has shown promise but is still being refined for breast cancer compared to its successes in other cancers, such as melanoma. [15] For instance, the addition of pembrolizumab, an immunotherapy agent, to neoadjuvant chemotherapy has been evaluated in the phase III KEYNOTE-522 trial, demonstrating improved pathological complete response (pCR) rates for patients with triple-negative breast cancer (TNBC).[12]

Targeted Therapies

Targeted therapies have revolutionized the treatment landscape for breast cancer, particularly for subtypes such as HER2-positive breast cancer. The development of antibody-drug conjugates (ADCs), such as Trodelvy, Enhertu, and Kadcyla, exemplifies this progress. These therapies involve antibodies that specifically target cancer cells while delivering cytotoxic agents, thereby enhancing treatment efficacy and minimizing side effects.[15] Research continues into optimizing ADCs with various combinations of payloads and targets, indicating a trend toward personalized treatment approaches.

Hormonal and Chemotherapy Treatments

Hormonal therapies, including tamoxifen and aromatase inhibitors, remain standard for

hormone receptor-positive breast cancer. Additionally, CDK4/6 inhibitors, mTOR inhibitors, and PIK3CA inhibitors are among the targeted therapies utilized in conjunction with chemotherapy and surgery.[12] The integration of these therapies is often tailored based on the individual patient's response and the molecular characteristics of the tumor.

Role of Clinical Trials

All patients with metastatic breast cancer are considered candidates for ongoing clinical trials, which play a crucial role in advancing treatment options. Participation in clinical trials allows for access to novel therapies and contributes to the broader understanding of effective treatment strategies for various breast cancer subtypes.- [12]

Immunotherapy and Future Directions

While immunotherapy is currently utilized mainly in selected patients with TNBC, there is ongoing research aimed at enhancing its effectiveness across all breast cancer subtypes. The immune system's ability to adapt offers potential for developing therapies that can evolve in response to cancer changes, marking a significant shift in treatment paradigms.[15] Continued investigation into the mechanisms of resistance and the potential for combination therapies will be critical in optimizing immunotherapy for breast cancer patients.

Prognosis

Overview of Prognostic Factors

Prognosis in breast cancer is influenced by a variety of factors including tumor characteristics, patient demographics, and treatment modalities. Key prognostic indicators include hormone receptor status, tumor size, and the presence of metastatic disease at diagnosis[12].

Overdiagnosis and Overtreatment

One significant aspect of breast cancer prognosis is the issue of overdiagnosis, which occurs when screening identifies cancers that are unlikely to become symptomatic or threaten the patient's health during their lifetime[16][17]. Estimates of overdiagnosis rates from randomized controlled trials range from approximately 11% to 19%, indicating that a considerable proportion of diagnosed cases may not require treatment[- 16]. This phenomenon leads to overtreatment, where patients undergo unnecessary interventions for

indolent lesions, complicating the overall understanding of survival outcomes[17].

Treatment and Survival Outcomes

Recent studies have highlighted the equivalence in survival rates among various treatment strategies, including standard breast-conserving surgery[12]. Evidence suggests that patients categorized into different groups based on hormone receptor status show similar disease control outcomes, although comprehensive data supporting these findings are still lacking. For patients with high clinical risk but low genomic risk, chemotherapy does provide some survival benefits, emphasizing the importance of tailored treatment approaches[12].

Disparities in Prognosis

Health disparities significantly impact breast cancer prognosis, particularly among minority populations. Research indicates that socioeconomic factors, access to healthcare, and the impact of systemic racism contribute to higher mortality rates and poorer outcomes among certain demographic groups, including Black women[18][- 19]. Notably, Black women have higher rates of aggressive breast cancer subtypes such as triple-negative breast cancer, which complicates their treatment and overall prognosis[19].

Lifestyle Factors

Lifestyle choices also play a critical role in breast cancer prognosis. Factors such as weight management, exercise, dietary habits, smoking, and alcohol consumption are associated with disease outcomes and can influence survival rates[20]. Future research aimed at understanding the interaction between lifestyle factors and genetic predispositions may provide insights into improving prognosis for diverse patient populations[20].

Prevention

Breast cancer prevention involves a combination of lifestyle modifications, medical interventions, and awareness of risk factors. By adopting strategies to minimize risks and enhance protective factors, individuals can potentially lower their chances of developing breast cancer.

Lifestyle Modifications

Adopting a healthy lifestyle is a crucial aspect of breast cancer prevention.

1. **Regular Exercise:** Engaging in physical activity can help maintain a healthy weight and may lower breast cancer risk[21].

2. **Healthy Diet:** A balanced diet that includes a variety of vegetables, fruits, and whole grains has been associated with reduced cancer risk. Limiting intake of high-calorie and processed foods is also beneficial[21][20].
3. **Alcohol Consumption:** Research indicates that even moderate alcohol consumption can increase breast cancer risk. It is advisable for women to limit their intake to no more than one alcoholic drink per day[8].
4. **Avoiding Smoking:** Quitting smoking can decrease the risk of developing breast cancer and other related health conditions[22].

Risk Factors and Protective Factors

Breast cancer risk is influenced by a variety of factors, including age, genetics, and lifestyle choices. The primary risk factor is being female, with older age also significantly increasing risk; for example, a 30-year-old woman has about a 1 in 175 chance of being diagnosed with breast cancer in the next decade, while a 70-year-old woman's chance rises to 1 in 9[23]. Additionally, personal and family medical histories, such as previous breast cancer diagnoses or benign breast disease, contribute to elevated risk levels[23].

Conversely, certain protective factors can help reduce the risk of breast cancer. These include engaging in regular physical activity, maintaining a healthy weight, consuming a diet rich in fruits and vegetables, and limiting alcohol intake[24][21]. Evidence suggests that breastfeeding for several months postpartum may also confer additional protective benefits against breast cancer[8].

Medical Interventions

For women at high risk, particularly those with BRCA mutations, preventive measures may include chemoprevention or surgical options such as mastectomy[24]. Hormonal treatments can also be discussed with healthcare providers to mitigate risks associated with menopause-related hormone therapies[8].

Screening and Clinical Trials

Regular screening is vital for early detection and management of breast cancer. Screening modalities, such as mammography and clinical breast examinations, are recommended for women, although guidelines regarding the age and frequency of screenings may vary among medical organizations[24]. Additionally, cancer prevention clinical trials continue to

investigate new strategies to reduce breast cancer risk, including lifestyle interventions and the use of medications or supplements[23][24].

Emotional Well-Being and Support Systems

Emotional well-being is a crucial aspect of the breast cancer journey, affecting both patients and their caregivers. The challenges associated with diagnosis, treatment, and survivorship can lead to feelings of uncertainty, fear, and isolation, making it essential for individuals to seek out supportive networks and self-care practices.

Importance of Support Groups

Support groups provide a vital resource for those affected by breast cancer. The American Cancer Society offers various programs and services aimed at assisting individuals during and after treatment, including free online support groups for those who have completed their treatment within the past 18 months[25][26]. Such connections help individuals share experiences and foster a sense of community, which can significantly enhance emotional resilience.

Self-Care Strategies

Engaging in self-care is fundamental to maintaining emotional well-being. It involves actively pursuing one's own needs and making lifestyle changes that promote health. Although there are no guaranteed ways to prevent breast cancer, adopting healthier habits such as nutritious eating, regular exercise, and stress-reducing techniques can improve overall well-being[22][27]. Personalized approaches to self-care can help individuals feel empowered in their health journeys.

Addressing Disparities in Care

Emotional support also intersects with issues of health equity. Research indicates that racial disparities exist in breast cancer care, with Black and Hispanic patients often reporting negative experiences in healthcare settings, which can exacerbate feelings of distress[19]. It is essential to ensure that all patients have access to com- passionate care and support, as these factors can significantly influence emotional well-being and treatment outcomes.

Resources and Research

The National Cancer Institute (NCI) supports research that addresses the emotional and psychological impacts of breast cancer and its treatments. Investigations into the effects on

functioning, emotional health, and caregiver experiences are ongoing, and findings from these studies aim to enhance the support systems available to survivors[28]. Additionally, numerous free resources exist to connect individuals with local and online support networks, providing opportunities for emotional and practical assistance[29].

Research and Future Directions

Overview of Current Research Efforts

Research plays a pivotal role in advancing our understanding and treatment of breast cancer. Throughout 2023, significant strides have been made in various aspects of breast cancer research, focusing on improving treatment outcomes and discovering innovative methods to predict disease progression[30][28]. Scientists are investigating the biological mechanisms underlying breast cancer, aiming to develop targeted therapies that can enhance the efficacy of existing treatments and reduce resistance to therapy[30].

Innovations in Treatment

Targeting Resistance Mechanisms

One of the notable breakthroughs in early 2023 involved researchers from the University of Manchester, led by Dr. Ahmet Ucar, who identified the RAC1B protein as a key factor contributing to treatment resistance and cancer spread[30]. This finding could pave the way for new therapeutic strategies aimed at inhibiting this protein, potentially leading to better patient outcomes.

Immunotherapy Developments

The landscape of immunotherapy for breast cancer continues to evolve. A phase 3 clinical trial called OptimICE-PCR is currently exploring whether monitoring patients after surgery, as opposed to continuing immunotherapy, is effective in preventing cancer recurrence in those whose initial treatment eliminated detectable disease[31]. This research seeks to identify which patients can safely reduce their treatment while still achieving favorable outcomes.

Enhancing Screening Techniques

Breast cancer screening remains a vital area of research. Current efforts are focused on refining screening methods such as mammography, MRI, and ultrasound to improve early detection rates, particularly for those at average risk[28]. Innovative technologies, including tomosynthesis, are being investigated to enhance the accuracy of screenings and reduce false

positives, which can lead to unnecessary stress for patients[17].

Future Directions

The future of breast cancer research is bright, with ongoing studies exploring person- alized cancer vaccines and precision oncology[32]. These approaches aim to tailor treatment to the individual's unique cancer profile, which may enhance efficacy and minimize side effects. Moreover, research is ongoing to assess the long-term impacts of novel therapies, particularly for patients with triple-negative breast cancer (TNBC) who may benefit from new treatment regimens[31].

Collaborative Research Efforts

Institutions like Memorial Sloan Kettering Cancer Center are at the forefront of breast cancer research, conducting clinical trials that evaluate emerging therapies and their potential impacts on patient care[33]. These collaborative efforts are essential for translating laboratory findings into clinical applications, ensuring that patients receive the most effective and innovative treatments available.

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