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Current Trends in the Prevention and Management of Breast Cancer

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ABSTRACT

Breast cancer has become a global health challenge, with rising incidence and mortality rates, especially in developing countries. Current clinical practices are changing with new therapies and artificial intelligence (AI). Consequently, this review explores and summarizes emerging treatment modalities essential for breast cancer prevention and management, including the roles of AI and machine learning. We conducted a comprehensive review of PubMed and Google Scholar databases to gather insights into breast cancer epidemiology, prevention strategies, current treatment modalities, AI and machine learning applications, and disparities in care.

Breast cancer's risk factors include non-modifiable (e.g., age, family history) and modifiable factors (e.g., lifestyle choices). Prevention strategies encompass primary, secondary, and tertiary levels of prevention, which focus on lifestyle modifications, early detection methods such as mammography and genetic testing, and personalized care, respectively. Management options have evolved from surgery, chemotherapy, and radiation therapy to targeted therapies and immunotherapy. AI and machine learning technologies have advanced early detection, prognosis prediction with personalized treatments, and improved patient outcomes. However, driven by access barriers and socio-economic factors, disparities in breast cancer care persist among racial and ethnic minority groups. Breast cancer prevention and management require a multifaceted approach, including risk reduction, early detection, personalized treatment, and addressing disparities. AI and machine learning offer promising tools for enhancing breast cancer care, but ethical and social considerations must be addressed. Reducing disparities in breast cancer outcomes demands community-based interventions and improved access to care.

KEYWORDS: Breast cancer, Prevention, Management, Artificial Intelligence, Machine Learning

INTRODUCTION

The second most common cause of cancer death in women worldwide and the most prevalent cancer in women is breast cancer.[1,2] Its incidence and prevalence are steadily rising, especially in developing and less developed countries.[3-5] As a result, a paradigm shift in preventative measures is necessary due to its dramatically rising incidence. A proactive approach to identifying specific women at higher risk for breast cancer is essential because it reduces the overall incidence and improves the overall quality of life and outcome of these women. However, only a few preventative interventions have been put in place despite the rising frequency, with the exception of the identification and monitoring of high-risk women with BRCA1 and BRCA2 mutations.[6] This is because the prevention of this disease is not without its challenges. For prevention to become a firmly established component of breast cancer management, obstacles such as adequate tools for identifying women at risk, a clear definition of what high risk is, effective patient communication about the disease, and identification of the optimal and adequate intervention that respects the balance between benefits in risk reduction and harm from potential medication side effects must be addressed.[1] Current clinical practices dictate early detection of cancers through mammography screening and treating newly diagnosed tumors. However, inadequate infrastructure, poor health-seeking behavior, and scarce healthcare resources have made it difficult to manage the growing number of breast cancer patients.[7] As a result, the success of prevention initiatives or management strategies heavily depends on an ambitious interdisciplinary approach devoted to the potential high-yield gain of preventing the development of breast cancer or successfully treating it.[8] Subsequently, this article aims to identify the current trends for improved breast cancer prevention and to discuss current knowledge on effective management, both of which are capable of lowering the incidence of the disease.

EPIDEMIOLOGY

The World Health Organization estimates that breast cancer accounts for 19.6 million Disability-Adjusted Life Years

(DALYs) out of the 107.8 million DALYs caused by malignant neoplasms.[9] With 2.26 million new cases in 2020, breast cancer is the most frequently diagnosed malignancy in women worldwide.[10] In addition to being the most prevalent malignancy in women, it is also responsible for most deaths from cancer. In 2020, for example, breast cancer caused 684,996 deaths worldwide at a rate of 13.6/100,000 when adjusted for age.[10] However, while developed countries have the greatest incidence rates, about 63% of all deaths worldwide occur in Asia and Africa.[10] This is because in developed countries, the majority of breast cancer patients survive due to early detection and treatment. However, this is not the case for many women in developing countries who present at a later stage of the disease.[11]

RISK FACTORS

There are a substantial number of risk factors for breast cancer, including both modifiable and non-modifiable ones. Non-modifiable factors include female sex, older age, a positive family history of breast or ovarian cancer particularly in first-degree relatives, black race, pregnancy and breastfeeding, menopause, increased density of the breast tissue, previous history of breast cancer, and previous radiation therapy. Modifiable risk factors include hormonal replacement therapy, diethylstilbestrol use, physical inactivity, obesity, alcohol intake, smoking, excessive exposure to artificial light and intake of processed food.[12]

PREVENTION

The prevention of breast cancer can be addressed at the different levels of disease prevention which are, the primary, secondary, and tertiary levels of prevention.

PRIMARY PREVENTION

Primary prevention methods aim to reduce the incidence of breast cancer by preventing exposure to the modifiable risk factors that lead to the development of breast cancer.[13] It involves lifestyle modifications such as healthy eating, exercising according to recommended levels, weight management, avoiding or reducing contact with environmental toxins such as pesticides and industrial chemicals, like Bisphenol A (BPA), encouraging breastfeeding, discouraging smoking and moderate alcohol intake.[14-18]

According to the Continuous Updated Project, 2018 on Diet, Nutrition, Physical Activity, and Breast Cancer, daily moderate to intense exercise lowers the risk of developing breast cancer by about 20-30%, especially in postmenopausal women.[19,20] In addition, the consumption of diets rich in whole grains, fruits, vegetables, and unsaturated fats also reduces the risk of developing breast cancer.

Additionally, an emphasis on the cautious use of hormone replacement therapy such as administration of the lowest effective dose for the shortest duration, or using estrogen-alone therapy rather than combined estrogen and progesterone therapy to alleviate the symptoms of menopause reduces the risk of developing breast cancer.[21,22]

However, there is no clinical evidence that altering modifiable lifestyle variables can prevent breast cancer.[1] This may be because many of the risk factors for breast cancer are not modifiable and have poorly defined pathologic mechanisms.

SECONDARY PREVENTION

Breast cancer screening and early detection are the cornerstone of secondary prevention methods. The goal of screening is to identify breast cancer at a stage when a surgical cure is likely. Traditionally, this includes small breast cancers (less than 1 cm) that are node negative and with no evidence of distant spread.[23] Breast cancer screening modalities are critical for early detection and diagnosis, effective treatment, and they ultimately improve the prognosis in individuals who have the disease. Secondary prevention efforts include breast self-examination (BSE), clinical breast examination, mammography, and other and other advanced digital imaging modalities such as Digital Breast Tomosynthesis (DBT), Contrast-Enhanced Mammography (CEM), and Molecular Breast Imaging (MBI). Others include genetic Screening and Counseling and the use of breast cancer risk Assessment Tools.

BSE is a simple, non-invasive technique that women can perform on themselves to detect any lumps or changes in their breast tissue. However, while many current medical literatures question the effectiveness and suitability of routine BSE, it is still the best routinely employed secondary prevention strategy with no absolute contraindications.[24,25] Additionally, as part of a multimodal approach, a clinical breast examination performed by a healthcare provider would corroborate findings detected on self-examination.

Mammography, on the other hand, is the most common and longest-established imaging technique to screen for breast cancer. It is a highly sensitive diagnostic tool with a sensitivity ranging between 69% to 87%. Routine mammography screening started in middle age reduces the risk of breast cancer mortality.[26] And, in very much rare, high-risk cases such as in women with mammographic breast density, a positive family history, or high-penetrance genetic predisposition, earlier and more frequent screening is highly beneficial.[27,28] Other imaging modalities, such as ultrasound and magnetic resonance imaging

may also be useful as adjuncts to confirm suspicions seen on mammography.[29]

Genetic testing also demonstrates BRCA1 and BRCA2 gene mutations that by extension identify individuals with an increased risk of developing breast cancer. The National Comprehensive Cancer Network (NCCN) recommends genetic testing for individuals with a positive family history as well as the provision of vital information about prevention options, and further screening recommendations.[30]

Several risk assessment tools have also been developed to estimate the probability of developing breast cancer in asymptomatic women. The Breast Cancer Risk Assessment Tool (BCRAT), for example, which was developed by the National Cancer Institute (NCI) in conjunction with the National Surgical Adjuvant Breast and Bowel Project (NSABP), is a widely used risk assessment tool that estimates an individual's five-year and lifetime risk of breast cancer based on factors such as age, family history, and reproductive history.[31] It is also useful in determining the eligibility of high-risk individuals for chemoprevention.[32] However, its effectiveness is limited to predicting breast cancer cases in specific risk factor strata, with questionable accuracy at the individual level.[33]

Breast cancer chemoprevention refers to the use of pharmacologic or natural agents to prevent the development of invasive breast cancer by blocking DNA damage that initiates carcinogenesis, or arresting or reversing the progression of premalignant cells. The success of clinical trials in high-risk groups suggests that chemoprevention is a rational and suitable secondary prevention strategy.[34]

Also, the use of Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene has paved the way as one of the therapeutic interventions in the prevention of breast cancer.[35-37] SERMs are estrogen receptor agonists and antagonists that reduce the incidence of ER-positive primary breast cancer by up to 50%.[34-38] Aromatase inhibitors (AIs) like anastrozole and exemestane (a recently established chemo prophylactic) are another anti-estrogen class of drug used. However, the effectiveness of these agents is limited to hormonally responsive breast cancer.[34,39]

Surgical prophylaxis such as mastectomy and oophorectomy has also been attempted to prevent the onset of cancer in women who are found to be mutation-positive on screening.[40] Bilateral mastectomy in particular, is highly effective in reducing the risk of breast cancer in women with deleterious BRCA 1, BRCA2, TP53, PALB2, CDH1, or PTE mutations.[41] And this method has grown in popularity as a medium of breast cancer risk and recurrence reduction. Although surgical prophylaxis is primarily a component of secondary prevention, it, however, has some tertiary prevention elements-recurrence reduction.

TERTIARY PREVENTION

Tertiary prevention is targeted at improving the quality of life following the subsequent development of breast cancer. It includes effective management, surveillance against breast cancer recurrence, screening for new breast tumor growths, and management of the physical and psychosocial effects of breast cancer and its sequel.

Psychosocial interventions and survivorship care are important to manage the psychosocial aspect of breast cancer. Counseling, support groups, and mindfulness-based techniques help manage stress, anxiety, depression, and other psychological symptoms that may be associated with breast cancer. Additionally, they help navigate and ease emotional distress while building resilience and promoting overall wellness.[42]

Adjuvant therapy such as chemotherapy, radiation therapy, and hormone therapy has also been confirmed to improve survival rates and reduce the risk of recurrence of breast cancer. It, in fact, is recommended for women with lymph node-positive or high-risk, lymph node-negative breast cancer.[42] Adjuvant radiation therapy minimizes the risk of local recurrence after breast-conserving surgery. Endocrine therapy, on the other hand, also prevents recurrence in patients with hormone receptor-positive breast cancer. Typically, combination chemotherapy regimens are standard recommendations in the adjuvant setting, to maximize the chance of a cure.[44]

MANAGEMENT OF BREAST CANCERS

With the burgeoning incidence of breast cancer diagnosis and mortality among women, conventional treatments have continued to evolve with promising potential. Typically, proposed conventional treatment methods include surgery, chemotherapy, radiotherapy, hormone therapy, and other targeted therapies. Before commencing treatment, the surgeon should individualize the patient and take into consideration the patient's fitness for surgery, the ability of the patient to bear the financial burden, coexisting comorbidities in the patient, and other prevailing factors.

Surgery is generally recommended depending on the size, type, and location of the tumor. It can be a lumpectomy or mastectomy. Standard surgical practice mandates the surgeon to ensure the excised tissue has clear margins of cancer.[35] Without clear margins, further operations might be scheduled for complete removal. Currently, advanced surgical techniques like sentinel lymph node (SLN) dissection have been effective in reducing the postoperative side effects while removing fewer lymph nodes.

Radiation therapy or chemotherapy can also be done. Radiation therapy uses high-energy beams to kill cancer cells without damaging healthy cells while chemotherapy involves the use of medications to kill cancer cells. They can either be given initially as neo-adjuvant therapy to shrink a tumor before definitive surgery is carried out or after surgery to destroy the remaining cancer cells and prevent recurrence.

However, these conventional therapeutic interventions still cause many side effects that may affect bodily function, body composition, psychological status, and the overall quality of life of the patient.[45] Chemotherapy, for instance, is notorious for resulting in hair loss, anemia, extreme fatigue, weight loss or loss of appetite, nausea, vomiting, and decreased cognitive function. Therefore, complementary and alternative methods of management have been recommended to alleviate the side effects and improve the quality of life of patients.[46] These methods have been reported as efficacious when used in conjunction with conventional treatments.[47]

Emerging modalities of treating breast cancer have also been explored to improve the outcome of the disease, from targeted therapies to immunotherapy to cancer vaccines.

HER2-targeted therapy, for example, is an advancement in the treatment of HER2-positive breast cancer.[48] It involves the use of Tyrosine Kinase Inhibitors (TKIs) and Antibody-Drug Conjugates (ADCs). TKIs inhibit the activity of tyrosine kinase, a component of the HER2 signaling pathway. This in turn down-regulates the HER2 receptor and subsequently halts the growth of breast cancer cells. ADCs meanwhile are drugs that contain a monoclonal antibody that binds to HER2. Once the ADC-antigen complex is internalized, lysosomal enzymes cleave it and release the cytotoxic drug to trigger targeted cell death. Several clinical trials have demonstrated the efficacy of HER2-targeted therapies. For instance, the EMILIA trial of ado-trastuzumab emtansine (T-DM1), an ADC, provided a significant improvement in progression-free survival and overall survival over the combination of trastuzumab and docetaxel therapy for patients with metastatic HER2-positive breast cancer.[48] However, despite the successes of ADCs, mechanisms of resistance to ADCs have been observed in clinical use that need to be understood to improve outcomes.[48,49]

The use of CDK4/6 inhibitors to induce cell cycle arrest by targeting the CDK enzymes is another example of one of the emerging modalities of managing breast cancer. Cyclin-dependent kinases (CDKs) are regulatory enzymes in cell proliferation that are essential for the progression of breast cancer cell growth. CDK4/6 inhibitors, however, are used in combination with endocrine therapy, and this combination therapy has been successful in the treatment of advanced ER positive variants thus bypassing the resistance of cancer cells to endocrine therapy.[50,51] The PALOMA-2 clinical trial, for example, provides proof of a higher progression-free survival rate for the combination of palbociclib (CDK4/6 inhibitor) and letrozole (aromatase inhibitor) than letrozole alone in the first-line treatment of advanced ER positive breast cancer.[50] This is probably because the CDK4/6 inhibitors-endocrine therapy combination provides a more efficient blockade of the cell cycle.[52,53] However, resistance to some CDK4/6 Inhibitors has also been noticed recently.[53]

The phosphatidylinositol 3-kinase (PI3K)/ Protein Kinase B (AKT)/ mammalian target of rapamycin (mTOR) pathway dysregulation is also associated with resistance and progression of breast cancer. PI3K/AKT/mTOR pathway inhibitors such as everolimus, have been approved though some are in preclinical trials for the treatment of breast cancer, either as monotherapy or in combination with other agents.[54] Additionally, sufficient evidence demonstrates that combining inhibitors of this pathway with CDK4/6 inhibitors delays the development of resistance to CDK4/6 inhibitors and provides a more efficient blockade of the cell cycle.[53] The combination of PI3K inhibitors and endocrine therapy is also being explored but data on clinical efficacy is limited to HR+/HER2- breast cancers.[51,54]

Immunotherapy is also another emerging modality in the treatment of breast cancer. Immune checkpoint inhibitors, such as programmed cell death 1 (PD-1) and programmed cell death ligand-1 (PD-L1) inhibitors, are the main clinical benefit of exploiting the immune system. The rationale is to block the interaction between PD-1 and PD-L 1 which is responsible for the cytotoxic secretion and anti-tumor immune degeneration in tumor cells.[55]

Clinical trials Impassion130 investigated the efficacy of combining atezolizumab, a PD-L1 inhibitor, with chemotherapy as opposed to using chemotherapy alone. The results showed that this combination significantly improved the prognosis in patients with unresectable, locally advanced, or metastatic triple-negative breast check (TNBC) when compared to chemotherapy alone.[55] However, not all patients respond to immune checkpoint inhibitors, and sometimes, resistance develops even after an initial response. Subsequently, several ongoing researches are investigating how to overcome resistance to immune checkpoint inhibitors.[55]

Chimeric antigen receptor (CAR) T cell therapy has also shown promise in the management of breast cancer. It uses laboratory-engineered T cells that express a CAR, to get the T lymphocytes to fight cancer cells by targeting a specific tumor antigen. CAR-T cell therapy has been clinically experimented in hematologic malignancies but is still in the early stages of development for breast cancer.[55] Ongoing research is focused on identifying breast cancer-associated antigens that can be

targeted by CAR-T cells and improving the efficacy and safety of this approach.

THE USE OF AI AND MACHINE LEARNING IN BREAST CANCER DETECTION AND MANAGEMENT

With the aid of artificial intelligence (AI) and machine learning (ML), breast cancer screening, diagnosis and management have improved.[56,57] Here are the various applications of AI and ML in breast cancer detection and management.

EARLY DETECTION AND SCREENING

The Use of AI in analyzing mammograms, digital pathology images and cytology slides with accuracy:

Mammography is the most widely used screening tool for breast cancer. However, interpreting mammograms can be daunting. AI algorithms have shown promise in improving the accuracy of mammogram analysis by assisting radiologists in detecting suspicious lesions. These algorithms can analyze large volumes of mammographic data and identify patterns that may be overlooked. AI systems can use deep learning to continuously learn and improve their ability to detect early signs of breast cancer. Additionally, AI algorithms can assist pathologists in detecting cancerous cells and assessing tumor characteristics.[58]

TREATMENT PERSONALIZATION

Every breast cancer patient is unique, and treatment plans should be tailored to individual characteristics and needs. AI and ML algorithms can develop personalized treatment plans by analyzing patient data, including genetic information and clinical parameters.[59] AI algorithms can predict treatment responses for each patient and identify the most effective interventions. This personalized approach can improve treatment outcomes, minimize side effects, and enhance patient experience.

DRUG DISCOVERY AND DEVELOPMENT

AI algorithms can identify potential drug candidates for breast cancer therapies by analyzing vast amounts of biomedical data, including genomic data, protein structures, and drug interactions.[59] These algorithms can predict the effectiveness and safety of new drug molecules, speeding up the discovery process and reducing reliance on trial and error. AI can also assist in repurposing existing drugs for breast cancer treatment, maximizing the potential of available therapeutic options.

PREDICTIVE MODELS FOR PATIENT PROGNOSIS

Predicting patient outcomes is crucial for treatment planning and decision-making.[60] AI and ML models can analyze patient data, including clinical parameters, genetic information, and treatment history, to develop predictive models for patient prognosis. These models can estimate the likelihood of disease progression, recurrence, or response to treatment, helping healthcare professionals make informed decisions.

IMPROVING POST-TREATMENT QUALITY OF LIFE

AI can also improve the post-treatment quality of life for breast cancer survivors. By analyzing patient-reported outcomes, wearable device data, and social determinants of health, AI algorithms can identify interventions and support systems that can enhance recovery. These algorithms can provide personalized lifestyle modifications, psychological support, and result-oriented recommendations.

DISPARITIES IN BREAST CANCER PREVENTION AND MANAGEMENT

Breast cancer disparate outcomes exist, with racial and ethnic minority groups showing lower rates of early detection and survival. Access to care, social determinants of health, and community outreach are the major categories of factors that contribute to these variances. For example, Social, economic, and cultural factors are responsible for Black-White disparities in breast cancer mortality, mistrust, and community barriers that prevent young African American women from benefiting from available tools for early detection of breast and cervical cancer, and Asians and African Americans also experience breast cancer barriers and unfavorable outcomes due to specific cultural practices and poor health-seeking behaviors.[61,62]

However, strategies such as community navigation, access to prevention, and early detection services, community-partnered clinical trials, and mentorship programs can improve access to early detection strategies and targeted interventions.

FUTURE PERSPECTIVES

Emerging treatments for breast cancer, such as cancer vaccines as monotherapy in premalignant or adjuvant settings, antibody-drug conjugates, immunotherapy, and CAR-T cell therapies provide the promise for metastatic breast cancer as demonstrated in the PANACEA study.[63-65] Also, Mediator Subunit 1 (MED1), a unique, tissue-specific cofactor and ER coactivator that mediates breast cancer metastasis and

treatment resistance has been identified as a potential target for breast cancer subtypes with specific mutations. The co-expression of MED1 and HER2 could serve as a biomarker for identifying patients who may have resistance to endocrine therapies.[66]

CONCLUSION

Breast cancer is becoming increasingly becoming common everywhere, but especially in developing nations.[1] The identification of those who are at risk and routine screening of these people can aid in the disease's prevention. The application of cutting-edge screening and treatment techniques as well as a holistic management strategy for those who have breast cancer or are at risk will also open up new avenues for the treatment and prevention of breast cancer.

Additionally, there is a need to recognise that AI and machine learnrecognizemprove the accuracy of screening and diagnosis, make treatment personalized, and enhance patient outcomes. However, addressing its ethical and social implications are essential to ensuring equitable access, data privacy, and transparency. With ongoing research and advancements, AI and machine learning will continue to shape the future of breast cancer detection and management.

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