https://doi.org/10.59459/1859-1655/JMM.345

CIRCULATING PROTEINS AS DIAGNOSTIC BIOMARKERS IN BREAST CANCER

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ABSTRACT

Purpose: *Summary of tumor-produced circulating proteins as biomarkers in breast cancer (BC) detection.*

Subjects and method: *A meta-analysis of 50 researches on protein biomarkers in BC diagnosis.*

Results: *Many studies have shown that tumors continuously release components such as protein, RNA, and DNA into the bloodstream during apotosis. There are different protein markers, as tissue markers and serum markers involved assisting diagnosis, but none of them can independently establish the final diagnotic BC at an early stage. Therefore, scientific communities have been putting lots of effort to discover biomarkers for better identifying this malignant disease at earlier stages.*

Keywords: Breast cancer, biomarkers, diagnosis, protein.

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Receipt date: October 27, 2023; scientific review: November 2023; accepted: December 15, 2023.

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1. INTRODUCTIONS

Despite the advancement of many approaches in diagnosis, BC is the leading cancer diagnosed worldwide and the main cause of cancer death in women [1]. Among of various BC identifying platforms (figure 1), imaging techniques are central diagnosis tools for either establishing the final diagnosis or/ and patients' follow-up [2, 3]. Mammography (MG) is commonly used for screening of breast tumors, although it has some limitations, such as a low sensitivity for cancer detection in younger females with dense breasts and radiation exposure [2, 4, 5]. It has also reported nearly 30% of unnecessary tumor biopsy processes due to high rates of over-diagnosis of MG [2]. Besides, MRI is found as other powerful diagnostic tool for BC with high-cost, and the use of iodine-based contrast can cause toxicity. Therefore, novel biomarkers are needed to complement defects of present screening systems.

Currently, traditional serum biomarkers such as CEA, CA15-3, CA27-29 which are recommend for disease and therapy monitoring although lack of sensitivity and accuracy [3].

In 2013, the the US Food and Drug Administration (FDA) approved the CellSearch system for measuring circulating cancer cells (CTCs) to monitor advanced metastatic BC. FoundtionOne Liquid CDx was also authorized to detect genomic alterations from patients'blood in multiple solid tumors and applying for tageted therapy. Regardless of the growing acceptance in clinical, liquid biopsy testing is now confined to advanced-stage cancer management [6, 7]. Clinical adoption is currently restricted, particularly in BC detection, while a deeper understanding of liquid biopsy is predicted to offer a possibility for its effective use in clinical practice.

In this review, we summarized the growing evidence of circulating proteins that are data specific for BC and could be applied in clinical setting as a potential strategy for early detecting malignant breast tumors.

2. SUBJECTS AND METHODS

2.1. Subjects

We obtained 250 published articles. After removing duplicates, 121 publications were assessed for relevancy based on their titles and abstracts. We eliminated 109 articles that did not meet our inclusion criteria. The remaining 50 papers underwent full-text retrieval to ensure they were eligible for the final analysis. The final analysis contained 12 articles that matched the review's inclusion criteria.

- *Inclusion criteria*: Diagnostic test studies using serum or plasma proteins for breast cancer diagnosis at early stage, peer-reviewed articles on our topic of interest.

- *Exclusion criteria*: Studies were excluded if (a) the sample used for analysis was not blood (b) samples were analyzed post-surgery or post-therapy, and (c) autoantibody detection was not applied for early detection/ diagnosis.

2.2. Methods

- *Search criteria:* PubMed/MEDLINE, Scopus, Proquest, Ovid SP, and Cochrane Library were searched for relevant articles. Key words used were 'breast cancer', 'breast carcinoma', 'serum',

'biomarker', 'blood', 'screening', 'detection', 'early detection', and 'diagnosis'. The search was updated till December 2022.

- *Quality assessment of included studies*: Full text articles of the selected studies were assessed for quality with the help of a tailored quality Assessment of diagnostic accuracy studies (QUADAS)-2 tool.

- *Data analysis*: Primary exploratory analyses were carried out with RevMan 5.3. This included quality assessment summary of eligible studies, producing paired forest plots of sensitivity and specificity and summary receiver operating characteristic (SROC) curves.

3. RESULTS AND DISCUSSIONS

Many analyses have shown that practically all tumors leak their constituents into the bloodstream; so, blood may be utilized to examine biomolecules derived from tumors [8]. Researches have concentrated on blood-based biomarkers, such as proteins reviewed previously as well as listed in table 1, which are less intrusive, convenient to determine routinely, and appear to be an option for BC screening [9,10].

Table 1. Summary of sensitivity and specificity of circulating proteins in diagnosis of BC.

Biomarkers	Stage	Subject	Sample	Techniques	Se	Sp	AUC	References
Trx1	I-IV	106	Serum	ELISA	97.17%	94.15%	0.99	Youn Ju Lee et al. 2022 [11]
IL-7	I-III	213	Serum	ELISA	88.9%	90.9%	0.942	Faton Sermaxhaj et al. 2022 [12]
ITGA2B, FLNA, RAP1A, TLN-1	I-IIIa	60	Serum	Nano-particle	100%	85%	0.93	Fredolini và CS sự. 2020 [13]
8-iso-PGF2α	I-IV	65	Serum	ELISA	100%	99.2%	0.999	Essam Eldin Mohamed Nour Eldin et al. 2020 [14]
CEACAM1, resistin, visfatin	I-IV	135	Serum	ELISA	93.3% 83.3% 80.0%	82.5% 97.5% 85.2%	0.92 0.96 0.86	Tarek MK Motawi et al. 2020 [15]
MUC2	I-IV	127	Serum	ELISA	74.8%	75%	0.82	Suleyman Bademler et al. 2019 [16]
CEBPA, EP55, GATA3, HRAS, PTCH1, RalA	I-IV	120	Serum	Protein microarray	78.9%	90.2%	0.916	Cuipeng Qiu et al. 2021 [17]
CCN1	I-III	544	Plasma	ELISA	80%	99 %	0.901	Kai Bartkowiak et al. 2022 [18]
Ang-2	I-III	143	Serum	ELISA	78.3%	77%	0.836	Ping Li et al. 2015 [19]
GAL3, PAK2, PHB2, RACK1, RUVBL1	I-III	114	Serum	ELISA	66%	87%	0.81	Jeroˆme Lacombe et al. 2013 [20]
CA15-3, CYFRA21-1, TFF1	I-III	60	Serum	ELISA	95%	83.3%	0.892	Feng Xue et al. 2022 [21]
N-glycans	I-IV	328	Serum	MALDI-TOF mass spectroscopy	82.3%	84.1 %	0.93	Sae Byul Lee et al. 2020 [22]

- Thioredoxin 1 (Trx1): Trx1 regulates transcription factor DNA binding activity, which is crucial for cancer cell growth [23]. Despite the fact that Trx1 is likely expressed in a range of malignancies as well as in women without cancer, the most significant difference in Trx1 levels between sera from women without cancer and cancer participants was discovered in BC [26]. According to a recent study, the cut-off value for Trx1 for distinguishing BC patients from the group of women without cancer was 11.4 ng/ml, with sensitivity and specificity of 97.17 and 94.15%, respectively. Notably, in combination with mammography, the test exhibited a outstanding diagnostic performance with the sensitivity and specificity escalated to 98.06 and 100.0%, respectively. Moreover, BC patients were identified based on the level of Trx1 in their sera, which was unaffected by age, stage, histological grade and molecular subtypes [11].

- Interleukin-7 (IL-7): IL-7 is a cytokine that is extremely important to the immune system. It promotes lymphocyte development in the thymus

and lymph node organogenesis, as well as the maintenance of activated T cells in secondary lymphoid organs. Because IL-7 is responsible for T lymphocyte development, growth, and maturation, a low level of T lymphocytes in cancer patients may be one reason for the increase in circulating IL-7 levels. It is now known that IL-7 promotes the growth of a variety of cancers [27]. However, there is a scarcity of data comparing serum IL-7 levels in early BC (EBC) patients to healthy controls. In a study conducted on 213 BC patients, researchers discovered that EBC patients had significantly higher IL-7 serum levels than healthy control cases ($p < 0.001$). IL-7 serum levels, on the other hand, have not been linked to tumor size, lymph node metastasis, or tumor progression regardless of age or menopausal status of the patients [12]

- 8-Iso-prostaglandin F2α (8-iso-PGF2α): Increased lipid peroxidation and the absence of antioxidants, combined with oxidative stress, have been related to breast tumorigenesis in BC studies [26, 27]. Lipid peroxidation is the most well researched free radical-inducing process linked to cancer, assisting in the creation of numerous relatively stable breakdown products, such as isoprostanes, which serve as indirect cellular pro-oxidant indicators in bodily fluids [28-31]. Because of structural stability, nondietary and endogenous antioxidant-modulated characteristics, and simplicity of detection in bodily fluids, 8-iso-PGF2 is recognized as a noninvasive analytical technique for detecting endogenous lipid peroxidation [32]. As a result, they may accurately represent the body's oxidative stress. In 2019, by analysis serum 8-iso-PGF2α in 65 malignant BC, a high diagnostic performance of this test in BC was reported (AUC = 0.999, sensitivity = 100%, specificity = 99.2% at a cutoff value of 36.18 pg/mL). Additonnally, Serum 8-iso-PGF2 was found to be positively correlated with carcinoembryonic antigen ($r = 0.74$, $p = 0.001$) and cancer antigen 15-3 ($r = 0.80$, $p = 0.001$) but disconnect with the progression of the BC stages [14].

- Carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM1), resistin and visfatin: Endothelial cells, B cells, interleukin activated T cells, the gastrointestinal system, the breast, the prostate, and the endometrial all generate CEACAM1. It was identified to influence cellular proliferation, apoptosis, angiogenesis, invasion, and migration to regulate tumor formation [33]. Resistin participates in autocrine and paracrine cell signaling and may shed light on cancer origin, development, regression, and persistence pathways [34]. Visfatin is implicated in inflammation, a variety of metabolic and stress responses, and cellular energy consumption [35]. Visfatin, according to Park and colleagues, increased the levels of NF-B p65 and Notch1 in BC cells [36]. Another study reveals that higher visfatin levels may accelerate BC development and impair medication effectiveness in BC patients. The serum levels of CEACAM1, resistin, visfatin in 135 patients with BC were quantified through ELISA in 2020. BC patients showed larger amounts of CEACAM1, resistin, and visfatin than the normal control and benign groups. These biomarkers' cutoff values, sensitivities, and specificities were effective in early separating BC from controls. Furthermore, serum visfatin levels are higher as tumor size and BC stage increased [15]. An earlier study revealed that the mean serum visfatin level was vastly higher in BC patients than in controls, indicating that it may be used as a biomarker for postmenopausal women [37].

- Membrane-bound mucin 2 (MUC2): MUCs (membrane-bound mucins) are cell surface receptors for a range of signaling pathways, the expression of which changes in a variety of clinical settings, including cancer. Mucin's particular glycosylation pattern causes hypersecretion in cancer, where it serves as a binding substrate for a variety of growth factors and cytokines, boosting malignant cell proliferation and metastasis via many signaling pathways [38]. MUC2 is a secretory mucin found mostly in the digestive and respiratory systems. MUC2 upregulation has been seen in pancreatic, breast, colorectal and prostate mucinous carcinomas [39-42]**.** Suleyman Bademler et al. used ELISA to measured the levels of MUC2 in 127 BC sera. BC patients had a considerably higher median serum MUC2 level than controls (198 vs. 54 ng/mL, $p< 0.001$). MUC2 levels in the blood were not related to survival ($p = 0.65$). Although blood MUC2 levels may be diagnostic, no predictive or prognostic effect in survival in BC patients was found [16].

- Cellular communication network factor 1 (CCN1): CCN1, also known as cysteine-rich angiogenic inducer 61, is an extracellular matrix-associated signaling protein of the CCN family. Through interactions with cell surface integrin receptors, CCN1 governs a wide range of biological activities, including cell adhesion, migration, and differentiation [43]. Kai Bartkowiak et al. used an ELISA to assess plasma CCN1 levels in 544 women with BC at the time of first diagnosis, prior to neoadjuvant treatment or surgery. Clinical blood samples from patients with BC and age-adjusted healthy controls were analyzed for cancer detection, yielding an overall specificity of 99.0% and sensitivity of 80.0%. Surprisingly, CCN1 was already present in 81.5% of small T1 tumors, but CCN1 concentrations in individuals with benign breast lesions were below the detection threshold for BC [18].

- Angiopoietin-2 (Ang-2): Angiopoietins (Angs) are endothelial growth factors that have been demonstrated to bind to the endothelium-specific tyrosine receptor Tie-2. Angiopoietin 2 (Ang-2) was discovered as an antagonist for Ang-1 activation of Tie2, which influences vascular stability. Increased Ang-2 expression has been associated to the invasive and metastatic properties of various types of human cancers, including breast tumors [46]. Sfiligoi C et al. previously discovered that elevated Ang-2 expression in BC tissues was associated with lymph node invasion and short survival [45].

In a study conducted in 2014, the serum Ang-2 concentration was investigated through ELISA. The team found that the concentration of serum Ang-2 was substantially greater in BC patients than in healthy controls (3171 ± 1024 vs. 1800 ± 874 pg/ml, $p < 0.0001$). With an area under the curve (AUC) of 0.836 ($p = 0.001$, 95% confidence interval: 0.787-0.885), blood level of Ang-2 exhibited a sensitivity of 78.3% and a specificity of 77.0% for discriminating BC patients from healthy controls at the ideal cut-off (2558.5 pg/ml). Furthermore, the high Ang-2 expression patients had considerably shorter 5-year DFS and 5-year OS than those with low Ang-2 expression (46.0% vs. 68.7%; $p = 0.029$; 55.9% vs. 80.3%; $p = 0.018$, respectively) [19].

- N-glycans: N-glycans have critical roles in the development and progression of cancer. Because specific glycoproteins are produced or shed by tumors, serum can contain tumor-associated glycan patterns as well as alterations in protein glycosylation reflecting the host response. According to emerging evidence, protein glycosylation changes in serum have been seen in a number of malignancies, including BC [46]. Sae Byul Lee et al. used MALDI-TOF mass spectroscopy to examine the diagnostic potential of serum N-glycan in 2020. Highly effective pattern identification of patients with invasive ductal carcinoma, with extremely excellent diagnostic performance (area under the curve: 0.93 and 95% confidence interval: 0.917-0.947). Based on N-glycan profiles, effective stage-specific separation of BC subjects (n=256) from healthy participants (n = 311) was obtained with 82.3% specificity, 84.1% sensitivity, and 82.8% accuracy for stage 1 BC and identified hormone receptor-2 and lymph node invasion subtypes [22].

- ITGA2B (integrin subunit alpha IIb), FLNA (Filamin A), RAP1A (Ras-associated protein-1A), TLN-1 (Talin-1): Previous researches have demonstrated that a individual tumormarker frequently fails to capture sensitivity and specificity in determining a specific malignancy, which can be raised in both normal people and in benign diseases. As a result, a collection of biomarkers was evaluated in order to identify the panel with the greatest accuracy in early identifying BC patients from women without cancer [10]. In Claudia Fredolini et al. study, affinity hydrogel nanoparticles coupled with LC-MS/MS analysis was deployed to measure low abundance proteins in serum samples from invasive ductal carcinoma (IDC) patients. A highly specific and sensitive protein signature suggestive of early-stage BC was identified by using a nanoparticle-based protein enrichment method, with no false positives when comparing normal participants. These indicators have previously been described in the context of cell-ECM interaction and tumor microenvironment biology. In the finding batch, 56 proteins were found to be elevated in blood samples from IDC patients, with 32 of these proteins being unique to IDC. A subset of these proteins was validated in an independent cohort of early-stage T1a BC patients, yielding a panel of four proteins, ITGA2B (integrin subunit alpha IIb), FLNA (Filamin A), RAP1A (Ras-associated protein-1A), and TLN-1 (Talin-1) that classified BC patients with 100% sensitivity and 85% specificity (AUC of 0.93) [13].

- Autoantibodies: Evidence of circulating autoantibodies in cancer patients' sera has offered prospects for using the immune system as a generator of cancer biomarkers in recent years. The immune response in cancer patients is initiated by the release of proteins from tumors, which emerge months to years before the clinical diagnosis of a tumor, making serum autoantibody analysis an excellent tool for early cancer detection. However, when employed as a standalone diagnostic assay, most serum autoantibodies have insufficient sensitivity and/or specificity to be used as reliable screening tools [10]. A suggestion has been made to integrate various reactive autoantibodies into a panel test to attain the best degree of accuracy while including the histological heterogeneity of cancer. This method has been verified in numerous separate groups of patients with lung, colorectal, ovarian, and prostate cancer [47]. Although autoantibody biomarkers have been discovered in BC, the majority of them have only been reported in late-stage tumors. Recently research reported an autoantibody panel which might be beneficial as a diagnostic tool in early-stage invasive BC and noninvasive BC screening capabilities. It may be extremely effective as a supplement to mammography for women with dense breasts. Among sixty-seven antigens were discovered that triggered a distinct humoral response in BC, five indicators (GAL3, PAK2, PHB2, RACK1 and RUVBL1) were pooled, they significantly distinguished early-stage cancer from healthy subjects (AUC = 0.81; 95% CI [0.74-0.86]). This value was particularly high in node-negative early-stage primary BC (AUC = 0.81; 95% CI [0.72-0.88]) and ductal carcinoma in situ women (AUC = 0.85; 95% CI [0.76-0.95]) [20]. Additionally, A protein microarray was utilised in another study to detect possible tumor-associated autoantibodies (TAAb) in sera of 319 preoperative and postoperative. A panel of six TAAb (CEBPA, CEP55, GATA3, HRAS, PTCH1, RalA) has the capacity to identify BC with an AUC of 0.916 (78.9% sensitivity, 90.2% specificity). The AUC of the panel was 0.920 and 0.934 for discriminating stage I-II and patients under the age of 50 from healthy group, respectively [17].

- CA15-3, CYFRA21-1, TFF1: CA15-3 and CYFRA21-1 are frequent serological markers. CA15-3 is a characteristic serum marker for BC and is helpful in guiding BC diagnosis and surveillance, but CYFRA21-1 has some sensitivity for progressive BC and can complement CA15-3 in clinical examination [48]. Furthermore, current research has discovered TFF1- a member of the trefoil factor family, which plays a significant part in a variety of physiological activities in the body; normally, it is less expressed in the mammary gland, and overexpression causes female estrogen inequality problem and raising the proliferation of breast tissue cells and eventually

causing BC [49]. TFF1 can be employed in the diagnosis and efficacy evaluation of BC. Integrating breasts MRI with serum CA15-3, CYFRA21-1, and TFF1 has high efficacy in identifying BC, according to Feng Xue et al. observation in 2022, and may be used in clinical diagnosis of BC. The levels of CA15-3, CYFRA21-1, and TFF1 were distinguishable between the BC, benign, and normal groups (33.81 ± 12.46 vs 19.02 ± 6.47 vs 9.55 ± 2.64, 4.08 ± 1.41 vs 1.96 ± 1.19 vs 0.99 ± 0.21, 1.39 ± 0.54 vs 1.04 ± 0.26 vs 0.89 ± 0.12, $p < 0.05$); A coordinated test diagnosed 57 BC patients with a sensitivity of 95.0%, specificity of 83.3%, positive predictive value of 74.0%, negative predictive value of 97.1%, accuracy rate of 87.2%, and AUC of 0.892, inferring that the combined test had a significantly higher diagnostic performance than a single testing by CA15-3, CYFRA21-1, TFF1, or MRI [21].

4. CONCLUSIONS

In terms of early diagnosis and screening for breast cancer, various blood-based indicators are anticipated to be clinically employed as easily accessible and less invasive alternatives or supplements to conventional screening procedures such as mammography. Several plasma- and serum-based indicators have superior sensitivity and specificity than imaging-based approaches or traditional biomarkers CA15-3, CA27-29, making them excellent diagnostic tools for breast cancer, as reported in the literatures**.** Based on the evidence given by multiple observational studies, it is certain that circulating biomarkers offer significant potential, albeit with a small number of subjects**.** Therefore, more testing on independent sample sets from multicenter clinical trials comprising large series of breast cancer patients is required to give greater proof of these biomarkers' relevance for BC screening and early diagnosis.

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