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Scoping Review

ctDNA versus mammography for breast cancer diagnosis in women aged more than 40 years old: A scoping review

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Abstract

Breast cancer remains a major public health concern, with mammography being the gold standard for early detection. However, mammography has limitations, including false positives, discomfort, and limited accessibility in resource-limited settings. Circulating tumor DNA (ctDNA) is an emerging biomarker that offers a non-invasive alternative for breast cancer diagnosis. The aim of this study was to evaluate whether ctDNA has comparable sensitivity and specificity to mammography in detecting breast cancer among suspected patients. A scoping review was conducted following the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) guidelines. A comprehensive literature search was performed in four databases (PubMed, Scopus, EMBASE, and EBSCO) as of September 13, 2023. Studies were included if they assessed ctDNA for breast cancer detection in suspected patients aged ≥40 years and compared its diagnostic performance with mammography. Five reviewers independently screened studies, extracted data, and performed critical appraisal using the Centre for Evidence-Based Medicine (CEBM) tools. The synthesis focused on sensitivity, specificity, and diagnostic performance. A total of five studies met the eligibility criteria, including three meta-analyses and two cross-sectional studies. The sensitivity of ctDNA ranged from 31.08% to 94%, while specificity ranged from 79% to 89%. The meta-analyses reported higher sensitivity (75–94%) and specificity (79–89%) compared to an individual cross-sectional study, which reported a lower sensitivity of 31.08% but a comparable specificity of 86.36%. The findings suggest ctDNA's potential as a diagnostic tool for breast cancer detection in suspected patients. It may serve as a non-invasive alternative or adjunct to mammography. This is particularly relevant in settings where traditional imaging methods are less accessible. However, variations in study quality, risk of bias, and patient selection criteria warrant future validation.

Keywords: Breast cancer, circulating tumor DNA, mammography, sensitivity, specificity

Introduction

Breast cancer is a malignant growth of cells that starts in the ducts or lobules of the breast gland. Early breast cancer is usually asymptomatic. As the cancer cells grow, the patient may accidentally discover a lump in the breast tissue. In advanced breast cancer, it may be presented with peau d'orange, ulceration, or fixation to the chest wall [1]. Breast cancer remains a major public health problem worldwide, especially for women. In the year of 2020, there were 2.3 million women diagnosed with breast cancer, with 685.000 deaths globally [2]. In line with the current situation

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in Indonesia, breast cancer ranks first among the most prevalent cancers, with more than 68,858 cases and 22,430 deaths [3]. The high number of deaths from this disease is attributed to the scarcity of early detection programs. This leads to a high proportion of women presenting with late-stage disease at diagnosis, as well as delays associated with treatment [4]. In fact, 43% of deaths from breast cancer can be prevented if patients regularly undergo breast cancer screening and avoid various risk factors [5].

The gold standard for diagnosing breast cancer is mammography. Although it is the gold standard, this examination has many side effects such as a high false positive rate, pain, and radiation risk. Moreover, mammography cannot be performed in rural areas that do not have adequate equipment [5,6]. Currently, circulating tumor DNA (ctDNA) is being discussed and has the potential to become a biomarker for breast cancer detection. CtDNA carries many features of the original tumor and can be analyzed from a simple, non-invasive blood extraction [7]. It has a variable half-life in the human's body circulation, ranging from 15 minutes to several hours. This makes it an appealing biomarker for cancer diagnosis, as it can provide real-time information about the molecular tumor genotype and the existing tumor burden [8]. It is faster, lower in cost, and has a lower risk of complications compared to mammography [7]. Despite the potential of this biomarker for breast cancer diagnosis, there have been mixed results in studies of its effectiveness [7,8]. Therefore, the aim of this study was to evaluate the diagnostic value of ctDNA biomarkers in diagnosing breast cancer compared to mammography.

Methods

Study design

This study used scoping review to answer the following research question: "Does ctDNA have comparable sensitivity or specificity to mammography in breast cancer detection on suspected patients?" The reporting of this scoping review followed preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) [9].

Searching strategy

Literature search was conducted by five authors (SA, ABS, CM, FN, KRL). The literature search was carried out until September 13, 2023. The search was conducted in four databases: PubMed, Scopus, EMBASE, and EBSCO. The keywords used for the search were "CT-DNA," "Breast cancer," and "biomarker," utilizing synonyms and MeSH terms when possible. The literature search strategy is presented in **Table 1**.

Table 1. Searching strategy in each database

Database	Search strategy	Hits
PubMed	((“Circulating Tumor DNA”[MeSH Terms] OR ctDNA OR ct-DNA) AND (“Biomarkers[MeSH Terms] OR "biological marker") AND (“Breast cancer[MeSH Terms] OR "mammary cancer")	238
Scopus	TITLE-ABS-KEY (("Circulating tumor DNA" OR ctDNA OR ct-DNA) AND (biomarker OR "biological marker") AND ("breast cancer" OR "breast neoplasm" OR "mammary cancer")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACT KEYWORD , "Article")) AND (LIMIT-TO (LANGUAGE , "English"))	275
Embase	'circulating tumor DNA':ab,ti AND (biomarker:ab,ti OR 'biological marker':ab,ti) AND ('breast cancer':ab,ti OR 'breast neoplasm':ab,ti OR 'mammary cancer':ab,ti)	189
EBSCO	(“Circulating tumor DNA”) AND (biomarker OR biomarkers OR “biological marker” OR “biological markers”) AND (“breast cancer” OR “breast neoplasm” OR “breast carcinoma” OR “breast tumor”)	68

Eligibility criteria

The eligibility criteria for this study encompass specific inclusion and exclusion criteria. Inclusion criteria included studies that involve female patients who are suspected to have breast cancer and utilize ctDNA as an intervention. The study under consideration should have compared ctDNA to mammography as part of its methodology. The primary outcomes of interest in this investigation are the sensitivity and specificity of ctDNA. The eligible study designs were limited to systematic reviews and meta-analyses that draw upon cross-sectional studies or those that employ a cross-sectional design. Conversely, exclusion criteria pertain to factors that render a study ineligible for

inclusion. These encompass studies conducted in languages other than English, as the focus here is on English-language research. Additionally, articles published in magazines, news outlets, or conference proceedings are excluded from the scope of this study. Lastly, studies that do not include patients who are at least 40 years old will be excluded from the analysis.

Selection strategies

Articles showing up in the search result subsequently went through a selection process, including automated duplicate removals on Rayyan.ai (https://www.rayyan.ai). Thereafter, the records were subjected to the screening of titles and abstracts and subsequent full-text screening. Screening of titles, abstracts, and full texts was carried out based on eligibility criteria. These selection stages were performed by five independent authors (SA, ABS, CM, FN, KRL), and any discrepancies were resolved through discussion and voting.

Critical appraisal method

The Centre for Evidence-Based Medicine (CEBM) appraisal tools [10] were used to evaluate the quality of evidence included in this evidence-based case report (EBCR) systematically. CEBM appraisal sheets for randomized controlled trials (RCTs) and systematic review sheets were used with respect to each study type. As for the RCT critical appraisal sheet, the quality was evaluated within the domains of internal validity (mainly focusing on randomization, blinding, and comparability) and clinical importance (study findings). Furthermore, systematic reviews were evaluated with regard to the domains of a comprehensive and appropriate search strategy, validity, and heterogeneity of included studies, as well as the conclusion drawn by the review.9

Data synthesis

Data synthesis involved systematically extracting and organizing findings related to sensitivity, specificity, and overall diagnostic performance of ctDNA and mammography. Five independent reviewers (SA, ABS, CM, FN, KRL) assessed study methodologies, extracted diagnostic accuracy metrics, and compared results to ensure consistency and validity. Discrepancies were resolved through discussion and consensus. The final synthesis presented a structured comparison of diagnostic accuracy, variations across studies, and gaps in the literature.

Results

Literature search result

In this study, a literature search was conducted based on the search strategy and eligibility criteria. Five studies were identified and critically appraised. The majority of the studies were excluded because they were not relevant to the research question. The summary of the identification and selection of the eligible literature is presented in **Figure 1**.

Study characteristics

Five studies were appraised in this study, three of which were meta-analyses. Neither of the other two studies was included in the meta-analysis after we carefully read the full text of each study. The characteristics of each study are presented in **Table 2**.

Table 2. Characteristics of studies eligible based on the criteria in this review

Study	Type of study	Intervention	Comparison	Population	Sample size	LoE
Wang *et al.*, 2021 [11]	Cross-sectional	ctDNA	Mammography and biopsy	Patient with suspected breast cancer from bi-rads	555	2B
Jimenez-Rodriguez., 2022 [12]	Cross-sectional	ctDNA	Mammography	Patients with bi-rads 4C/5	97	2B
Yu *et al.*, 2019 [13]	Meta-analysis	ctDNA	Mammography	Patient with suspected BC	1807	2A
Guo *et al.*, 2021 [14]	Meta-analysis	ctDNA	Mammography	Patient with suspected BC	7198	2A

Study	Type of study	Intervention	Comparison	Population	Sample size	LoE
Lin *et al.*, 2017 [15]	Meta-analysis	ctDNA	Mammography	Patient with suspected BC	3018	2A

LoE: Level of evidence

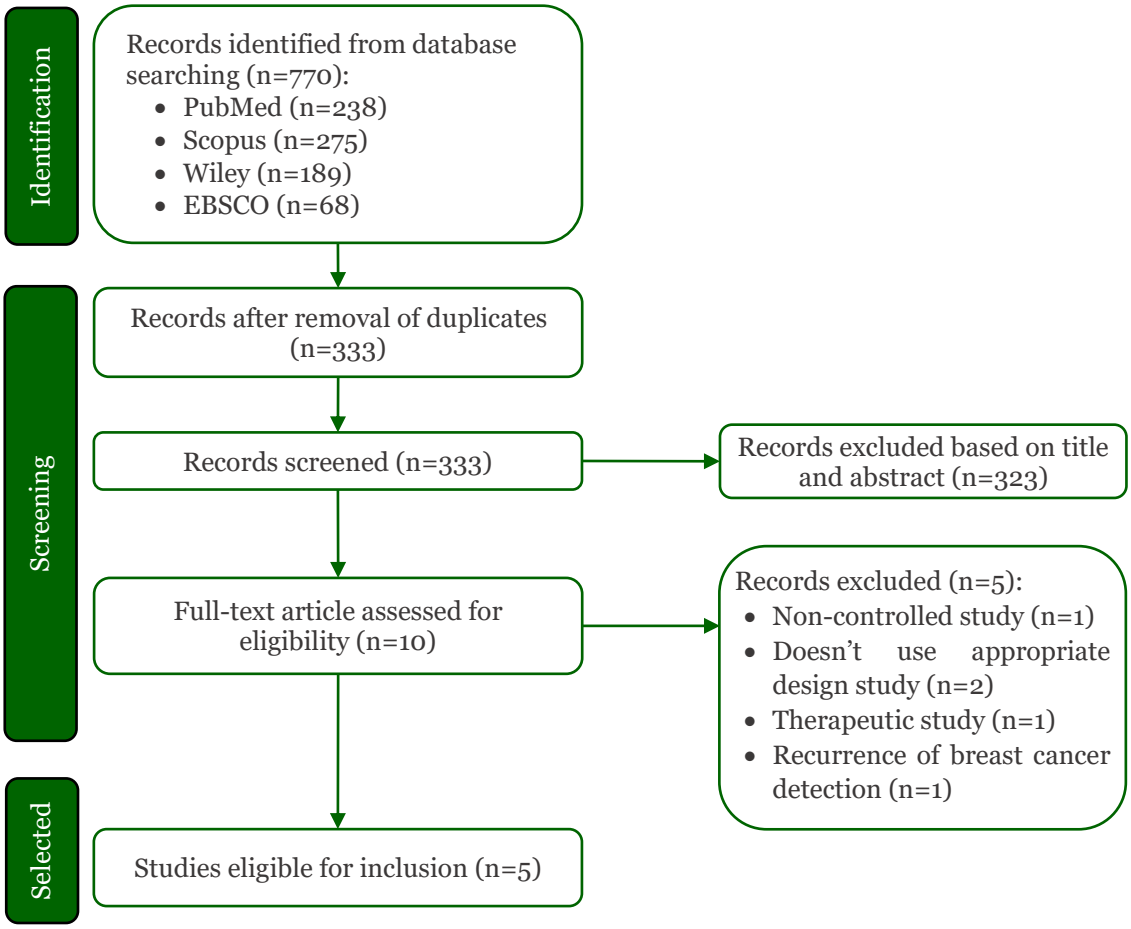

Figure 1. Flow chart summarizing the selection of studies reporting the comparison between ctDNA and mammography.

Results of critical appraisal

The validity of each study was checked using the criteria of gold standard, blinding, and appropriateness of the population which is presented in **Table 3**. After the appraisal, we concluded that one cross-sectional study [11] was not valid because the gold standard test (mammography) was not applied to all subjects. Therefore, this study included only one primary study and three systematic reviews on the importance of appraisal. In the primary study, the sensitivity and specificity of ctDNA were 31.08% and 86.36%, respectively, with a positive predictive value (PPV) of 88.46% and negative predictive value (NPV) of 55.56%. The sensitivity of ctDNA ranged from 75% to 94% and the specificity from 79% to 89% in three meta-analysis studies [12–15]. The clinical significance results are presented in **Table 4**.

Table 3. Critical appraisal results for the validity of the diagnostic cross-sectional study

Study	LoE	Validity Criteria			
		Gold standard	Blinding	Appropriate population	Applied to all subjects
Wang *et al.*, 2021 [11]	2b	Yes	Yes	Yes	No
Jimenez-Rodriguez *et al.*, 2022 [12]	2b	Yes	No	Yes	Yes
Yu *et al.*, 2019 [13]	2a	Yes	Yes	No	Yes
Guo *et al.*, 2021 [14]	2a	Yes	Yes	No	Yes
Lin *et al.*, 2017 [15]	2a	Yes	Yes	No	Yes

LoE: Level of evidence

Table 4. Critical importance of the diagnostic study

Study	Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR (%)	Pre-test prob (%)	Pre-test odds (%)	Post-test prob (%)	Post-test odds (%)
Jimenez-Rodriguez *et al.,* 2022 [12]	31.08	86.36	88.46	55.56	2.28/0.80	77.31	3.41	7.76/ 2.72	0.89/ 0.73
Yu *et al.,* 2019 [13]	94	89	92.6	90.77	8.55/0.07	77.31	3.41	29.12/ 0.23	0.97 /0.19
Guo *et al.,* 2021 [14]	80	88	90.5	75.32	6.67/0.23	77.31	3.41	22.71 /0.77	0.96/ 0.44
Lin *et al.,* 2017 [15]	75	79	84.32	67.7	3.57/0.32	77.31	3.41	12.17/ 1.08	0.92 /0.52

LR: Likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; Sn: sensitivity; Sp: specificity

Discussion

The present evidence-based case report's aim was to identify whether the sensitivity and specificity of ctDNA is as good as mammography for breast cancer diagnosis in suspected patients. Our main findings showed that the sensitivity and specificity of ctDNA ranged from 31.08% to 94% and 79% to 89%, respectively. We critically appraised five studies according to our predetermined selection criteria. We considered one individual study and three meta-analyses to be valid. The other individual study is not valid because not all subjects were assessed by mammography as its reference standard [11]. However, there are other studies that need to be highlighted too. The blinding was not mentioned in the individual study [12]. In all meta-analyses by Yu *et al.* [13], Guo *et al.* [14], and Lin *et al.* [15], not all of the included studies were of high quality. According to Yu *et al.*, most studies were of moderate to high quality; however, the index test in 12 out of 13 studies had a high risk of bias, despite the overall quality of the included studies being generally robust [13]. In Guo Q (2021), all components of risk of bias were either unclear or had a high risk, particularly in patient selection [14]. Nevertheless, the majority of the enrolled studies fulfilled the baseline criteria. In Lin *et al.*, two studies included fewer than 20 cancer patients, which may have contributed to the poor robustness [15]. Also, the inclusion of only English-language studies might have introduced bias to the analysis.

In terms of the importance of the studies, all of them reported high specificity for ct-DNA in diagnosing breast cancer. The individual study reported a specificity of 86.36%, while the meta-analyses showed pooled specificities of 89% [13], 88% [14], and 79% [15]. This high specificity indicates the potential of ct-DNA in diagnosing breast cancer in suspected patients. However, the sensitivity varied across studies, with the individual study reporting a sensitivity of 31.08%, while the meta-analyses showed sensitivities of 94% [13], 80% [14], and 85% [15]. Jimenez-Rodriguez *et al.* reported lower sensitivity, attributed to challenges in detecting ctDNA in localized breast cancer, even in pretreatment blood samples [12]. The PPV and NPV ranged from 84.32% to 92.6% and 55.56% to 90.77%, respectively [12–15].

Currently, mammography, as the gold standard method used for early detection of breast cancer, can reduce mortality by up to 30% [13]. However, 13% of breast cancer was not detected while using full-field digital mammography due to some factors such as overlapping with dense fibroglandular tissue, tumor size, and patient's age [16,17]. Mammography screening is recommended for the general population ages 40 or older [18]. Women with possible hereditary risk of breast cancer are recommended to start screening at a younger age [19]. In addition, mammography may cause over-diagnosis and radiation-induced disease in false positive cases. The limitations of mammography can also be seen in the small percentage of cases that require additional testing to detect specific areas of the breast. False negative cases also occur in approximately 1 in 8 patients, especially with dense breast tissue [20].

Based on the five studies we appraised, ctDNA detection as a diagnosis tool for breast cancer offers several advantages. Some of the advantages of ctDNA include its ability to detect residual disease and identify resistance to certain drugs, allowing for the application of early diagnosis [21]. The high level of accuracy and specificity in the qualitative analysis of tumors also play an important role in confirming breast cancer in suspected patients, although there is a level of inconsistency that still needs to be further investigated in a larger study [22]. The development

and growth of the disease can also be determined based on ctDNA analysis [21]. This diagnostic tool is easy to use, rapid, and non-invasive [15]. ctDNA has relatively good sensitivity (except in the study by Jimenez-Rodriguez *et al* [12].) and high specificity [23].

Based on the information presented, ctDNA can be considered as a diagnostic tool, with clinical considerations taken into account. To improve sensitivity, larger studies with appropriate populations are needed to clarify the consistency of this diagnostic tool. However, its specificity for diagnosis appears promising. In Indonesia, there is potential for high adoption due to its simplicity and potential cost-effectiveness, especially considering the economic differences in the region, which may lead to future price reductions for this tool.

Conclusion

In conclusion, the sensitivity and specificity of ctDNA are comparable to those of mammography for diagnosing breast cancer in suspected patients. Circulating tumor DNA (ctDNA) can be used as an additional diagnosis tool, particularly for individuals aged 40 years and older, due to its high specificity. While mammography remains the primary diagnostic method, ctDNA offers a valuable complement. Currently, ctDNA is not widely used in Indonesia, as it is not yet a standard diagnostic tool. However, it holds significant potential for broader implementation in the country due to its simplicity, non-invasive nature, and availability of relatively affordable equipment, such as polymerase chain reaction.

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Nothing to declare.

Competing interests

Nothing to declare.

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Underlying data

All underlying data have been presented in this article.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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