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Circulating Protein Biomarkers in Breast Cancer: Clinical Significance and Integration with Molecular Signature

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1. Abstract

Breast cancer is biologically heterogeneous; the best way to manage the disease is to have biomarkers that represent the fixed molecular phenotype of the tumor in addition to a dynamic over time behavior of the tumor. Measurable protein circulating biomarkers, which are readily available in the minimally invasive blood, provide insight into tumor burden, shedding, microenvironment interactions, and host response. The presence of these markers, including CA 15-3 and CA 27.29, has historically been used to monitor metastatic disease. In contrast, serum HER2 extracellular domain (sHER2 ECD) and circulating tumor cells (CTCs) have also been found to be prognostic or predictive in some settings. The technology of proteomics and immunoassay has increased the repertoire of candidate circulating proteins, such as immune-related cytokines, extracellular matrix proteins, and tumor-derived antigens. Nevertheless, a low number of these candidates have been adopted into clinical practice. On the other hand, the central focus of therapy stratification in breast cancer at an early stage is tissue-based molecular assays, including the 21-gene (Oncotype DX) and 70-gene (MammaPrint) signature. Hence, the combination of dynamic serology markers and static tissue genomic profiles can potentially offer personalized and responsive management of patients. This review critically covers and discusses known and novel circulating protein biomarkers, discusses technical and clinical issues, as well as suggests a model of combining serological biomarkers with molecular signatures in the future management of breast cancer.

2. Introduction

Breast cancer is not a disease, but a group of biologically and clinically diverse subtypes determined by hormone receptor status (estrogen receptor -ER and progesterone receptor -PR). Conventionally, clinical decision-making based on clinical biomarkers in breast cancer has been heavily based on tissue-based assays. These tests, though, are a one-time picture of the biology of the tumor (biopsy or surgery), and fail to capture any dynamic changes that happen throughout treatment or as the tumor devel-

ops. A less invasive option is circulating biomarkers, which are released by tumor cells or by the host as a result of the tumor, and which can be used to provide real-time disease monitoring. Various circulating proteins are now emerging as promising biomarkers with the development of ELISA and multiplex immunoassays, and mass-spectometers proteomics. This review synthesizes current evidence on circulating protein biomarkers in breast cancer and how they may complement tissue-based molecular signatures (Table 1).

Table 1

Biomarker / Assay	Type	Clinical / Investigational Use	Strengths	Limitations
CA 15-3, CA 27.29	Serum protein (MUC1)	Monitoring metastatic disease	Widely available; minimally invasive; serial measurement possible	Low sensitivity for early disease; poor specificity; inter-assay variability
sHER2 ECD	Serum protein (HER2 shed domain)	Prognosis, monitoring, and possible therapy selection	Reflects tumor HER2 shedding, dynamic over time, and prognostic data in meta-analyses	Variable shedding; assay cut-offs not standardized; not yet guideline-recommended
CTC enumeration (CellSearch or other platforms)	Cellular	Prognosis (PFS, OS); potential disease monitoring	Prognostic across early & metastatic disease; non-invasive; serial sampling	Rare cells, low sensitivity; platform variability; no standard clinical guidelines for action
Proteomic candidate panels (cytokines, ECM proteins, tumor antigens)	Serum/plasma proteins	Research / emerging prognostic/predictive biomarkers	Potential to reflect microenvironment, immune response, and metastasis biology	Low specificity; high variability; lack of standardization; limited validation
Tissue ER / PR / HER2 (IHC / FISH)	Tissue biomarker	Therapy selection (endocrine / anti-HER2)	Standard, validated, guideline-driven	Static; requires tissue; cannot capture dynamic changes
uPA / PAI-1 (tumor extract)	Tissue protein	Prognosis in node-negative early BC; guide chemo decisions	Level-1 evidence from prospective trials	Requires fresh/frozen tissue; not universally available; not blood-based
Gene-expression signatures (Oncotype DX, MammaPrint)	Tissue-derived mRNA panels	Risk stratification; adjuvant chemotherapy decisions	Validated prognostic and predictive value; widely used	Static, single-timepoint; tissue requirement; cost
Germline markers (e.g., DPYD genotype)	Germline DNA / enzyme assay	Pharmacogenetic guidance (e.g., 5-FU toxicity)	Predict therapy toxicity; improves safety	Not tumor-specific; does not inform disease biology

3. Classical Circulating Proteins Biomarkers

3.1. CA 15-3 and CA 27.29

CA 15 and CA 27.29 are MUC1-derived circulating markers commonly measured in breast cancer. They are, however, less sensitive and specific than required to screen or diagnose at an early stage. Consequently, clinical do not recommend these markers for routine recurrence surveillance; they are mainly used in metastatic disease [1]. Although serial trends could be useful in the metastatic environment, CA 15-3 and CA 27.29 lack sufficient use as single markers due to limited analytical reliability.

3.2. Other Classical Serum Markers: Cytokeratin Fragments, CEA.

Carcinoma serum markers like carcinoembryonic antigen (CEA), cytokeratin fragments (e.g., CYFRA 21-1) have also been tested in breast cancer. On the same note, the cytokeratin fragments have been explored but lack clinical utility [2,3]. Consequently, CA 15-3/CA 27.29 are the only classical serum protein biomarkers that can be used consistently, albeit not extensively, clinically, namely, in the metastatic setting.

3.3. HER2 ECD and Emerging Serum Markers

Serum HER2 Extracellular Domain sHER2 ECD) One such potentially useful next-generation serum biomarker is the extracellular domain of HER2 (sHER2 ECD), which can be released by tumor cells into the bloodstream. In a meta-analysis of 23 studies (~8,230 patients), increased baseline sHER2 ECD was correlated with a significantly worse overall survival (HR 2.28, 95% CI 2.002.61) and progression-free, disease-free and time-to-progression endpoints [4]. These results imply that sHER2 ECD could be useful in forecasting the prognosis and predicting the choice or follow-up of HER2-targeted therapies, such as trastuzumab, but not necessarily TKIs. Some studies suggest changes over time may have prognostic value [5]. Lack of cut-off consistency and assay variation limit clinical adoption.

3.4. Additional Emerging Serum Markers: MMPs, VEGF, ECM and Immune Proteins.

- Matrix metalloproteinases (MMPs, principally, MMP-9) are linked with extracellular degradation, invasion and metastasis. In some studies, the MMP-9 in patients with brain metastasis was higher than in [6].

- Angiogenic factors include vascular endothelial growth factor (VEGF). High levels of VEGF in circulation could indicate neovascularization in proliferating tumors.
- Extracellular matrix and adhesive protein (e.g., osteopontin), which are associated with metastasis and bad prognosis in a number of cancers, such as breast cancer [7].
- Antigen proteins of tumor or cell surface, i.e., mesothelin (in some triple-negative or HER2-negative cancer) [8,9].
- Immune-related proteins: cytokines of inflammation (e.g. IL-6, IL-8), chemokines, acute-phase proteins; they may indicate tumor-induced inflammation, immune suppression or activation - particularly in microenvironment and metastatic niche biology.

None of these has so far acquired routine clinical application in breast cancer in spite of intensive research. Some of the reasons are high inter-individual and pre-analytical variability (e.g., sample collection, storage), absence of standardized assays, low specificity (many of them are increased in non-cancer inflammatory or benign conditions) and no large-scale validation. Therefore, sHER2 ECD is the most plausible pewter-generation active serum mark in the meantime.

4. Liquid Biopsy and Circulating Tumor Cells (CTCs)

4.1. Prognostic Value of CTE Enumeration

Enumeration of circulating tumor cells (CTCs) using the CellSearch system, which is FDA approved, has been widely researched in the case of breast cancer. This prognostic value was confirmed by many other studies afterwards, and it resulted in meta-analyses. A large meta-analysis of 49 (6,825 patients) studies demonstrated that the existence of CTCs was connected with the absence of survival in early and metastatic conditions (DFS HR 2.86, OS HR 2.78 early disease, PFS HR 1.78, OS HR 2.33 metastatic disease) [10]. The other meta-analysis used metastatic breast cancer (MBC) (24 studies, 3,701 patients) and found that high CTC counts are associated with poor treatment response (RR 0.56), poor PFS (RR 0.64) and poor OS (RR 0.69) [11]. Longitudinal studies also indicate that the early alteration in CTE count, e.g., following the start of therapy, can give an indicator of the radiological response or progression, a sort of real-time biomarker. Notably, CTC counting provides dynamic data and can solve the constraints of the traditional tissue biopsies: sampling is minimally invasive, can be repeated, and can indicate tumor progression, resistance to therapy, or new clone development.

4.2. Limitations and Challenges of CTC-based Biomarkers

Nonetheless, there are many obstacles to the widespread use of CTCs:

- Poor sensitivity and infrequency — CTCs are infrequent (they may be only a fraction in 7.5 mL blood), and thus detection is sensitive to enrichment and technical factors. Even though the approved CellSearch by the FDA is based on EpCAM (epithelial cell adhesion molecule) expression, cells that had undergone epithelial-mesenchymal transition (EMT) could suppress EpCAM and escape detection. Recent studies emphasize that new approaches (microfluidic, physical enrichment) can be used to achieve higher detection rates, yet most of them apply unvalidated cut-off points and non-homogeneous protocols [12].
- Heterogeneity of CTCs - CTCs may be heterogeneous (genetically and phenotypically), and they may form clustered groups (CTC clusters), thus making biology and prognosis more complex. Other studies indicate that CTC clusters are linked to worse outcomes as compared to single CTCs [13].
- Standardization and reproducibility - inter-laboratory variability, variation in definitions of both CTC-positive and the multiplicity of platforms, make comparability challenging.
- Poor clinical utility in areas other than prognosis - although numerous studies report other clinical utilities correlate with survival, few studies have demonstrated that altering therapy on the basis of CTC counts enhances survival, and many prospective studies examining whether CTC-directed therapy can add to survival or quality of life continue.

Therefore, similar to circulating proteins, CTCs are very promising but yet to be confirmed as a standard-of-care biomarker beyond research or specialized centers.

4.3. Proteomics-Identified Novel Circulating Biomarkers

Many putative circulating proteins have been proposed as breast cancer biomarkers with the progress in high-throughput proteomics (mass spectrometry, multiplex immunoassays) and bioinformatics and represent tumor biology, microenvironment remodelling, immune response, invasion, angiogenesis, and resistance to therapy.

Some of the most researched (or promising) of these are:

- Extracellular matrix and invasion proteins: Osteopontin (OPN), matrix metalloproteinases (e.g., MMP-9), collagens, adhesion molecules. High serum or plasma osteopontin has also been linked to metastasis, resistance to therapy, and worse outcomes in retrospective cohorts, but the data are still not consistent (Xu et al., 2015) [7]. The level of MMP-9, potentially in conjunction with sHER2, was elevated in patients with breast cancer who had brain metastases [14].
- Tumor-associated antigens / cell-surface proteins: Mesothelin protein has been a target in serum or exosomal mesothelin as a biomarker, but it is only validated in a limited number of studies [8], with respect to triple-negative breast cancer.
- Growth factor ligands and binding proteins: Circulating amphiregulin (AREG), proliferative signaling or endocrine resistance or microenvironmental modulation may be represented by insulin-like growth factor binding proteins (IGFBP2/3).
- Immune and inflammatory proteins: Cytokines (e.g., IL-6, IL-8), chemokines, acute-phase proteins - indicative of tumor-induced inflammation, immune suppression or activation, or host response. These indicators may indicate a change in the microenvironment or the premature metastatic niche.

• Proteomic signatures or protein panels: A few studies have employed a mass-spec-generated protein panel of proteins (e.g., a combination of ECM proteins, secreted glycoproteins, and acute phase reactants) to investigate prognostic or diagnostic signatures. Nevertheless, not many of them have been independently validated or prospectively tested.

• In spite of the fertile proteomic discovery space, there have been barriers to the translation of proteomic discoveries to clinical use:

• Standardization of assays: There is a large amount of studies in which various platforms (mass spec, ELISA, Luminex), sample types (serum and plasma), and processing protocols (resulting in varying results) are used.

• Pre-analytical variability: Protein concentrations can be highly influenced by sample collection, handling, storage, freeze-thaw cycles, hemolysis, time-to-processing and comorbidities in the patient (e.g., inflammation, infection).

• Low specificity: Numerous candidate proteins are not cancer-specific (e.g., cytokines, ECM proteins) and whose increase may be observed in benign disease, inflammation or even normal physiologic conditions (aging, comorbidities).

• Absence of high-scale validation: The majority of the studies are small, retrospective, or exploratory. Seldom have there been large, well-controlled, prospective cohort studies (including longitudinal sampling, standardized procedures and clinically relevant endpoints) that have been completed.

• Lack of clarity regarding incremental value: It is still unclear whether candidate proteomic markers provide any meaningful additional prognostic/predictive value to already existing clinical, pathological, and molecular (tissue) markers. Clinical adoption will not happen without showing incremental value.

• Therefore, despite the fact that proteomics is a good and promising field in discovering biomarkers, at present, the clinical potential of CTCs or sHER2 ECD cannot be substituted or comparable to a novel proteomic circulating protein.

4.4. Tissue Biomarkers: Receptor, Genomic Signatures, uPA/PAI-1 - Clinical Context

4.4.1. ER / PR / HER2 (IHC/FISH)

ER, PR and HER2 expression in tumor tissue continues to be the basis of breast cancer phenotyping to govern therapy with endocrine agents or anti-HER2 therapy. Their predictive and prognostic value is well established, and they remain the determinants of the first-line therapy (e.g., endocrine therapy, trastuzumab).

4.4.2. uPA / PAI-1 (Tissue Extracts)

One of the strongest prognostic markers, which has been validated in early, node-negative breast cancer, is serine protease urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1, in tumor tissue extracts. It has been demonstrated by prospective studies and pooled analyses that high levels of uPA/PAI-1 are associated with higher chances of recurrence and can be used to determine patients who benefit from adjuvant chemotherapy [15,16]. Due to this reason, certain expert panels in Europe indicate the uPA/PAI-1 using measurement in order to inform adjuvant therapy, but large-scale use is hindered by technical requirements (fresh/frozen tissue, use of specific ELISA, pre-analytical requirements). This is used as an example benchmark: a biomarker with high prognostic value, which has been confirmed in a prospective study, incorporated into medical practice.

4.5. Gene-Expression Signatures (Oncotype DX, MammaPrint)

Molecular assays, Tissue-based 21-gene recurrence score (Oncotype DX) and 70-gene signature (MammaPrint) have revolutionized the systemic therapy decision-making in early breast cancer. These genomic signatures continue to feature in the center of therapy stratification since they were clinically verified and supported by guidelines. Hence, the use of tissue-based molecular assays cannot exclude the use of dynamic biomarkers, into which circulating proteins and liquid biopsy come into the picture.

4.6. Integrative Model: A Consortium of Circulating Biomarkers and Molecular Signatures

4.6.1. Possible Clinical Situ(s)

Scenario A: A patient who has a low-risk gene signature (e.g., low Oncotype DX) and ER+, HER2 is with low-stage breast cancer initiates adjuvant endocrine therapy. sHER2 baseline is negative, CTCs absent. Follow-up: A rise in sHER2 ECD or a new appearance of CTCs could instigate an imaging or earlier intervention before radiologic manifestation.

Scenario B: When a patient on trastuzumab-based therapy with HER2+ metastatic disease experiences a decrease in the sHER2 and CTC counts, this can be considered a response, and therapy should be switched (e.g., TKI or another anti-HER2 agent should be used); however, increasing sHER2 or re-emerging CTCs might indicate acquired resistance, and the therapy should be changed.

Scenario C: A patient with tumor tissue that did not lend itself to repeat biopsy (e.g., bone-only metastasis). Serial liquid biopsies (sHER2, CTCs, proteomic markers) provide a non-invasive means to monitor illness and direct treatment.

This type of an integrative model may allow customized, dynamic, affordable, and patient-centered management.

4.7. Difficulties, Constraints, and Problematic Matters

Although the integrated model looks promising, there are a number of daunting challenges that should be overcome before it becomes a possibility in routine practice.

1. Assay Standardization and Validation Assay standardization is essential because it allows the researcher to determine the precise scale of the targeted outcome and to evaluate the precision of the method employed to measure the outcome<|human|>Assay Standardization and Validation. Assay standardization is necessary since it gives the researcher the ability to ascertain the

exact magnitude of the intended outcome and to determine the accuracy of the procedure used in gauging the outcome.

Circulating Proteins: There is no consistency in the results due to variability in sample collection, processing, storage, freeze-thaw cycles, and platform (ELISA, Luminex, mass-spec). Most proteomic candidate studies do not have standard operating procedures or controls for reproducibility.

CTCs: There is variable sensitivity and specificity with various enrichment and detection methods (EpCAM-based, size-based, microfluidic, immunomagnetic, etc.). Non-EpCAM-expressing (e.g., EMT phenotype) cells might escape detection. The clusters of CTC make even more complicated the process of enumerating and there is no standardized approach or cut-off to do this across centers (Anderson & Anderson, 2002).

Absence of Prospective Validation: Most of the potential biomarkers of proteomics have not yet been tested in a prospective study, nor on a small scale. Few large and multicenter, prospective studies with standardized protocol, serial sampling and meaningful clinical endpoints (relapse, survival, therapy response) have ever been published. In the absence of such data, clinical utility will be merely hypothetical.

2. Clinical Confounding and Biological Specificity.

Most of the circulating proteins (e.g., cytokines, ECM proteins) are not cancer-specific and may be increased by inflammation, benign disease, comorbid conditions (e.g., liver disease, arthritis), or even physiological processes (aging, tissue remodelling). This lacks specificity in regard to their usefulness as cancer biomarkers. It is still a significant challenge to define a clinically meaningful signal (tumor-associated) vs a noise (non-cancer-associated) signal.

3. Evidence of Clinical Utility.

There is not enough evidence to demonstrate that a biomarker is correlated with prognosis or that it is correlated with tumor burden. Clinically, it is whether or not biomarker-informed decisions, such as changed imaging, change or switch of therapy, or escalation or de-escalation of the same, result in better patient-important outcomes (longer survival, improved quality of life, cost-effectiveness). Up to now, there have been limited trials that have occurred testing biomarker-guided management strategies; therefore, the translational value is unclear.

4. Clinical Workflow Integration.

The proposal of a multi-marker, dynamic monitoring system creates practical, ethical and economic concerns:

- Complexity of interpretation: Oncologists require simple, practical thresholds and guidelines (e.g., when to change imaging or therapy).
- Patient compliance: Doing blood draws periodically can be tedious.
- Benefits Cost-effectiveness: Frequent liquid biopsy + proteomic panels can be costly; incremental benefit versus cost must be considered by payers and health systems.
- Regulatory approval: Biomarkers should undergo regulatory procedures of diagnostic/prognostic tests (analytic validity, clinical validity, clinical utility), such as quality control and standardization.

5. Future Prospects and Research Areas

In order to achieve the promise of circulating biomarker protein in the management of breast cancer as an integrated disease, the following actions are to be given priority:

- Prospective, multicenter, large-scale, circulating biomarker (proteins, CTCs) design trials, in which circulating biomarkers (proteins, CTCs) are collected serially.
- Standardization of assays - establish agreement on sample collection, processing, storage, assay platforms (e.g., tested mass-spec pipelines or immunoassays), cut-off values, and metrics of reporting. Potential formation of global biomarker consortia or reference laboratories.
- Creation of multi-analyte panels - including circulating proteins, CTC enumeration/phenotype, ctDNA (when available), and perhaps exosomal proteins, along with combining it with clinical and molecular (tissue) data, to generate powerful, multi-dimensional prognostic/predictive signatures.
- Potential trials of biomarker-guided therapy - test the hypothesis that interventions based on biomarker changes (e.g., therapy escalation, imaging, earlier salvage therapy) are beneficial to patients compared to standard-of-care.
- Regulatory and Clinical guideline development - once proven, codify guidelines regarding the application of circulating biomarkers (who, when, level, what to do) in order to help unlock clinical uptake and payment.

6. Conclusion

Circulating protein biomarkers - in combination with CTC enumeration - have great potential to change the management of breast cancer to dynamic and responsive, pertinent care and no longer a static/snapshot management decision. Up to now, a limited number of circulating markers (CA 15-3/CA 27.29, sHER2 ECD, CTCs) have attained clinical applicability - even these have significant weaknesses. Proteomic discovery has provided a plethora of candidate biomarkers, and clinical translation needs to be done with solid validation, assay standardization and added value to the currently employed tissue-based predictors. Tissue-based biomarkers ER, PR, HER2, uPA/PAI-1, and gene-expression signatures will not be rendered redundant in the stratification of the baseline and therapy choices. The future of biomarkers is to have integrated biomarker workflows, with baseline molecular profiles and longitudinal, minimally invasive liquid biopsy monitoring. When applied scientifically, proven assays and properly designed clinical trials, such as integrative schemes, can help in better early detection of relapse, altering therapy based on evidence, early detection of resistance or micro-metastatic disease, and eventually, improving patient

outcomes. The 5-10 years are critical: these concerted studies, collaboration with other countries, and regulatory avenues can decide whether circulating protein biomarker panels, potentially with the addition of CTCs, ctDNA, and tissue molecular data, will become regular elements of personalized breast cancer care.

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