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Early Detection of Breast Cancer: Advances in Clinical Screening and Diagnostic Strategies

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Abstract

Breast cancer remains a major global health challenge, with approximately 2.3 million new cases and 670,000 deaths reported in 2022, and projections indicating a rise to 3.2 million cases and 1.1 million deaths annually by 2050. Disparities in mortality are stark, driven by late-stage diagnoses and limited access in low- and middle-income countries, where survival rates are significantly lower than in high-income settings. This review examines recent advances in early detection and diagnostic strategies, including the transition from 2D digital mammography to Digital Breast Tomosynthesis (DBT) and synthetic 2D mammography, which improve sensitivity (up to 86–90%) and reduce recall rates, particularly in dense breasts. Supplemental modalities such as Automated Breast Ultrasound (ABUS) and Contrast-Enhanced Mammography (CEM) enhance detection in dense tissue, with CEM offering comparable sensitivity to MRI (98.9%) but superior specificity. The shift toward personalized, risk-based screening, supported by trials like WISDOM, incorporates genetic testing, polygenic risk scores (PRS), and breast density to optimize screening protocols and reduce unnecessary interventions. Artificial intelligence (AI) applications, including deep learning for lesion detection and independent reading, demonstrate substantial improvements in cancer detection rates (up to 29% increase) and workflow efficiency. Emerging liquid biopsy techniques, utilizing circulating tumor DNA (ctDNA) and exosomes, enable non-invasive molecular detection with high AUC values (e.g., 0.96 for early-stage disease). In low-resource settings, portable AI-supported tools, mobile units, and task-shifting address access gaps. These integrated, multi-modal approaches, aligned with the Global Breast Cancer Initiative (GBCI) goal of 2.5% annual mortality reduction, hold promise for closing survival disparities and averting millions of deaths by 2040.

Keywords: Breast Cancer, Early Detection, Digital Breast Tomosynthesis, Automated Breast Ultrasound, Contrast-Enhanced Mammography, Personalized Screening, Polygenic Risk Scores, artificial intelligence, liquid biopsy, global breast cancer initiative

Introduction

The global landscape of female breast cancer is characterized by a relentless upward trajectory in both incidence and mortality, necessitating a fundamental reassessment of current screening and diagnostic paradigms (Dlamini, 2025). As of early 2025, data released by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) underscore a public

health crisis that is no longer confined to high-income nations (World Health Organization, 2025). In 2022 alone, approximately 2.3 million new cases were diagnosed, resulting in 670,000 deaths. Projections for the year 2050 suggest a catastrophic expansion of this burden, with annual new cases expected to reach 3.2 million a nearly 40% increase and deaths projected to climb to 1.1 million (United Nations News, 2025). These statistics translate to a reality where, globally, every minute four women are diagnosed with breast cancer and one woman dies from the disease (Kim et al., 2025). The distribution of this disease is intricately linked to the Human Development Index (HDI). While the highest age standardized incidence rates are found in very high HDI regions, such as Australia, New Zealand, and Northern Europe (exceeding 100 cases per 100,000 women), the mortality rates tell a different story (Rygiel, 2023). In low-income countries, more than half of the women diagnosed with breast cancer die from it, compared to a survival rate of 83% in high-income countries (United Nations News, 2025). This disparity is driven by the prevalence of late-stage diagnoses, limited access to high-quality treatment, and the rising incidence of early-onset breast cancer in transitioning economies (Biswas, 2025).

Table 1: Global Breast Cancer Burden and Projections by HDI and Region

Region / Metric	2022 Incidence (Cases)	2022 Mortality (Deaths)	2050 Projected Incidence	2050 Projected Mortality
Global Total	2.3 Million	670,000	3.2 Million	1.1 Million
High HDI Regions	~100 per 100k	~17% mortality	20-30% Increase	~10-15% Increase
Low HDI Regions	~27 per 100k	>50% mortality	40-60% Increase	60-80% Increase
Sub-Saharan Africa	<30 per 100k	High	Accelerated Growth	High Early-Onset

The rising burden in younger populations (under age 50) is particularly concerning, as these cases often involve more aggressive phenotypes and contribute significantly to disability-adjusted life years (Abudulai, 2014). Historical data showed an annual incidence increase of 1% to 5% in a majority of countries surveyed (Kim et al., 2025). Consequently, the Global Breast Cancer Initiative (GBCI) has established a target of reducing mortality by 2.5% per year, which could avert 2.5 million deaths by 2040 (Sage, 2021).

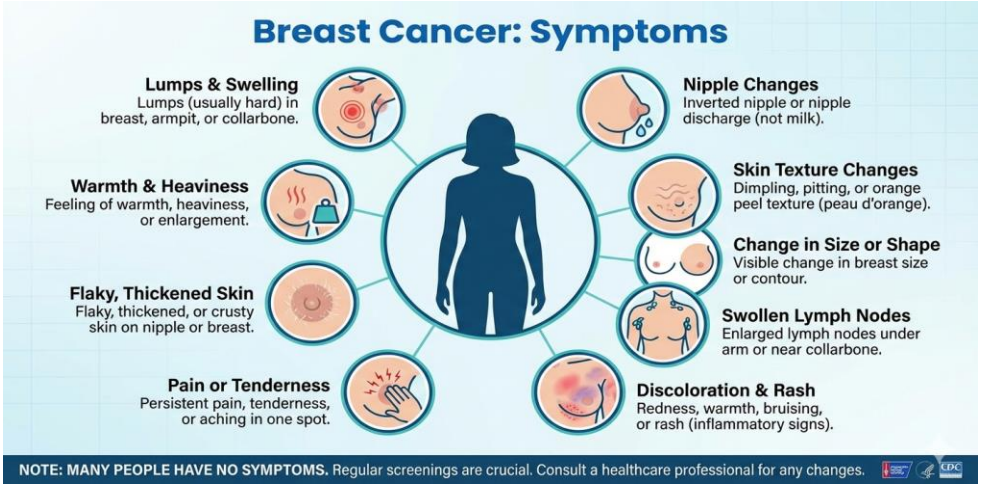

Figure 2: Physical Manifestations and Clinical Symptoms of Breast Cancer

The Evolution of Radiographic Screening: From 2D to 3D Modalities

For decades, digital mammography (DM) has served as the gold standard for population-level screening. Evidence suggests that nationwide screening recommendations have contributed to 25% of the total reduction in breast cancer mortality over the past 35 years (Alabousi et al., 2021). However, the inherent limitations of 2D mammography, specifically the "masking effect" of overlapping fibroglandular tissue, have driven the clinical transition toward Digital Breast Tomosynthesis (DBT) (Liu et al., 2025).

Performance Metrics of Digital Breast Tomosynthesis

DBT, or 3D mammography, addresses tissue superimposition by acquiring multiple images at various angles. Recent meta-analyses reveal significant improvements in diagnostic performance. The pooled sensitivity for DBT is estimated at 86%, notably higher than the 80% associated with conventional DM (Marshall et al., 2022). This increased sensitivity does not come at the expense of specificity; in many cohorts, DBT has demonstrated a significant reduction in recall rates with an absolute risk difference of -1.51% and a corresponding increase in specificity of 1.56% (Gao et al., 2021).

Table 2: Performance Metrics of Digital Breast Tomosynthesis Compared to Digital Mammography

Imaging Modality	Sensitivity (95% CI)	Specificity (95% CI)	Recall Rate Change
Digital Mammography (DM)	80% (76-84%)	96% (95-97%)	Baseline
DBT (Standalone)	86% (81-90%)	96% (95-98%)	Reduced
DM + DBT (Combination)	90% (85-94%)	Lower than DM	Increased Recall
Synthetic 2D + DBT	Comparable to DM+DBT	Comparable to DM+DBT	Reduced Dose

The clinical utility of DBT is most pronounced in women with dense breast tissue. Despite these advantages, the impact of DBT on interval cancer rates (ICR) remains a subject of debate. While DBT identifies more invasive cancers at an earlier stage, some meta-analyses have yet to show a statistically significant reduction in ICR, necessitating further long-term investigation (Libesman et al., 2025).

Radiation Management and Synthetic Mammography

A primary concern in the adoption of DBT is the increased radiation dose. To mitigate this, Synthetic 2D Mammography (S2D) was developed. S2D uses the 3D data set from the DBT scan to reconstruct a 2D image, eliminating the need for a separate digital exposure (Hamad et al., 2024). Meta-analyses have confirmed that the combination of DBT and S2D offers a cancer detection rate (CDR) that is significantly higher than DM alone with a difference of 2.03 per 1000 examinations while maintaining a radiation profile similar to traditional 2D mammography (Heywang-Köbrunner et al., 2022).

Supplemental Screening Strategies for Dense Breast Tissue

Breast density is one of the most significant independent risk factors for the development of breast cancer, as women with extremely dense breasts face a four- to sixfold higher risk than those with fatty breasts (Gupta et al., 2025). Furthermore, density severely compromises the sensitivity of mammography, which can drop to as low as 30-62% in extremely dense tissue. This has led to the emergence of supplemental screening modalities, most notably Automated Breast Ultrasound (ABUS) and Contrast-Enhanced Mammography (CEM) (Covington, 2021).

Clinical Utility of Automated Breast Ultrasound (ABUS)

ABUS was approved by the FDA as a supplemental screening tool specifically for women with dense breasts. Unlike handheld ultrasound (HHUS), which is operator-dependent, ABUS utilizes a standardized transducer to capture a full 3D volume of the breast (Paul et al., 2025).

Table 3: Comparison of Automated and Handheld Ultrasound Features

Feature	Automated Breast Ultrasound (ABUS)	Handheld Ultrasound (HHUS)
Sensitivity (Dense Breast)	72-81% (Incremental)	Comparable
Cancer Detection Rate	+1.9 to 7.7 per 1,000	+2.0 to 4.0 per 1,000
Unique Imaging Signs	Retraction Phenomenon	Acoustic Shadowing
Display Modes	Coronal View (Stellate Pattern)	Transverse/Sagittal
Operator Dependency	Low	High

Research indicates that adding ABUS to screening mammography can double the cancer detection rate in dense breasts, from 3.6 per 1,000 to 7.2 per 1,000. A striking 93% of the additional cancers found by ABUS are invasive and predominantly node-negative (Melnikow et al., 2016). Unique features of ABUS include the "retraction phenomenon," visualized in the coronal view as a stellate pattern around a lesion, which has a specificity of 96-100% for malignancy (Łuczyńska et al., 2022).

Contrast-Enhanced Mammography (CEM) and MRI Comparisons

Contrast-Enhanced Mammography (CEM) utilizes dual-energy imaging and iodinated contrast material to identify areas of increased vascularity (RSNA, 2025). Recent comparative studies between CEM and Magnetic Resonance Imaging (MRI) have shown that CEM is a highly viable, lower-cost alternative. In a 2025 study of 301 breast lesions, the sensitivity of CEM was found to be identical to MRI at 98.9% (Tucunduva et al., 2025). CEM also demonstrated a more favorable specificity profile 78.5% for CEM vs. 72.7% for MRI potentially leading to fewer unnecessary biopsies (Frontiers in Oncology, 2025).

Table 4: Diagnostic Parameter Comparison of CEM and MRI Performance

Diagnostic Parameter	CEM Performance	MRI Performance
Sensitivity	98.9%	98.9%
Specificity	78.5%	72.7%
Accuracy	90.7%	88.4%
AUC	0.887	0.858

Beyond general screening, CEM has shown utility in discriminating low-suspicion lesions. For BI-RADS Category 4A lesions, CEM achieved a 100% accuracy rate compared to 61.9% for MRI in certain trials. For women eligible for supplemental MRI screening who cannot access it, CEM serves as a robust alternative that improves the overall area under the curve (AUC) from 0.73 (DBT alone) to 0.92 (Pan et al., 2025).

The Paradigm Shift: Personalized, Risk-Based Screening

The historical model of screening has relied heavily on age-based criteria, but the growing understanding of individual genetic and lifestyle risks is shifting the field toward personalized medicine. The most comprehensive evidence for this shift comes from the Women Informed to Screen Depending on Measures of Risk (WISDOM) study (Shieh et al., 2025).

Insights from the WISDOM Trial

The WISDOM trial compared a risk-based screening approach incorporating age, genetics, health history, lifestyle, and breast density to standard annual mammography. The study found that personalized screening could reduce the frequency of screenings for low-risk women without increasing the incidence of advanced-stage cancers (Fiscalini et al., 2024).

Table 5: WISDOM Trial Risk Categorization and Screening Protocols

Risk Category	Proportion	Protocol
Lowest Risk	26%	Delayed start (age 50)
Average Risk	62%	Biennial screening
Elevated Risk	8%	Annual screening
Highest Risk	2%	Bi-annual (Mammography + MRI)

One of the most critical findings from WISDOM was that 30% of women who carried pathogenic genetic variants (like BRCA1/2) did not report a family history of the disease. Furthermore, the study integrated Polygenic Risk Scores (PRS), which account for hundreds of small DNA changes. This addition shifted the risk level of 12% to 14% of participants, underscoring the necessity of genetic assessment for all women (Riddle et al., 2024).

Polygenic Risk and Individualized Assessment

The use of a 313-SNP PRS has been validated to establish risk groups from 0 to 10 times the population average. Women in the top 1% of the PRS distribution have a lifetime risk of approximately 32.6%, roughly four times that of the average woman (Buonomo et al., 2021). This shift toward "risk-adapted screening" allows for the allocation of intensive resources, such as MRI, to those who need them most while sparing low-risk women from unnecessary procedures (Stegel et al., 2022).

Artificial Intelligence in the Diagnostic Ecosystem

Artificial Intelligence (AI), particularly deep learning and convolutional neural networks (CNNs), is now a functional component of modern breast cancer diagnostics (Lang et al., 2025).

Deep Learning and Independent Image Interpretation

Advanced deep learning architectures are being used to process scans with high accuracy. The MASAI trial demonstrated that AI-supported mammography screening detected 29% more cancers than traditional human interpretation. In retrospective analyses, advanced AI solutions flagged 32% of cancer cases that were initially interpreted as "negative" by radiologists (Hologic, Inc., 2025).

Table 6: Clinical Impact and Performance Benchmarks of AI Functions

AI Function	Clinical Impact	Performance Benchmark
Lesion Detection	Reduces missed cancers	~90% localization accuracy
Independent Reader	Offsets radiologist shortage	Non-inferior to double-reading
Triage	Filters out normal cases	Reduces workload by ~30-50%
Histopathology	Analyzes whole-slide images	High precision for lymph node status

AI is particularly effective in identifying subtle patterns in dense breast tissue. Hybrid models have achieved accuracies of 96.79% in ultrasound image classification (Matta et al., 2022). Furthermore, AI-driven risk models, such as Prognosia Breast, utilize mammographic textures to predict five-year risk 2.2 times more accurately than standard questionnaire-based models (Prognosia Inc., 2025).

Surgical Planning and Explainable AI (XAI)

One of the most innovative applications is the "Transformer neck" model, which predicts the likelihood of axillary lymph node metastasis from the primary mammogram. This tool could potentially allow 40% of patients to skip unnecessary sentinel lymph node biopsies (Laish et al., 2021). To foster trust, "Explainable AI" (XAI) techniques are being integrated to provide transparency into the features such as tumor boundaries that drive an AI's prediction (Tuan, 2024).

Liquid Biopsy and Molecular Interception

Liquid biopsy represents the frontier of early detection, shifting focus to detecting molecular fragments in circulation. These tests analyze circulating tumor DNA (ctDNA) and extracellular vesicles (exosomes) from a blood or saliva sample (Jiang et al., 2025).

Circulating Tumor DNA and Exosomal Cargo

Multi-cancer early detection (MCED) assays utilize ctDNA methylation patterns to identify the tissue of origin. In early-stage breast cancer, liquid biopsy has demonstrated the ability to detect ctDNA before tumors are visible on standard imaging. Furthermore, exosomes carry a "molecular cargo" of proteins and RNA that reflect the tumor's biology (Horrmann et al., 2025).

Table 7: Circulating Biomarker Categories and Clinical Utility

Biomarker Category	Primary Modality	Clinical Utility
ctDNA	Targeted Methylation	MCED, Screening, Recurrence
Exosomes	Multi-omics (Proteomics)	Treatment Response, Monitoring
Salivary Metabolites	LC-MS/MS	Non-invasive preliminary screening
Plasma Proteome	Mass Spectrometry	AUC 0.96 for early-stage BC

A 2025 proteomics study achieved an AUC of 0.96 in identifying breast cancer patients (Stages 0-2) using plasma samples. The classifier maintained over 85% sensitivity even in women with high breast density. Similarly, salivary metabolomics has identified biomarkers like 2-aminonicotinic acid and theobromine, offering a non-invasive triage option for large-scale screening (Bovis et al., 2022).

Bridging the Global Access Gap: Innovations for Low-Resource Settings

The projected increase in breast cancer mortality is most acute in low- and middle-income countries. Innovation in these regions focuses on portable, AI-driven diagnostic tools (BMJ, 2025).

AI-Supported Portable Diagnostics

In regions lacking radiologists, AI-supported point-of-care tools allow non-specialist healthcare workers to perform screenings. For example, AI algorithms can interpret portable ultrasound sweeps of the breast or analyze thermal images (thermography) for preliminary risk assessment (Manoj et al., 2026).

Table 8: Diagnostic Innovations and Implementation Strategies for Low-Resource Settings

Innovation	Implementation Strategy	Benefit
Mobile Screening Vans	Portable equipment + AI software	Reaches rural populations
Offline AI Algorithms	Edge computing on mobile devices	Operates without internet/power
AI Thermography	Radiation-free thermal sensors	Triage tool in low-resource clinics
Task-Shifting	AI-guided interpretation	Empowers nurses and technicians

Despite the potential of these tools, significant barriers remain. AI models trained on Western datasets often degrade in performance when applied to diverse populations. Furthermore, the lack

of regulatory frameworks and consistent power complicates the deployment of cloud-based AI (Lang et al., 2025)

Synthesis and Future Outlook

The landscape of breast cancer detection is moving toward a highly integrated, multi-modal diagnostic ecosystem. The convergence of 3D imaging (DBT), molecular profiling (liquid biopsy), and machine intelligence (AI) is transforming the clinical pathway (Ahuchogu, 2025). The shift toward personalized, risk-based screening as pioneered by the WISDOM study offers the opportunity to maximize the benefits of screening while minimizing its harms. By incorporating genetic markers and polygenic risk scores, clinicians can identify high-risk individuals who require intensive surveillance while sparing low-risk populations from unnecessary procedures (Shieh et al., 2025). Artificial intelligence will continue to serve as the engine of this transformation, provided the successful implementation of these advances occurs on a global scale. The development of portable, offline, and ethnically diverse AI systems is essential to close the survival gap and meet mortality reduction targets set for 2050 (Kim et al., 2025).

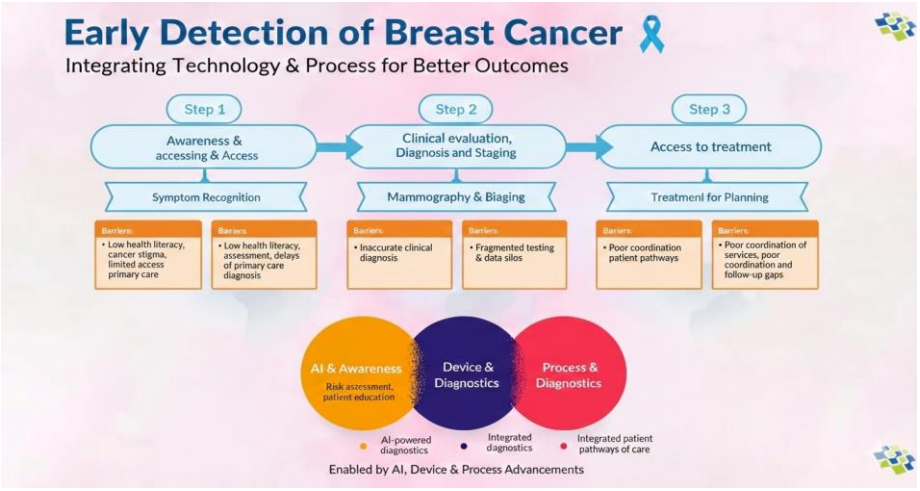

Figure 1: The Integrated Diagnostic Ecosystem: Barriers and Technological Enablers in Breast Cancer Care

Conclusions

The evolving landscape of breast cancer early detection is characterized by a convergence of advanced imaging, personalized risk stratification, artificial intelligence, and molecular innovations that collectively enhance diagnostic accuracy, reduce harms, and address global inequities. Technologies such as DBT combined with synthetic mammography, ABUS, CEM, and AI-driven tools significantly outperform traditional mammography, particularly in challenging cases like dense breasts, while risk-adapted screening models exemplified by the WISDOM trial enable tailored protocols that balance benefits and overdiagnosis. Liquid biopsy and related molecular approaches herald a future of pre-clinical interception, offering non-invasive, high-sensitivity options for screening and monitoring. In low-resource environments, portable and offline AI solutions represent critical steps toward equitable access. Successful global implementation of these advances supported by diverse training data, regulatory frameworks, and investment in infrastructure will be essential to meet the GBCI target of a 2.5% annual mortality reduction and prevent an estimated 2.5 million deaths by 2040. Continued research, international collaboration, and adaptation to diverse populations will be key to transforming breast cancer from a life-threatening disease into one that is increasingly detectable and manageable at early, curable stages.

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