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Understanding the Role of Liquid Biopsies in the Early Detection of Breast Cancer

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Abstract

Breast Cancer (BC) remains a significant global health challenge, with early detection playing a crucial role in improving survival rates. Traditional detection methods such as mammography, MRI, and biopsies have limitations that impact the timely diagnosis of early-stage BC. This review focuses on the potential of liquid biopsies, specifically Circulating Tumor DNA (ctDNA) analysis, as a non-invasive alternative for early breast cancer detection. Liquid biopsies offer advantages in terms of non-invasiveness and the ability to be repeated over time, providing valuable insights into tumor genetics. However, current ctDNA assays face challenges, particularly in detecting early-stage cancers due to low ctDNA levels. The review examines recent advancements in ctDNA research, including the role of key genetic mutations and copy number alterations, and highlights the need for improved assay sensitivity and specificity. It also explores the promise of tumor-informed approaches, despite their higher costs and longer development times. The integration of ctDNA analysis into clinical practice holds potential for enhancing early detection and personalizing treatment, with implications extending to other malignancies as well. Continued research and technological innovations are essential to overcoming current limitations and advancing the field of cancer detection and treatment.

Keywords: Breast cancer • ctDNA • Liquid biopsies

Introduction

In 2022, around 2.3 million women worldwide were diagnosed with Breast Cancer (BC) [1]. BC is the second most common cancer in women, with melanoma being the most common [2]. Beginning as a growth of cells in the breast. Triple-negative breast cancer, which lacks estrogen, progesterone, and HER2 receptors, is more challenging to treat and is often managed with chemotherapy and emerging targeted tissue, the most common types of BC are invasive ductal carcinoma and invasive lobular carcinoma [3]. When diagnosed in its earliest stage, almost all women with breast cancer survive for five or more years. However, when BC is diagnosed at its latest stages, the survival rate drops to around three in 10 women [4]. Currently, BC in early stage I or stage II is diagnosed in 65% of women - 27% of women are diagnosed after having progressed to stage III BC, and 6% of women are diagnosed at stage IV [5].

Breast cancer is further classified based on the presence of specific molecular markers that influence treatment and prognosis. The most common subtypes include estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Positive (HER2+), and Triple-Negative Breast Cancer (TNBC). ER+ breast cancer, which accounts for approximately 70% of cases, is driven by estrogen and is typically treated with hormone therapies such as tamoxifen or aromatase inhibitors. HER2+ breast cancer, characterized by overexpression of the HER2 protein, is often treated with targeted therapies like trastuzumabtherapies. Additionally, Ductal Carcinoma *In Situ* (DCIS) is a non-invasive form of breast cancer that remains confined to the ducts and does not invade surrounding breast tissue. DCIS is often detected through screening and is generally treated with surgery and radiation [3].

Consequently, early detection of BC is vital for patient survival. Presently, the most common BC detection method is the mammography screening test. Yet, mammograms miss about 20% of breast cancers, resulting in false-negative results that delay treatment [3]. Other detection methods for BC include Magnetic Resonance Imaging (MRI), thermography, and tissue sampling [6]. However, breast MRIs have a higher likelihood of leading to "false positive" test results, which may lead to unneeded breast biopsies [7]. Breast thermographies are not effective enough to act as a standalone test for detecting BC, particularly early-stage BC [8]. Finally, breast biopsies are the most invasive detection method and come with risks, such as bruising, swelling, infection, and/or bleeding at the biopsy site [9]. As can be seen, current BC detection methods are not sufficient, especially in early detection. New methods should be considered, one of which is the liquid biopsy.

A liquid biopsy is a method of sampling and analyzing body fluid, such as blood and urine, that contains tumor-derived materials. Various biomarkers have been found in blood including tumor DNA, RNA, Circulating Tumor Cells (CTCs), or Extracellular Vehicles (EVs). circulating tumor DNA (ctDNA) is part of cell-free DNA (cfDNA) that tumor cells release through necrosis or apoptosis (REFERENCES). CtDNA can also be released into the bloodstream by CTCs - tumor cells that metastasize into the circulation or are shed from tumors [10]. Liquid biopsies have the advantage of being noninvasive as materials are often obtained through blood draws or urine collection, making it an attractive alternative to methods like a tumor biopsy. For examples in cases where the tissue is inaccessible such as the brain. They also offer the possibility of being repeated over time, which would allow for longitudinal minoring during treatment and potentially identify Minimal Residual Disease (MRD) [11]. In addition, liquid biopsy offers the potential to identify resistance mutations and better understand tumor evolution. This review provides an updated outlook on liquid biopsy applications specifically in the early diagnosis of breast cancer (Figure 1).

Related works

Due to the high incidence of breast cancer around the world, many

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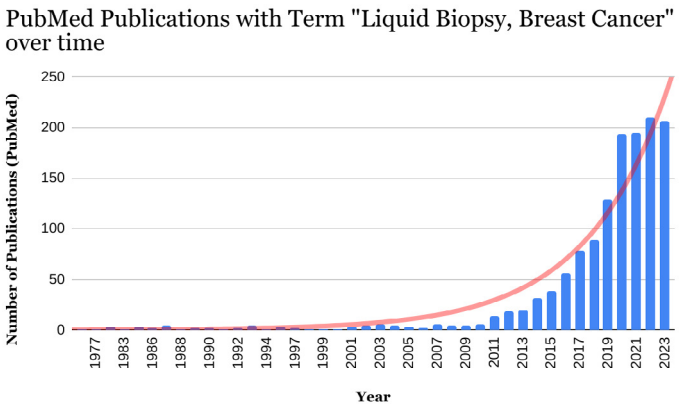

Figure 1. PubMed publications with key-word search term "liquid biopsy, breast cancer" over the years. The number of publications with keyword terms started to rise in 2011 and has seen exponential growth since the aforementioned year.

studies have been conducted related to improving its management, many of which list liquid biopsies as a potential clinical application. Two of such studies are described below. In a study led by Alimirzaie S, et al. [12], the advantages and limitations of liquid biopsy in breast cancer were reviewed, and areas that require further research were highlighted. The study mentioned the potential in early diagnosis and screening of breast cancer using liquid biopsies, in addition to other benefits like serial sampling and monitoring of response to treatment. The use of ctDNA was also covered: ctDNA collected in liquid biopsies has the potential to be sequenced to genetically profile the tumor, enhancing personalized treatment. Finally, the study described how ctDNA detection after the tumor is surgically resected can allow for earlier detection of a relapse in breast cancer.

In a study led by Yang J, et al. [13], the importance of creating predictive biomarkers in patient selection for immunotherapy is illuminated. The study continues by identifying liquid biopsy as a method to identify patients who would most likely have favorable outcomes from immunotherapy, and then specifically discusses the value liquid biopsy has toward breast cancer immunotherapy. Furthermore, the limitations of liquid biopsy in breast cancer are also mentioned. Using ctDNA as a biomarker can be a challenge because of its low concentration in fluids, particularly when it comes to small tumors - the study cites ctDNA levels to be as low as 0.01% of cfDNA. The work presented in these papers builds on previous research to examine the potential of liquid biopsy in breast cancer treatment. While earlier work focused on topics such as liquid biopsy's relation to immunotherapy, or its role in predicting relapse possibilities, the focus of this review is to deep dive into the potential use of liquid biopsies in the early detection of breast cancer. Furthermore, there is a strong emphasis on the genetic biomarkers associated with breast cancer

Objective

The primary objective of this review is to investigate the role of liquid biopsies in the early detection of breast cancer. The mechanisms of liquid biopsies are examined, as well as the genetic nature of breast cancer. These two aspects can then be reviewed together to determine a course for the role of liquid biopsies in early detection. Figure 2 below visually shows the conventional steps of the liquid biopsy.

Methodology

Literature in numerous journals relating to breast cancer and liquid biopsies was assessed for this review that have been published in the year between 2019 to 2024. The National Cancer Institute's GDC Data Portal was used for data collection on prominent genes in breast cancer. PubMed was used to find relevant research papers, as well as to assess the popularity of liquid biopsy research throughout the decades. As can be seen in the table below, recent research in ctDNA early detection in breast cancer has limited. However, the majority of the studies involve late stage and/or metastatic breast cancer, with little focus on early stage BC, likely because tumor burden is relatively low during the first stages of breast cancer. Thus, more sensitive approaches need to be developed for the early detection of BC, which is what this review will focus on (Table 1).

Results

Recent advancements over the past five years in the use of circulating tumor DNA (ctDNA) as a biomarker for the early detection of breast cancer reveal both promising potential and significant challenges. The molecular characterization of breast cancer often emphasizes either copy number alterations or specific mutations. Notably, early-stage breast cancers present with low ctDNA. Breast cancer can be categorized based on its molecular characteristics, including mutations and copy number alterations. The TCGA data highlights the most frequently mutated genes in breast cancer, such as TP53, PIK3CA, and BRCA1. These mutations play a crucial role in defining the disease's molecular landscape. Subtypes like Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC) have distinct genetic profiles. For example, ILC is often associated with mutations in the CDH1 gene, while IDC may present with mutations in PIK3CA (Figure 3).

ctDNA and liquid biopsies

Recent studies demonstrate that while ctDNA can indicate the presence of mutations and copy number changes associated with breast cancer, the assays currently available are not sufficiently sensitive for reliable early-stage detection such as tumor fraction of less than 1%. The need for more advanced assays is evident, as existing technologies struggle to detect ctDNA at low levels typically seen in early-stage cancers. The only approach that allows the detection of tumor fraction at a few parts per million is currently based on informed tumor sequencing by pre-identifying the personalized mutations of the patient in the tumor genome [14].

Tumor-informed approaches

To overcome the limitations of current ctDNA assays, tumor-informed approaches are being explored. These methods utilize the genetic information from a patient's specific tumor to enhance assay sensitivity and specificity. Although these approaches offer increased precision, they require more time and resources for development, making them less accessible in routine clinical practice.

FDA-approved drug treatments

In the context of breast cancer treatment, several FDA-approved drugs highlight the importance of molecular characterization

- Tamoxifen is a well-established treatment for estrogen receptor-positive breast cancer.

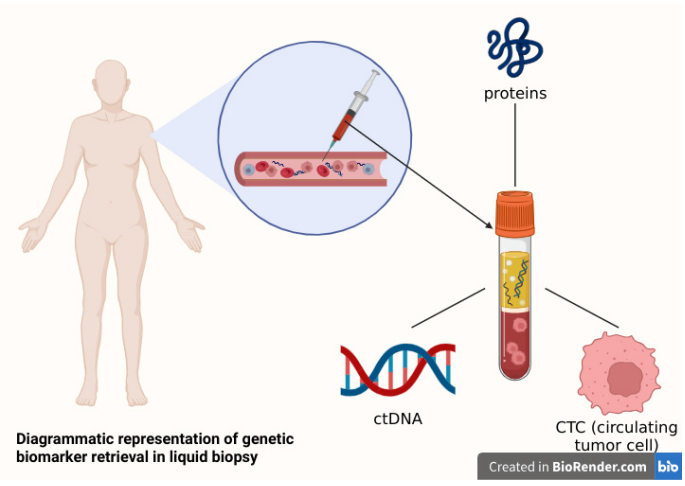

Figure 2. Diagrammatic representation of genetic biomarker retrieval in a liquid biopsy sample from a patient with breast cancer.

Table 1. Recent research in ctDNA early detection in breast cancer.

Work	Primary Authors	Year	Biomarker	NGS Method	Stage of Cancer	# of Cases
Comparison of tumor-informed and tumor-naïve sequencing assays for ctDNA detection in breast cancer	Angela Santonja, Wendy Cooper	2023	ctDNA	Tumor-informed and Tumor-naïve assays	4 early, 3 late	7
Hybrid capture-based genomic profiling of circulating tumor DNA from patients with estrogen receptor-positive metastatic breast cancer	J H Chung	2017	ctDNA	Hybrid capture-based genomic profiling	metastatic ER-positive breast cancer	254
Modeling clonal structure over narrow time frames via circulating tumor DNA in metastatic breast cancer	Zachary T Weber	2021	ctDNA	whole exome sequencing, ultra-low pass whole genome sequencing, 396-gene targeted panel sequencing	metastatic triple-negative breast cancer	7
Circulating tumour DNA in metastatic breast cancer to guide clinical trial enrolment and precision oncology: A cohort study	Andjelija Zivanovic Bujak	2020	ctDNA	targeted panel sequencing, low-coverage whole-genome sequencing	metastatic breast cancer	234
Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): A multicentre, multicohort, phase 2a, platform trial	Nicholas C Turner	2020	ctDNA	digital PCR, targeted sequencing	advanced breast cancer	1051
Clinical significance of gene mutation in ctDNA analysis for hormone receptor-positive metastatic breast cancer	Tomoko Shibayama	2020	ctDNA	Oncomine Breast cfDNA assay	HR-positive metastatic breast cancer	56
Circulating tumor DNA profiling from breast cancer screening through to metastatic disease	Karen Page	2021	ctDNA	Oncomine Breast cfDNA assay	127 healthy controls, 28 ductal carcinoma in situ, 60 primary breast cancers, 47 primary breast cancer on follow-up, and 111 metastatic breast cancers	373
The use of serial circulating tumor dna to detect resistance alterations in progressive metastatic breast cancer	Saya Jacob	2021	ctDNA	Guardant360 next-generation sequencing assay	metastatic breast cancer	255
Early evaluation of circulating tumor DNA as marker of therapeutic efficacy and prognosis in breast cancer patients during primary systemic therapy	Ru Wang	2024	ctDNA	Targeted capture approach	stage 2, stage 3	72
Variant allele frequency in circulating tumor DNA correlated with tumor disease burden and predicted outcomes in patients with advanced breast cancer	Jianxin Zhong	2024	ctDNA	harmonized 152-gene PredicineCARE™ NGS assay	advanced breast cancer	184
Phase II trial of delta-tocotrienol in neoadjuvant breast cancer with evaluation of treatment response using ctDNA	Ina Mathilde Kjær	2023	ctDNA	multiplex digital droplet polymerase chain reaction	newly diagnosed, histologically verified breast cancer	80
Potential value of ctDNA monitoring in metastatic HR+/HER2 - breast cancer: Longitudinal ctDNA analysis in the phase Ib MONALEESASIA trial	Joanne Chiu	2023	ctDNA	targeted next-generation sequencing panel of 572 cancer-related genes	HR-positive, HER2-negative advanced breast cancer	87
Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer: Preplanned Secondary Analysis of the BRE12-158 Randomized Clinical Trial	Milan Radovich	2020	ctDNA	FoundationACT or FoundationOneLiquid Assay	early-stage triple-negative breast cancer	196
Clinical factors associated with circulating tumor DNA (ctDNA) in primary breast cancer	Yidong Zhou	2019	ctDNA	targeted sequencing	primary breast cancer	71
The circulating tumor DNA (ctDNA) alteration level predicts therapeutic response in metastatic breast cancer: Novel prognostic indexes based on ctDNA	Binliang Liu	2022	ctDNA	target-capture deep sequencing	metastatic breast cancer	223

- Olaparib targets BRCA1/2 mutations and represents a tailored approach based on specific genetic profiles.

These treatments underscore the significance of understanding the molecular basis of breast cancer, which is crucial for developing personalized therapeutic strategies.

Discussion

The primary goal of this review was to assess the current state of ctDNA as a biomarker for the early detection of breast cancer and to highlight the progress made in this field. Recent findings show that while ctDNA holds significant promise, the existing assays are not yet adequate for early detection due to their limited sensitivity. The challenges are particularly pronounced in early-stage cancers where ctDNA levels are low of tumor DNA. The novelty of this review lies in its focus on recent developments and the specific application of ctDNA in early breast cancer detection. The results indicate that while ctDNA can provide valuable information about the tumor's molecular characteristics, current technologies need further refinement to improve sensitivity.

Given the limitations of current ctDNA assays, there is a critical need for

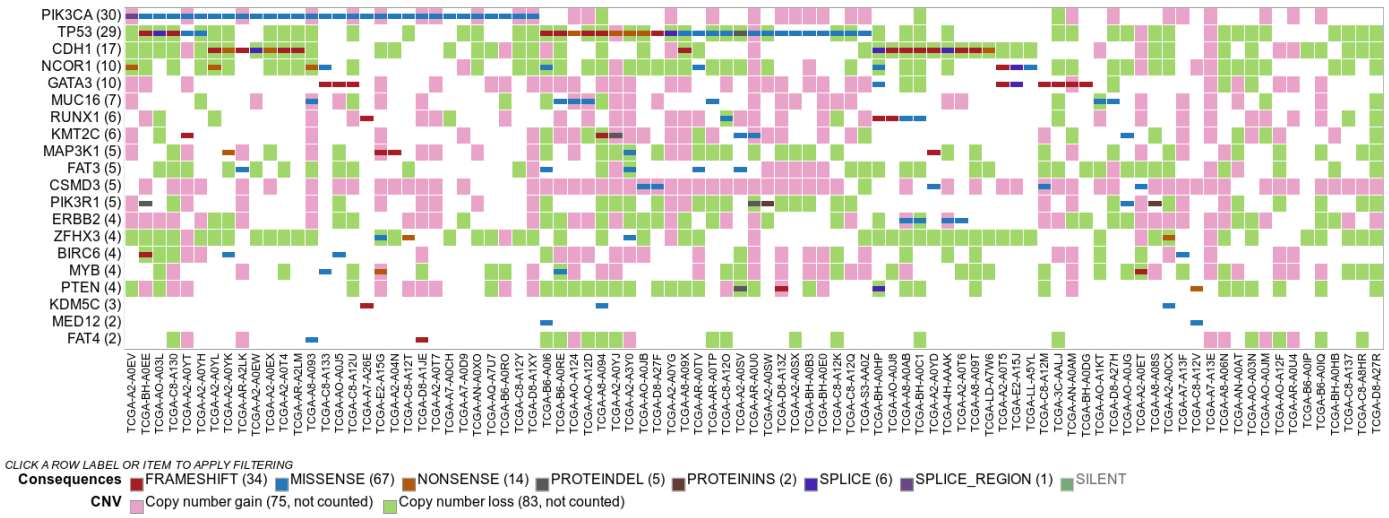

Figure 3. The 20 most mutated genes in breast cancer cohort identified from tumour biopsies on the National Cancer Institute's GDC Data Portal. Cohort consisted of "Disease Type: ductal and lobular neoplasms, Gender: female, Tissue Type: tumor, Primary Site: breast, Preservation Method: ffpe, Tumor Descriptor: primary, Data Category: copy number variation & simple nucleotide variation, Experimental Strategy: WGS, Platform: illumina, Access: open, Program: TCGA".

more sensitive and specific methods. Tumor-informed approaches, despite being more costly and time-consuming, represent a promising direction for enhancing assay performance. As the field progresses, these advanced methods could significantly improve the early detection of breast cancer, potentially transforming patient outcomes by enabling earlier and more accurate diagnosis. The implications of these advancements extend beyond breast cancer, offering valuable insights for other cancers, such as ovarian cancer, which also suffers from late-stage diagnosis and a need for effective noninvasive biomarkers for earlier detection but also more monitoring of the disease. In summary, while ctDNA has the potential to revolutionize early breast cancer detection, ongoing research and technological development are essential to address current limitations and enhance the effectiveness of liquid biopsies.

Conclusion

The pursuit of effective early detection methods for Breast Cancer (BC) is critical, given its high incidence and the marked improvement in survival rates with early diagnosis. Despite advancements in detection technologies, current methods such as mammography, MRI, and biopsies have limitations that hinder the timely diagnosis of early-stage breast cancer. Liquid biopsies, particularly those analyzing circulating tumor DNA (ctDNA), represent a promising alternative due to their non-invasive nature and potential for repeated use.

This review highlights the progress and ongoing challenges associated with using ctDNA for early breast cancer detection. Recent research underscores the potential of ctDNA to provide valuable insights into the tumor's genetic profile and to detect molecular changes indicative of breast cancer. However, the sensitivity of ctDNA assays remains a significant obstacle, especially for early-stage cancers where ctDNA levels are low. The molecular characterization of breast cancer, including the identification of key mutations and copy number alterations, is essential for understanding tumor biology and tailoring treatment strategies. The data from TCGA illustrate the role of mutations in genes such as TP53, PIK3CA, and BRCA1, and highlight differences between breast cancer subtypes like Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC). These insights are critical for leveraging ctDNA in a clinical setting.

Despite the promising developments, current ctDNA assays are not yet sufficiently sensitive for reliable early detection of breast cancer. The review emphasizes the need for more refined methods, such as tumor-informed approaches, which could potentially enhance assay sensitivity and specificity. These advanced techniques, though promising, come with higher costs and longer development times, posing challenges for their widespread implementation. The FDA-approved treatments for breast cancer, including Tamoxifen and Olaparib, underscore the importance of molecular characterization in personalizing therapy. The integration of ctDNA analysis into clinical practice could significantly impact patient outcomes by enabling earlier diagnosis and more precise treatment decisions. The implications of this research extend beyond breast cancer to other malignancies, such as ovarian cancer, which also faces challenges related to late-stage diagnosis. The development of effective noninvasive biomarkers for such cancers is crucial for improving early detection and treatment.

In conclusion, while ctDNA offers a potentially transformative approach to early breast cancer detection, further research and technological advancements are needed to overcome current limitations. Continued exploration of tumor-informed ctDNA assays and other innovative technologies will be crucial in enhancing the sensitivity and reliability of early detection methods. By addressing these challenges, we can move closer to achieving earlier diagnosis, improving patient outcomes by offering a personalized approach by satisfying patients based on their tumor genomic profile. Ultimately this will empower patients and clinicians to make informed decisions and advance the field of cancer detection and precision medicine.

Acknowledgement

None.

Conflict of Interest

None.

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