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Review

Preventive Strategies and Screening Protocols for Early Detection of Breast Cancer

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Abstract

Breast cancer is a critical global health issue, with around 2.3 million new cases annually. Risk factors include genetic predispositions, hormonal influences, and lifestyle choices. Preventive measures have evolved, particularly for women with BRCA1/2 mutations, though their uptake varies. Recent guidelines aim to expand testing criteria, enabling earlier identification of high-risk individuals. While treatments have advanced, especially for early-stage cancers through multimodal approaches, metastatic breast cancer remains challenging to cure. The World Health Organization emphasizes the importance of early diagnosis and screening, particularly in low- and middle-income countries where late-stage diagnoses are more common. Ongoing research focuses on preventive strategies such as diet, exercise, and chemoprevention. Innovative diagnostic tools and targeted therapies, including nanoparticle-based methods, show promise for earlier detection and personalized treatment. Enhancing both preventive measures and management strategies is crucial for improving outcomes and reducing the global burden of breast cancer. Addressing these factors comprehensively is essential for effective breast cancer control worldwide.

Keywords: *breast cancer, risk factors, preventive measures, screening, early diagnosis, metastatic cancer, diagnostic tools*

Introduction

Breast cancer is still a significant worldwide health concern, with approximately 2.3 million new diagnoses each year (1). The risk of developing this disease is influenced by factors including genetic predisposition, hormonal levels, lifestyle choices, and benign breast conditions. Among these, genetic factors such as pathogenic mutations in breast cancer gene 1 (BRCA1) and BRCA2 genes significantly increase susceptibility. Endogenous hormones affected by age at menarche, menopause, parity, and breastfeeding duration along with exogenous hormones from contraceptives and hormone replacement therapy, also play a critical role. Additionally, lifestyle factors like high alcohol consumption, smoking, physical inactivity, and anthropometric factors including higher body weight and increased central fat are associated with increased risk (2).

These risk factors and their impact on breast cancer development and subtypes advances (3), preventive measures have become more targeted. Women with BRCA1/2 mutations may choose prophylactic bilateral mastectomy or chemoprophylaxis with tamoxifen or other selective oestrogen receptor modulators, although uptake of these measures is limited. Historically, high-risk groups have been identified through family history or ancestry linked to BRCA1/2 variants, such as Jewish descent. Currently, genetic testing is reserved for women with breast cancer, particularly those with triple-negative, bilateral, or young-onset disease, and is often offered only if there is a family history of the disease (2). However, the 2019 US Preventive Services Task Force guidelines have expanded testing criteria to include women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer, as well as those with ancestry associated with BRCA1/2 variants (4).

The molecular diversity of breast cancer necessitates a variety of treatment approaches, including biologically targeted therapies and treatment de-escalation to minimize adverse effects (5). To enhance early detection of breast cancer, the World Health Organization advocates for two strategies: early diagnosis of symptomatic disease and screening for asymptomatic individuals (6). In low- and middle-income countries (LMICs), where many women are diagnosed at advanced stages, promoting early diagnosis is crucial before establishing population-based screening programs. Early diagnosis can improve patient outcomes, as even the most effective screening programs may miss a considerable proportion of cases. Thus, prioritizing early diagnosis is essential until appropriate screening infrastructure is in place.

This knowledge is critical for making informed decisions about investments, planning, and policy development to ensure efficient breast cancer prevention and care. The Breast Health Global Initiative (BHGI) has developed resource-stratified guidelines for breast cancer detection, providing a framework for health planners and policymakers (7, 8). This approach underscores the importance of ongoing evaluation and improvement to maintain high-quality care.

While advancements in treatment have improved outcomes for early-stage breast cancer, which now has a cure rate of 70–80% due to multimodal therapy, metastatic breast cancer remains incurable with current treatments. Nonetheless, it is manageable with a focus on extending survival, controlling symptoms, and minimizing treatment-related toxicity to enhance quality of life (5).

Review

Breast cancer originates from the abnormal proliferation and division of cells, primarily due to mutations in regulatory genes (9). These genes are categorized into three types: oncogenes, proto-oncogenes, and tumour suppressor genes. Proto-oncogenes, when mutated, become oncogenes, and produce oncoproteins that disrupt cell cycle regulation and genomic stability, leading to uncontrolled growth. Tumour suppressor genes, crucial for DNA repair, if mutated, cause cell division abnormalities. These disruptions contribute to cancer progression from preneoplastic lesions to metastatic disease (9, 10).

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Breast cancer is the most common malignancy globally, with early detection improving treatment outcomes. Metastasis primarily affects the lungs, liver, bones, and brain. The progression involves cell invasion, intravasation into blood vessels, extravasation into tissues, colonization, and distant spread. Intravasation disrupts endothelial cell junctions with the help of macrophages and tumour-cell interactions. Extravasation requires specific factors for cell movement through endothelial junctions (9).

Metastatic breast cancer in the brain can be categorized into three types based on anatomy: leptomeningeal metastasis, parenchymal metastasis, and choroid plexus metastasis. Parenchymal metastasis is the most common, accounting for 78% of cases, with solitary metastases making up 14%. Leptomeningeal metastasis occurs in about 8% of cases, while choroid plexus metastasis is rare (11).

Diagnosis

Women presenting with breast symptoms or changes, such as a lump, localized pain, nipple symptoms, or skin alterations, require a thorough diagnostic evaluation. This also applies to women recalled for additional testing following positive screening mammography. The diagnosis of breast cancer relies on a triple test approach, which includes clinical examination, imaging typically mammography and/or ultrasonography, and needle biopsy (5). The diagnostic process involves executing the components of the triple test, considering the patient's characteristics and presentation. This assessment should be completed prior to initiating treatment. An accurate assessment is crucial for distinguishing between breast cancer and benign conditions such as fibroadenoma or normal breast changes. Proper evaluation ensures that patients with benign conditions or normal changes can be reassured or managed with follow-up, thus avoiding unnecessary surgical intervention.

Ultrasonography is widely employed to evaluate localized symptoms and is often used as the initial imaging modality in younger women. It is effective for identifying and characterizing abnormalities detected during screening and is commonly used for imaging-guided percutaneous biopsies. Additionally, breast ultrasonography can be utilized to characterize and biopsy axillary lymph nodes in women suspected of having breast cancer (12). Magnetic Resonance Imaging (MRI) is also part of the imaging evaluation, particularly for specific clinical situations. MRI is recommended when conventional imaging tests yield inconclusive or discordant results, for assessing women with breast implants, and for evaluating cases with axillary nodal metastases but no detectable breast tumour (13, 14). Preoperative MRI is sometimes used for staging newly diagnosed breast cancer; however, its benefit in improving clinical outcomes is debated due to limited evidence (14). MRI is particularly advised for the preoperative assessment of newly diagnosed invasive lobular cancers (13).

Pathological Reporting

A standardized synoptic pathology report with a checklist after biopsy is strongly recommended for comprehensive and consistent breast cancer diagnosis **(Table 1)** (5).

Table 1. Essential Components of the Pathology Report for Invasive Carcinoma (5).

Category	Summary
Histotype	Includes major subtypes like invasive carcinomas of no special type and lobular carcinomas, guiding treatment, and prognosis.
Histological Grade	Determined by the Elston-Ellis system, which assesses tubule formation, nuclear size, and mitotic count, reflecting tumor aggressiveness.
Theranostic Biomarkers	Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) are key biomarkers, assessed via immunohistochemistry. Proliferation marker is used for ER-positive, HER2-negative cancers.
Vascular Invasion and Margins	Vascular invasion correlates with metastases. Margins should be free of cancer; positive margins need further surgery.
Lymph Node Status and Stage	Lymph node status is assessed by sentinel biopsy or axillary dissection. TNM staging system classifies the extent of disease.

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Diagnostic potential of nanoparticles in breast cancer

Recent advancements in nanotechnology have revolutionized cancer diagnostics (15, 16). Nanoparticles, thanks to their specialized surface chemistry and structural adaptability, can preferentially accumulate in tumor tissues, enhancing diagnostic sensitivity and specificity (15, 17). Current blood tests and imaging procedures are being improved with innovative nanoparticle-based techniques. Examples include the use of iron oxide nanoparticles (IONPs) for brain metastasis imaging (18), self-illuminating nanoprobes for identifying tumor-infiltrating neutrophils (19), adenosine triphosphate (ATP)-responsive superparamagnetic iron oxide nanoparticles (SPIOs) (20), and peptide-functionalized magnetic nanoparticles to detect HER2 on circulating tumor cells (21). For instance, Du et al. used ultrasmall IONPs, modified with a peptide from phage display (BRBP1), to achieve precise imaging of breast cancer brain metastasis (18). These IONPs showed high binding affinity for breast cancer cells in the brain, providing improved imaging contrast and detection accuracy for metastasis. Similarly, Zheng et al. developed a novel nanoprobe for lung metastasis detection, utilizing self-illuminating nanoprobes that target neutrophil infiltration, a key early indicator of metastasis. This approach achieved 98% sensitivity and 96% specificity (19). These examples underscore the significant potential of nanoparticle-based imaging techniques in early metastasis detection and their promise in enhancing personalized breast cancer treatment.

Wang G et al. advanced the field of dual-modality imaging by utilizing superparamagnetic iron oxide nanoparticles (SPIOs) (20). These nanoparticles, which respond to ATP, can detect high metabolic activity in tumours. When introduced into the body, they accumulate in metastatic lymph nodes and produce strong molecular fluorescence. This approach also offers deep tissue penetration, enhancing the sensitivity of metastatic disease detection (20). Complementing this technique, Liang et al. used photodynamic therapy (PDT) for early detection and precise treatment initiation. Their method involved an optical microfiber sensor integrated with gold nanorods and black phosphorus (22).

In addition to imaging metastasis, nanoparticle-based platforms are showing promise in detecting circulating tumour cells (CTCs). Analysing CTCs provides crucial insights into metastasis and cancer progression (23). Early detection of CTCs is essential for starting personalized therapies on time, potentially improving patient outcomes. Wang M et al. developed a fluorescent technique using peptide-functionalized magnetic nanoparticles to quantify HER2 on CTCs (21). This technique not only quantifies CTCs but also offers prognostic information that could guide therapy decisions and enhance patient outcomes.

Systemic toxicity and immune reactions from nanoparticle interactions with biological systems necessitate rigorous safety evaluations (22).

Preventive strategies for breast cancer

Diet and exercise

A growing body of evidence supports that dietary and physical activity modifications play a significant role in reducing breast cancer risk. Studies indicate that consuming a diet low in saturated fats and high in fiber can mitigate the risk of developing breast cancer. Diets rich in fruits, vegetables, and whole grains, coupled with regular physical activity, are associated with a lower incidence of breast cancer. Regular exercise contributes to overall health and helps maintain a healthy weight, further reducing risk factors associated with breast cancer (24, 25).

Alcohol consumption

Alcohol consumption is a well-established risk factor for breast cancer, with research demonstrating that even moderate alcohol intake can increase the likelihood of developing the disease. Studies consistently highlight the association between alcohol and elevated breast cancer risk, prompting recommendations to limit alcohol consumption as a preventive measure. Adhering to these guidelines can help reduce the

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risk of breast cancer and contribute to overall cancer prevention efforts (2).

Weight management

Obesity is another significant risk factor for breast cancer, particularly in postmenopausal women. Excess body weight is linked to higher levels of oestrogen and other hormones that may promote breast cancer growth. Maintaining a healthy weight through a balanced diet and regular physical activity is crucial for reducing breast cancer risk. Weight management strategies should focus on achieving and sustaining a healthy weight, which includes a combination of caloric control, healthy eating patterns, and consistent physical exercise (2).

Chemoprevention with Anti-Oestrogens

Prospective randomized controlled trials (RCTs) assessing primary prevention of breast cancer with selective oestrogen receptor modulators or aromatase inhibitors have consistently demonstrated a reduction in the incidence of hormone receptor-positive breast cancer subtypes (2). However, to prevent one case of breast cancer over the next 20 years, 22 women would need to take tamoxifen daily for 5 years (26).

The significant adverse effects associated with anti-oestrogens, combined with the lack of overall or breast cancer-specific survival benefits and no reduction in the incidence of aggressive, hormone receptor-negative breast cancers, make it challenging to determine whether it is more effective to use these drugs for preventive purposes in healthy women or to reserve them for adjuvant treatment of diagnosed cases. Nonetheless, the US Preventive Services Task Force has noted that serious adverse effects, such as thrombosis and endometrial cancer, are rare, and common toxicities, like vasomotor symptoms, are reversible and only slightly more frequent in those on active treatment compared to those on placebo in the RCTs (27). As a result, several international guidelines recommend the use of anti-oestrogens for chemoprevention in women at elevated risk of breast cancer (2). Future RCTs will need to determine if improved risk stratification can reduce the number of healthy women required to take anti-oestrogens to achieve the same preventive benefits.

Surgical prevention

Prophylactic bilateral mastectomy is the most effective method for preventing breast cancer and decreasing breast cancer-specific mortality among the small percentage of women approximately 3% with a germline pathogenic BRCA1/2 variant (2). Nipple-sparing mastectomies are considered a safe option for these women and do not adversely affect the risk reduction (28). However, general complications associated with this procedure include wound dehiscence, infection, implant loss, flap necrosis, asymmetry, and capsular contracture (29). The overall complication rate for nipple-sparing mastectomies has been reported as 22.3%, with a nipple necrosis rate of 5.9% (30).

Despite its effectiveness, surgical prevention can lead to other complications and adverse effects, such as psychological distress related to changes in body image and poses resource-related implications. Therefore, it is essential to evaluate the clinical utility, feasibility, and acceptability of surgical prevention to determine the appropriate risk threshold for intervention (2).

Other preventive strategies

In recent years, several new potential targets for breast cancer prevention have emerged. Notably, progesterone plays a crucial role in the development of aggressive breast cancers. A meta-analysis of 58 studies found that women using menopausal hormone therapy containing progesterone had a higher incidence of breast cancer and a greater likelihood of advanced-stage disease compared to women using oestrogen-only treatments or no hormone therapy (31). Additionally, women on progesterone-containing therapy were more likely to die from breast cancer than those receiving oestrogen-only treatments (32).

The role of progesterone in breast carcinogenesis is further supported by findings that women with germline pathogenic BRCA1/2 variants have higher levels of luteal phase progesterone compared to carriers of non-pathogenic BRCA1/2 variants (33).

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Elevated progesterone levels lead to increased receptor activator of nuclear factor-κB ligand (RANKL) and decreased levels of its antagonist, osteoprotegerin, which promotes the expansion of ER and progesterone receptor-negative mammary stem cells, potentially leading to breast cancer (2).

Further evidence comes from a case-control study suggesting that moderate use of dietary supplements containing folic acid and vitamin B12 may offer protection against BRCA1/2-associated breast cancer (34). Other potential chemotherapeutic agents for risk reduction include aspirin, metformin, and statins; however, clinical trial evidence supporting these strategies is currently lacking. Denosumab, a fully humanized monoclonal antibody targeting Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL), has demonstrated the ability to reduce breast epithelial cell proliferation in premenopausal women (35). Nevertheless, it does not appear to affect the incidence of contralateral breast cancer in postmenopausal women (36).

Future directions

To advance preventive strategies and screening protocols for early detection of breast cancer, several key areas require focus. Research should continue to refine and expand genetic testing guidelines to identify high-risk individuals earlier, particularly in diverse populations. Developing and validating innovative diagnostic tools, such as nanoparticle-based methods, holds promise for enhancing early detection. Additionally, integrating lifestyle modifications and targeted chemoprevention strategies into public health guidelines could further reduce breast cancer risk. Emphasis on personalized treatment approaches and addressing disparities in screening access, particularly in low- and middle-income countries, will be critical for improving global outcomes. Continued investigation into novel biomarkers and therapeutic agents will also be essential for advancing breast cancer prevention and management.

Conclusion

Early detection and preventive strategies are crucial for reducing breast cancer mortality. While advancements in screening and diagnostic tools have improved outcomes, ongoing research is needed to refine these methods and address challenges, especially for high-risk populations. Integrating effective preventive measures, targeted therapies, and personalized approaches will enhance breast cancer management and patient outcomes globally.

Disclosures

Author Contributions

The author has reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Ethics Statement

Not applicable

Consent for publications

Not applicable

Data Availability

All data is provided within the manuscript.

Conflict of interest

The authors declare no competing interest.

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