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A MINI REVIEW ON BREAST CANCER

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ABSTRACT

Breast cancer is among the major culprits of cancer-related death in women; it is complex and highly heterogeneous. Traditionally defined in terms of tissue of origin, modern classification emphasized molecular markers, such as hormone receptors and HER2 (human epidermal growth factor receptor 2) status, that drove the treatment approach. Hormone receptor-positive, HER2-positive, and triple-negative breast cancers broadly characterize three main subtypes, with distinctly different recurrence risks, treatment responses, and survival rates. In nonmetastatic cases, curative treatment and recurrence prevention are prioritized, while metastatic cases focus on life extension and control of life-threatening symptoms. Their molecular bases unveil mechanisms such as epithelial-mesenchymal transition, loss of cell adhesion, and immune evasion, which ultimately enable the metastasis of malignant cells to secondary organs like bones, liver, and lungs. This study emphasizes on causes, diagnosis methods and various treatments of breast cancer.

Keywords: Breast cancer, Immunotherapy, Hormone therapy, Estrogen receptor, Epithelial-mesenchymal transition.

INTRODUCTION

It involves uncontrolled proliferation and growth of cells that find ways to battle the body's natural regulatory mechanisms. Traditionally, cancers have been categorized according to the comfort of their origin from a tissue or organ, but an increasing number are being classified based on the molecular properties of cancer cells. Recent technological advances have permitted high-resolution, high-throughput molecular analysis of different forms of cancers. (9) Cancerous tumors invade local tissues and may spread, by way of the lymphatic or blood system, to far-body areas to generate new tumors, a process referred to as metastasis; hence the name malignant. While many cancers are associated with solid tumors, blood cancers like leukemia generally do not involve the growth of solid masses. (NCI)

Breast cancer is categorized into three subtypes: hormone receptor-positive/ERBB2-negative (70%), ERBB2-positive (15%-20%), and triple-negative (15%). Nonmetastatic at diagnosis, the treatment aims to eliminate the tumor and prevent recurrence. Triple-negative has a higher recurrence risk and lower 5-year survival rate. Treatments vary by subtype and often involve surgery, chemotherapy, endocrine therapy, and radiation. Metastatic cases focus on life extension. (17). Breast cancer was the first human tumor to benefit from targeted therapies, with notable successes such as estrogen receptor down regulators (tamoxifen and aromatase inhibitors) and HER2 antagonists (Herceptin). While numerous other targeted treatments are in development, certain intrinsic features of breast cancer biology can hinder the effectiveness of these strategies. (6)

Advances in mammography, magnetic resonance imaging, and the identification of additional biomarkers have further broadened the modalities for breast cancer detection and monitoring towards improving treatment outcomes. The identification of mutations in BRCA1 and BRCA2, however, was pivotal to understanding hereditary breast cancer risks and tumor aggressiveness. The modern management of this affliction using endocrine treatment, immunotherapy, and targeted agents has indeed advanced remarkably; however, challenges persist, especially in the case of metastatic diagnosis and in providing worldwide access to state-of-the-art treatment. Actions to prevent and intervene early in breast cancer are critical in reducing breast cancer incidence, and it will require collaborative partnership between medicine, science, and public health to enhance global survivorship outcomes, and create access to care.

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STATISTICAL DATA (% OF BREAST CANCER)

Age-standardized rates (ASR) are a summary measure of disease rates that a population would have if it had a standard age structure. This standardization is necessary when comparing populations that differ in age structure, as age significantly influences the risk of dying from cancer. In 2022, global breast cancer incidence and rates for women show France had the highest overall rate, followed by Cyprus. Worldwide, there were 2,296,840 cases with an ASR of 46.8 per 100,000. China reported 357,161 cases (ASR 33.0), the United States had 274,375 cases (ASR 95.9), and India reported 192,020 cases (ASR 26.6). Other notable countries include Brazil with 94,728 cases (ASR 63.1), Japan with 91,916 cases (ASR 74.4), and Russia with 78,839 cases (ASR 57.7). Germany reported 74,016 cases (ASR 77.0), Indonesia had 66,271 cases (ASR 41.8), France (metropolitan) reported 65,659 cases (ASR 105.4), and the United Kingdom had 58,756 cases (ASR 94.0). Regarding breast cancer mortality in 2022, the total global deaths were 666,103, with an ASR of 12.7 per 100,000. India reported the highest number of deaths at 98,337 (ASR 13.7), followed by China with 74,986 deaths (ASR 6.1), and the United States with 42,900 deaths (ASR 12.2). Other countries with significant mortality include Indonesia with 22,598 deaths (ASR 14.4), Brazil with 22,189 deaths (ASR 13.9), and Russia with 22,115 deaths (ASR 13.6). Germany reported 20,601 deaths (ASR 15.8), Japan had 17,638 deaths (ASR 9.7), Nigeria reported 16,332 deaths (ASR 26.8), and Pakistan had 15,552 deaths (ASR 18.6) [WCRF].

MECHANISM OF BREAST CANCER

Tumor metastasis is a multi-step process involving local invasion, intravasation, migration through lymphatics or blood vessels,

extravasation, and colonization, leading to metastases in distant organs. This process is influenced by the interactions between tumor cells and the tumor microenvironment, which includes various non-cancerous cells and extracellular components [10].

Breast cancer cells often spread early in tumor development, independently of primary tumor progression. Different breast cancer subtypes prefer different metastatic sites due to distinct molecular mechanisms. All subtypes can develop bone metastasis, but the incidence varies: luminal subtypes have a higher incidence of bone metastasis compared to HER2-positive and basal-like subtypes. Luminal B and basal-like subtypes are more likely to metastasize to the lungs, while HER2-positive subtypes often metastasize to the liver. Basal-like tumors have higher rates of brain, lung, and distant lymph node metastases but lower rates of liver and bone metastasis [15,8].

The first step in metastasis involves tumor cells breaking away from the primary tumor and migrating into the bloodstream, reducing their cell adhesion through epithelial-mesenchymal transition (EMT). EMT increases cell mobility by transitioning from epithelial to mesenchymal traits. Integrin-mediated interactions and increased blood vessel permeability aid in this migration.[5, 16]

Once in the bloodstream, circulating tumor cells face the challenge of penetrating blood vessel walls, facilitated by platelets and white blood cells. Selection ligands on tumor cells, angiopoietin-like 4 induced by TGFβ/SMAD signaling, and chemokines in target tissues enhance their ability to invade and establish in new environments. [8]

Adjusting to new environments, circulating tumor cells must interact with the extracellular matrix and new microenvironment to form metastases. Tumor-stroma interactions in early invasion stages further promote metastasis development. [3]

DIFFERENT CAUSES OF BREAST CANCER (GENETICAL AND ENVIRONMENTAL)

Breast cancer is a multifaceted disease that is the second-leading cause of cancer-related deaths among women. Statistically speaking, various factors-including genetics and environmental influences have been shown to be correlated with the initiation and development of breast cancer. [7] Typically speaking, in or cases of human breast cancer, genetic alterations are invoked in the course of somatic cells of the breast. On occasion, susceptibility to the disease will be inherited. It is hoped that the identification of genes influencing inherited breast cancer will also facilitate recognizing early lesions, a crucial aspect in the rise of breast cancer in the population at large. [4] The BRCA1 gene, located on chromosome 17, was the first gene strongly associated with hereditary breast cancer, having been discovered through linkage analysis in affected families as early as 1990. The BRCA2 gene was mapped to chromosome 13 by 1994. [14]Tumors resulting from BRCA1 mutations typically exhibit a basal-like phenotype, have a high histologic grade, and do not commonly express the estrogen receptor (ER), progesterone receptor (PR), or Her2/neu. These are referred to as triple-negative tumors. [11]

BRCA1 and BRCA2 mutations are inherited in an autosomal dominant manner but function recessively at the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair. Female carriers of BRCA1 or BRCA2 mutations have a 50%–85% lifetime risk of developing breast cancer. [14]

VARIOUS DIAGNOSIS FOR BREAST CANCER

Early diagnosis is crucial for effective treatment. Among the diagnostic platforms, imaging techniques are paramount, providing valuable data on breast cancer patients. Techniques such as mammography, magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and single-photon emission computed tomography (SPECT) are vital for diagnosing and monitoring breast cancer at various stages[7]. Additionally, biochemical biomarkers, including proteins, DNA, mRNA, and microRNAs, offer new diagnostic and therapeutic tools. This summary highlights various imaging techniques and biochemical biomarkers used for diagnosing breast cancer, with a special focus on microRNAs and exosomes as emerging diagnostic and therapeutic biomarkers for monitoring the disease. [7]

ADVANCE TREATMENTS FOR BREAST CANCER

Hormone Therapy

Endocrine therapy is typically divided into three categories. The first class includes Selective Estrogen Receptor Modulators (SERMs), with tamoxifen being a prominent example. SERMs act as competitive inhibitors of estrogen binding to estrogen receptors (ER) and exhibit either agonist or antagonist effects depending on the target tissue. These drugs inhibit estrogen binding and prevent ER signaling. While SERMs effectively block the activation function AF2 domain, they cannot block the AF1 domain of ERα, which can lead to agonist activity and limit their effectiveness. [12]

Immunotherapy

They're immune checkpoint inhibitors, PD-1 and PD-L1 inhibitors, as well as HER2-directed monoclonal antibody therapies currently used in the pharmaceutical treatment of breasts. [2]Immune checkpoint inhibitors (ICI) interfere with the signal that inhibits T cells by preventing the binding of the checkpoint signals to their partners. They thereby unleash the T cells to kill those cells that are meant to be destroyed. The PD-1/PD-L1 pathway isamong others used by cancer cells to elude immune detection. ICIs block PD-L1 binding to PD-1, allowing T cells to identify cancer cells as targets for aberration. In turn, ICIs derivatives are less dragging for the immune system and fully unleash its capacity to target cancer cells previously invisible or tolerated. On the downside, this mode of action can also provoke irAEs, leading to the development of severe, irreversible and sometimes fatal autoimmune processes.[13]

PREVENTION

Meaningful progress against breast cancer comes with extending survival and increasing cancer-free lifetimes while starting at the forefront of prevention. Everyone has a role to play, starting with the clinicians and researchers down to funders, community planners, educators, parents, and individuals alike. While new cancer treatments have been that much celebrated, the cure for advanced breast cancer still remains a formidable challenge. Moreover, the availability of costly tests and treatments is poor across low- and middle-income countries where breast cancer rates are soaring. [1]

CONCLUSION

Breast cancer remains a significant health challenge, characterized by its diverse subtypes and complex biological mechanisms. The disease's classification has evolved from a focus on the organ of

origin to molecular characteristics, allowing for more targeted and effective treatment strategies. Despite significant advancements in technology and therapies, such as the development of hormone receptor down-regulators and HER2 antagonists, breast cancer continues to present hurdles, particularly in its metastatic stages. The statistics underscore the global burden of breast cancer, with substantial incidence and mortality rates across various countries. This data highlights the importance of early detection and diagnosis through advanced imaging techniques and biochemical biomarkers. The identification of genetic factors like BRCA1 and BRCA2 has also been pivotal in understanding and managing hereditary breast cancer risks. Advanced treatments, including endocrine therapy and immunotherapy, offer promising avenues for improving patient outcomes. However, these therapies come with their own set of challenges, including potential adverse effects and the need for more accessible solutions in lower-income regions.

Ultimately, prevention and early detection are critical in combating breast cancer. It requires a collective effort from all sectors—medical professionals, researchers, policymakers, educators, and the public—to continue making strides toward reducing the incidence and impact of this disease. As we progress, ensuring equitable access to advanced treatments and preventive measures will be essential in achieving long-term success in the fight against breast cancer.

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