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MiniReview

Overview of Early Detection for Breast Cancer: Current Status and Future Perspectives

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Abstract

Cancer remains a formidable challenge in our modern society, and breast cancer has emerged as the most prevalent form of cancer among women worldwide. Timely detection of breast cancer holds immense potential for improving the lives of countless women globally. In this comprehensive review, we delve into the multifaceted factors that contribute to the prevalence of breast cancer among women from diverse socioeconomic backgrounds. We explored the intricate interplay of genetics, lifestyle choices, and environmental influences that contribute to breast cancer susceptibility. Additionally, we discussed the well-established screening methods, particularly mammography, which has revolutionized the early detection of breast cancer. Moreover, we highlight the advancements in the development of biomarkers that offer a simple and convenient alternative to overcome the limitations of mammography. Furthermore, we examine the pivotal role that artificial intelligence plays in enhancing breast cancer detection, presenting its potential to revolutionize diagnostic approaches and improve overall outcomes. Through this review, we aim to provide valuable insights into the various aspects of breast cancer detection, facilitating informed decision-making and advancing the fight against this formidable disease.

Keywords: breast cancer, early detection, risk factor, biomarkers, artificial intelligence

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1 INTRODUCTION

Cancer poses a significant and pressing public health challenge on a global scale, with a staggering 10 million lives lost to this disease in 2020[1]. Ranking as the second leading cause of death worldwide, cancer accounts for one in every six deaths[2]. Among the various forms of cancer, breast cancer stands out as the most widespread and is responsible for the highest mortality rate among women[3]. In the United States alone, 339,250 cases of breast cancer were reported in 2022[4]. These statistics underscore the urgent need for enhanced awareness, prevention, and effective interventions to combat this pervasive disease and safeguard the well-being of individuals worldwide.

While effective prevention methods for breast cancer are still lacking, early detection plays a crucial role in improving outcomes and minimizing treatment costs. The utilization of mammograms and regular self-breast exams is indispensable in identifying early irregularities before tumors become advanced. In addition to these screening methods, significant advancements have been made in the development of biomarkers for early detection. These biomarkers offer non-invasive and convenient approaches to detect breast cancer at its earliest stages, enhancing the potential for successful intervention and treatment[5].

This review aims to provide a summary of the risk factors associated with breast cancer, as well as an overview of current and emerging methods for early detection. Furthermore, we delve into the role of artificial intelligence in the detection of breast cancer, highlighting its potential contributions to improving diagnostic accuracy and efficiency. By exploring these key aspects, we aim to contribute to the understanding of breast cancer detection strategies and pave the way for further advancements in this field.

2 RISK FACTORS OF BREAST CANCER

Age, familial history, and reproductive factors are among the most influential risk factors for breast cancer. Additionally, lifestyle and hormonal factors have been implicated in breast cancer risk, although the existing data is inconclusive and inconsistent[6]. A comprehensive list of the factors known to impact breast cancer risk in the population can be found in Table 1.

3 PRACTICALITIES OF SCREENING

Breast cancer currently lacks a definitive cure, highlighting the significance of secondary prevention through early detection and screening as the most practical and effective approach for women worldwide. Clinical trials have consistently demonstrated that screen-detected, nonpalpable tumors measuring ≤15mm exhibit the most favorable prognosis[8-13]. Three cost-effective, reliable, and readily available methods are currently employed for early detection and screening of breast cancer: full-field digital mammography[14,15], clinical breast exams (CBE)[16-18], and breast awareness combined with breast self-examination (BSE)[19-21]. Among these methods, mammography is the most widely utilized modality[22-24], employing low-dose X-rays of the breast[25] and serving as the initial diagnostic tool for breast cancer detection[26]. With its broad population reach, mammography remains a popular screening method for identifying initial breast cancer symptoms[27,28].

In addition to the standard practice of mammography screening, high-risk women can benefit from the implementation of adjunctive imaging procedures. These include ultrasound[29], breast magnetic resonance imaging (MRI)[30], breast thermography (BT)[31], positron emission tomography (PET), computed tomography (CT)[32], and histopathology (HP)[33] (Table 2). These complementary imaging techniques offer valuable insights and contribute to a more comprehensive approach in the detection and evaluation of breast abnormalities.

4 ROLE OF BIOMARKERS IN EARLY DETECTION OF BREAST CANCER

Despite the widespread use of mammogram screening for breast cancer, concerns regarding high false-positive and false-negative rates, as well as radiation exposure, have persisted[41-45]. In recent years, the advent of “omics” strategies has led to significant advancements in the quest for non-invasive biomarkers for early-stage breast cancer diagnosis. Various biomarkers, including circulating carcinoma antigens, circulating tumor cells (CTCs), circulating cell-free tumor nucleic acids (DNA or RNA), circulating microRNAs (miRNA), and circulating extracellular vesicles (EVs) in peripheral blood, nipple aspirate fluid (NAF), sweat, urine, and tears, as well as volatile organic compounds (VOCs) in breath, have emerged as potential non-invasive diagnostic markers to complement current clinical approaches and enhance early detection of breast cancer (Table 3)[46,47]. These promising biomarkers offer the potential for improved accuracy and convenience in breast cancer diagnosis, addressing some of the limitations associated with mammography.

Besides these non-invasive biomarkers, biopsy samples are obtained through invasive methods to determine if cells are cancerous, as well as the presence of hormone receptors and other markers influencing treatment options. Estrogen receptor alpha (ERα) and epidermal growth factor 2 (ErbB2/HER2) are key biomarkers in breast cancer. ERα is expressed in about 70% of invasive breast cancers, activating growth pathways. Progesterone receptor (PR) is also indicative of ER signaling. ER-positive or PR-positive breast cancers are treated with endocrine agents to inhibit ER signaling. ErbB2 is amplified or overexpressed in around 20% of breast cancers, with targeted therapy benefiting patients[40].

5 ADVANCES IN ARTIFICIAL INTELLIGENCE TECHNOLOGY IN RELATION TO EARLY DETECTION

The advent of advanced medical imaging modalities and technologies has significantly contributed to the early detection of breast cancer and the reduction of patient mortality rates. However, the interpretation of breast images remains challenging due to the inherent

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Table 1. Risk Factors Related to Breast Cancer in the World[7]

Risk Factors		Effect
Demographic	Age	Predisposing
	Blood group	Controversial
Reproductive	Age of menarche	Controversial
	Late age of menopause	Predisposing
	Full-term pregnancy	Protective
	Abortion	Controversial
	Ovulatory menstrual cycle	Protective
	Pregnancy characteristics	Protective, Predisposing
Hormonal	Hormonal contraceptive methods	Predisposing
	Ovulation-stimulating drugs	Controversial
	Postmenopausal hormone therapy	Predisposing
Hereditary	Genetic factors	Predisposing
	Positive family history of breast cancer	Predisposing
Breast related	Lesser lactation duration	Protective
	More breast density	Controversial
	Benign breast disorders	Predisposing
Lifestyle	Obesity and overweight	Predisposing
	Alcohol consumption	Predisposing
	Smoking	Predisposing
	Coffee	Controversial
	Diet	Predisposing
	More physical activity	Protective
	Vitamin D	Protective
	Duration of sleep	Controversial
Others	Air pollution	Predisposing
	Night work	Predisposing
	Socioeconomic status	Predisposing
	Diabetes	Predisposing
	Radiation	Predisposing

heterogeneity of breast tumors and fibro-glandular tissue. This heterogeneity poses obstacles in terms of achieving high sensitivity and specificity in cancer detection, leading to substantial inter-reader variability. To address these clinical challenges, researchers have dedicated their efforts to developing computer-aided detection and / or diagnosis (CAD) schemes for breast imaging, aiming to provide radiologists with decision-making support tools. Recent breakthroughs in technologies include high-throughput radiomics feature analysis and AI-based deep transfer learning. Radiomics involves extracting quantitative features from images or specific regions of interest using pattern recognition algorithms. These features provide numerical descriptions of geometrical and physical properties of the image. In oncology, features such as tumor size, shape, intensity, and texture are used to comprehensively characterize tumors, forming the radiomics signature[49]. Radiomics is based on the hypothesis that these features reflect underlying genetic and molecular mechanisms, offering insights at the epistemological level[49-53].

These technical progresses have facilitated the development of numerous CAD schemes and prediction models for various research tasks in breast cancer. These tasks include predicting cancer risk, assessing the likelihood of malignancy, determining tumor subtypes, staging, prognosis, and treatment response[53-55]. These advancements hold great promise in enhancing the accuracy and efficiency of breast cancer diagnosis, offering valuable support to healthcare professionals in clinical practice.

Although AI has made significant advancements in

Table 2. Summary of Adjunctive Imaging Procedures

Imaging Procedure	Description
Automated breast ultrasound (ABUS) acquisition systems	The FDA has granted approval for the use of ABUS in whole-breast screening. This approval applies specifically to women with dense breasts who have previously received negative mammography results and have not undergone surgery or biopsy. ABUS has demonstrated an enhanced detection rate for breast cancer, leading to improved workflow and reduced examination time[34].
Dynamic contrast-enhanced (DCE) MRI	DCE-MRI is a noninvasive diagnostic method for suspected malignant breast lesions, offering a relatively high diagnostic sensitivity and specificity[35]. Its three-dimensional nature enables the visualization of disease extent, angiogenic properties, and lesion heterogeneity. DCE-MRI also has the capability to detect changes in angiogenic properties before morphological alterations occur, making it a valuable tool for predicting treatment response prior to therapy initiation or during early treatment stages[36].
BT	BT utilizes an infrared (IR) camera to measure the surface temperature of the breasts, subsequently identifying areas with atypical temperature patterns through image post-processing. This contactless, noninvasive, and nonionizing adjunct technique provides a valuable tool for breast cancer screening. IR breast thermography offers a safe and efficient method to assess breast health, aiding in the detection of potential abnormalities without direct physical contact[37].
PET	PET is a powerful imaging technique that enables the visualization of regions with increased metabolic activity in the body. PET scans play a crucial role in assessing the extent of cancer spread once the presence of cancer has been established[38].
CT	CT is an imaging technique that utilizes multiple X-ray projections taken from various angles by rotating the X-ray tube around the body. This process generates cross-sectional images of internal body areas[32]. CT produces highly detailed 3D images with significantly improved contrast compared to conventional mammography[37].
HP	HP involves the meticulous examination and thorough evaluation of a biopsy sample by an expert pathologist to study the growth of cancer in organs[39]. When other detection methods are inconclusive, a biopsy remains the definitive approach for diagnosing breast cancer[40].

developing automated systems for medical image analysis and disease predictions, there are important challenges that need to be addressed before its integration into clinical practices. Limited availability of comprehensive and annotated datasets, along with the necessity for robust ethical regulations, are key concerns. Another critical issue is the "black box" nature of AI algorithms, which lack transparency and fail to provide explanations for their decisions or predictions. In breast cancer diagnosis, radiologists and physicians prefer to understand the rationale behind decisions rather than relying on opaque recommendations from AI-based systems. The lack of explainability, coupled with concerns about losing control over decision-making, often leads to skepticism among physicians regarding AI-based prediction / diagnosis systems. To gain physicians' trust and ensure the reliability of AI-driven decisions, it is crucial to provide clear explanations for the decisions made, especially in the context of disease prediction[56-58].

6 CONCLUSION

Breast cancer is influenced by various risk factors, including age, positive family history, obesity, and more. To screen for breast cancer, mammography, CBE, and BSE are commonly employed modalities. Among them, mammography is the most widely used. Additionally, non-invasive biomarkers offer a noninvasive and convenient approach to supplement traditional methods for early breast cancer detection. Biomarkers in biopsy provide important insights for cancer treatment and prognosis. Researchers have invested significant efforts in developing AI-powered methods for the detection and diagnosis of breast images, aiming to assist radiologists in making informed decisions. However, further research is necessary to validate these advanced techniques through large-scale trials, ensuring their effectiveness and reliability.

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Conflicts of Interest
The authors declared no conflict of interest.

Author Contribution
Wang P and Chen J wrote the manuscript. Wang P, Chen J and Zhao W contributed to the original draft preparation, review and editing. All authors read and approved the manuscript for submission.

Abbreviation List
ABUS, Automated breast ultrasound
BSE, Breast self-examination
BT, Breast thermography
CAD, Computer-aided detection and / or diagnosis
CBE, Clinical breast exams
CT, Computed tomography
CTC, Circulating tumor cells
DCE, Dynamic contrast-enhanced
ERα, Estrogen receptor alpha
EVs, Extracellular vesicles
HP, Histopathology

Table 3. Pros and Cons of Potential Non-invasive Biomarkers for Early Detection of Breast Cancer[48]

Sources	Types	Importance	Limitations
Peripheral blood	Circulating carcinoma proteins	These markers are primarily employed to monitor therapeutic response in patients with advanced disease.	Accurate prediction of early-stage breast cancer cannot be achieved solely with these markers. Combining them with other factors, including tumor-associated autoantibodies, clinical patient characteristics, or breast imaging results, is necessary for effective detection. However, detection sensitivity still needs further enhancements.
	Circulating tumor cells	CTCs above a cut-off level of five cells per 7.5mL blood are associated with reduced survival, highlighting their value as a prognostic biomarker.	Due to low sensitivity and reproducibility, the measurement of CTCs is not currently recommended for breast cancer diagnosis.
	Circulating cell-free tumor DNA	Elevated levels of ctDNA are associated with advanced-stage breast cancer and metastasis, while ctDNA mutation analyses show promise for early-stage tumor detection. Additionally, methylation and fragmentation patterns of cfDNA hold potential for breast cancer detection.	The majority of cfDNA originates from normal cells due to cell death. In patients with early-stage cancers, ctDNA constitutes less than 0.1% of total cfDNA and is highly variable. Therefore, the development of a highly sensitive technique for ctDNA detection remains crucial.
	Circulating miRNAs	Combining certain circulating miRNAs has the ability to differentiate breast cancer from normal and healthy controls.	Consistency among the identified circulating miRNA panels for breast cancer diagnosis is limited, and no panels of circulating miRNAs are currently suitable for clinical diagnosis of breast cancer.
	Extracellular vesicles	Analyzing cancer-related contents within EVs holds potential for early-stage breast cancer diagnosis.	Challenges persist in the identification and isolation of EVs, including potential contamination with cells and platelet remnants. Our understanding of EVs is still limited, and further research is needed to elucidate the precise molecular mechanisms underlying their biogenesis, release, and functions.
	Metabolites and lipids	Detection of breast cancer can be achieved using a panel of metabolites or serum free fatty acids.	It is important to validate these findings in further studies.
	Multi-analyte tests	Combining multiple blood marker assays for cancer detection and localization improves accuracy.	The sensitivity of multi-analyte tests in breast cancer detection remains low.
Other body fluids	Urine	Protein, metabolite, miRNA, and other cellular component alterations in urine hold potential as indicators of breast cancer.	Urinary biomarkers reported thus far are still in the discovery phase and require validation of their specificity and sensitivity through cohort studies.
	Breath	Breath VOC tests offer a promising approach for breast cancer screening. These non-invasive, painless, safe, and cost-effective tests have the potential to reduce the reliance on mammograms in clinics for screening and monitoring breast cancer.	Factors such as breath collection methods, patient physiology, test environments, and analysis methods can influence the accuracy of VOC breath test results. Therefore, standardized procedures are still necessary to enhance the reliability of these tests.
	NAF	The color and specific biomarkers in NAF hold potential for breast cancer diagnosis. NAF collection is simple, quick, reliable, and reproducible, as it is directly derived from the breast ductal system.	Improvements are needed in NAF sample collection methods, sample volume normalization, and analysis standardization to establish an accurate screening approach using breast cancer-specific biomarkers.
	Tears	Tear sample collection is a minimally invasive approach for health monitoring, as tears can be easily obtained from the eyes inside or outside the clinic.	The concentration of certain molecules in tears is typically lower compared to blood.
	Apocrine sweat	Apocrine sweat sample collection is a minimally invasive approach for cancer testing.	Sweat-based cancer tests are currently underutilized and lack clinical validation

IR, Infrared
miRNA, MicroRNA
MRI, Magnetic resonance imaging
NAF, Nipple aspirate fluid
PET, Positron emission tomography
PR, Progesterone receptor
VOC, Volatile organic compounds

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