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FUTURE DIRECTIONS IN BREAST CANCER DIAGNOSIS: THE EXPANDING LANDSCAPE OF LIQUID BIOPSY- BASED BIOMARKERS

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Abstract

Breast cancer diagnosis is advancing through liquid biopsy, a minimally invasive method analyzing tumor-derived biomarkers in blood. Circulating tumor DNA (ctDNA), CTCs, EVs, and ncRNAs offer real-time insights into tumor dynamics, resistance, and subtypes. ctDNA enables early detection of recurrence, while ncRNA signatures guide prognosis and therapy. Integration with genomic strategies, such as using PARP inhibitors in BRCA1/2-deficient tumors, enhances treatment precision. This approach exploits synthetic lethality, selectively killing cancer cells while sparing normal ones. Emerging AI-driven multi-omics platforms promise personalized monitoring. Together, these innovations are reshaping breast cancer care.

Keywords

Liquid biopsy, Breast cancer, Circulating tumor DNA (ctDNA), Non-coding RNAs, Extracellular vesicles (EVs)

Breast cancer continues to be the most frequently diagnosed malignancy among women globally, posing significant diagnostic and therapeutic challenges. Breast pain, or mastalgia, is a common symptom that can affect individuals of all ages and may arise from a range of physiological, pathological, or external factors. It can be cyclical, related to hormonal fluctuations, or non-cyclical, stemming from issues such as infections, cysts, trauma, or even musculoskeletal conditions. Identifying the underlying cause is essential for proper diagnosis and effective treatment (figure 1) (1). Traditional biopsy methods, while informative, are limited by their invasiveness, sampling bias, and inability to capture tumor heterogeneity or monitor disease progression in real time (2). Liquid biopsy**,** a minimally invasive approach that analyzes circulating tumor-derived components in biological fluids, has emerged as a transformative tool in breast cancer diagnosis, prognosis, and treatment monitoring (3).

Recent advancements in liquid biopsy-based biomarkers are revolutionizing the early diagnosis, therapeutic monitoring, and recurrence detection of breast cancer. Among the most promising markers, circulating tumor DNA (ctDNA) provides a real-time snapshot of tumor evolution (4). CtDNA harbors genetic alterations, such as ESR1 mutations, associated with therapeutic resistance, especially in hormone receptor-positive breast cancers. Its ability to dynamically reflect tumor burden and molecular changes allows for earlier detection of recurrence than conventional imaging modalities (5).

Circulating tumor cells (CTCs), another valuable component, offer phenotypic and genotypic insights that can inform prognosis and treatment response. Meanwhile, extracellular vesicles (EVs), particularly exosomes, serve as stable carriers of tumor-derived DNA, RNA, and proteins. These vesicles not only facilitate early detection and

molecular subtyping including in aggressive forms such as triple-negative breast cancer but also participate in tumor progression and immune evasion (6).

Additionally, non-coding RNAs (ncRNAs) are emerging as powerful diagnostic and prognostic biomarkers. Specific signatures, such as miR-21, miR-155, and miR-10b, have been linked to breast cancer progression and therapeutic response, while long non-coding RNAs and circular RNAs offer novel opportunities for detecting resistance mechanisms and guiding precision oncology (7).

The integration of liquid biopsy approaches with insights into synthetic lethality mechanisms, such as those targeting BRCA1/2-deficient tumors using PARP inhibitors, further enhances the landscape of personalized medicine in breast cancer. As illustrated in the figure, normal cells with functional BRCA1/2 can repair double-strand DNA breaks, allowing cell survival despite PARP inhibition (8). In contrast, tumor cells harboring BRCA1/2 mutations are unable to repair the accumulating DNA damage caused by PARP inhibition, leading to synthetic lethality and selective tumor cell death. This approach not only exemplifies the clinical utility of biomarker driven therapies but also underscores the relevance of integrating genomic context with circulating biomarkers for optimal treatment stratification (9) (Figure 2).

These emerging biomarker modalities when integrated with advanced therapeutic strategies are paving the way for more precise, non-invasive, and dynamic management of breast cancer. Future directions in this evolving field focus on the integration of multi-omics platforms (genomics, transcriptomics, proteomics, and metabolomics) with liquid biopsy to provide a holistic view of tumor biology. Machine learning and artificial intelligence (AI) algorithms are being developed to analyze complex datasets and identify predictive biomarker signatures. Furthermore, combining liquid biopsy with imaging modalities and clinical data could usher in an era of real-time, personalized oncology.

Figure 1 this diagram illustrates various causes of breast pain.
It includes hormonal changes, trauma or surgery, and hormonal therapies.
Other causes shown are lactation conditions, cysts, inflammation, and cancer.
Musculoskeletal issues are also depicted as potential non-breast-related sources.

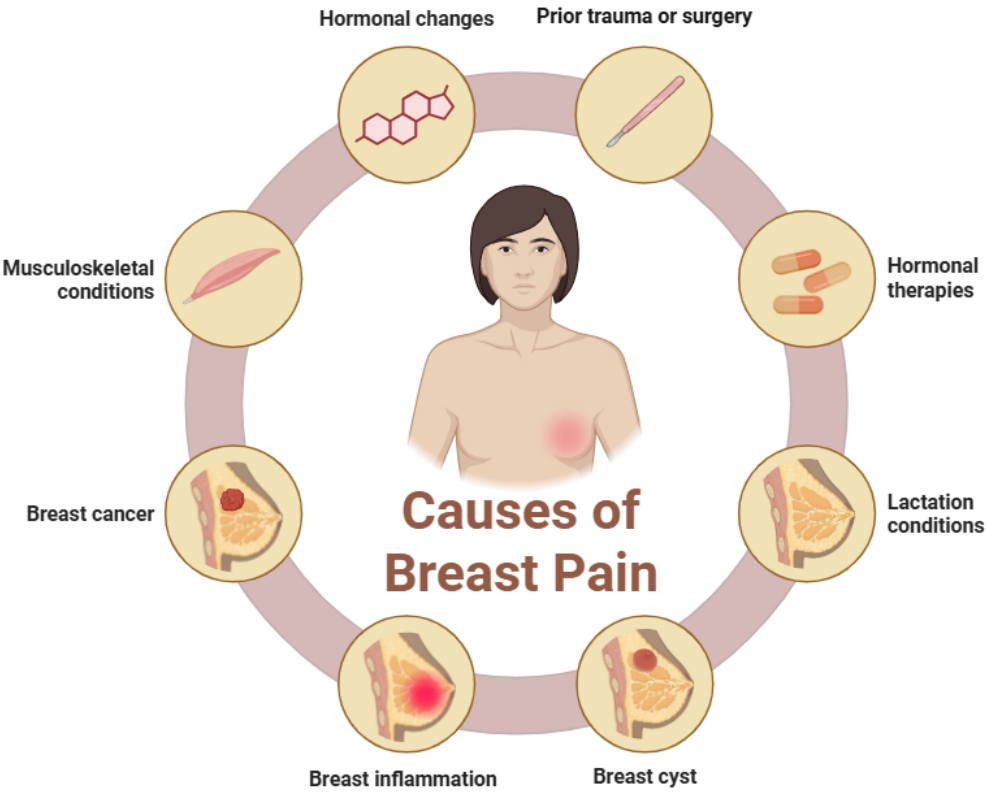
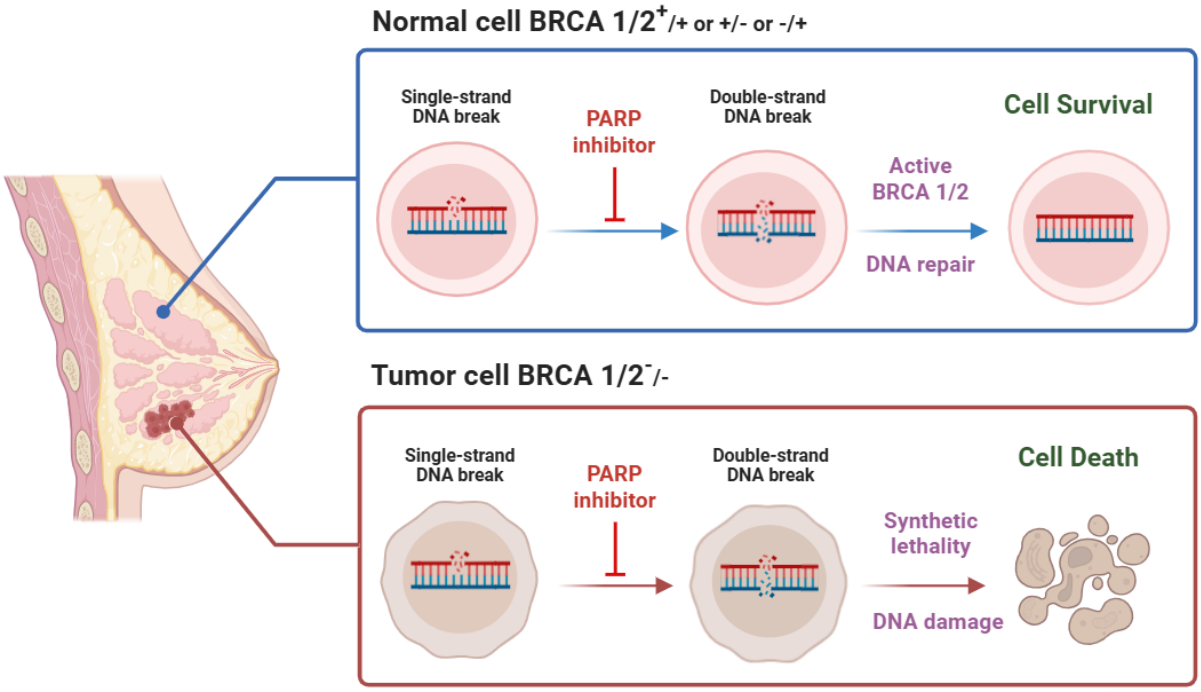


Figure 2 this diagram illustrates the mechanism of PARP inhibitors in cells with different BRCA1/2 statuses. In normal cells with functional BRCA1/2, DNA damage is repaired, allowing cell survival. In tumor cells lacking BRCA1/2 function, PARP inhibition leads to DNA damage accumulation and synthetic lethality, resulting in cell death.



Biomarker Type	Function/Role	Clinical Application	Reference
Circulating Tumor DNA (ctDNA)	Contains tumor-specific genetic alterations (e.g., ESR1 mutations)	Early detection, monitoring resistance, recurrence prediction	(4), (5)
Circulating Tumor Cells (CTCs)	Provide phenotypic and genotypic tumor data	Prognostic indicator, guides treatment decisions	(6)
Extracellular Vesicles (EVs)	Carry DNA, RNA, proteins; involved in tumor progression and immune evasion	Molecular subtyping, early detection, especially for aggressive subtypes	(6)
Non-coding RNAs (ncRNAs)	Includes miR-21, miR-155, miR-10b; linked to progression and therapy response	Diagnostic and prognostic biomarker; resistance mechanism indicator	(7)
PARP Inhibitors in BRCA1/2 Deficiency	Induce synthetic lethality by exploiting defective DNA repair	Precision therapy for BRCA-mutant breast cancer	(8), (9), (10)

Table 1 this table summarizes key liquid biopsy-based biomarkers used in breast cancer diagnosis and management. It highlights their biological roles, clinical applications, and supporting references. The integration of these biomarkers with genomic insights enables more precise and personalized treatment strategies.

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