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Sex Differences in Breast Cancer: Implications for Immunotherapy and Combination Treatments

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ABSTRACT

Background: Sex differences in breast cancer are critical determinants of tumor biology, treatment responses, and clinical outcomes. Despite breast cancer's predominance in women, men are also affected, with distinct biological and clinical characteristics. However, research on sex-specific influences in breast cancer remains limited, particularly regarding immunotherapy and combination treatments.

Objectives: This study explores the molecular, genetic, and immune-related mechanisms underlying sex differences in breast cancer. It evaluates the implications for immunotherapy and combination treatments and emphasizes the need for personalized, sex-specific therapeutic approaches.

Methods: A comprehensive review of current literature was conducted to examine sex differences in breast cancer, focusing on hormonal, genetic, and immunological mechanisms. Research on immune response variations and clinical trial data related to breast cancer treatment outcomes was analyzed. Evidence from studies on immunotherapy and combination treatment strategies was reviewed to identify sex-specific outcomes, therapeutic challenges, and potential personalized treatment approaches.

Results: Sex hormones, chromosomal differences, and immune system variations significantly influence tumor behavior and therapeutic responses. Men and women exhibit different outcomes with immune checkpoint inhibitors, with variations in efficacy and adverse effects. Combination treatments involving immunotherapy and hormonal or chemotherapy-based approaches show potential but require sex-specific considerations.

Conclusions: Sex differences must be recognized as a critical determinant in breast cancer treatment. Integrating sex as a biological variable in clinical trials and developing sex-specific biomarkers can enhance personalized medicine. Future research should prioritize sex-stratified studies to improve therapeutic precision and outcomes for all patients.

INTRODUCTION

Breast cancer remains one of the most significant global health challenges, affecting millions of lives each year. In 2020 alone, an estimated 2.3 million new cases and 685,000 deaths were reported worldwide, making it the most frequently diagnosed cancer globally [1]. While in 2023, the American Cancer Society estimated 300,590 new breast cancer cases in the United States, with 297,790 in females and 2,800 in males, resulting in an anticipated 43,700 deaths (43,170 women and 530 men). Traditionally viewed as a disease predominantly affecting women, it ranks as the leading cancer type among women and the second most common cause of cancer-related deaths among females. Women face a lifetime risk of 1 in 8 of developing breast cancer, while the risk for men is significantly lower, at approximately 1 in 833 [2]. Despite accounting for only about 1% of all breast cancer diagnoses, male breast cancer (MBC) has shown a steady increase in incidence, rising from 0.85 per 100,000 in 1975 to 1.28 per 100,000 in 2020 according to Surveillance, Epidemiology, and End Results (SEER) data [1].

The limited screening and lower awareness of male breast cancer have contributed to delayed diagnoses, often resulting in more advanced stages of the disease at the time of presentation. In contrast, significant progress in understanding female breast cancer has led to more effective screening programs, early detection strategies, and tailored treatments that have improved outcomes. Despite these advances, the underrepresentation of males in clinical trials and breast cancer research has sustained gaps in knowledge regarding sex-specific differences that influence breast cancer pathophysiology and therapeutic outcomes [3].

Emerging evidence highlights the importance of hormonal, genetic, and immune-related variations between males and females in shaping disease progression and treatment responses. Among the genetic factors,

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BRCA1 and BRCA2 mutations are critical drivers of hereditary breast cancer. However, the risk profiles associated with these mutations differ significantly between sexes. In men, BRCA2 mutations are more strongly associated with breast cancer, conferring a 6% to 12% lifetime risk, while BRCA1 mutations are less common, with an estimated risk of 1% to 5% [4]. In contrast, women with a BRCA1 mutation face a 55% to 72% lifetime risk of developing breast cancer, compared to a 45% to 69% risk for those with a BRCA2 mutation [4].

Sex as a biological variable influences cancer development and immune response dynamics. Female patients typically exhibit stronger immune responses due to the modulatory effects of estrogen, which enhances immune surveillance, while males often show higher levels of systemic inflammation driven by testosterone [3]. These differences have profound implications for the effectiveness of immunotherapies, including immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways. Studies have shown that women may experience greater efficacy but also higher rates of immune-related toxicities compared to men [5]. Current therapeutic strategies largely overlook these differences, relying on a one-size-fits-all approach that may lead to suboptimal outcomes. Furthermore, male breast cancer often presents with more advanced disease at diagnosis and exhibits distinct patterns of hormone receptor expression, complicating treatment decisions [6].

Despite the clear rationale for integrating sex-based considerations into breast cancer research, significant gaps remain. Clinical trials historically underrepresent male participants, and many studies do not report sex-stratified outcomes [2]. This limits the generalizability of findings and impedes progress in developing precision treatments. Addressing this disparity requires intentional inclusion of both sexes in clinical research, along with the development of sex-specific biomarkers to predict therapeutic efficacy and adverse effects. Personalized medicine that accounts for biological sex can reduce disparities and enhance outcomes, making it a vital component of future cancer treatment strategies.

In short, Understanding and addressing sex differences in breast cancer is crucial for advancing precision oncology. Incorporating sex as a fundamental variable in clinical trials, developing tailored treatment regimens, and leveraging biomarkers to guide therapy will ensure more equitable and effective care for both men and women. Future research must prioritize sex-stratified data and personalized approaches to fully realize the potential of modern immunotherapy and combination treatments in breast cancer management.

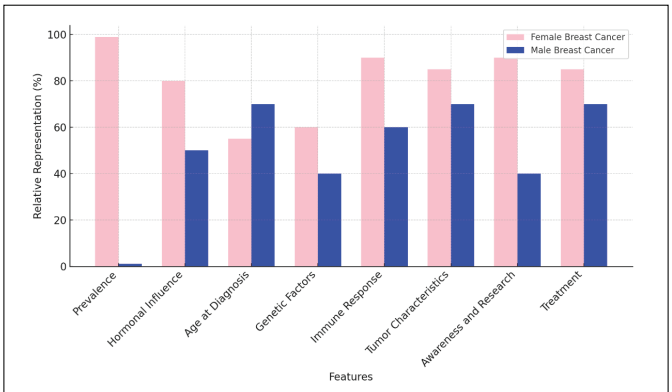

Figure 1: Comparison of Key Features in Female and Male Breast Cancer.

2. Biological and Molecular Basis of Sex Differences in Breast Cancer

Sex-based biological differences in breast cancer are driven by complex interactions of hormonal, genetic, and tumor microenvironmental factors. These elements collectively influence tumor behavior, progression, and response to therapy, underscoring the need for sex-specific research and treatment approaches.

Hormonal factors play a pivotal role in both the initiation and progression of breast cancer. Estrogen and progesterone are critical regulators of breast tissue proliferation. In female breast cancer, estrogen promotes cell proliferation by binding to estrogen receptors (ER), activating pathways that enhance tumor growth [7]. In contrast, androgen and its receptor (AR) are involved in a more complex, context-dependent manner in male breast cancer. The balance between androgenic and estrogenic activity influences tumorigenesis differently between sexes. Studies indicate that male breast cancer tends to have a higher proportion of estrogen receptor-positive (ER+) tumors compared to women, leading to distinct hormonal therapy responses [2],[4].

Genetic and epigenetic mechanisms further differentiate male and female breast cancer susceptibility. Variations in sex chromosomes are linked to differential gene expression. The presence of a second X chromosome in females provides a potential genetic buffer, contributing to lower mutation rates in critical tumor suppressor genes like BRCA1 and BRCA2 [8]. BRCA2 mutations are more common in male breast cancer cases than BRCA1, reflecting differences in genetic predisposition between sexes [2]. Epigenetic modifications, including DNA methylation and histone modifications, exhibit sex-specific patterns that influence gene regulation and cancer risk. Emerging studies reveal distinct methylation profiles associated with sex-based gene expression differences in breast cancer [9].

The tumor microenvironment (TME) further amplifies sex-related differences in breast cancer outcomes. Male and female TMEs differ in the composition of stromal cells, cytokine signaling, and immune cell infiltration. Estrogen significantly modulates immune activity by regulating the expression of cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α), contributing to a more immunosuppressive environment in females [4]. Conversely, the reduced estrogen levels in men may impact the recruitment and function of immune cells differently, resulting in unique immunotherapy responses [1]. These differences underscore the need for personalized approaches that consider the tumor microenvironment in treatment planning. Addressing these biological and molecular differences is imperative to advancing breast cancer management. Incorporating sex as a variable in clinical research will enhance therapeutic strategies and lead to more precise, individualized treatments for both male and female breast cancer patients.

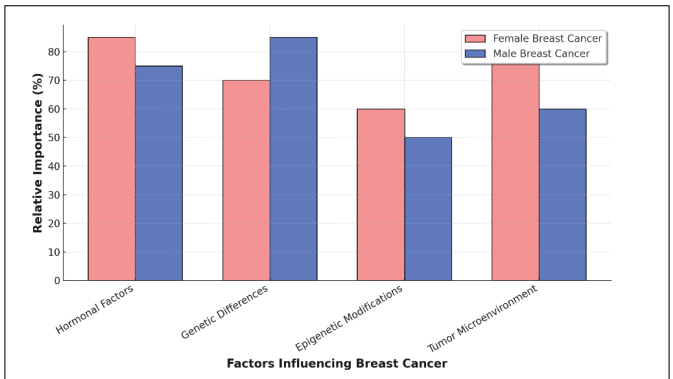

Figure 2: Different factors influencing breast cancer in male and female.

3. Immunotherapy in Breast Cancer: A Sex-Specific Perspective

Immunotherapy has emerged as a promising treatment modality for various cancers, including breast cancer, aiming to harness the immune system's ability to recognize and attack tumor cells. However, sex-specific differences in immune system function and responses to immunotherapy highlight the need for tailored approaches to optimize therapeutic outcomes for both men and women.

Checkpoint inhibitors, including PD-1/PD-L1 and CTLA-4 inhibitors, are at the forefront of current immunotherapy strategies. These agents disrupt the inhibitory signals that prevent T cells from attacking cancer cells, restoring their ability to target tumors [10]. In breast cancer, PD-L1 expression is a significant biomarker guiding the use of checkpoint inhibitors, particularly in triple-negative breast cancer (TNBC) [11]. Additionally, adoptive T-cell therapies, such as chimeric antigen receptor (CAR) T cells, and experimental cancer vaccines are being explored to enhance the immune response in breast cancer patients [12][13].

Sex differences in immune system function are well-documented and influence cancer progression and treatment outcomes. Females generally exhibit stronger adaptive immune responses, driven by enhanced T-cell activity and higher antibody production. This heightened immune vigilance contributes to better responses to certain immunotherapies but also increases susceptibility to autoimmune conditions [14]. In contrast, males demonstrate a greater propensity for inflammatory responses, influenced by higher circulating levels of pro-inflammatory cytokines such as IL-6 and TNF-α. Sex hormones further modulate immune function, with estrogen enhancing the expression of PD-1 on T cells, potentially affecting checkpoint inhibitor efficacy [4]. Conversely, androgens have been linked to immune

suppression, which may contribute to differential outcomes in male breast cancer patients.

Clinical outcomes of immunotherapy reveal notable sex-based variations. Data from clinical trials indicate that female patients often experience higher overall response rates (ORRs) to checkpoint inhibitors but also exhibit increased immune-related adverse effects (irAEs), including thyroid dysfunction and colitis [4]. In contrast, males may experience lower response rates but a different spectrum of toxicities, potentially due to variations in immune cell infiltration and checkpoint activity regulation. The KEYNOTE-119 trial, investigating pembrolizumab in metastatic TNBC, highlighted a trend toward more favorable responses in female subsets with higher PD-L1 expression [15]. However, the limited data on male breast cancer underscore a critical research gap that must be addressed to develop equitable immunotherapy guidelines.

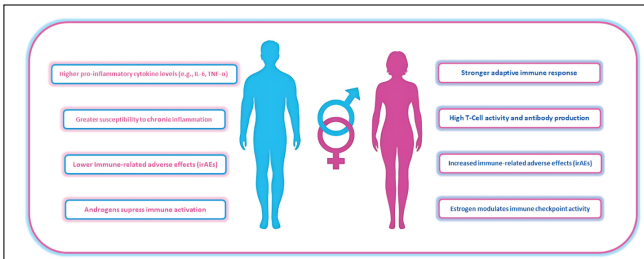

Figure 3: Immunotherapy modalities and sex-specific immune factors in breast cancer.

4. Combination Treatments and Personalized Approaches

The evolving landscape of breast cancer treatment emphasizes the integration of multiple therapeutic strategies to enhance efficacy and overcome resistance. Sex-specific considerations are increasingly recognized as pivotal in optimizing combination treatments and advancing personalized medicine.

Hormonal therapy, traditionally a cornerstone in hormone receptor-positive breast cancer, shows promise when combined with immunotherapy. Estrogen receptor antagonists like tamoxifen and aromatase inhibitors modulate the tumor microenvironment by altering cytokine profiles and immune cell infiltration. This dual modulation can enhance immune checkpoint inhibition, thereby boosting the anti-tumor immune response [12]. In preclinical studies, combining immune checkpoint inhibitors with hormone-blocking agents improved T-cell recruitment and activation, indicating potential synergy in sex-specific therapeutic regimens [16]. However, differences in estrogen and androgen receptor signaling pathways necessitate careful tailoring of these combinations for men and women.

The integration of chemotherapy and radiation with immunotherapy further broadens the therapeutic horizon. Chemotherapeutic agents such as cyclophosphamide and doxorubicin, along with radiation, induce immunogenic cell death, enhancing antigen presentation and T-cell priming [17]. Clinical trials reveal that women often experience stronger immune-related toxicities than men, potentially due to heightened immune reactivity. Conversely, men may require more aggressive combination regimens due to their lower baseline immune activation [4]. These findings highlight the importance of sex-based dosing and toxicity management to optimize patient outcomes.

Targeted therapies, particularly HER2 inhibitors like trastuzumab, demonstrate significant potential when paired with immunotherapeutic approaches. HER2 overexpression modulates immune signaling, and dual targeting with checkpoint inhibitors augments tumor eradication [18]. Emerging strategies involve sex-specific biomarker-driven combinations, considering differential HER2 expression and immune profiles between men and women. Precision medicine approaches incorporating genomic, hormonal, and immune factors are crucial for refining these regimens, ensuring that therapeutic interventions align with the unique biology of each patient. Combination treatments that incorporate hormonal, chemotherapeutic, and targeted therapies with immunotherapy hold immense promise. By integrating sex-specific biological insights into these strategies, personalized breast cancer treatment can achieve greater precision and improved clinical outcomes.

5. Challenges in Addressing Sex Differences in Breast Cancer

Despite advancements in understanding breast cancer biology, significant challenges remain in addressing sex-specific disparities. Research and clinical gaps hinder comprehensive insights into how biological sex influences disease progression and treatment outcomes. Historically, breast cancer has been perceived as a predominantly female disease, resulting in the chronic underrepresentation of males in research. Male breast cancer accounts for approximately 1% of all breast cancer cases, yet most clinical trials lack sufficient male participants to draw meaningful conclusions about sex-specific treatment efficacy [2]. This limitation constrains the ability to generalize findings and hampers efforts to develop tailored therapeutic strategies for male patients.

The biological complexity underlying sex differences further complicates research. The interplay of hormonal, genetic, and environmental factors contributes to multifactorial variations in tumor development and progression. Estrogen and androgen receptor pathways, differential immune responses, and variations in epigenetic regulation present unique challenges in isolating sex-specific influences. For example, while estrogen is a major driver in female breast cancer, androgen receptor signaling may play a more nuanced role in males, requiring distinct therapeutic considerations [19]. Understanding these intricacies demands robust study designs that account for diverse biological variables while distinguishing sex-based factors from broader genetic and environmental influences.

Ethical and practical considerations also pose barriers to addressing sex differences in clinical practice. Allocating resources for sex-specific studies must be balanced against the need for broader population-wide research. The push for personalized medicine, while promising, introduces challenges in integrating individualized approaches into standard care models. Cost constraints, access to genomic testing, and limited infrastructure for precision medicine hinder widespread adoption. Furthermore, ethical questions arise regarding the equitable distribution of research funding and clinical resources between sexes, especially given the rarity of male breast cancer.

Addressing these challenges requires a multifaceted approach. Increasing male representation in clinical trials, fostering collaborations that prioritize sex-based analyses, and leveraging advanced technologies such as machine learning to analyze complex biological data are critical steps forward. In parallel, education and policy advocacy are essential to overcome systemic barriers and embed personalized, sex-specific strategies within standard treatment paradigms. Only through concerted efforts can we achieve equitable and effective care for all breast cancer patients.

6. Clinical Implications and Future Directions

Incorporating sex as a biological variable in breast cancer research is paramount to improving clinical outcomes for both men and women. Historically, clinical studies have been skewed toward female participants, neglecting the unique biological and therapeutic needs of males. The integration of sex-based analyses into preclinical and clinical research frameworks is essential to address this gap. Such analyses can reveal critical differences in hormone receptor activity, immune responses, and genetic pathways that influence disease progression. Developing sex-specific biomarkers to predict treatment response and guide therapeutic choices will enable more precise and personalized treatment plans. For instance, molecular markers that account for androgen receptor expression in males or variations in immune checkpoint activity in females could revolutionize treatment stratification and monitoring [4].

Advancing personalized medicine requires designing tailored immunotherapy and combination regimens that reflect sex-specific biology. The interplay of hormonal, genetic, and immune factors necessitates a nuanced approach to drug development and clinical management. Personalized strategies should incorporate sex-specific data from comprehensive genetic, hormonal, and immunological profiles. Collaborative efforts across disciplines, including oncologists, immunologists, and geneticists, are critical to creating dynamic treatment models that adapt to the biological nuances of each patient. Policies that promote equity in clinical trial design, ensuring balanced male and female participation, are also key to generating robust, generalizable data [12].

Translational research must prioritize bridging preclinical insights with clinical applications. Many promising discoveries related to sex differences remain confined to laboratory models due to a lack of translational frameworks. Designing clinical trials that explicitly test sex-based hypotheses can accelerate the adoption of findings into practice. Furthermore, long-term monitoring of sex-specific treatment outcomes is essential to evaluate the effectiveness and safety of interventions in diverse populations. Data collection efforts should extend beyond short-term efficacy to include quality-of-life measures, recurrence rates, and survival outcomes for both sexes [16].

Conclusion

In conclusion, recognizing and addressing sex differences in breast cancer is vital for enhancing treatment efficacy and achieving personalized care for

all patients. The distinct hormonal, genetic, and immune factors influencing disease progression and therapeutic response between men and women necessitate tailored approaches. Sex-specific immunotherapy and combination treatments hold transformative potential, but their success depends on robust research, equitable clinical trial representation, and policy-driven initiatives. By integrating sex-based analyses into oncology, fostering multidisciplinary collaboration, and prioritizing translational research, the future of breast cancer treatment can become more precise, inclusive, and effective.

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