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Advances in Molecular Subtype-Based Precision Therapy and Strategies to Overcome Resistance in Breast Cancer

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Abstract

Breast cancer is a leading cause of cancer-related morbidity and mortality, characterized by significant biological and molecular heterogeneity. Molecular subtypes—including luminal A, luminal B, HER2-enriched, and triple-negative—inform prognosis and guide precision therapies. Despite advances with endocrine agents, HER2-targeted therapies, PARP inhibitors, and immune checkpoint inhibitors, therapeutic resistance remains a major challenge, driven by intratumoral heterogeneity, cancer stem cell plasticity, and tumor microenvironmental factors. Genomic profiling, liquid biopsies, combination and adaptive strategies, and next-generation antibody-drug conjugates are emerging to overcome resistance and optimize outcomes. Additionally, novel immunotherapies and artificial intelligence (AI)–assisted decision-making support individualized treatment selection. This review summarizes recent advances, from molecular characterization to precision-guided interventions and strategies to counteract resistance, and emphasizes the integration of biological insights into personalized breast cancer management.

Keywords

breast cancer, molecular subtypes, precision therapy, resistance mechanisms, tumor heterogeneity

1. Introduction

Breast cancer continues to be a major global health burden, representing the most frequently diagnosed malignancy in women and accounting for a significant proportion of cancer-related morbidity and mortality worldwide. In 2022 alone, there were over 2.2 million new cases and more than 660,000 deaths attributed to breast cancer, with substantial regional disparities in incidence and mortality patterns across continents [1]. The likelihood of early diagnosis and a favorable outcome is strongly influenced by organized screening programs, especially mammography, which is associated with earlier detection and improved survival compared with symptomatic presentation [2]. Despite the declines in mortality observed in many high-resource settings due to widespread early detection and advanced multimodal therapies, low- and middle-income countries still experience a disproportionate burden of late-stage presentation and poorer outcomes, highlighting ongoing global inequities in access to preventive and therapeutic resources [1].

Breast cancer is not a single disease but a heterogeneous group of biological subtypes with distinct clinical behaviors. Molecular classification, including luminal A, luminal B, HER2-enriched, and triple-negative/basal-like subtypes, has provided refined prognostic stratification and informed therapeutic decisions, as these subtypes differ in hormone receptor and HER2 expression, proliferation markers, gene expression profiles, and response to treatment [1, 3]. This molecular understanding has driven the transition from a purely anatomical view of cancer to one that integrates biological complexity into clinical management.

Over the past century, therapeutic paradigms have shifted from radical surgery alone to systemic and targeted approaches grounded in molecular biology. The identification of hormone receptor dependence led to the development of endocrine therapies that significantly improved outcomes for hormone receptor–positive disease, and the discovery of HER2 gene amplification paved the way for HER2-targeted agents that transformed the prognosis of this aggressive subtype [3]. More recently, genomic profiling tools have enabled personalized risk stratification and tailored treatment selection, heralding the era of precision oncology in breast cancer care. This review synthesizes current knowledge from epidemiology to molecular mechanisms and clinical management strategies, emphasizing how deeper biological insights are continually shaping individualized treatment approaches and improving patient outcomes.

2. Molecular Subtypes and Tumor Heterogeneity

2.1 Molecular Subtypes of Breast Cancer

Breast cancer is a biologically heterogeneous disease composed of distinct molecular subtypes that differ in prognosis, cellular origin, and therapeutic vulnerabilities. Large-scale gene expression and genomic profiling studies have consistently classified tumors into luminal A, luminal B, HER2-enriched, basal-like, and rare subtypes. Each subtype demonstrates unique transcriptional programs, receptor expression profiles, and signaling pathway dependencies that guide clinical decision-making [4, 5]. In routine clinical practice, surrogate immunohistochemical (IHC) markers—ER, PR, HER2, and Ki-67—are used to approximate intrinsic subtypes, allowing subtype-directed therapy when comprehensive genomic assays are unavailable [6].

2.2 Intratumoral and Intertumoral Heterogeneity

Beyond classification, tumor heterogeneity represents the main challenge to effective precision therapy. Heterogeneity exists both between tumors of different patients (intertumoral) and within a single tumor (intratumoral), encompassing genetically distinct subclones with diverse phenotypes, metabolic states, and immune interactions [7, 8]. Single-cell and spatial transcriptomic analyses have revealed that even tumors assigned to a single subtype contain subpopulations with variable signaling dependencies, undermining therapies targeting a single dominant pathway [9, 10]. Resistant subclones may preexist or arise via epigenetic plasticity, reversible epithelial-to-mesenchymal transitions, or induction of a stem-like state, allowing escape from targeted inhibitors without new mutations [11].

2.3 Clinical Implications of Heterogeneity

The consequences of heterogeneity manifest as partial responses, adaptive resistance, and eventual relapse. Therapy-induced selective pressures enrich resistant subclones, reducing the efficacy of subsequent treatments. Spatial heterogeneity further contributes, as tumor niches with hypoxia, dense stroma, or immunosuppressive microenvironments protect resistant cells from both drug exposure and immune attack [12, 13]. Such complexity explains why therapies effective in preclinical models may fail in heterogeneous patient tumors and highlights the limitations of static subtype classification.

2.4 Strategies to Overcome Heterogeneity

Addressing tumor heterogeneity requires dynamic, multiscale strategies. Longitudinal monitoring, such as ctDNA liquid biopsies, provides real-time insights into evolving clonal populations and early detection of emerging resistance [14]. Rational combination therapies targeting multiple survival and adaptive pathways aim to suppress both dominant and minor subclones, while adaptive therapy approaches seek to modulate

selective pressure to delay resistance [15, 16]. Integrating spatial transcriptomics, single-cell multi-omics, and microenvironment mapping may enable the identification of resistant niches and the optimization of therapeutic regimens, advancing durable responses despite tumor complexity.

3. Tumor Microenvironment, Cancer Stem Cells, and Therapeutic Resistance in Breast Cancer

Breast tumors are not merely masses of malignant cells but complex ecosystems in which cancer cells interact dynamically with various stromal and immune components, collectively termed the tumor microenvironment (TME). This milieu plays a central role in therapeutic resistance through both physical barriers to drug delivery and biological cues that promote survival, immune evasion, and stem-like plasticity. A dense, desmoplastic extracellular matrix (ECM), largely remodeled by cancer-associated fibroblasts (CAFs), increases interstitial pressure and matrix stiffness, activating mechanosignaling pathways such as FAK/Src and YAP/TAZ that not only drive proliferation and invasion but also impair the penetration of chemotherapies and large biologics into the tumor parenchyma [17, 18]. CAF-secreted matrix proteins and cross-linking enzymes such as lysyl oxidase further reinforce this barrier, while CAF-derived soluble factors (e.g., IL-6, CXCL12) support cancer cell survival and can induce drug tolerance through paracrine signaling [19, 20].

Immune components of the TME also shape therapeutic outcomes. Tumor-associated macrophages (TAMs) often acquire an immunosuppressive phenotype that promotes angiogenesis and matrix remodeling, and they secrete factors that blunt the efficacy of cytotoxic therapies and checkpoint blockade [21]. Conversely, cytotoxic T lymphocytes (CD8+) correlate with better responses to immunotherapy, especially in triple-negative and HER2-positive breast cancers, while regulatory T cells and myeloid-derived suppressor cells (MDSCs) create inhibitory niches that limit anti-tumor immunity and contribute to resistance [22, 23].

Overlapping with the TME, cancer stem cells (CSCs) represent a subpopulation endowed with self-renewal, plasticity, and intrinsic resistance to diverse treatments. Breast CSCs, commonly characterized by CD44+/CD24−/low phenotypes and high ALDH1 activity, persist in hostile microenvironments and evade cytotoxic therapies, in part, through quiescence and enhanced DNA repair mechanisms, including upregulated ABC transporters that efflux drugs and robust damage-response pathways that repair therapy-induced lesions [24, 25]. CSCs can also enter a dormant state, allowing them to survive systemic therapy and later drive relapse and metastasis [26].

The interplay between CSCs and the TME further amplifies resistance: ECM stiffness and CAF-secreted cytokines promote stemness and epithelial-to-mesenchymal transition (EMT), while immunosuppressive niches protect CSCs from immune surveillance and immunotherapy, undermining even the latest targeted inhibitors and immune checkpoint blockade [27]. Efforts to therapeutically target CSCs include inhibitors of developmental pathways critical for maintenance (Notch, Wnt/β-catenin, Hedgehog) and strategies that force differentiation or enhance immune recognition of stem-like cells. However, effective clinical translation remains challenging [28, 29].

Understanding how the physical architecture of the TME and the biology of CSCs contribute to drug penetration barriers, immune evasion, and intrinsic resistance highlights the need for combinatorial approaches that remodel the microenvironment, sensitize CSCs, and restore effective anti-tumor immunity to overcome treatment failure in breast cancer.

4. Genomic Profiling for Treatment De-escalation

Genomic profiling plays a central role in guiding adjuvant therapy decisions for breast cancer, particularly in early-stage, hormone receptor–positive, HER2-negative disease. Unlike traditional diagnostic approaches, genomic assays provide predictive information that allows clinicians to tailor treatment intensity to a patient's molecular characteristics, thereby avoiding unnecessary chemotherapy and enhancing individualized, precise treatment.

Several genomic assays have been developed to guide adjuvant therapy decisions in ER-positive breast cancer, including Oncotype DX, a 21-gene assay that generates a Recurrence Score (RS) for node-negative

disease and predicts both distant recurrence risk and chemotherapy benefit [30, 31]; MammaPrint, a 70-gene microarray-based assay that stratifies tumors as “Low Risk” or “High Risk” for node-negative and select node-positive patients [32, 33]; Prosigna (PAM50), which determines intrinsic subtype and provides a Risk of Recurrence (ROR) score[34]; and EndoPredict, a 12-gene assay integrating molecular and clinical parameters to predict late distant recurrence in ER-positive patients [35]. Overall, genomic profiling represents a shift from empirical treatment toward precision medicine, enabling adjuvant therapy to balance efficacy and toxicity and providing breast cancer patients with a safer and more effective individualized treatment approach.

Multigene expression assays provide prognostic and, more importantly, predictive information to guide adjuvant chemotherapy decisions.

5. Systemic Therapies by Breast Cancer Subtype: Precision Approaches and Resistance Mechanisms

Treatment of breast cancer has increasingly shifted from a uniform approach to subtype-specific systemic therapies, guided by molecular characteristics, genomic profiling, and emerging targeted agents. For each disease subtype, therapeutic strategies now focus on overcoming resistance mechanisms, optimizing efficacy, and minimizing toxicity.

5.1 Hormone Receptor–Positive/HER2-Negative Breast Cancer (HR+/HER2-)

Endocrine therapy remains the backbone of treatment for ER-positive disease. Genomic assays, such as Oncotype DX, guide adjuvant chemotherapy decisions and help identify patients suitable for treatment de-escalation. In advanced or high-risk disease, targeted agents have significantly improved outcomes. CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) block the cyclin D-CDK4/6 complex, halting cell cycle progression and improving both progression-free and overall survival. Additional targeted therapies include PI3K inhibitors (alpelisib) for PIK3CA-mutated tumors and mTOR inhibitors (everolimus) for endocrine-resistant disease. PARP inhibitors are employed in patients with germline BRCA mutations, exploiting homologous recombination deficiency to induce synthetic lethality [36, 37]

5.2 HER2-Positive Breast Cancer

Antibody-drug conjugates (ADCs) have transformed HER2-targeted therapy, particularly in overcoming resistance to traditional monoclonal antibodies. T-DM1 (trastuzumab emtansine) combines trastuzumab with the cytotoxic payload DM1 and demonstrated improved progression-free and overall survival compared with standard therapy in patients previously treated with trastuzumab and a taxane [38]. Resistance to T-DM1 can arise from reduced HER2 expression, altered intracellular trafficking, or limited payload delivery due to its non-cleavable linker [39].

Next-generation ADCs, such as trastuzumab deruxtecan (T-DXd), use cleavable linkers and potent topoisomerase I inhibitor payloads, with higher drug-to-antibody ratios and a membrane-permeable payload that produces a bystander effect. This allows killing of both high- and low-HER2-expressing tumor cells. In the DESTINY-Breast03 trial, T-DXd significantly improved progression-free survival and response rates compared with T-DM1, demonstrating its ability to overcome resistance to earlier ADCs [40]. Tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib) remain valuable for patients progressing on antibody therapy and for CNS-active disease.

5.3 Triple-Negative Breast Cancer (TNBC)

TNBC lacks ER, PR, and HER2 expression, limiting traditional targeted therapy options. Immune checkpoint inhibitors (ICIs) have reshaped treatment for specific subgroups. The KEYNOTE-522 trial demonstrated that adding the PD-1 inhibitor pembrolizumab to neoadjuvant chemotherapy, followed by adjuvant pembrolizumab, significantly improved pathological complete response (pCR) and event-free survival in early-stage TNBC [41]. In metastatic TNBC, pembrolizumab plus chemotherapy improved overall survival in PD-L1-positive tumors, reflecting TNBC’s inherent immunogenicity [42].

PARP inhibitors, such as olaparib and talazoparib, exploit synthetic lethality in germline BRCA1/2-mutated TNBC by inhibiting single-strand DNA repair, leading to tumor cell death. Clinical studies have demonstrated significant improvements in progression-free survival compared with standard chemotherapy in BRCA-mutant metastatic TNBC^8. Together, pembrolizumab and PARP inhibitors illustrate a shift from empiric chemotherapy to biology-driven, subtype-specific treatment strategies.

6. Conclusion

The journey in understanding and treating breast cancer has been one of remarkable progress, moving from a one-size-fits-all approach rooted in anatomy to a nuanced, molecularly driven, and increasingly personalized discipline. The delineation of intrinsic subtypes has provided the fundamental roadmap for therapy development. The success of targeted agents like trastuzumab, PARP inhibitors, and CDK4/6 inhibitors exemplifies the power of translating basic biological insights into clinical practice.

However, significant challenges persist. Therapeutic resistance, whether intrinsic or acquired, remains the principal obstacle to curing advanced disease. Overcoming it will require a deeper understanding of tumor evolution, clonal heterogeneity, and the complex adaptive responses of the TME. Metastasis, particularly to the brain, is still largely incurable and demands more effective strategies to target dormant cells and overcome the blood-brain barrier. While immunotherapy has made inroads in TNBC, response rates are still limited, and predictive biomarkers beyond PD-L1 are urgently needed to identify beneficiaries and overcome immune evasion mechanisms.

The future of breast cancer diagnosis and treatment is advancing toward greater precision, real-time monitoring, and intelligent support. Minimally invasive liquid biopsies, including circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), have demonstrated the ability to dynamically reflect tumor clonal evolution, therapeutic response, and minimal residual disease, offering more sensitive insight into tumor heterogeneity and resistance mechanisms compared with traditional tissue biopsies, and holding promise for early relapse detection and informed re-treatment decisions [43, 44]. Antibody-drug conjugates (ADCs), which direct potent cytotoxic payloads to tumor cells, continue to evolve as a novel targeted strategy. While first-generation ADCs such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) revolutionized HER2-positive disease treatment, next-generation constructs with optimized antibodies, linkers, and payloads are expanding efficacy into HER2-low subgroups and other molecular subtypes, including ADCs targeting TROP2 and other novel antigens, which overcome limitations related to antigen heterogeneity and drug resistance and have shown improved progression-free and overall survival in diverse patient populations. The re-conceptualization of HER2 expression as a continuum rather than a binary category, together with the successful application of ADCs in HER2-low breast cancer, has broadened the population eligible for effective targeted therapies and highlights the need for updated diagnostic standards and refined molecular classification schemes [45, 46].

In parallel, novel immunotherapeutic strategies are under active investigation. Beyond enhanced use of immune checkpoint inhibitors in subtypes such as triple-negative breast cancer (TNBC), emerging modalities, including cancer vaccines and adoptive cell therapies (e.g., CAR-T cells, tumor-infiltrating lymphocytes), aim to more effectively activate or reprogram antitumor immunity, with multi-omic biomarkers increasingly used to predict immunotherapy response and optimize regimen selection. Furthermore, artificial intelligence (AI) and machine learning are being widely applied in breast cancer diagnosis and treatment decision-making, improving imaging interpretation, integrating pathology, genomic, and multi-omic datasets, and enabling more accurate prediction of treatment response, molecular subtyping, and clinical outcomes to support personalized treatment strategies [47]. While further clinical validation and standardization are needed, the integration of these technologies holds promise for dynamic management of breast cancer—from early detection and resistance tracking to precision-guided therapy—ushering in an era of intelligent, patient-centered oncology care.

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