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Emerging Role And Mechanism of Markers in Breast Cancer

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Abstract
Breast cancer is among the most common cancers worldwide, primarily affecting women but also occurring in men. While its exact cause remains unknown, several risk factors have been identified, including age, family history, genetic mutations (BRCA1, BRCA2), hormonal influences, lifestyle, and environmental exposures. Recent research has highlighted various genetic, epigenetic, and proteasomal markers that improve diagnosis and treatment. Key biomarkers include BRCA1/BRCA2, Ki67, p53, Cyclin D1 mutation, TP53 mutation, HER2 amplification, DNA methylation patterns, microRNAs (miRNAs), and androgen receptors (ARs). These markers play a crucial role in personalized medicine, enabling precise diagnosis and tailored therapies. For instance, HER2 amplification helps determine suitability for targeted treatments like trastuzumab. Similarly, miRNAs regulate gene expression, offering insights into tumor behavior and therapeutic response. Despite advancements, identifying the most effective biomarkers remains a challenge for researchers and clinicians. Optimizing these markers could enhance treatment strategies, reduce costs, and improve patient outcomes. Ongoing investigations into emerging biomarkers may lead to better interventions, ultimately supporting breast cancer management and care.

Keywords
Breast Cancer, BRCA1/BRCA2, Triple-Negative Breast Cancer (TNBC), miRNAs, Precision Medicine, Liquid Biopsies

Introduction

Breast cancer is a global health problem and a leading cause of cancer-related death in women. Breast cancer, including its various subtypes, is characterized by its association with biological and medical conditions. Early detection and treatment are important to reduce mortality. The global spread of breast cancer requires extensive research into its causes, diagnosis, and treatment. According to the World Health Organization, there are approximately 2.3 million new cancer cases each year, accounting for 11.7% of

all cancer cases worldwide. International collaborations and clinical trials have improved our understanding and led to the identification of important biomarkers and treatment strategies [1]. Raising awareness about breast cancer through awareness campaigns and education has increased the rate of early detection. Services including self-examination, mammograms and regular check-ups encourage people to seek timely treatment.The importance of understanding breast cancer lies in its impact on public health. Comprehensive research into its molecular underpinnings can guide the development of personalized treatment approaches, improving patient outcomes and quality of life. Breast cancer is caused by genetic and epigenetic changes that affect cellular processes. Mutations in tumor suppressor genes such as BRCA1 and TP53 and changes in genes such as DNA methylation play an important role in cancer. These changes lead to uncontrolled cell proliferation, invasion, and metastasis. Cyclin D1 is a cell cycle regulator that is frequently overexpressed in breast cancer, causing cell cycle disruption and tumor growth [2,3]. Biomarkers are measurable indicators of biological processes, pathogenic organisms, or pharmacological responses. In breast cancer, biomarkers aid in diagnosis, prognosis, and treatment decisions. They include genetic markers such as BRCA mutations, epigenetic markers such as DNA methylation, proteasome markers such as HER2 overexpression, and proteins such as p53 and cyclin D1. These biomarkers help stratify patients and guide treatment strategies.The interaction between cancer and biomarkers is important for understanding the disease. Biomarkers provide information about cancer biology and allow patients to be stratified for treatment. For example, HER2-positive tumors respond well to trastuzumab, demonstrating the clinical utility of a biomarker-driven approach. In addition, p53 mutations are common in many breast cancers, especially in stage III tumors, and are associated with poor prognosis [4]. Overexpression of cyclin D1 is associated with hormone receptor-positive isoforms and may serve as a target for endocrine therapy[5]. Common signs and symptoms of breast cancer include palpable lumps, changes in breast shape or size, skin dimpling, nipple discharge, and localized pain. Advanced cases may present with systemic symptoms like weight loss and fatigue. Early recognition of these signs is crucial for prompt intervention. Treatment modalities for breast cancer include surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. The choice of treatment depends on the tumor subtype, stage, and patient characteristics. Multidisciplinary approaches have shown improved efficacy in managing the disease. Drugs used to treat cancer range from chemotherapy drugs such as doxorubicin and paclitaxel to treatments such as trastuzumab and PARP inhibitors. Hormone therapy, such as tamoxifen and aromatase inhibitors, are effective in the hormone receptor-positive subtype. Emerging drugs, including cyclin-dependent kinase (CDK) inhibitors that target the cyclin D1 pathway, have been investigated in clinical trials and hold promise for providing new treatments [6].

Prevalence Rate of Breast Cancer: Breast cancer is one of the most common cancers worldwide, significantly contributing to cancer-related morbidity and mortality:

1. **Global Prevalence**: As of 2020, breast cancer was the most diagnosed cancer globally, with 2.3 million new cases, accounting for 11.7% of all cancer cases [7].
2. **Regional Prevalence**:
    a. **Developed Countries**: Higher prevalence due to longer life expectancy, increased screening, and lifestyle changes. For example, in the United States, approximately 264,000 cases are diagnosed annually, with 42,000 deaths [8].
    b. **Developing Countries**: Rapidly increasing prevalence due to urbanization, changing reproductive patterns, and limited access to healthcare. In India, the age-standardized incidence rate is 25.8 per 100,000 women [9].
3. **Gender-Specific Prevalence**: While predominantly affecting women, breast cancer also occurs in men, constituting about 1% of all breast cancer diagnoses [10].

4. **Age-Specific Prevalence**: The risk of breast cancer increases with age, with the highest incidence in women aged 50 and older. Younger women (below 40) represent 5–7% of cases but often present more aggressive forms [11].

1. Emerging Biomarkers in Breast Cancer: Biomarkers play a crucial role in diagnosing, predicting prognosis, and guiding treatment strategies for breast cancer. They can be broadly categorized into genetic, epigenetic, and proteomic markers:

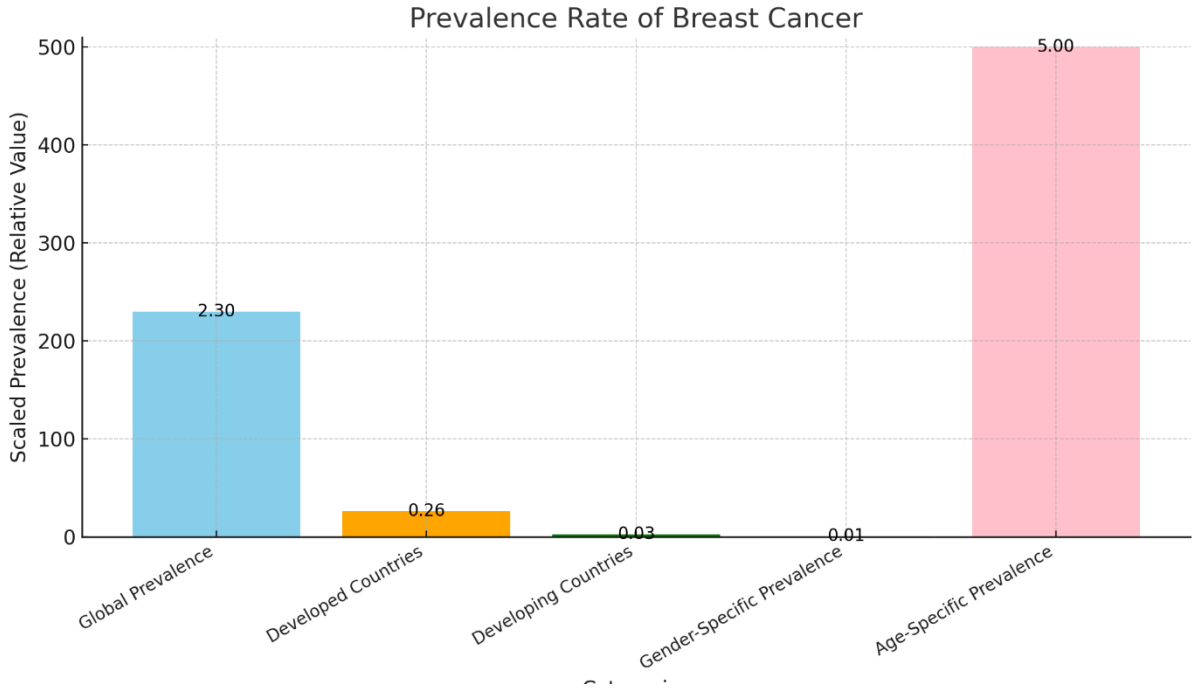

Figure 1: Prevalence Rate of Breast Cancer

Genetic Markers:

- **BRCA1/BRCA2**: Mutations in BRCA1/BRCA2 increase breast cancer risk by impairing DNA repair mechanisms through homologous recombination. Individuals with these mutations face a lifetime breast cancer risk of up to 72% [12,13].
- **TP53 Mutations**: Found in approximately 20% of breast cancer cases, TP53 mutations are associated with aggressive tumor phenotypes and poor prognosis [13].
- **HER2 Amplification**: HER2-positive breast cancer accounts for 15–20% of all cases and is linked to increased tumor growth and metastasis [14].

Epigenetic Markers:

- **DNA Methylation**: Aberrant methylation of tumor suppressor genes, such as RASSF1A, is frequently observed in breast cancer. Methylation analysis is emerging as a non-invasive diagnostic tool [15].
- **MicroRNAs (miRNAs)**: MiRNAs like miR-21 and miR-155 act as oncogenes by modulating pathways related to apoptosis and immune evasion [11,12].

Proteomic Markers:

- **Ki67**: A marker of cell proliferation, Ki67 is widely used to assess tumor aggressiveness and guide treatment decisions [16].
- **p53 and CyclinD1**: These markers regulate cell cycle progression and apoptosis. Altered expression is indicative of poor treatment outcomes [17].

- **Androgen Receptor (AR)**: While traditionally studied in prostate cancer, AR expression in breast cancer has gained attention for its potential as a therapeutic target, particularly in triple-negative breast cancer (TNBC) [18].

Significance: By categorizing breast cancer subtypes, these biomarkers enable tailored therapeutic approaches, improving outcomes for patients with aggressive or recurrent disease [16].

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2. Role and Mechanisms of Key Biomarkers: Biomarkers do not merely serve as diagnostic tools but also provide insights into the molecular mechanisms driving breast cancer:

- **BRCA1/BRCA2**: These genes encode proteins essential for homologous recombination repair. Loss-of-function mutations lead to genomic instability, increasing susceptibility to DNA-damaging agents like PARP inhibitors [6,7].
- **HER2**: Amplification of HER2 drives oncogenic signaling through pathways like PI3K-AKT and MAPK, leading to increased tumor proliferation and survival. HER2-targeted therapies like trastuzumab inhibit these pathways, reducing tumor growth [9,17].
- **miRNAs**: MiR-155 downregulates tumor suppressor genes, while let-7 family miRNAs suppress oncogenic pathways. These regulatory RNAs are crucial in maintaining tumor plasticity and promoting metastasis [11,18].
- **Ki67**: Elevated Ki67 expression reflects high cellular proliferation and is associated with poor prognosis. However, its prognostic utility varies between molecular subtypes of breast cancer [13].
- **p53**: Loss of p53 function impairs apoptosis, allowing cancer cells to evade programmed cell death, a hallmark of tumorigenesis [14].

Clinical Insights: Understanding these mechanisms facilitates the development of biomarkers not only for early detection but also for predicting response to therapies like immunotherapy and targeted treatments [19].

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3. Diagnostic and Therapeutic Applications: Biomarkers have revolutionized the clinical management of breast cancer through their application in diagnostics, treatment, and prognostication:

Diagnostics:

- **HER2 Testing**: HER2 testing using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) is standard for identifying candidates for trastuzumab therapy [9,17].
- **Liquid Biopsies**: Non-invasive methods like liquid biopsies analyze circulating tumor DNA (ctDNA), enabling early detection and monitoring of minimal residual disease [20].

Therapeutics:

- **HER2-Targeted Therapies**: Drugs like trastuzumab and pertuzumab specifically inhibit HER2 signaling, significantly improving survival in HER2-positive patients [17,21].
- **PARP Inhibitors**: Olaparib and talazoparib target BRCA-mutant cancers by exploiting defects in DNA repair mechanisms [6,22].
- **miRNA-Based Therapies**: Therapeutic approaches aim to restore normal miRNA function by either inhibiting oncogenic miRNAs or mimicking tumor-suppressive miRNAs [11,23].

Prognostics: Markers like Ki67 and p53 are used to stratify patients into low-risk and high-risk groups, guiding the need for adjuvant therapies [13,14].

Advances: Integrating biomarkers into clinical workflows has significantly improved the precision of breast cancer treatment, offering new hope for patients with advanced or resistant disease [19,24].

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4. Challenges and Future Directions: Despite significant progress, several challenges impede the full realization of biomarker potential:

Challenges:

- **Tumor Heterogeneity**: Genetic and molecular differences within tumors complicate the identification of universal biomarkers [25].
- **Validation Standards**: The lack of standardized protocols for biomarker validation limits their clinical utility [26].
- **Triple-Negative Breast Cancer (TNBC)**: This subtype lacks established therapeutic targets, necessitating novel biomarkers to guide treatment [15,27].

Future Directions:

- **Multi-Omics Integration**: Combining genomics, proteomics, and metabolomics offers a holistic view of tumor biology, paving the way for novel biomarker discovery [28].
- **Artificial Intelligence (AI)**: AI-driven platforms analyze complex datasets to uncover biomarker patterns and predict therapeutic responses [29].
- **Liquid Biopsies**: Advances in detecting ctDNA and exosomal RNA are enabling real-time tumor monitoring, particularly in metastatic settings [20,30].
- **Immunotherapy Markers**: Identifying biomarkers like PD-L1 and tumor mutation burden could enhance patient selection for immune checkpoint inhibitors [31].

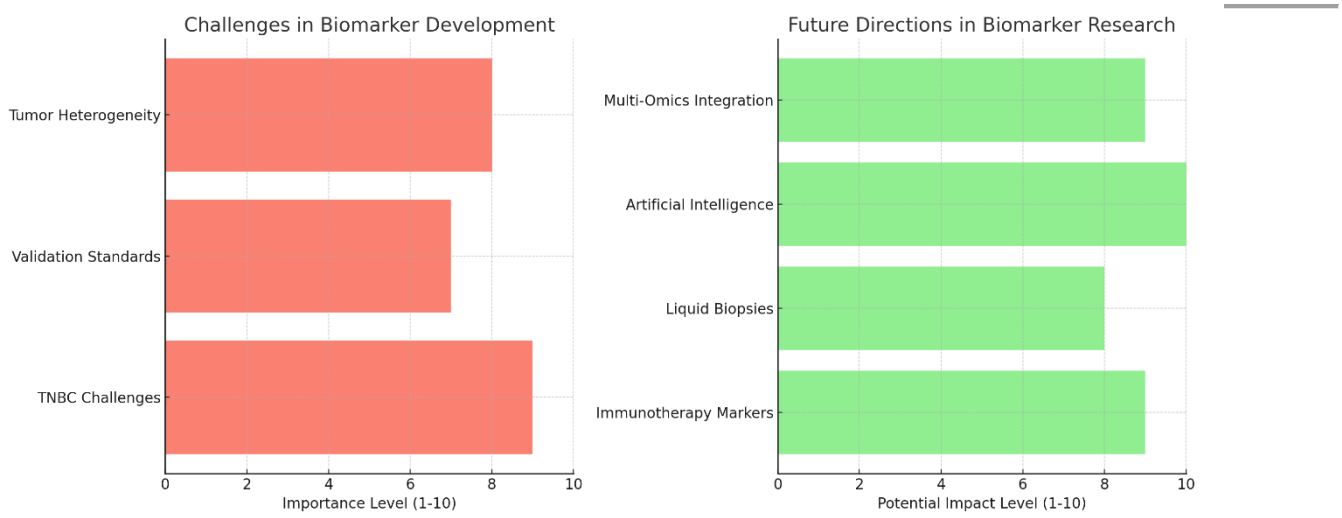

Figure 2: challenges and Future Directions in Biomarker Research

Conclusion: Breast cancer remains a major problem worldwide, with 2.3 million new cases each year, making it the most common cancer and leading cause of cancer worldwide [37]. Its prevalence varies by region; developing countries face higher costs due to increasing life expectancy and living conditions, while developing countries are exacerbated by rapid urbanization and limited access to healthcare [38,39]. Although breast cancer primarily affects women, it also affects men, albeit at a lower rate, accounting for approximately 1% of all diagnoses [40]. The discovery of cancer biomarkers is important for diagnosis, prognosis, and treatment. Genetic markers such as BRCA1/BRCA2, TP53, and HER2 amplification play an important role in determining risk and tailoring treatment. For example, HER2-targeting therapies, such as trastuzumab, have improved the prognosis of HER2-positive patients [41,42]. Similarly, epigenetic markers such as DNA methylation and miRNA provide information about tumor behavior and have become important tools for noninvasive diagnosis and targeted therapy [43,44]. Proteasome markers

including Ki67, p53, and androgen receptor (AR) further support patient outcomes and improve self-healing strategies [45]. Competition. Tumor heterogeneity affects the universal use of biomarkers, and the lack of formal acceptance criteria hinders their integration into routine therapy [46,47]. The lack of clear therapeutic targets, especially in triple-negative breast cancer (TNBC), indicates an urgent need for novel biomarker discovery [48]. Future directions in cancer research include the integration of multi-omics technologies to provide comprehensive biomarker data and the use of artificial intelligence to analyze difficult information to help make clear and immediate decisions [49,50]. The increasing use of biopsy fluid and immunotherapies such as PD-L1 is expected to change the breast cancer treatment landscape. These innovations, combined with continued efforts in precision medicine, demonstrate the potential to reduce the global burden of cancer and improve patient outcomes. An integrated approach that includes research, clinical practice, and technology is essential to overcome current challenges and advance progress [51].

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