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Review

The future of blood-based biomarkers for the early detection of breast cancer

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Abstract Breast cancer (BC) is the most frequently diagnosed cancer and the most common cause of cancer-related mortality among women worldwide. Despite the extensive use of mammography as the gold standard for BC screening, the occurrences of false-positive and false-negative mammograms, as well as overdiagnosis, remain a concern in breast oncology. Thus, there is a need to identify reliable biomarkers from an easily accessible source that could generate cost-effective assays feasible for routine screening. Blood-based biomarkers may offer an alternative non-invasive strategy to improve cancer screening. Although none of the currently used blood-based biomarkers are sensitive enough for the early detection of BC, a plethora of significant findings pertaining to the development of screening tools using blood-based biomarkers have emerged in recent years. Promising candidate biomarkers such as proteins, autoantibodies, miRNAs, nucleic acid methylation, metabolites and lipids have shown great potential for detecting BC, including detection at the pre-invasive and early stages of the disease. Nevertheless, blood-based biomarkers for BC screening are still at the early phases of development, and various clinical and preclinical issues need to be addressed before these biomarkers can be used clinically. This review summarises the latest discoveries for harnessing blood-based biomarkers as novel BC screening tools, as well as discusses the limitations and challenges that need to be overcome before the translation of their use from the bench to the bedside.
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1. Introduction

Breast cancer (BC) screening plays a significant role in improving the outcomes of BC patients as patients detected early have a significantly better prognosis [1–3]. Mammography is currently the main tool and gold standard for BC screening, but it has several well-known drawbacks including being poor at detecting cancer in dense breasts, which is common in younger women, as well as high rates of false positives, and overdiagnosis [4–7]. This review summarises blood-based BC biomarkers with a primary focus on biomarkers shown to have early detection or diagnostic potential, as reported in the literature over the past 5 years. We conducted a comprehensive literature review on blood-based biomarkers for early detection of BC, published in PubMed from 2013 to 2017. A total of 3914 papers were retrieved by a search with keywords 'breast cancer, blood, serum, plasma, screening, early detection and diagnosis'. Filtering was further performed to select papers that were published in scientific journals with an impact factor of two and above. After reviewing the titles and abstracts, 88 original articles of relevance to the early detection of BC were selected for thorough reading, and 43 papers were finally chosen based on the promising performance of the blood-based biomarkers in the initial studies.

In addition to reporting an account of biomarker candidates in this review, the limitations and challenges encountered in biomarker research, the translation into the clinical setting and recent advances in next-generation sequencing (NGS) of circulating tumour DNA (ctDNA) are discussed. A list of promising biomarkers with information regarding the study design and diagnostic performance is presented in Table 1, together with an illustration of the types of biomarkers identified from serum, plasma, buffy coat, and whole blood being shown in Fig. 1. All biomarker studies discussed in the present review are retrospective studies unless stated otherwise in text and in Table 1.

Biomarkers encompass substances associated with or released from tumour tissue, substances released by other tissues in response to tumours, and physiological markers or other markers that can be visualised using imaging technology [8]. A cancer screening blood test incorporating blood-based biomarkers for determining the absence or presence of malignancy could be an attractive, observer-independent, cost-effective and readily accessible option.

To date, there are no blood-based biomarkers in clinical practice for BC screening, early detection or diagnosis [9,10]. Biomarkers that are currently in clinical use are for the prevention, prognosis, prediction and monitoring of BC. The *BRCA1* and *BCRA2* genes are well-recognised high penetrance genes in hereditary BC [11] that are used for genetic screening of individuals with a high susceptibility to the inherited malignancy [9]. Other classical blood-based biomarkers available for BC, such as carcinoembryonic antigen (CEA), gene products of *MUC1* (e.g. cancer antigen [CA] 15-3 and CA 27.29), circulating cytokeratins (CKs) (e.g. tissue plasminogen activator and tissue polypeptide-specific antigen) and soluble human epidermal growth factor receptor 2), are limited to assessing disease progression, predicting and monitoring treatment response and recurrence [10,12,13]. Notably, their clinical value remains controversial due to their lack of specificity and sensitivity.

2. Screening and diagnostic blood-based biomarkers under current research

2.1. Proteins

Circulating proteins have been a sought-after choice of biomarker for tumour detection, including BC. The integration of blood proteomics, such as enzyme-linked immunosorbent assay (ELISA) and mass spectrometry, allows the comprehensive and systemic examination of the blood proteome under physiological and pathological conditions, leading to the discovery of various protein biomarkers that offer improvement in BC detection. Recently, the panel of trefoil factor (TFF) 1, TFF2 and TFF3 has been shown to be promising biomarkers for BC screening due to their impressive discriminative ability and differential expression for each protein in the serum of BC patients compared to healthy individuals [14]. The glycoproteins of the mucins (MUC) family and CKs of intermediate filaments are two well-known groups that produce several classical BC biomarkers. For example, the CA 15-3 assay is currently used for treatment monitoring [13], whereas CKs 8, 18 and 19, have been suggested as markers for the early stages of BC although their effectiveness are hampered due to a lack of sensitivity [15]. For the first time, the concentration ratio value of serum epithelial membrane antigen (EMA, also known as MUC1) and CK1 have been suggested as potential diagnostic markers particularly for early-stage BC detection, and the diagnostic ability of this novel combination was found to be superior to their counterpart, CA 15-3 [16].

In addition, other circulating protein biomarkers with adequate discriminative ability have been discovered by ELISA. Among them are a single-marker diagnostic model of pleiotrophin (PTN) [17], and two-marker models such as combinations of human epididymis secretory protein 4 (HE4) with microRNA (miRNA) miR-127-3p [18], vascular endothelial growth factor (VEGF) with CA 15-3 [19] and human anterior gradient (AGR) 2 with AGR3 [20]. For the identification of triple-negative BC (TNBC), serum apolipoprotein C-I (apoC-I) has shown its potential in diagnosis

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