LGJDX ISSN No: 1008-0562 Journal Of Liaoning Technical University Natural Science Edition

BREAST CANCER: THE KEY ROLE OF EARLY DETECTION IN ENHANCING CONTROL AND CARE

ADENIJI, Oluwabunmi Mercy
Department of Nursing,
College of Medicine and Health Sciences,
Afe Babalola University
Ado Ekiti, Ekiti State

Prof. Rev. Sr. OGUNKORODE, Agatha Olufunke
Department of Nursing,
College of Medicine and Health Sciences,
Afe Babalola University
Ado Ekiti, Ekiti State

Prof. OKAFOR, Uchendi Fidelis
Department of Nursing,
University of Benin,
Benin City, Edo State

OWOLABI, Wuraola Foluke
Department of Nursing,
College of Medicine and Health Sciences,
Afe Babalola University
Ado Ekiti, Ekiti State

Abstract

This literature-based review provides a comprehensive examination of breast cancer research, focusing on epidemiology, pathogenesis, risk factors, early detection, and survival rates. A literature based search strategy was employed, utilizing databases such as PubMed, Google Scholar, Scopus, and Web of Science, with search terms including "breast cancer epidemiology," "risk factors," and "early detection methods." Studies published between 2000 and 2024 were selected based on rigorous inclusion criteria, including peer-reviewed articles, systematic reviews, and meta-analyses. The review synthesized data from selected studies, highlighting trends in incidence and mortality, the role of genetic factors like BRCA1 and HER2, and the impact of various risk factors, including age, family history, and lifestyle. It also evaluated the effectiveness of early detection methods, such as mammography and MRI, and analyzed survival rates in relation to early diagnosis and treatment advancements. The findings were integrated to offer a detailed overview of current knowledge on breast cancer, adhering to PRISMA guidelines. The review concludes with a discussion of implications for public health and clinical practice, identifying gaps and suggesting directions for future research.

Keywords: Breast Cancer, Epidemiological Data, Pathogenesis, Risk Factors, Early Detection

Introduction

Breast cancer remains one of the most prevalent and challenging health concerns worldwide, with significant disparities in incidence and outcomes between high-income and low- and middle-income countries (LMICs). Despite advances in treatment and increased awareness, the burden of breast cancer continues to grow, particularly in developing regions where healthcare infrastructure and resources are often inadequate (Globocan, 2021). Early detection is pivotal in enhancing breast cancer control and care, as it can lead to timely and more effective treatment, thereby improving survival rates (Ferlay et al., 2020). In developed countries, extensive screening programs and public health initiatives have significantly contributed to early detection and reduced mortality rates (Sharp et al., 2019). However, in LMICs, various factors such as limited access to healthcare, cultural barriers, and lack of awareness impede early diagnosis, resulting in a higher prevalence of advanced-stage breast cancer at presentation (Rodriguez et al., 2017). Studies have demonstrated that delays in diagnosis and treatment, often exceeding three months from symptom discovery, are associated with poorer survival outcomes (Richards et al., 2014). These delays are multifaceted, involving patient-related factors such as delays in seeking medical attention and systemic issues within the healthcare infrastructure (Caplan, 2016).

Educational programs tailored to address cultural sensitivities and enhance public knowledge about breast cancer are essential for the success of early detection initiatives (Kreps, 2018). Such programs must emphasize that breast cancer is highly treatable when detected early, thereby encouraging women to seek timely medical advice and participate in regular screening activities. Additionally, investment in healthcare infrastructure, including the training of healthcare providers and the provision of affordable screening methods like mammography, is critical for improving early detection rates in LMICs (Galukande et al., 2021).

Moreover, it is essential to understand and address the underlying reasons for late-stage diagnosis in these regions. Research indicates that enhancing access to quality healthcare and implementing effective breast health programs can significantly improve outcomes (Barchuk et al., 2018). As mammography screening has been shown to reduce breast cancer mortality

by at least 20%, expanding such services in LMICs is a vital step towards mitigating the disease's impact (Ferlay et al., 2020).

This study highlights the global and regional prevalence and mortality rates of breast cancer, emphasizing disparities between high-income and low-income countries such as Nigeria. The document elucidates factors contributing to high mortality rates in Sub-Saharan Africa, including inadequate awareness and healthcare infrastructure. It discusses risk factors associated with breast cancer, such as genetic mutations (BRCA1, BRCA2), lifestyle choices, and reproductive factors. The pathogenesis section explores tumor microenvironments and the role of cancer stem cells in drug resistance and metastasis. Additionally, the write-up underscores the importance of early detection and screening in improving prognosis and reducing mortality, with specific reference to methods like mammography and MRI. Lastly, it outlines the impact of genetic and epigenetic changes on breast cancer development, presenting key genes and signaling pathways involved in tumor progression.

Methodology

The methodology for this literature-based review was designed to provide a thorough and systematic examination of the existing research on breast cancer. The review began with a comprehensive search strategy, utilizing electronic databases such as PubMed, Google Scholar, Scopus, and Web of Science. Search terms included "breast cancer epidemiology," "breast cancer pathogenesis," "risk factors for breast cancer," "early detection of breast cancer," and "breast cancer survival rates," along with additional keywords like "BRCA1," "HER2," and "screening methods" to refine the results. The search was restricted to articles published between 2000 and 2024 to ensure the inclusion of recent and relevant studies.

To select appropriate literature, specific inclusion and exclusion criteria were established. Only peer-reviewed articles, systematic reviews, and meta-analyses related to breast cancer were included. The review focused on studies providing data on incidence, mortality, pathogenesis, risk factors, early detection, and survival rates. Articles published in English were selected, while studies on non-breast cancer malignancies, those lacking original data or comprehensive reviews, and non-English publications were excluded.

Key information was meticulously extracted from the chosen articles. This included epidemiological data on the incidence, mortality rates, and prevalence of breast cancer globally and in specific regions, such as Nigeria and Sub-Saharan Africa. The review also

focused on the pathogenesis of breast cancer, including mechanisms of tumor initiation and progression and the roles of genetic factors like BRCA1 and HER2. Additionally, the review examined various risk factors, such as age, family history, reproductive factors, estrogen exposure, and lifestyle choices. Early detection methods, including mammography, MRI, and clinical breast examination, were evaluated for their efficacy. Furthermore, survival rates and factors influencing survival, such as early detection and treatment advancements, were analyzed.

Data from the selected studies were synthesized through a comparative analysis, identifying common trends, discrepancies, and gaps in the literature. The findings were integrated to provide a comprehensive overview of breast cancer, organized into thematic categories like epidemiological trends, risk factors, and detection methods. This structured presentation facilitated a clear understanding of the current state of knowledge on breast cancer. The quality of the included studies was assessed using established criteria, such as the Critical Appraisal Skills Programme (CASP) checklists, which evaluate methodological rigor, sample size, data accuracy, and relevance. This assessment ensured that only high-quality studies contributed to the review.

Epidemiology and Pathogenesis of Breast Cancer

Breast cancer has emerged as one of the most frequently diagnosed malignancies worldwide, representing nearly 12% of all cancer cases globally in 2020. Although the disease can also affect males, these cases account for less than 1% of all incidences (Fox et al., 2022). In 2020, approximately 2.3 million women were diagnosed with breast cancer, resulting in 685,000 deaths globally. By the end of 2020, there were 7.8 million women alive who had been diagnosed with breast cancer in the previous five years, making it the most prevalent malignancy globally (Ferlay et al., 2020; 2023).

In Nigeria, high mortality rates from breast cancer persist due to inadequate population awareness, poor health-seeking behaviors, and low levels of female education and empowerment, coupled with a suboptimal health system that results in insufficient treatment services (Atara et al., 2022). Although the incidence of breast cancer in Sub-Saharan Africa appears relatively low, survival rates are generally poor due to other competing public health challenges. Africa, aside from Asia, has the highest age-standardized mortality rate for breast cancer compared to other continents with higher incidence rates. Nigeria, in particular, has

the highest breast cancer mortality rate, with a prevalence rate of 69.1 per 100,000 and a mortality rate of 6.23 per 100,000 based on data from the Institute of Health Metrics Evaluation (IHME, 2022). Breast cancer remains the most common malignancy among women in Nigeria, accounting for 28,380 (22.7%) of all new cancer cases (Globocan, 2020).

In contrast, mortality rates from breast cancer have been declining in many high-income countries, a change attributable to greater population awareness, early detection, timely diagnosis, and effective treatment strategies. This paper aims to demonstrate that early detection is crucial for expanding control and care of breast cancer. Breast cancer is a significant concern in women's health, being the most common type of cancer after lung cancer and the second leading cause of cancer-related death among women in high-income countries. Globally, breast cancer accounts for 11.7% of all cancer incidences among women, making it the second most common type of non-skin cancer after lung cancer and the fifth most common cause of cancer death (WHO, 2020; 2023). In 2004, breast cancer was responsible for 519,000 deaths worldwide (7% of cancer deaths and almost 1% of all deaths). In North America, the 5-year relative survival rate for breast cancer patients exceeds 80% due to timely detection (Siegel et al., 2022).

Breast cancer is about 100 times more common in women than in men, although males tend to have poorer outcomes due to delays in diagnosis. Most breast cancer cases occur in women, with the number of cases being 100 times higher in women than in men (Sonnenschein & Soto, 2016). Cancer cells closely resemble the cells of the organism from which they originated, having similar DNA and RNA, which is why they are not often detected by the immune system, especially if it is weakened (Siegel et al., 2017). Breast cancer is a metastatic disease, commonly spreading to distant organs such as the bone, liver, lung, and brain, which primarily accounts for its incurability (Siegel et al., 2017; Sood et al., 2020). Although the incidence rate of breast cancer in America increases annually, the mortality rate decreases due to widespread early screenings and advanced medical therapies. Biological therapies developed in recent years have also proven beneficial for breast cancer (Siegel et al., 2017).

Early diagnosis of breast cancer can lead to a favorable prognosis and high survival rates. Mammography is a widely used screening method that helps detect breast cancer early and effectively reduce mortality. Other screening methods, such as Magnetic Resonance Imaging (MRI), which is more sensitive than mammography, have also been implemented and studied

over the last decade. Numerous risk factors, such as sex, aging, estrogen, family history, gene mutations, and unhealthy lifestyle choices, can increase the likelihood of developing breast cancer.

Breast tumors typically begin with ductal hyperproliferation and can develop into benign tumors or even metastatic carcinomas after constant exposure to various carcinogenic factors. Tumor microenvironments, such as stromal influences or macrophages, play crucial roles in breast cancer initiation and progression. For instance, the mammary gland of rats can develop neoplasms when only the stroma is exposed to carcinogens, not the extracellular matrix or epithelium (Sonnenschein & Soto, 2016). Macrophages can create a mutagenic inflammatory microenvironment, promoting angiogenesis and enabling cancer cells to escape immune rejection (Zhang et al., 2017). Different DNA methylation patterns observed between normal and tumor-associated microenvironments indicate that epigenetic modifications in the tumor microenvironment can promote carcinogenesis (Valenti et al., 2017).

A new subclass of malignant cells within tumors, known as cancer stem cells (CSCs), has been identified and is associated with tumor initiation, escape, and recurrence. This small population of cells, which may develop from stem cells or progenitor cells in normal tissues, has self-renewal abilities and is resistant to conventional therapies such as chemotherapy and radiotherapy (Zhang et al., 2017). Breast cancer stem cells (BCSCs) were first identified by Ai Hajj (2003), and even as few as 100 BCSCs could form new tumors in immune-compromised mice. BCSCs are more likely to originate from luminal epithelial progenitors rather than from basal stem cells (Valenti et al., 2017). Signaling pathways, including Notch, Hedgehog, p53 (Tumor Protein 53), and PI3K (Phosphatidylinositol-3 kinase), are involved in the self-renewal, proliferation, and invasion of BCSCs (Valenti et al., 2017; El Helou et al., 2017; Shukla et al., 2017).

Drug resistance is a significant challenge in breast cancer treatment. Accumulating evidence indicates that BCSCs are responsible for drug resistance, causing relapse and metastasis in breast cancer patients (Zheng et al., 2021). Therefore, eliminating BCSCs could reverse drug resistance and improve drug efficacy, benefiting breast cancer patients. Understanding the proliferation, resistance mechanisms, and separation of BCSCs in breast cancer therapy is crucial for developing BCSC-targeted therapeutic strategies. It is essential to focus on BCSC-targeted strategies to overcome drug resistance in clinical therapies (Harbeck & Gnant, 2017). Some breast cancer cells exhibit intrinsic drug resistance, while others acquire resistance after

initially being drug-sensitive, leading to chemotherapy resistance and tumor recurrence (Abad et al., 2020; Eiro et al., 2019).

Two hypothetical theories explain breast cancer initiation and progression: the cancer stem cell theory and the stochastic theory. The cancer stem cell theory suggests that all tumor subtypes derive from the same stem cells or progenitor cells. Acquired genetic and epigenetic mutations in these cells lead to different tumor phenotypes. The stochastic theory posits that each tumor subtype originates from a single cell type, with random mutations accumulating and transforming cells into tumor cells. Although both theories have substantial support, neither fully explains the origin of human breast cancer

Genes Related to Breast Cancer

Breast cancer is a complex disease influenced by the interplay of various genetic factors. Numerous genes have been identified in relation to breast cancer, with mutations and abnormal amplification of both oncogenes and tumor suppressor genes playing crucial roles in tumor initiation and progression. Among these, BRCA1 and BRCA2 are well-known tumor suppressor genes associated with breast cancer risk (Barchuk et al., 2018).

BRCA1 and BRCA2 are located on chromosomes 17q21 and 13q12, respectively, and encode proteins that suppress tumor formation. A deficiency in BRCA1 disrupts cell cycle checkpoints, causes abnormal centrosome duplication, genetic instability, and ultimately leads to apoptosis (Edge et al., 2014). The expression of BRCA1 is regulated by pocket proteins such as p130, p107, and the retinoblastoma protein in an E2F-dependent manner. Furthermore, the BRCA1 gene forms a regulatory loop between its promoter, introns, and terminator regions (Ferlay et al., 2020). The BRCA2 protein is essential for recombination repair in DNA double-strand breaks by interacting with RAD51 and DMC1 (Galukande et al., 2021). BRCA2-associated breast cancers are often high-grade invasive ductal carcinomas with a luminal phenotype (Globocan, 2021). Mutations in BRCA1 or BRCA2 significantly increase breast cancer risk, accounting for about 20-25% of hereditary breast cancers and 5-10% of all breast cancers (Gulzar et al., 2019). A meta-analysis revealed that women over 70 years carrying BRCA1 or BRCA2 mutations have a breast cancer risk ratio of 57% and 49%, respectively (Institute of Health Metrics Evaluation, n.d.).

The human epidermal growth factor receptor 2 (HER2), also known as c-erbB-2, is an oncogene located on chromosome 17q12. The homolog in mice, Neu, was first identified in

3-methylcholanthrene induced rat neuroblastoma cells (Khan et al., 2018). HER2 gene expression is primarily activated through gene amplification and rearrangement. The HER2 protein, part of the tyrosine kinase family, forms heterodimers with other ligand-bound EGFR family members such as HER3 and HER4, activating downstream signaling pathways (Langenhoven et al., 2016). Overexpression of HER2, found in about 20% of primary breast cancers, increases cancer stem cells through the PTEN/Akt/mTORC1 signaling pathway, indicating poor clinical outcomes (Mitra & Dey, 2016).

The epidermal growth factor receptor (EGFR), also known as c-erbB-1 or HER1, is located on chromosome 7p12. The EGFR protein, a cell surface glycoprotein of the tyrosine kinase family, is activated by binding to ligands such as EGF and TGF-α. EGFR activation triggers downstream signaling pathways like PI3K, Ras-Raf-MAPK, and JNK, promoting cell proliferation, invasion, and angiogenesis while protecting cells from apoptosis (Rodriguez et al., 2017). Overexpression of EGFR is observed in more than 30% of inflammatory breast cancer (IBC) cases, a particularly aggressive breast cancer subtype. EGFR-positive IBC patients generally have a poorer prognosis compared to those with EGFR-negative tumors (Saeed et al., 2021). Additionally, over half of triple-negative breast cancer (TNBC) cases, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 amplification, exhibit EGFR overexpression (Sharp et al., 2019).

The c-Myc gene, located on chromosome 8q24, encodes the Myc protein, a transcription factor containing the bHLH/LZ domain. Myc protein regulates approximately 15% of all genes by binding to the E-box consensus and recruiting histone acetyltransferases or DNA methyltransferases (Sood et al., 2020). Myc-regulated genes, such as MTA1, hTERT, and PEG10, play crucial roles in breast cancer initiation and progression. Overexpression of c-Myc is predominantly seen in high-grade, invasive breast carcinomas, while benign tissues show no c-Myc amplification (World Health Organization, 2020).

The Ras gene family includes H-ras, K-ras, and N-ras, located on chromosomes 11p15, 12p12, and 1p22, respectively. Proteins encoded by these genes belong to the small GTP-binding protein superfamily (Zhang et al., 2018). Point mutations commonly lead to overexpression of Ras genes, with most mutations being missense mutations at the GTP binding domain. Although Ras protein mutations are infrequent in breast cancer (<5%), abnormalities in Ras signaling pathways are observed in both benign and malignant mammary tissues (Zheng et al., 2021). H-ras, in particular, can cooperate with BMI1 to

promote proliferation, invasion, and inhibit apoptosis in breast cancer cells (Ferlay et al., 2023). Overexpression of H-ras is detected in both primary and advanced breast cancer patients, indicating a poor prognosis (Globocan, 2018).

Risk Factors of Breast Cancer

Breast cancer is influenced by a variety of risk factors, including age, family history, reproductive factors, estrogen, and lifestyle choices, as highlighted in a pyramid chart representing these risks. Effective prevention strategies encompass screening methods such as mammography and MRI, chemoprevention using selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), as well as biological prevention with drugs like Herceptin and pertuzumab. Immunotherapy, particularly PD1/PDL1 inhibitors, shows promise in treating triple-negative breast cancer (TNBC) (Saeed et al., 2021; Sood et al., 2020).

Aging, alongside sex, is a significant risk factor for breast cancer, with incidence rates increasing with age. In the United States, a striking 99.3% and 71.2% of breast cancer-associated deaths in 2016 occurred in women over 40 and 60 years of age, respectively (Siegel et al., 2022). In Nigeria, the highest incidence is observed in the 60-69 age group (Fatiregun et al., 2020). Given these statistics, early mammography screenings for women aged 40 and older are crucial in early detection and management of the disease (Globocan, 2018).

Family history plays a critical role in breast cancer risk, with nearly 25% of cases linked to familial predispositions (Brewer et al., 2017). Women with a first-degree relative diagnosed with breast cancer face a 1.75-fold increased risk, which escalates to 2.5-fold or higher with two or more affected relatives (Brewer et al., 2017). This heightened susceptibility is partly due to mutations in breast cancer-related genes such as BRCA1 and BRCA2, underscoring the importance of genetic counseling and testing (Khan et al., 2018).

Reproductive factors significantly impact breast cancer risk. Early menarche, late menopause, late age at first pregnancy, and low parity are associated with increased risk. Each year of delayed menopause raises the risk by 3%, while each year of delayed menarche or each additional birth reduces the risk by 5% and 10%, respectively (Hall & Valten, 2017). A Norwegian cohort study reported a hazard ratio (HR) of 1.54 for women having their first child at age 35 or older compared to those who gave birth before age 20 (Dall & Britt, 2017).

Furthermore, reproductive factors are closely linked with estrogen receptor (ER) status, affecting the odds ratios (OR) for ER+ and ER- breast cancer based on parity and age at first birth (Dall & Britt, 2017). A study among Nigerian women showed that prolonged breastfeeding significantly lowers breast cancer odds, particularly in younger women and those with ER- breast cancer (Azubuike et al., 2022).

Both endogenous and exogenous estrogens are implicated in breast cancer risk. Endogenous estrogen, produced by the ovaries in premenopausal women, can be reduced by ovariectomy (Soroush et al., 2016). Exogenous estrogens, from oral contraceptives and hormone replacement therapy (HRT), also contribute to risk. Despite advancements in contraceptive formulations, African American and Iranian women still face an OR higher than 1.5 (Soroush et al., 2016). However, discontinuing oral contraceptives for more than ten years negates this risk (Horn & Vatten, 2017). HRT, widely used for menopausal symptoms, has been shown to increase breast cancer risk, with the Million Women Study reporting a relative risk (RR) of 1.66 for current users (Liu et al., 2016). Asian cohort studies also reflect elevated hazard ratios (HRs) after extended HRT use (Liu et al., 2016).

Lifestyle choices, such as alcohol consumption and high dietary fat intake, significantly affect breast cancer risk. Alcohol elevates estrogen-related hormone levels, with a meta-analysis revealing a 32% increased risk for those consuming 35-44 grams of alcohol daily, and a 7.1% increase for every additional 10 grams per day (Jung et al., 2016). The modern Western diet, high in saturated fats, is associated with increased mortality and poor prognosis in breast cancer patients (Knight et al., 2017). Although the link between smoking and breast cancer remains debated, mutagens from cigarette smoke have been detected in non-lactating breast fluid. Women who both smoke and drink have a higher risk (RR=1.54), and early-age smoking poses a significant risk (Gaudet et al., 2017). Therefore, lifestyle modifications are critical for reducing breast cancer risk (World Health Organization, 2020).

In conclusion, the multifaceted nature of breast cancer risk factors necessitates comprehensive prevention and early detection strategies. Aging, family history, reproductive factors, estrogen exposure, and lifestyle choices collectively shape breast cancer risk profiles, emphasizing the need for personalized screening and prevention efforts to mitigate the impact of this pervasive disease (Ferlay et al., 2020; Globocan, 2021).

Early Detection of Breast Cancer

Early detection of breast cancer involves identifying the disease at its initial stages (0, I, or II), where treatment tends to be more effective. This process relies on "early diagnosis" approaches and "screening" specific subgroups without breast symptoms (Ferlay et al., 2020). Both methods aim to shift the stage distribution of diagnosed cancers towards earlier stages, enhancing the chances of successful treatment (Barchuk et al., 2018). The primary objective of an early detection program is to diagnose over 60% of invasive breast cancer cases at stages I or II (Globocan, 2021). Enhancing early detection through increased screening and timely diagnosis is essential, as delays can lead to more advanced and complicated disease states (Siegel et al., 2022).

Early diagnosis serves as a strategic alternative to systematic screening, necessitating changes in health-seeking behaviors among women. This can be achieved by educating communities on the early symptoms of breast cancer and the importance of prompt detection (Saeed et al., 2021). Training healthcare providers to recognize symptoms and ensuring timely referrals and access to quality diagnostic facilities are crucial components of early diagnosis (Langenhoven et al., 2016). Although screening is complex and resource-intensive, focusing on symptomatic women makes early diagnosis more feasible and affordable (Zhang et al., 2018). Despite its limitations, early diagnosis can significantly improve breast cancer survival rates and patients' quality of life (Edge et al., 2014).

Raising public awareness about breast cancer, including its signs and symptoms, is vital for early medical intervention. This can be achieved through media campaigns, workshops, and community-based programs led by healthcare professionals (Rodriguez et al., 2017). Educating the public on healthy lifestyle choices, such as reducing sugary drink consumption and promoting regular exercise, can also play a role in prevention (World Health Organization, 2020). Schools should provide nutritional guidance and promote physical activities to instill healthy habits from a young age (Galukande et al., 2021). Civil society organizations and frontline healthcare providers play a critical role in disseminating health promotion messages (Sharp et al., 2019). Screening for breast cancer involves systematic examinations of asymptomatic women to detect cancers at in situ or early invasive stages, aiming to reduce mortality (Ferlay et al., 2020).

Breast self-examination (BSE) is a cost-effective and straightforward method that women can perform themselves. It involves inspecting and feeling the breasts for any abnormalities, such as lumps or changes in size or texture (Khan et al., 2018). Regular BSE can enhance the

chances of early detection and improve survival rates (Zheng et al., 2021). Clinical breast assessment (CBA) involves a series of clinical tools for early diagnosis at the primary care level. It includes taking a medical history and performing a general examination to identify any changes in the breast (Sood et al., 2020). Clinical breast examination (CBE), a component of CBA, involves visual inspection and palpation of the breast and surrounding areas by a healthcare provider (Mitra & Dey, 2016). While CBE is simpler and requires less equipment than mammography, its sensitivity is lower, and it often leads to unnecessary diagnostic investigations (Ferlay et al., 2023).

Early diagnosis programs are the foundation of breast cancer detection efforts. They encourage individuals with early symptoms to seek care and undergo diagnostic evaluations, distinguishing them from screening programs targeting asymptomatic women (Globocan, 2018). Mammography, an X-ray examination of the breast, is the most commonly recommended screening method and is essential for early detection (Gulzar et al., 2019). For young women, imaging evaluations should be conducted by experienced professionals to ensure accurate diagnosis (Institute of Health Metrics Evaluation, n.d.). Prompt diagnosis is crucial when suspicious abnormalities are identified, emphasizing the need for timely imaging and intervention (Zhang et al., 2018).

Improving Breast Cancer Survival

The ideal goal for addressing breast cancer should be reducing its incidence, yet the options are limited and long-term, particularly for low- and middle-income countries (LMICs). Some lifestyle modifications, such as regular exercise, healthy dietary habits, and avoiding postmenopausal hormone replacement therapy, can significantly impact breast cancer incidence (Sood et al., 2020). Efforts should focus on mitigating these risk factors to reduce breast cancer risk. However, even with robust prevention strategies, the incidence of breast cancer is likely to rise in most developing countries due to changes in reproductive patterns, reduced physical activity, and increased life expectancy (Globocan, 2021).

Another crucial priority should be increasing survival rates through early detection and timely treatment, which can lead to substantial improvements in survival, particularly in developing countries (Barchuk et al., 2018). Enhanced education about breast cancer and expanded healthcare coverage could significantly improve survival rates, as observed in developed regions (Rodriguez et al., 2017). Educational initiatives must highlight that breast cancer is

often curable when detected early, diagnosed accurately, and treated appropriately (Kreps, 2018). For optimal success, these programs need to adapt to potential cultural barriers surrounding breast cancer diagnosis in LMICs (Caplan, 2016).

Research on why breast cancer patients in LMICs are diagnosed at advanced stages remains scarce. Studies from developed countries show an association between delays of more than three months from symptom discovery to treatment initiation and advanced clinical stages of breast cancer, as well as reduced survival rates (Richards et al., 2014; Galukande et al., 2021). This delay influences disease progression, subsequently affecting survival (Langenhoven et al., 2016). Additionally, there are significant knowledge gaps regarding breast cancer structure and processes in most LMICs. Available data indicate a substantial need for improved access to and quality of care to enhance breast cancer outcomes (Saeed et al., 2021).

Investment in breast cancer control in LMICs is urgently needed, as increasing screening coverage is a critical step toward reducing breast cancer mortality (Ferlay et al., 2020). Mammography remains the standard of care in breast cancer screening, and early detection combined with appropriate diagnosis is essential for achieving favorable outcomes. Clinical studies have shown that mammography screening can reduce breast cancer mortality by at least 20% (Ferlay et al., 2020). However, supporting any screening program requires sustainable funding, project management, trained physicians, and affordable care. Most populations in LMICs rely on public healthcare systems, which affects timely tumor diagnosis and treatment (Sharp et al., 2019).

Over the past decade, cancer healthcare programs have started gaining priority in LMICs. However, late-stage diagnosis continues to impede improvements in breast cancer outcomes, diminishing the importance of early detection (Siegel et al., 2022). In some developing countries, screening mammograms are not affordable for all at-risk women, and the coverage provided by the health system is insufficient (Globocan, 2018). Despite acknowledging diagnosis and treatment delays as detrimental to survival, there is a lack of studies investigating the reasons behind better survival outcomes, a concept that has been recognized since the early 20th century (Gulzar et al., 2019).

Historically, Dr. William Halsted, an American surgeon renowned for introducing radical mastectomy, suggested that while the cure of breast cancer was improbable, early operation

could lead to probable outcomes (Mitra & Dey, 2016). For almost seventy years, research on delays in breast cancer treatment has been contradictory, either supporting or refuting an association with survival. Yet, the consensus among physicians, researchers, and patients over the past century has been to avoid medical attention upon discovering cancer symptoms (Zheng et al., 2021).

In 1999, Richards and colleagues clarified the relationship between global delay and survival through a meta-analysis of observational studies published between 1907 and 1996, demonstrating that women with delays longer than three months had shorter survival compared to those who commenced treatment within three months of symptom discovery (Edge et al., 2014). This study remains one of the strongest pieces of evidence available. Furthermore, care delay has been categorized into patient delay (PD) and health system delay (SD) (Caplan, 2016). PD corresponds to the delay in seeking medical attention after symptom discovery, while SD pertains to delays within the healthcare system.

The oncology field defines global delay as an interval of more than three months between symptom discovery and treatment initiation, with longer delays linked to reduced survival (Langenhoven et al., 2016). Delays between three and six months may not drastically impact survival, but increased delay time correlates with clinical progression, decreasing survival rates (Galukande et al., 2021). Despite the unpredictable and heterogeneous nature of breast cancer, studies have shown reduced mortality with earlier diagnosis. Therefore, since breast cancer cannot be entirely prevented, efforts should focus on early and adequate diagnosis and treatment (Ferlay et al., 2020).

Pack and Gallo described two types of delays in 1938: PD as an interval of three months or more between symptom detection and medical consultation, and health system delay when treatment initiation takes longer than a month post-consultation (Saeed et al., 2021). This model, though widely accepted, has been recently questioned by many authors as reductionist and dualistic, solely based on survival and considering delays as independent factors. There is a growing consensus that a more comprehensive understanding of these delays is necessary to improve breast cancer outcomes in LMICs (Rodriguez et al., 2017).

Conclusion

Breast cancer, from a global perspective, has emerged as one of the most frequently diagnosed forms of cancer worldwide, constituting nearly 12% of all cancer cases and leading

as the primary cause of cancer deaths among women. It stands as the most prevalent cancer among women in 158 out of 183 countries and the leading cause of female cancer-related deaths in 107 of those countries. This prominence underscores the critical need for ministries of health globally to prioritize breast cancer as a significant public health issue.

Addressing breast cancer is not merely a health imperative but also a gender equity and human rights issue. Women hold central roles in society, and protecting them from breast cancer also safeguards their families, communities, and the economy at large. The burden of avoidable breast cancer deaths disproportionately affects low- and middle-income countries (LMICs), where over 70% of breast cancer deaths are premature, occurring in individuals under 70 years of age. The disparity is stark, with five-year breast cancer survival rates exceeding 90% in high-income countries (HICs), compared to 66% in India and 40% in South Africa. In sub-Saharan Africa, where half of all breast cancer deaths occur in individuals under 50 years of age, the death of 100 women from breast cancer at this young age can result in 210 children becoming maternal orphans. The chronic social disruption and financial harm from breast cancer will continue to impact LMICs for generations if current trends remain unchecked, with the cancer burden projected to increase to 2.74 million new cases and 1.04 million deaths by 2040.

Significant improvements in breast cancer outcomes have been achieved over the past four decades, with 20 countries successfully reducing breast cancer mortality by at least 2% per year for three consecutive years. However, higher fatality rates in LMICs and among disadvantaged populations are largely due to late-stage diagnosis and limited access to quality treatment. In several LMICs, this issue is compounded by a lack of awareness regarding the benefits of early detection and effective therapies. There is a pressing need to strengthen health systems to respond to the growing burden of breast cancer, using sustainable, cost-effective, and equitable early detection and treatment services, particularly in LMICs. These efforts must be integrated within a community-health framework that engages primary care facilities and secondary and tertiary care centers.

Improving breast cancer outcomes requires a concerted and innovative approach to ensure that women are aware of common symptoms and understand the necessity of consulting healthcare providers if any symptoms arise. Primary healthcare providers should be trained to perform quality clinical examinations of symptomatic women. Systematic clinical breast exams by appropriately trained providers have a high negative predictive value and can

efficiently rule out the presence of disease. Women with abnormalities on clinical examination should have access to diagnostic imaging, followed by diagnostic confirmation with either core needle biopsy (CNB) or fine-needle aspiration cytology (FNAC). CNB is advantageous in providing tissue for immunohistochemistry and diagnosing conditions like atypical ductal hyperplasia and in situ carcinomas, whereas FNAC is rapid, simpler logistically, and more acceptable to patients, with marginally lower sensitivity and specificity than CNB.

Establishing breast ultrasound and guided FNAC facilities at the secondary level of care can significantly enhance early diagnosis of breast cancers in healthcare settings. It is crucial to monitor existing screening activities in countries with national recommendations for mammography-based or clinical breast examination (CBE)-based screening. Proper evaluation of these programs will not only improve the quality of services but also generate valuable evidence on the effectiveness of screening in countries undergoing transition.

Breast cancer is curable at an early stage. Enhancing surgical care with a multidisciplinary approach, ensuring the availability of good-quality anesthesia facilities, improving histopathology and basic immunohistochemistry capacities, and providing access to tamoxifen for estrogen receptor-positive tumors and cytotoxic chemotherapy for more biologically aggressive cancers can have a substantial impact on breast cancer survival. Policymakers must commit and invest rationally to save the lives of thousands of women currently succumbing to a curable cancer

References

Barchuk, A., Bespalov, A., Huhtala, H., Chimed, T., Laricheva, I., & Belyaev, A. (2018). Breast and cervical cancer incidence and mortality trends in Russia 1980-2013. *Cancer Epidemiology, 55*, 73–80.

Edge, J., Buccimazza, I., Cubasch, H., & Panieri, E. (2014). The challenges of managing breast cancer in the developing world—a perspective from sub-Saharan Africa. *South African Medical Journal, 104*, 377–379. https://doi.org/10.7196/SAMJ.8249

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mercy, L., & Pineros, M. (2020; 2023). Cancer today. Lyon International Agency for Research on Cancer. https://gco.iarc.fr/today (accessed 3rd January 2023)

Ferlay, J., Laveisanne, M., Ervik, M., Lam, F., Colombet, M., & Mercy, L. (2020; 2023). Cancer tomorrow. Lyon International Agency for Research on Cancer. https://gco.iarc.fr/today (accessed 3rd January 2023)

Galukande, M., Schuz, J., Anderson, B. O., Zietsman, A., & Adisa, C. (2021). Maternally orphan children and intergenerational concerns associated with breast cancer deaths among women in sub-Saharan Africa. *JAMA Oncology, 7*(2), 285-89.

Globocan. (2021). Global cancer observatory. Available from: https://gco.iarc.fr/today/data/factsheets/populations/586-pakistan-fact-sheets.pdf

Globocan. (2018). Nigeria Cancer Fact Sheet. https://gco.iarc.fr/today/data/factsheets/populations/566-nigeria-fact-sheets.pdf

Gulzar, F., Akhtar, M. S., Sadiq, R., Bashir, S., Jamil, S., & Baig, S. M. (2019). Identifying the reasons for delayed presentation of Pakistani breast cancer patients at a tertiary care hospital. *Cancer Management and Research, 11*(4), 1087–96. https://doi.org/10.2147/CMAR.S180388

Institute of Health Metrics Evaluation (IHME). (n.d.). https://vizhub.healthdata.org/gbd-compare/ (accessed on July 15, 2022)

Khan, R. T., Siddique, A., Shahid, N., Khokher, S., & Fatima, W. (2018). Breast cancer risk associated with genes encoding DNA repair MRN complex: A study from Punjab, Pakistan. *Breast Cancer, 25*(3), 350–5. https://doi.org/10.1007/s12282-018-0837-9

Langenhoven, L., Barnardt, P., Neugut, A. I., & Jacobson, J. S. (2016). Phenotype and treatment of breast cancer in HIV-positive and -negative women in Cape Town, South Africa. *Journal of Global Oncology, 2*(5), 284–91.

Mitra, S., & Dey, P. (2016). Fine-needle aspiration and core biopsy in the diagnosis of breast lesions: A comparison and review of the literature. *CytoJournal, 13*, 18.

Rodriguez, E. L., Molina, C., Rivera Franco, M. M., & Campos Castro, A. (2017). Breast self-exam and patient interval associate with advanced breast cancer and treatment delay in Mexican women. *Clinical and Translational Oncology, 19*, 1276–1282. https://doi.org/10.1007/s12094-017-1666-6

Saeed, S., Asim, M., & Sohail, M. M. (2021). Fears and barriers: Problems in breast cancer diagnosis and treatment in Pakistan. *BMC Women's Health, 21*(1), 1-10. https://doi.org/10.1186/s12905-021-01293-6

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jermal, A. (2022). Cancer statistics. *CA: A Cancer Journal for Clinicians, 72*, 7-33. https://doi.org/10.3322/caac.21708 https://pubmed.ncbi.nlm.nih.gov/35020204/ (accessed 6th February 2023)

Sharp, J. W., Hippe, D. S., Nakigudde, G., Anderson, B. O., Muyinda, Z., & Molina, Y. (2019). Modifiable patient-related barriers and their association with breast cancer detection practices among Ugandan women without a diagnosis of breast cancer. *PLoS One, 14*, e0217938. https://doi.org/10.1371/journal.pone.0217938

Sood, A. K., Nemeth, M., Wang, J., Wu, Y., & Gandhi, S. (2020). Opportunities for antigen discovery in metastatic breast cancer. *Frontiers in Immunology*. https://doi.org/10.3389/fimmu.2020.570049

World Health Organization. (2020). e-Library of Evidence for Nutrition Actions (eLENA). Reducing consumption of sugar sweetened beverages to reduce the risk of unhealthy weight gain in adults. Available from: https://www.who.int/elena/bbc/ssbs_adult_weight/en/

Zhang, X., Lin, X., Tan, Y., Zhu, Y., Wang, H., & Feng, R. (2018). A multicenter hospital-based diagnosis study of automated breast ultrasound system in detecting breast cancer among Chinese women. *China Journal of Cancer Research, 30*, 231–9.

Zheng, Q., Zhang, M., Zhou, F., Zhang, L., & Meng, X. (2021). Breast cancer stem cells traits and drug resistance. *Pharmacology of Anti-Cancer Drugs, 11*. https://doi.org/10.3389/fphar.2020.599965