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Review Article

An Overview Of Breast Cancer: Pathogenesis, Histology, Epidemiology, Risk Factors, Diagnosis, Prevention And Treatment

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ABSTRACT

Breast cancer remains the most prevalent cancer among women globally, accounting for significant morbidity and mortality. This article reviews the complex pathogenesis, clinical challenges, and advances in screening, diagnosis, and treatment of breast cancer. It highlights the insidious nature of certain breast cancer types that metastasize early despite initial benign characteristics. Emphasis is placed on the importance of early detection through organized screening programs, exemplified by Denmark's mammography initiatives, which have demonstrated reduced mortality rates. The role of the tumor microenvironment in cancer progression, including epigenetic factors and the influence of stromal cells, is explored. The article also addresses persistent clinical questions, such as tumor recurrence and therapeutic resistance, underscoring the heterogeneity of the disease. Comprehensive insights into risk factors, including age, geographical variation, and familial history, are presented, alongside an evaluation of current diagnostic tools and therapeutic options. Advances in systemic therapies, including chemotherapy, endocrine treatment, and targeted therapies, are discussed, highlighting their roles in improving patient outcomes. Ultimately, this article underscores the necessity for ongoing research to refine prevention strategies, enhance early detection, and develop personalized treatment approaches for breast cancer.

INTRODUCTION

In, breast cancer is the most common type of cancer. Approximately 25% of breast cancers are hidden and sneaky, developing slowly but metastasizing early, even though the majority are benign and treatable with surgery. Although recurrence is unavoidable and results in high fatality rates, current medicines considerably postpone the course of the tumor. The origin is where the seeds of breast cancer cell behavior are sowed. Mammary development is characterized by cell mobility and alterations in cell contact, as embryonic mammary cells possess invasive and

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motile characteristics [1].The bilayered epithelial structures that enclose a central lumen are called mammary ducts and alveoli, and they form cyclically during pregnancy. E-cadherin, which is also necessary for mammary cell survival, allows lumenal cells to adhere to one another [2].The main reason breast cancer is incurable is that it is a metastatic disease, meaning it can spread to distant organs like the brain, liver, bone, and lung. A high survival rate and favorable prognosis can result from early detection of the illness. Because breast cancer is discovered early in life, patients in North America have a 5-year relative survival rate of over 80% [3]. Although they are not genetically identical, cancer cells bear many similarities to the cells of the original organism. This explains why, especially if the immune system is compromised, they are rarely picked up by it [4]. A 29% decrease in breast cancer mortality was observed in women aged 50-69 at randomization in the five Swedish randomized trials that were analyzed over a five- to thirteen-year follow-up [5].Based on these findings, organized population-based mammography screening was implemented in 1991 in Denmark's capital city of Copenhagen [6]. Since then, there has been much discussion about the reliability of the trial findings and the necessity of mammography screening [7].It is not always easy to apply trial outcomes to standard medical care. It is therefore critical to investigate if the screening programs indeed lower breast cancer-related mortality.Out of the 16 administrative regions in Denmark, mammography screening was implemented in just 3. Thus, over the whole follow-up period, the regions lacking a mammography screening program serve as a natural control group. Furthermore, there has been less opportunistic screening [8]. We created a way to ascertain the impact of mammography service screening on breast cancer mortality by utilizing this "natural experiment," the Danish population as a whole, and health [9].

Pathogenesis

Breast tumors typically begin as hyperproliferation of the ducts, which is then continuously stimulated by several carcinogenic stimuli to develop into benign tumors or even metastatic carcinomas. Breast cancer begins and progresses because of tumor microenvironments such macrophages and stromal effects. When carcinogens were exposed to the stroma alone—not the extracellular matrix or the epithelium—the mammary gland of rats could develop neoplasms [10]. Indicating that epigenetic changes within the tumor microenvironment can facilitate carcinogenesis, distinct DNA methylation patterns have been found between the normal and tumsor-associated microenvironments [11]. There are two conjectures regarding the genesis and advancement of breast cancer: the stochastic theory and the cancer stem cell celltheory [12].

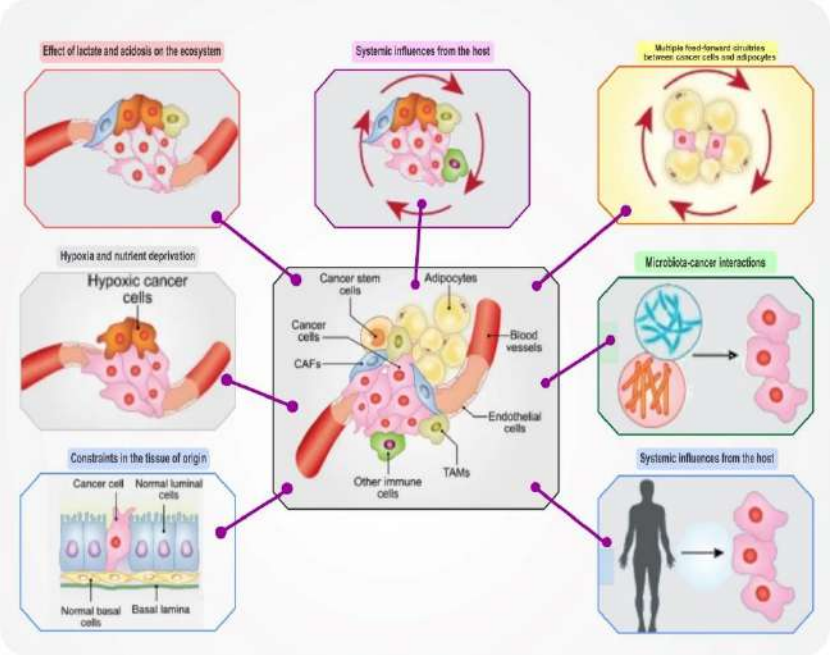

Fig no.1: Pathogenesis of breast cancer

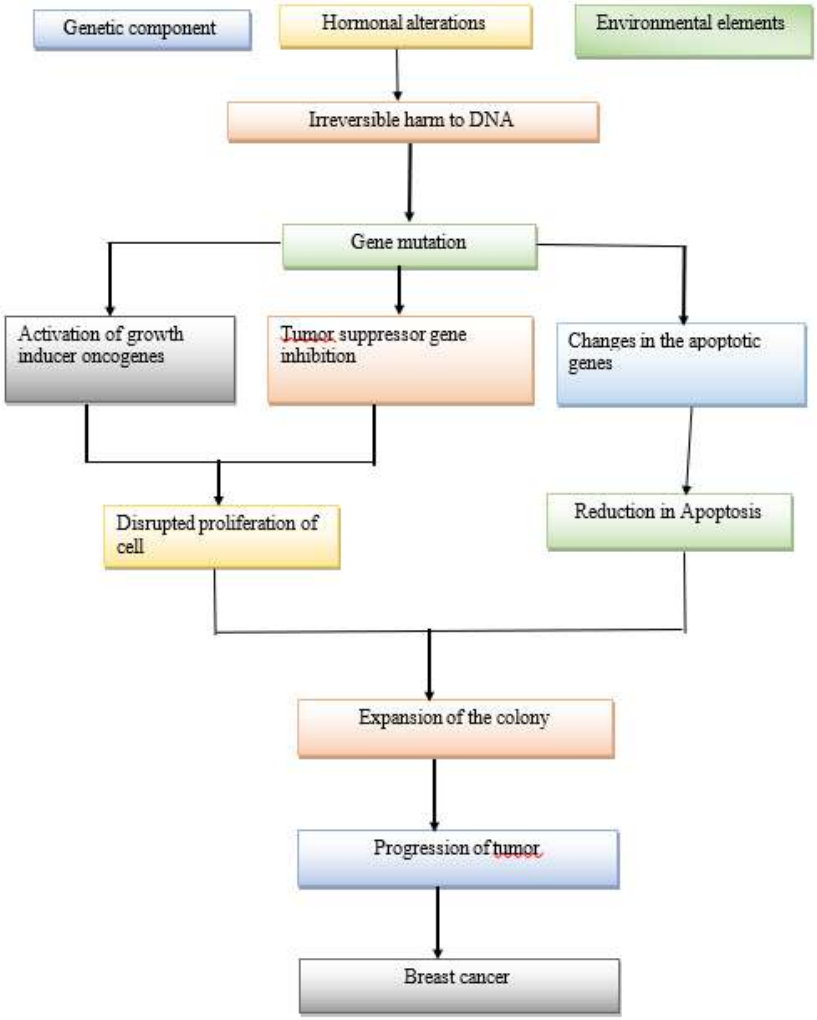

Fig.no.2 Pathophysiology of breast cancer

Primitive clinical and scientific issues and advances:

In women worldwide, breast cancer is the primary cause of cancer-related mortality [13]. Many important unsolved clinical and scientific issues persist despite tremendous advancements in the detection and treatment of breast cancer. These pertain to (a) tumor progression and recurrence (what causes it and how to predict it), (b) diagnosis (we need more sensitive and specific methods), (c) treatment (who should receive treatment and how), (d) prevention (who needs it and when), and (e) therapeutic resistance (how to predict, prevent, and overcome it). The fact that breast cancer is a highly heterogeneous illness at both the molecular and clinical levels makes fixing all of these issues more difficult [14].

The effects of microenvironment on the initiation and progression of breast cancer:

Breast cancer progresses through several pathological and clinical phases in its natural history. It begins with ductal hyperproliferation and then progresses to invasive and in situ carcinomas before metastatic disease develops [15].Certain alterations in the microenvironment of tumors seem to be irreversible, as stromal cells associated with tumors and normal cells retain their distinctions even when the patients' cells are removed and in vitro cultured [16].

Metastasis and invasion are essential steps in tumor progression:

The metastatic spread of primary tumors to distant organs and the conversion of DCIS to invasive carcinoma are important but poorly understood processes in the evolution of breast malignancies that alter therapeutic care and outcome dramatically. As of yet, these transitions have not been linked to any known genetic events. The diagnostic criterion that differentiates in situ carcinomas from invasive carcinomas, however, is the absence of the structured layer of myoepithelial cells [17]. These observations suggest that myoepithelial cells may be involved in the regulation of the progression of invasive cancer in situ, even though the physiological significance of these molecular alterations remains unclear [18]. Likewise, the advancement of metastasis could also be significantly influenced by microenvironmental factors. This theory is supported by observations made in a number of experimental systems. Changes in the extracellular matrix (ECM) of the mammary fat pad brought on by breastfeeding and involution accelerate the invasion and spread of breast cancer in mice and rats [19].

Mammary epithelial stem cell

The mammary gland is an exceptional organ that, even in adulthood, experiences significant remodeling and differentiation. While pregnancy causes substantial ductal branching and alveogenesis, hormonal changes throughout each menstrual cycle cause waves of proliferation in the mammary epithelium [20]. It is mainly unknown what molecular processes keep normal mammary stem cells stable and differentiated. Though the regulators of these several differentiation routes are still unknown, normal mammary epithelial stem cells are considered to give rise to luminal epithelial (both estrogen receptor–positive and –negative) and myoepithelial cells [21]. Various studies conducted on mice have revealed the presence of progenitor cells at all phases of mammary gland development, which can rebuild a functioning mammary gland upon transplantation into a recipient mouse's cleared fat pad (i.e., endogenous mammary epithelium removed) [22]. Using in vitro clonogenicity experiments as a gauge of "stemness," potential mammary epithelial progenitors in the human breast have been discovered. According to multiple studies, a subset of human mammary epithelial cells can grow into colonies in vitro and differentiate into both myoepithelial and luminal epithelial cells. As a result, these cells seem to be bipotential

mammary epithelial progenitors [23]. In both the mouse mammary gland and the human breast, a subset of mammary epithelial cells express ERs and PRs, indicating that hormones regulate the growth and function of the mammary gland [24].

Histological type of breast cancer

Breast cancer is a diverse illness that includes many unique entities with varying biological characteristics as well as clinical behaviours .[25]]Histological grade and histological type can be used to classify breast tumors into subgroups that are biologically and clinically significant [26].

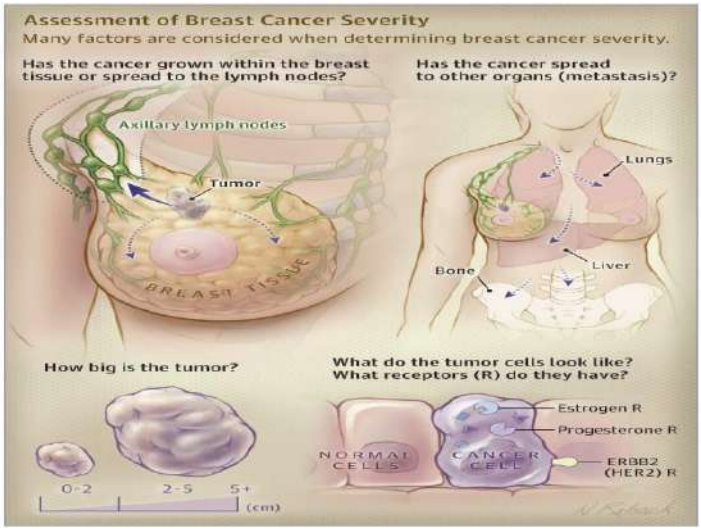

Fig no.3 Histology of breast cancer

Epidemiology

Across all global regions, regardless of per capita income, breast cancer is the most common cancer diagnosis for women.3, 4, 3 Approximately 1.7 million cases of breast cancer are diagnosed globally each year, which translates to one new case being identified every 18 seconds.3, 4, 3 On the other hand, incidence rates differ by almost four times, with higher incidence recorded in higher-income regions (92 per 100,000 in North America) and lower incidence recorded in lower-income regions (27 per 100,000 in Middle Africa) [27]. Breast cancer accounts for 18% of all female cancers and is the most frequent cancer in women, with one million new cases reported worldwide each year. The disease is the leading cause of death for women in the 40–50 age group, accounting for nearly a fifth of all deaths in this age group. The incidence among women over 50 approaches two per 1000 women annually in the United Kingdom, where age standardised incidence and mortality are the highest in the world. Over 14,000 deaths occur annually, with a notably high incidence among women aged 50-64, perhaps due to breast screening in this age range [28].

Risk factor

Age:

Before the menopause, when the rate of increase sharply slows down, the incidence of breast cancer rises with age, roughly doubling every ten years. Breast cancer occurs more frequently in younger people than lung cancer does. A flattening of the age-incidence curve occurs in certain countries following menopause.

Geographical variation:

Countries can differ by up to a factor of five in the age-adjusted incidence and death of breast cancer. Though it is still around five times larger, the gap between Far Eastern and Western nations is narrowing. According to studies on migrants from Japan to Hawaii, within one or two generations, the migrant population's rate of breast cancer equals that of the host country, suggesting that environmental variables outweigh hereditary factors.

Age at menarche and menopause:

An elevated risk of breast cancer exists for women who experience a late menopause or early onset of menstruation. Breast cancer is twice as common in women who naturally go through the menopause after the age of 55 as it is in those who go through it before the age of 45. At one extreme, the risk of breast cancer for women who get bilateral oophorectomy before the age of 35 is only 40% that of women who go through a natural menopause

Table no. 1 Established and probable risk factors for breast cancer

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	⩾2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	----
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight: Premenopausal	0.7	Body mass index >35

Age at first pregnancy:

Breast cancer incidence is higher throughout life in nulliparity and late age at first birth. When a woman has her first child after turning 30, her chance of developing breast cancer is almost double that of a woman who has her first child before turning 20. After the age of 35, women who become parents for the first time are the most at risk; in fact, their risk seems to be higher than that of nulliparous women. Further lowering the incidence of breast cancer is an early age at which a second kid is born.

Family history:

Genetic predisposition accounts for up to 10% of breast cancer cases in Western nations. Generally speaking, there is limited penetrance and autosomal dominant inheritance of breast cancer susceptibility. This implies that it can spread through either sex and that some family members may pass on the faulty gene even in the absence of their own cancer. The number of potential genes for breast cancer is yet unknown. The long arms of chromosomes 17 and 13, respectively, include the breast cancer genes BRCA1 and BRCA2, which have been found to be responsible for a significant percentage of very high risk families, or those where there have been four or more breast cancers in close relatives.[29] A woman who has a first-degree relative (mother, sister, or daughter) who was diagnosed with breast cancer before the age of 50 is at least twice as likely to have the disease herself; the higher the risk, the younger the relative was when she was diagnosed a woman who has a first-degree relative (mother, sister, or daughter) who was diagnosed with breast cancer before the age of 50 is at least twice as likely to have the disease herself; the higher the risk, the younger the relative was when she was diagnosed.

Diagnosis

Mammography:

Women who have no symptoms should get screened for breast cancer. When a woman exhibits indications or symptoms of breast cancer, she may get additional views during diagnostic mammography. The radiologist should be notified of any indication of malignancy along with the

request for a diagnostic mammography [30]. Breast cancer mortality rate is greatly reduced in women between the ages of 50 and 75 who have screenings. Screening women between 40 and 49 is debatable, despite the fact that preliminary research [31]. suggested that women who had mammograms would not have better survival rates; nevertheless, more recent research indicates that women in this age range who had mammograms had far lower death rates [32].

Ultrasonography:

When a palpable lump is poorly visible on a mammography, ultrasonographic screening can be used to distinguish between solid and cystic breast masses. When a mammography fails to show a palpable lump, ultrasonography can be particularly useful in young women with dense breast tissue. Because microcalcifications cannot be seen with ultrasonography and the yield of carcinomas is minimal, it should not be utilized for regular screening [33].

Prevention of breast cancer:

Screening as it is now done can lower mortality but not incidence, and only in a specific age range. Significant but small increases in survival have been brought about by therapy advances. There may be more opportunities for disease prevention if key components of the etiology of breast cancer are well understood.

Hormonal control:

Redirecting the hormonal milieu of women who are at risk is a viable path for primary prevention. A lower than anticipated number of contralateral breast cancers was observed during tamoxifen adjuvant treatment trials, indicating a potential function for the medication in breast cancer prevention [34].

Treatment

1.Surgery:

The two main surgical techniques that allow for the excision of breast malignant tissues are mastectomy and breast-conserving surgery (BCS). BCS, sometimes known as wide local excision, lumpectomy, quadrantectomy, or partial/segmental mastectomy, allows for the removal of malignant tissue while simultaneously preserving healthy breast tissue. It is frequently used in conjunction with oncoplasty, a type of plastic surgery.A mastectomy is the whole removal of the breast and is frequently accompanied by breast reconstruction right away. Axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) are used to remove the impacted lymph nodes. Despite the apparent increased benefits of BCS, patients who have undergone this treatment frequently exhibit a propensity to require a full mastectomy in the future [35].

2.Chemotherapy:

One systemic treatment for BC is chemotherapy, which can be adjuvant or neoadjuvant. Based on the unique characteristics of the breast tumor, the best option is determined; in cases of secondary breast cancer, chemotherapy may also be utilized. Carboplatin, cyclophosphamide,5-fluorouracil/capecitabine, taxanes (paclitaxel, docetaxel), and anthracyclines (doxorubicin, epirubicin) are among the medications used in treatment. Schemes 2-3 of these medications are applied concurrently. Given that distinct genetic subtypes of breast cancer react differently to preoperative chemotherapy, selecting the right medication is crucial [36].For women with node-positive cancer or tumors larger than 1 cm, chemotherapy is the standard of care. Diseases devoid of hormone receptors greater benefit from chemotherapy than there is a mone receptor-positive illness [37]. The decision to utilize chemotherapy is also influenced by factors including age and co-occurring conditions. The majority of research indicates a marginal benefit of using taxanes or anthracyclines instead of other chemotherapy treatments [38]. ‘In women whose malignancies overexpress ERBB2, in particular

[39]. According to a meta-analysis of 13 RCTs, supplementing an anthracycline-based regimen with a taxane increased overall survival (five-year risk reduction = 3 percent) and disease-free survival (five-year risk reduction = 5 percent) [40].

3.Radiation therapy:

Whole-breast radiation is usually administered after breast-conserving surgery to treat subclinical diseases. A review of ten randomized controlled trials (RCTs) comparing the rates of local recurrence five years after breast-conserving surgery with and without radiation revealed that radiation in addition to surgery significantly reduced the five-year rate of recurrence, regardless of the use of adjuvant systemic therapy (7 versus 26 percent; number needed to treat [NNT] = 5) and appeared to lower the 15-year breast cancer mortality risk (30.5 versus 35.9 percent; NNT = 18) [41]. As long as radiation is started within seven months of surgery, the timing of chemotherapy and radiation therapy does not seem to have a significant impact on survival or recurrence, according a comprehensive evaluation of three RCTs [42]. Shorter therapy regimens can be more appealing than radiation therapy, which is costly and time-consuming. Studies comparing compressed radiation schedules with biopsytherapy show positive five-year outcomes, but long-term data are scarce [43].

4.Adjuvant systemic therapies:

Adjuvant systemic therapies are given to most women with early-stage breast cancer. Chemotherapy, endocrine therapy, and tissue-targeted therapies improve definitive local therapy (radiation therapy, surgery, or both), which significantly reduces disease-specific death and cancer recurrence. Systemic therapy is most beneficial for node-positive diseases [44].

5.Endocrine therapy:

Agonists, gonadotropin-releasing hormone agonists, and SERMs are examples of endocrine treatments that block the production of estrogen. may inhibit the effects of estrogen, therefore stopping the stimulation of an susceptible to estrogen tumor. For premenopausal females, An oophorectomy or ovarian ablation could be explored. Cancers that are not curable with endocrine therapy hormone receptors absent. Throughout five years of therapy, Breast cancer mortality is decreased (absolutely) by tamoxifen Over a period of 15 years, risk reduction is 9.2%; NNT equals 11[45]. In all postmenopausal women with hormone receptor-positive breast cancer, aromatase inhibitors should be taken into consideration. They prevent androgens from being converted to estrogen in postmenopausal women, and studies consistently demonstrate that aromatase inhibitors lower the risk of relapse in early-stage breast cancer both in direct comparison to and following the completion of tamoxifen [46]. ‘A lot of women can tolerate aromatase inhibitors more so than tamoxifen [47]. Premenopausal women should not take aromatase inhibitors.

6.Tissue-Targeted Therapy:

Twenty to thirty percent of breast tumors that are in their early stages overexpress ERBB2 [48]. The prognosis for these cancers is typically worse. Women with node-positive and high-risk, node-negative breast cancers that overexpress ERBB2 can benefit from the addition of trastuzumab (Herceptin), a humanized anti-ERBB2 monoclonal antibody, to their chemotherapy regimen. This improves both disease-specific and overall survival [49]. However, the use of trotuzumab with anthracyclines should be done so cautiously, since 2 to 3 percent of patients will experience heart toxicity over the course of two years of treatment.

7.local therapy:

The response of the tumor after induction chemotherapy dictates the course of local therapy, which may include radiation therapy, mastectomy or breast conservation surgery, or both. Information from unsupervised prospective

research suggest that 50–90% of women with LACC have the potential to be successfully treated with breast-conserving surgery upon initiation of chemotherapy, despite the lack of completed randomized controlled trials in this area [50]. Surgery should only be performed if a complete resection can be achieved in patients whose cancer does not respond to induction chemotherapy. Factors such as lymph node involvement (more than three axillary, internal mammary, or clavicular nodes), residual pathologic tumors larger than 2 cm, multifocal residual disease, and lymphovascular invasion raise the risk of local recurrence after induction chemotherapy and, therefore, warrant mastectomy [51]. The majority of patients who present with LBC have clinically positive lymph nodes and require ALAN dissection. The detection rate of SLN biopsies performed after induction chemotherapy in patients with LBC who have clinically negative lymph nodes is comparable to that of early-stage breast cancer patients who do not receive induction chemotherapy [52]. Radiation therapy after surgery lowers the local recurrence rate, even in individuals who have achieved a clinically complete remission with induction chemotherapy [53].

CONCLUSION

In conclusion, breast cancer continues to pose a significant public health challenge, necessitating a multifaceted approach to address its complexities. Early detection through organized screening programs has proven effective in reducing mortality rates, emphasizing the critical role of proactive measures. Understanding the tumor microenvironment and the disease's heterogeneity is essential for tackling persistent issues like recurrence and therapeutic resistance. As research advances, there is a pressing need to refine prevention strategies and enhance personalized treatment options. Continued innovation in screening, diagnosis, and therapeutic approaches will be vital for improving patient outcomes and ultimately reducing the impact of breast cancer worldwide.

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