The Role of Multi-Omics in Breast Cancer Diagnosis and Research

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Abstract

Breast cancer is the most common malignancy among women and a leading cause of cancer-related mortality. Despite significant advances in detection and treatment, its molecular heterogeneity poses challenges in achieving accurate diagnosis and personalized therapies. Traditional diagnostic methods, based primarily on histopathology and genomics, fail to capture the full complexity of the disease. In response, multi-omics approaches, integrating genomics, transcriptomics, proteomics, and metabolomics, are emerging as powerful tools for comprehensive cancer profiling. These advanced methodologies enable the identification of novel biomarkers, improve diagnostic accuracy, and facilitate patient stratification for tailored treatments. This review explores the role of multi-omics in breast cancer diagnosis, emphasizing recent technological advancements and key findings that enhance early detection, prognosis, and treatment strategies. By providing a more complete molecular picture, multi-omics is paving the way for precision medicine, offering the potential for more effective and personalized breast cancer therapies.

Key words

breast cancer, omics techniques, genomics, proteomics, metabolomics

Introduction

Breast cancer remains the most prevalent malignancy among women and a major cause of cancer-related mortality globally. Despite advancements in early detection and treatment, the disease's heterogeneity presents challenges in accurate diagnosis and personalized therapy. Traditional diagnostic approaches, relying on histopathological examination and single-omics technologies like genomics, have been limited in capturing the full complexity of tumor biology. As a result, there is a growing need for more comprehensive methods to enhance diagnostic precision and guide therapeutic strategies.

The integration of multi-omics approaches—combining genomics, transcriptomics, proteomics, and metabolomics—offers a promising solution. These advanced techniques allow for a more complete molecular characterization of breast cancer, facilitating the discovery of novel biomarkers, improving diagnostic accuracy, and enabling the stratification of patients based on their specific tumor profiles. Recent studies employing integrative multi-omics methodologies, such as Multi-Omics Factor Analysis (MOFA+), have demonstrated their potential in refining breast cancer classification and improving clinical outcomes. Multi-omics approaches have the potential to revolutionize breast cancer diagnosis and treatment by integrating diverse omic data, such as genomics, proteomics, and metabolomics, to enable more accurate diagnosis, identification of biomarkers, and personalized therapies.

This review highlights the role of multi-omics in breast cancer diagnosis and patient management. We explore the latest technological advancements, key diagnostic biomarkers identified through multi-omics, and their clinical implications for early detection, prognosis, and personalized treatment. By providing a holistic understanding of the tumor microenvironment, multi-omics approaches are advancing precision oncology, bringing us closer to tailored therapies that improve patient outcomes.

Overview of Multi-Omics Technologies

Genomics plays a crucial role in understanding the molecular landscape of breast cancer by identifying genetic alterations that drive tumor initiation and progression. Key genomic features include DNA mutations, copy number variations (CNVs), and epigenetic modifications, all of

which contribute to tumor heterogeneity and influence treatment responses. Beyond their role in tumor biology, genomic techniques have become indispensable tools for breast cancer diagnosis and personalized treatment planning. Figure 1 illustrates the integration of multi-omics data to enhance the understanding of breast cancer biology. By combining genomics, transcriptomics, proteomics, and metabolomics, researchers can obtain a more comprehensive and detailed picture of the molecular mechanisms driving tumorigenesis. This integration enables the identification of new biomarkers and therapeutic targets, furthering personalized medicine approaches (Figure 1).

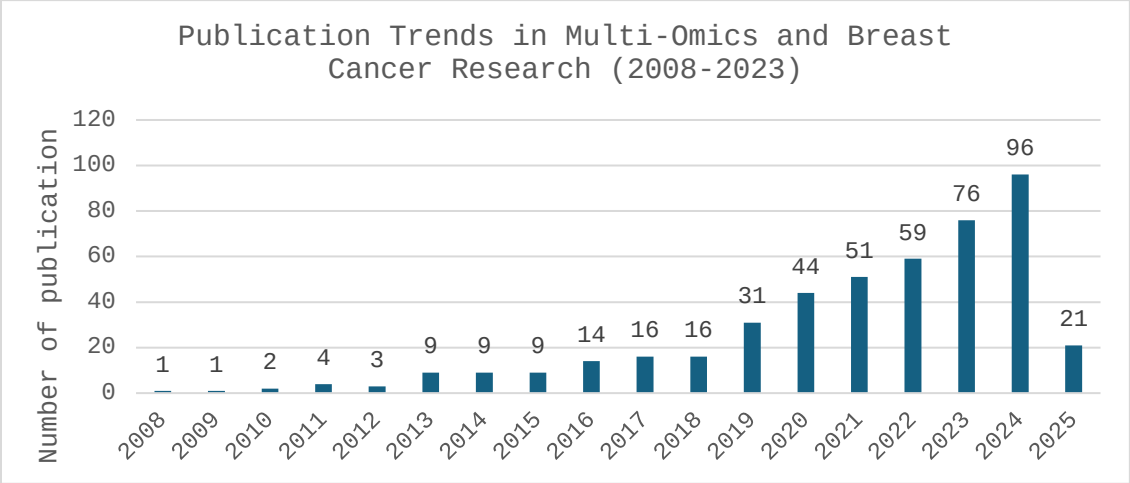

Figure 1. Trends in "Omics" Research on Breast Cancer.
This figure presents the results of a PubMed search for the query "omics [ti] AND breast cancer" conducted on March 14, 2025. The graph illustrates the number of publications related to the application of "omics" technologies in breast cancer research over the years.

With the rapid advancement of technologies such as next-generation sequencing (NGS) and liquid biopsy, genomic profiling has become more accessible and efficient. These innovations have significantly improved cancer detection and monitoring of cancer through tools like circulating tumor DNA (ctDNA) and plasma tumor DNA (ptDNA). These technologies allow for the comprehensive analysis of tumor DNA, facilitating the identification of critical mutations, CNVs, and epigenetic changes, even from small or hard-to-access tissue samples. Liquid biopsies, in particular, offer a non-invasive alternative to traditional tissue biopsies, enabling continuous monitoring of tumor evolution and therapy response.
Recent studies have shown the potential of ctDNA and ptDNA in breast cancer detection and monitoring, particularly with methods like droplet digital PCR (ddPCR) For instance, ddPCR has been used to detect PIK3CA mutations in ptDNA pre- and post-surgery, demonstrating its high sensitivity and specificity (93.3% and 100%, respectively) (1). ctDNA, detected using whole genome sequencing (WGS)-powered assays, further improved relapse detection with a lead time of 15 months before clinical relapse. Patients with undetectable ctDNA during follow-up did not relapse, underscoring the importance of ctDNA in monitoring minimal residual disease (MRD) and predicting outcomes in early breast cancer (2). These findings indicate the potential for ctDNA as a reliable biomarker for early relapse detection and personalized therapy.
Parallel with genomic profiling technologies, studies like those by Perou et al. have further advanced our understanding of breast cancer subtypes, identifying molecular classifications - luminal A, luminal B, HER2-enriched, and basal-like - that are now used in clinical settings to predict prognosis and guide therapy selection. Their study also found that gene expression within a tumor before and after chemotherapy remains more similar to itself than to other

tumors, highlighting genetic stability within individual tumors and genomic heterogeneity across cases (3). This work established a molecular taxonomy of breast cancer, now used in clinical settings through genomic assays to predict prognosis and guide therapy selection. This classification was expanded by Nik-Zainal et al., who identified recurrent somatic mutations in genes such as *TP53*, *PIK3CA*, and *GATA3*, which are crucial in tumor development (4).

Whole-genome and whole-exome sequencing approaches in breast cancer genomics revealed mutational signatures linked to DNA repair deficiencies, particularly in BRCA1/2-mutated breast cancers (4). Testing for germline BRCA1/2 mutations has an established predictive role in breast cancer risk assessment and treatment planning, as these mutations influence responsiveness to therapies like platinum-based chemotherapy and PARP inhibitors (5) Genetic testing for BRCA1/2 mutations is now a standard part of clinical practice, not only for identifying patients at increased risk but also for personalizing treatment (6). For example, patients with BRCA1/2 mutations are often treated with PARP inhibitors, such as olaparib, which exploit the DNA repair deficiencies in these tumors (7). NGS enables multigene sequencing, aiding treatment selection based on mutations in genes like PIK3CA and TP53, which guide PI3K inhibitor use (8,9). Other susceptibility genes, such as BARD1, BRIP1, CHEK2, and SMAD4, contribute to breast cancer risk and treatment stratification (10–15). Genomic assays like Oncotype DX and MammaPrint stratify patients based on recurrence risk and chemotherapy response, with machine learning models further enhancing their predictive accuracy (84.8% for MMP, 87.9% for ODX) (16,17).

In addition to somatic mutations, CNVs contribute to breast cancer heterogeneity by amplifying oncogenes (e.g., *HER2*, *MYC*) and deleting tumor suppressor genes (e.g., *PTEN*, *RB1*) (18)(19). These genomic alterations are now routinely assessed in clinical practice, with HER2 amplification serving as a key biomarker for trastuzumab-based targeted therapies (20). Technologies such as fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS) are widely used to detect these genomic changes and tailor treatment plans accordingly. Amplifications of *ESR1*, *PRDM14*, *MYC*, and *HER2* are associated with a higher mitotic index, while tumors with co-amplifications of *HER2/MYC*, *HER2/CCNE1*, and *EGFR/MYC* were significantly larger compared to tumors with amplifications of only one of these genes (21). These findings underscore the role of CNVs in shaping tumor phenotypes and influencing clinical outcomes. Moreover, a recent study by Cha et al. identified distinct CNVs enriched in metastatic breast cancer (MBC) across various metastatic sites, including *SMARCA4*, *TSC2*, *ATRX*, and *AURKA*, suggesting that these alterations may contribute to tumor organotropism and the heterogeneity of metastasis (22).

Epigenetic changes, including DNA methylation and histone modifications, regulate gene expression in breast cancer (23,24). Hypermethylation of tumor suppressor genes (e.g., CDH1, RASSF1A) and global hypomethylation contribute to cancer progression, while histone marks like H3K4me3 and H4K20me3 serve as prognostic indicators (25,26). Batra et al. analyzed DNA methylation in 1,538 breast cancer samples, revealing epigenomic instability, a tumor replication-linked clock, and cis-regulation of gene expression. Methylation changes in CpG islands correlated with tumor grade, TP53 mutations, and prognosis (27). Methylation-based biomarkers are being incorporated into liquid biopsy tests for non-invasive diagnosis. Transcriptomics further aids in identifying genes involved in cancer progression and therapy response, offering new biomarker and treatment strategies.

Proteogenomics integrates genomic, transcriptomic, and proteomic data, enhancing our understanding of cancer biology (28). Combining next-generation sequencing with mass spectrometry-based proteomics allows for deep protein quantification and post-translational modification analysis (29). Proteogenomic profiling has identified molecular vulnerabilities in breast cancer beyond genomic and transcriptomic data (30). Large-scale studies have characterized over 10,000 proteins and numerous phosphorylation/acetylation sites, revealing

clinically relevant biomarkers (31). Established tumor markers like MUC1 (32), HER2 (33), and CA 15-3 (34) aid in cancer detection and monitoring. Proteomic studies have also highlighted novel markers, such as MIF, EDIL-3, and fibronectin, for personalized diagnostics. Jeon et al. identified immune subtype-specific proteins, with Coronin-1A upregulated in immune-inflamed tumors and α-1-antitrypsin in immune-excluded tumors. Titin expression correlated with pathological complete response in immune-inflamed cases (35). A large-scale analysis of 300 FFPE breast cancer specimens quantified 4,214 proteins, uncovering distinct proteomic patterns in aggressive PAM50 basal-like and HER2-enriched subtypes, linked to immune and metabolic features (36).

Metabolomics, utilizing an untargeted approach, shows promise for breast cancer diagnosis. A study identified eight metabolic biomarkers linked to breast cancer risk, including 1,3-dibutyl-1-nitrosourea, 11-cis-eicosenoic acid, and L-histidine, highlighting alterations in fatty acid and amino acid metabolism (37). Further validation is required to confirm their clinical relevance. Metabolomic studies reveal significant changes in key metabolic pathways, such as glycolysis, lipid metabolism, and amino acid metabolism, which are strongly associated with breast cancer progression. Triple-negative breast cancer (TNBC) tissues exhibit increased intermediates of glycolysis, glycogenolysis, and TCA cycle metabolites compared to estrogen receptor (ER)-positive tissues (38). Additionally, lipid metabolism is profoundly dysregulated, with increased phospholipids like phosphatidylcholine and phosphatidylethanolamine, particularly in ER-negative cases (39). Amino acid metabolism also plays a key role in breast cancer, with elevated glutamine and glutamate levels supporting cancer cell energy production (40). Branched-chain amino acids (isoleucine, valine), crucial for gluconeogenesis, are increased in breast cancer patients (41). Metabolites linked to oxidative phosphorylation, such as taurine, pyruvate, and succinate, are significantly higher in breast cancer plasma, indicating mitochondrial dysfunction (42–44). Metabolomics also sheds light on the epigenetic regulation of triple-negative breast cancer (TNBC). CtBP2, an NADH-dependent transcriptional co-regulator, links metabolism to transcriptional reprogramming. Inhibiting CtBP2 reduces cell proliferation by altering redox balance, nucleotide synthesis, and reactive oxygen species (ROS) homeostasis (45). This underscores the role of metabolic reprogramming in oncogene regulation and suggests metabolic pathways as therapeutic targets. Recent studies highlight the potential of metabolomics in distinguishing breast cancer subtypes. An untargeted LC-HRMS analysis identified distinct metabolic signatures for luminal A, luminal B, HER2+, and TNBC, achieving high diagnostic accuracy (AUROC > 0.85) (46). These findings support metabolic profiling as a tool for subtype-specific diagnosis and personalized treatment strategies.

Clinical applications and challenges

Integrating genomics, proteomics, epigenomics, and metabolomics provides a comprehensive understanding of breast cancer, enabling biomarker discovery and targeted therapies (Figure 2). This multi-omics approach enhances tumor classification, early detection, and personalized treatment, improving patient outcomes. Machine learning algorithms facilitate multi-omics data integration, aiding clinicians in diagnosis, treatment selection, and relapse prediction. Advanced computational methods, including similarity-based and Bayesian approaches, help manage high-dimensional datasets, supporting personalized strategies (47). Despite its potential, multi-omics integration faces challenges. The complexity of biological diversity and data heterogeneity complicates AI-driven analyses, necessitating robust validation methods (48). Data quality and consistency issues, along with variability across sources, hinder reproducibility (49). High costs and the need for specialized expertise further limit clinical adoption. Moreover, seamless integration into clinical workflows requires collaboration between bioinformaticians, clinicians, and researchers. Developing intuitive tools that merge molecular data with clinical records is essential for effective decision-making.

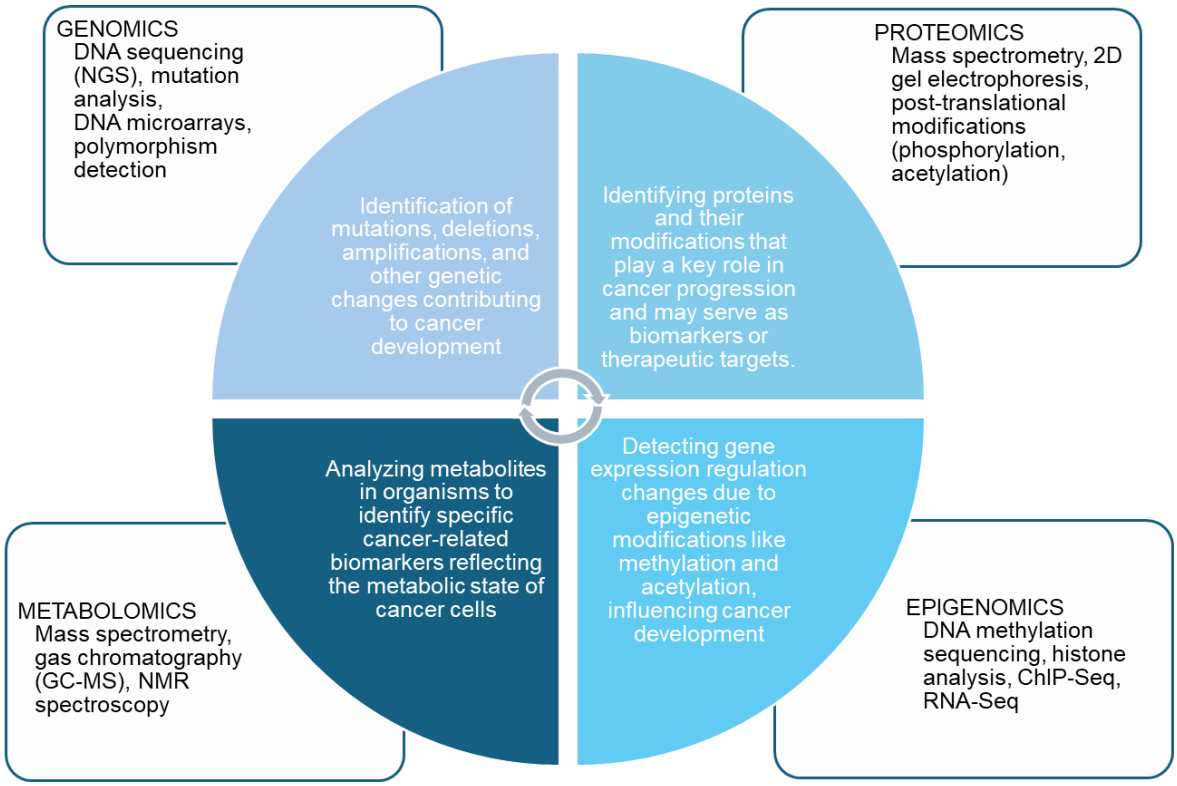

Figure 2. Integrated Approach to Cancer Biology Analysis Using Genomics, Proteomics, Epigenomics, and Metabolomics

This schematic diagram represents an integrated multiomics approach to cancer biology, illustrating the relationship between four key "omics" fields: genomics, proteomics, epigenomics, and metabolomics. Each circle corresponds to one of these fields, and their intersections highlight the integration of data to provide a comprehensive understanding of cancer development.

Conclusion

The integration of multi-omics technologies in breast cancer diagnosis represents a paradigm shift in precision oncology. By providing a comprehensive molecular characterization of tumors, multi-omics approaches offer enhanced diagnostic accuracy, improved patient stratification, and the potential for more personalized treatment strategies. While the integration of multi-omics data holds immense potential for improving clinical outcomes, several challenges remain before its widespread clinical application can be realized. Overcoming these challenges, including advancements in technology, data standardization, and collaboration across research and clinical domains, will be crucial for successful clinical implementation. As these hurdles are addressed, multi-omics technologies will continue to shape the future of breast cancer management, driving innovations in early detection, targeted therapies, and personalized oncology.

Conflict of interest statement

The authors declare no conflict of interest.

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