Breast Cancer Beyond Gender: Addressing the Reality of the Disease in Men

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Seminar Project

BIOL 405W

Sponsor: Dr. Osgood

Abstract:

This paper reviews the epidemiological risk factors, molecular pathogenesis, and standard treatment modalities for male breast cancer, highlighting the specific clinical roles of tamoxifen and GnRH analogs. Furthermore, it explores the psychological impact of the disease, with a particular focus on the social stigma experienced by the male population. Ultimately, this review emphasizes the critical need for more inclusive clinical trials to optimize treatment outcomes and improve the overall quality of life for male patients.

Perspective:

To address the realities of breast cancer in men, it is essential to recognize how the lack of research directly impacts diagnosis, treatment options, and overall quality of life within the male population. The limited scientific attention given to male breast cancer not only delays detection but also results in treatment strategies that are often adapted from female-centered studies. This gap highlights the urgent need for more inclusive research that accurately reflects the biological and psychosocial experiences of men, ultimately improving clinical outcomes and patient care.

Introduction:

Breast cancer is a disease that affects women, though it is important to recognize that it also occurs in men at much lower rates. Male breast cancer (MBC) makes up about 0.5-1% of all breast cancer cases worldwide, with an incidence of roughly 1.3 cases per 100,000 men each year (Sah et al., 2025). Men are diagnosed at an older age than women and often present with more advanced disease, mainly because of the lack of routine screening and limited awareness among patients and healthcare providers. This delay in diagnosis underscores the importance of proactive efforts and encourages healthcare providers to take responsibility for early detection and better patient outcomes. The fact that its global incidence has been gradually rising should encourage healthcare professionals and researchers to pay closer attention to this condition, highlighting the need for increased awareness and understanding (Sah et al., 2025).

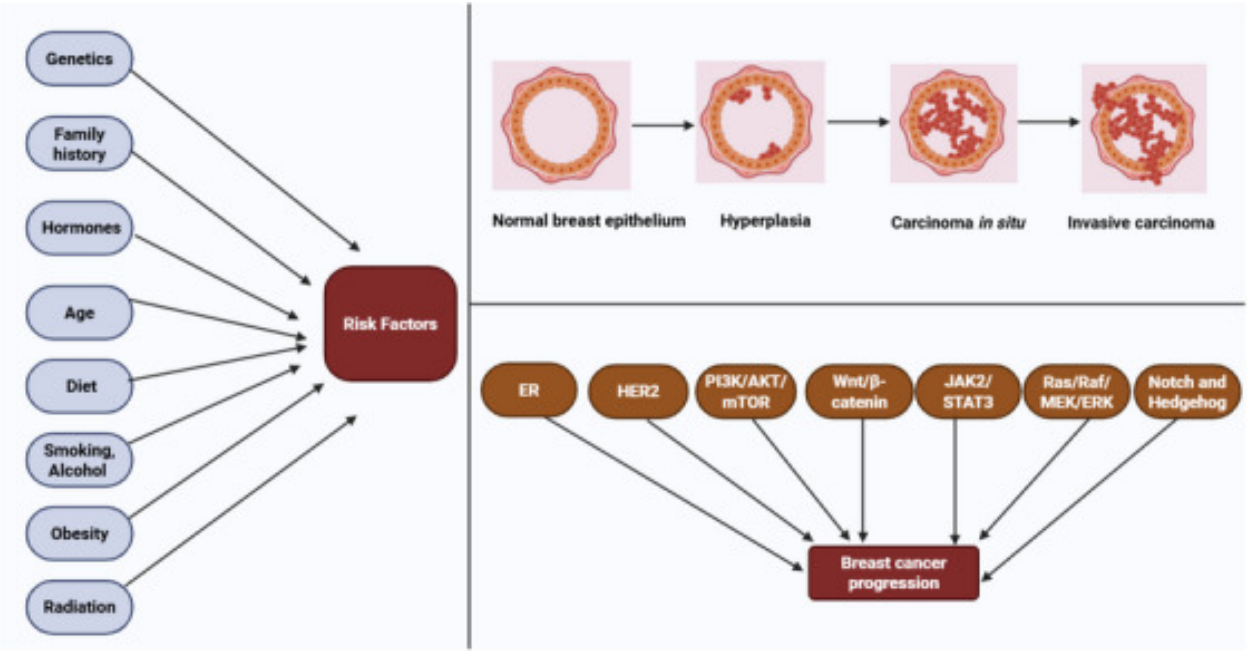
This paper examines the biological and molecular characteristics of male breast cancer, along with its clinical presentation, treatment options, surgical limitations, and impact on quality of life. Additionally, as the paper analyzes the disease beyond traditional gender assumptions, it aims to offer a more comprehensive understanding of male breast cancer and underscore the importance of improved research and targeted clinical approaches.

Molecular Pathogenesis

The initiation of breast cancer pathogenesis is a multifaceted process driven by a combination of environmental, lifestyle, and biological risk factors. External triggers such as smoking, alcohol consumption, diet, and radiation exposure, alongside intrinsic factors like aging and family history, create a physiological environment conducive to cellular transformation (Samad et al., 2025). These "triggers" act as catalysts for the transition of normal breast epithelium into hyperplasia, marking the beginning of a complex molecular journey toward malignancy (Samad et al., 2025).

At the core of this transformation are critical genetic mutations that disrupt normal cellular homeostatic mechanisms. The molecular drivers involve a dual-pronged attack: the gain-of-function in oncogenes and the loss-of-function in tumor suppressor genes (Samad et al., 2025). In a healthy state, these genes act as the cell's "quality control" system. For instance, TP53 (the "guardian of the genome") is responsible for sensing DNA damage and triggering either repair or apoptosis; when mutated, the cell loses its ability to self-destruct even when heavily damaged (Samad et al., 2025). Similarly, BRCA1 and BRCA2 are vital for repairing double-strand DNA breaks; their inactivation leads to a "mutator phenotype" where genetic errors accumulate rapidly (Samad et al., 2025). Furthermore, the loss of PTEN removes the natural inhibition of the PI3K signaling pathway, essentially leaving the "growth switch" permanently ON (Samad et al., 2025).

This genetic instability leads to the profound dysregulation of several key intracellular signaling pathways. As shown in the study (Figure 1), the abnormal activation of the ER, HER2, and PI3K/Akt/mTOR pathways provides signals that enable cells to bypass normal regulatory checkpoints (Samad et al., 2025). Furthermore, the involvement of the Wnt/β-catenin, JAK/STAT, Notch, and Hedgehog pathways fuels progression from carcinoma in situ to invasive carcinoma (Samad et al., 2025). This cascade of molecular signaling not only sustains tumor growth but also facilitates the invasive characteristics required for malignancy (Samad et al., 2025).



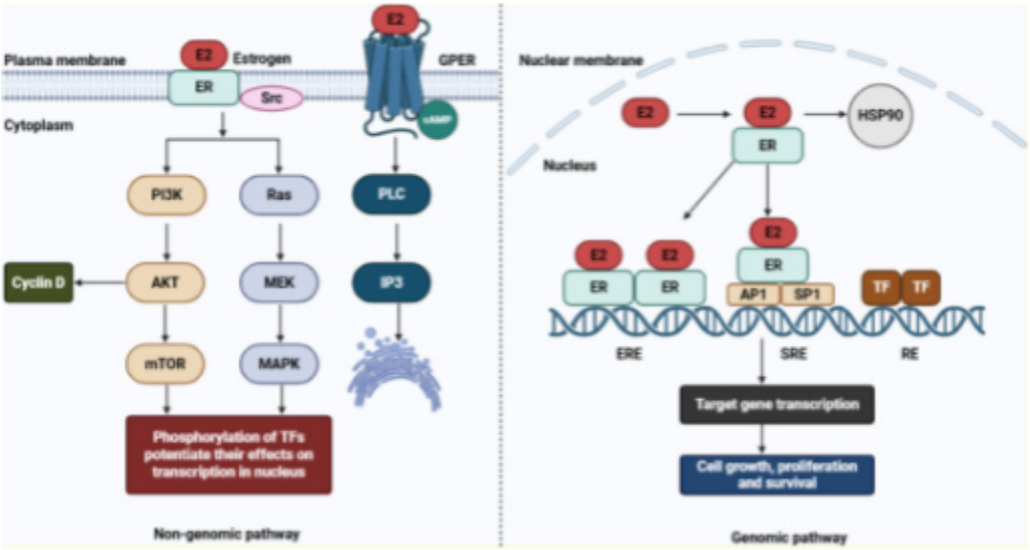
(Figure 1: Samad et al., 2025) An analysis of breast cancer development reveals a complex interplay between molecular and environmental drivers. The process is initiated by genetic mutations in oncogenes and tumor suppressor genes, along with the disruption of critical signaling pathways. This transformation shifts healthy breast epithelium toward hyperplasia, eventually advancing from a preinvasive state (carcinoma in situ) to malignant, invasive carcinoma.

Biological and Molecular Characteristics

Understanding the biological basis of male breast cancer is crucial for grasping its clinical behavior and progression. The most common histological subtype in men is invasive ductal carcinoma, making up over 90% of cases (Jamil et al., 2025). This type of cancer begins in the epithelial lining of the milk ducts. It is commonly seen in men with breast cancer due to the limited development of lobular breast structures, which makes other subtypes like invasive lobular carcinoma relatively rare (Bhardwaj et al., 2024). Compared to female breast cancer, male breast cancer shares several pathological features, including tumor classification and receptor-based

subtypes. However, men are more likely to present with advanced-stage disease because of delayed diagnosis and lower awareness (Bhardwaj et al., 2024).

A key biological feature of male breast cancer is its strong association with hormone receptor positivity. The majority of tumors are estrogen receptor (ER)-positive and progesterone receptor (PR)-positive, with studies indicating that approximately 80-90% of cases express these receptors (Jamil et al., 2025). This high prevalence suggests that tumor growth is largely driven by hormonal signaling pathways, particularly those involving estrogen, which has significant implications for targeted therapies. In contrast, human epidermal growth factor receptor 2 (HER2) overexpression is less common in men. Still, when present, it is linked to more aggressive tumor behavior and a poorer prognosis (Sah et al., 2025). The predominance of hormone receptor-positive tumors supports the use of endocrine therapies, which target these pathways, as illustrated in Figure 2. By visualizing the genomic and non-genomic signaling of the estrogen receptor, we can better understand how targeted treatments disrupt the mechanisms of tumor proliferation.



(Figure 2, Samad et al., 2025): The genomic and non-genomic signaling pathways of the Estrogen Receptor. These mechanisms drive the uncontrolled proliferation and survival of HR-positive breast cancer cells, which constitute the vast majority of male breast cancer diagnoses.

In addition to hormonal influences, genetic factors are crucial in the development of male breast cancer. A combination of genetic, hormonal, and environmental risk factors influences the

development of male breast cancer. Among these, mutations in BRCA2 represent the most significant genetic contributor, with carriers exhibiting a markedly increased lifetime risk compared to the general population (Fox et al., 2022). While BRCA1 mutations also contribute to risk, the impact is less pronounced in men (Fox et al., 2022). Additionally, other susceptibility genes, such as PALB2, CHEK2, and PTEN, have been identified as contributing factors, though they exert a lesser influence on male breast cancer (Sah et al., 2025). Recognizing these genetic factors is vital for advancing research, guiding genetic counseling, and developing targeted screening strategies to improve early detection and management.

Risk Factors, & Clinical Presentation

A multifactorial interplay of genetic, hormonal, and environmental risk factors influences the development of male breast cancer. Among these, mutations in the BRCA2 gene confer the highest-penetrance genetic risk, while other genes, such as PALB2 and ATM, contribute to moderate increases in susceptibility (Ter-Zakarian et al., 2025). A strong family history is also a notable risk factor, with nearly 20% of affected men reporting a relative with breast cancer.

Hormonal imbalance plays a central role in disease development. Conditions that increase estrogen levels or decrease testosterone—such as Klinefelter syndrome, obesity, liver disease, and hypogonadism—significantly elevate risk (Jamil et al., 2025). In addition, lifestyle and environmental factors, including chronic alcohol consumption, physical inactivity, and exposure to ionizing radiation, further contribute to disease susceptibility (Sah et al., 2025). Unlike women, men do not undergo routine breast cancer screening, which contributes to delayed detection and more advanced disease at diagnosis (Sah et al., 2025). This lack of screening, combined with limited awareness, significantly impacts clinical outcomes.

Clinically, male breast cancer most commonly presents as a painless, unilateral mass located beneath the nipple, occurring in approximately 85–90% of cases (Sah et al., 2025). Additional

symptoms may include nipple discharge, retraction, or skin changes such as dimpling (Sah et al., 2025). These signs are often misinterpreted as benign conditions, such as gynecomastia, leading to delays in seeking medical attention.

As a result, many men are diagnosed at later stages of the disease, often when tumors are larger or have already spread to regional lymph nodes. This delay underscores the importance of increasing awareness and improving early detection strategies in male populations.

Risk factors for male breast cancer

Risk factor	Description
Age	Increased risk with advancing age. The median age for male breast cancer diagnosis varies by ethnicity and race. Specifically, male breast cancer diagnosis median age was 70, 66, 65, and 64 for non-Hispanic white, non-Hispanic Pacific and Asian Islander, non-Hispanic black, and Hispanic men, respectively.
Hormonal imbalance	Higher levels of estrogen relative to androgen hormones can occur due to obesity, testicular atrophy, liver disease, or Klinefelter syndrome.
Radiation exposure	Increased risk in men treated with radiation therapy to the chest area, e.g., for lymphoma.
Family history/ Genetics	About 20% have a first-degree relative with breast cancer. Associated with BRCA2 mutations (accounts for ~10% of cases) and possibly CHEK2, PTEN, and PALB2 mutations.
Klinefelter syndrome	This is a rare genetic condition with an extra X chromosome, leading to hormonal imbalances and increased risk.
Obesity	High body mass index (BMI) is associated with 35% higher risk compared to low BMI.
Gynecomastia	The presence of excess breast tissue is associated with a 10-fold increased risk, independent of obesity and Klinefelter syndrome.
Alcohol consumption	Increased risk with higher alcohol intake.
Estrogen treatment	Prostate cancer treatment may increase breast cancer risk.

(Table 1, Jamil et al., 2025)

Surgical Management, Treatment Strategies, and Limitations

The management of male breast cancer involves a multimodal approach that includes surgery, systemic therapies, and radiation. Due to the rarity of the disease, most treatment

strategies are adapted from protocols established for female breast cancer, which presents challenges in optimizing care for male patients.

Surgery remains the cornerstone of treatment, with mastectomy being the most commonly performed procedure due to the limited amount of breast tissue in men. Although breast-conserving therapy may be an option in select cases, it is less frequently utilized, often as a result of later-stage diagnosis. The absence of routine screening contributes to larger tumor size at presentation, limiting less invasive surgical options.

Neoadjuvant therapies, particularly chemotherapy, may be used prior to surgery to reduce tumor size and improve surgical outcomes. However, men tend to have lower rates of pathologic complete response than women, which may affect the overall effectiveness of this approach (Jamil et al., 2025). Following surgery, adjuvant treatments such as radiation therapy are recommended in cases involving large tumors or lymph node involvement to reduce the risk of local recurrence.

Systemic therapies play a critical role in disease management, especially given the high prevalence of hormone receptor-positive tumors in men. Endocrine therapy, particularly tamoxifen, is the first-line treatment for estrogen receptor-positive cases and has demonstrated significant survival benefits (Bhardwaj et al., 2024). For patients who cannot tolerate tamoxifen, alternative regimens such as aromatase inhibitors combined with gonadotropin-releasing hormone analogs may be used (Bhardwaj et al., 2024). Chemotherapy, typically involving anthracyclines and taxanes, is reserved for patients with advanced or high-risk disease (Jamil et al., 2025). In addition, targeted therapies have expanded treatment options, with HER2-targeted agents such as trastuzumab and pertuzumab used in HER2-positive tumors, and emerging therapies including CDK4/6 inhibitors and PARP inhibitors showing promise (Sah et al., 2025).

Despite these advancements, treatment resistance remains a major challenge. Resistance to endocrine therapy may arise from alterations in estrogen receptor signaling, allowing tumor cells to continue proliferating despite treatment. Similarly, resistance to chemotherapy can develop through

tumor adaptation to cytotoxic stress, while resistance to targeted therapies is often driven by additional mutations that promote tumor survival and progression (Sah et al., 2025).

A significant limitation in the management of male breast cancer is the reliance on treatment strategies derived from female populations. The underrepresentation of men in clinical trials limits the development of male-specific guidelines and may reduce the effectiveness of current therapeutic approaches (Bhardwaj et al., 2024). Furthermore, delayed diagnosis often necessitates more aggressive surgical interventions, highlighting the need for improved awareness, earlier detection, and more targeted research focused on male patients.

Quality of Life and Psychosocial Impact

The diagnosis and treatment of male breast cancer extend beyond physical health, which significantly impacts men's quality of life and psychosocial well-being. One of the most significant aspects of survivorship in male breast cancer is the burden of treatment-related side effects. Endocrine therapy, particularly tamoxifen, is associated with a range of adverse effects such as hot flashes, mood changes, sexual dysfunction, and fatigue (Bhardwaj et al., 2024). Such side effects impact treatment adherence, wherein 25% of men discontinue therapy due to toxicity (Bhardwaj et al., 2024).

Sexual health represents another critical concern for males with breast cancer because they experience a proportional decrease in libido and erectile dysfunction, which results from hormonal treatment (Pyo et al., 2025). Physical changes, along with limited research, significantly reduce men's quality of life. Additionally, many men report body image distress following mastectomy due to visible scarring and changes in physical appearance, which can lead to decreased self-esteem and social withdrawal that affects the psychosocial functioning of men.

Furthermore, the perception that breast cancer is predominantly known as a female disease also contributes to feelings of stigma, isolation, and invisibility within healthcare settings (Pyo et al.,

2025). Not to mention, support systems for men with breast cancer are often limited, as most breast cancer resources and groups are designed for women, which leaves male patients with few options for emotional and social support (Bhardwaj et al., 2024). Another common thing that impacts quality of life in men is the psychological stress that comes from the fear of recurrence and metastasis. Concerns about disease progression and survival greatly take a toll on men's mental health, especially on younger male patients who experience more emotional burden in comparison to older male patients (Pyo et al., 2025).

Despite the limited support and research, studies suggest that overall global health status in men with breast cancer remains relatively high, which indicates that there are male patients who maintain functioning social and emotional well-being (Schroder et al., 2023). Nonetheless, there are specific symptoms— fatigue, insomnia, and pain– that continuously and greatly affect quality of life for men.

Discussion

The paper highlights the intricate and multifaceted nature of male breast cancer, emphasizing the important roles that biological, clinical, and psychosocial factors play in determining disease outcomes. The key biological features, such as a high prevalence of hormone receptor positivity and a strong association with BRCA2 mutations, underscore the need for recognition and validation by healthcare professionals and researchers. Such factors not only contribute to tumor development but also to clinical presentation and treatment response, as management depends on the tumor type.

A significant obstacle in managing male breast cancer lies in the reliance on treatment strategies that are largely derived from studies focused on female breast cancer, and due to the rarity of the disease in men, as well as the historical exclusion of clinical trials for male breast cancers, many therapeutic approaches are based on female breast cancer cases. This raises

concerns about the applicability of different treatments due to the distinct anatomical and biological differences between males and females, despite having similarities in receptors, causing breast cancer tumors. Moreover, as discussed, the condition of breast cancer detrimentally impacts the quality of life due to the stigma associated with breast cancer, which is perceived as a female disease, which was another factor in late diagnosis and an insufficient support system for men with breast cancer.

The overall findings heightened awareness, earlier detection, and the establishment of a research initiative to specifically target male breast cancer studies with emphasis on the need to improve the representation of men in clinical trials that would grasp the biology better and optimize treatment strategies, which are not derived from female breast cancer cases. Additionally, focusing on MBC would enhance supportive care and become a vital improvement for the quality of life in male breast cancer patients.

Conclusion

In conclusion, while male breast cancer shares a foundation of treatment with female breast cancer, it remains a distinct clinical entity that requires specialized attention. The high prevalence of estrogen-receptor-positive tumors and BRCA2 mutations underscores the importance of genetic screening as well as tailored therapies. Furthermore, the reliance on female-centered clinical data significantly presents a delay in diagnosis for men with breast cancer, along with the lack of a screening routine. Thus, improvement of male breast cancer necessitates two approaches: the initiation of male-centered clinical trials and the implementation of better supportive care that addresses the emotional burden of breast cancer.

References

Bhardwaj, P. V., Gupta, S., Elyash, A., & Teplinsky, E. (2024). Male Breast Cancer: A Review on Diagnosis, Treatment, and Survivorship. *Springer Nature* 26, 34–35.

Annotation - This review discusses the management and surveillance of male breast cancer, noting that treatment guidelines are largely adapted from female breast cancer despite biological differences. It highlights more extensive surgical approaches in men and worse stage-matched outcomes. It also emphasizes the limitations of imaging recommendations and the significant long-term physical and psychological impacts faced by male patients.

Fentiman, I.S., (2018). The biology of male breast cancer. *Science Direct* 38, 132–135.

Annotation - This article reviews the biological and molecular characteristics of male breast cancer, focusing on hormone receptors, genetic mutations, and molecular subtypes. It highlights differences between male and female breast cancer and discusses how genomic information may guide future targeted therapies.

Jamil, A., Siddique, R., Altaf, F., Warraich, D., Ahmed, F., and Qureshi, Z. (2025). Comprehensive review of male breast cancer: Understanding a rare condition. *Tech Science Press* 33, 1289-1300.

Annotation – This review examines the epidemiology, genetic risk factors, clinical presentation, and treatment of male breast cancer, highlighting BRCA2 mutations and hormonal imbalances as major contributors. It emphasizes late diagnosis, limited male-specific guidelines, and the unique psychosocial challenges faced by men. This source is useful for discussing research gaps and the need for improved screening, genetic counseling, and personalized treatment approaches in male breast cancer.

Pyo, Y., & Jeon, Y.S. (2025). Quality of life in male breast cancer patients: psychosocial impacts and therapeutic strategies. J. Men's Health *21*, 1–8.

Annotation - This article is a scoping review that examines how male breast cancer (MBC)—a rare but significant diagnosis—impacts a patient's quality of life (QOL). By analyzing studies published between 2010 and 2024, the authors identify three primary areas of concern: Physical Risks (the ongoing threat of tumor metastasis and local recurrence), Treatment Complications (the physical side effects stemming from chemotherapy and other therapeutic interventions), and Psychosocial Impact (significant distress related to body image, anxiety over life expectancy, and a general lack of male-specific support). The review concludes that while new targeted therapies are vital for survival, addressing the unique psychosocial needs of men is essential for improving their overall well-being and long-term recovery.

Sah, A.K., Choudhary, R.K., Sabrievna, V.A., Dzhuraevich, K.I., Abbas, A.M., Shalabi, M.G., Siddique, N.A., Alshammari, R.R., Trivedi, N., & Elshaikh, R.H. (2025). Male Breast Cancer: Epidemiology, Diagnosis, Molecular Mechanisms, Therapeutics, and Future Prospective. Oncol. Res. 34, 7.

Annotation - This comprehensive review examines the rising global incidence and unique biological landscape of male breast cancer (MBC), a rare malignancy often overshadowed by female-centric research. The authors highlight critical disparities in diagnosis, noting that the absence of routine screening often results in late-stage detection among older men. Key insights include the predominance of ER-positive/HER2-negative profiles and the significant role of *BRCA2* mutations. Furthermore, the article explores how precision oncology and artificial intelligence are revolutionizing management through multiomics and automated diagnostics. Ultimately, the paper underscores the urgent need for male-specific clinical trials to bridge the therapeutic gaps currently filled by extrapolation from existing data.

Samad, M.A., Ahmad, I., Khan, M.R., Suhail, M., Zughaibi, T.A., Al-Abbasi, F.A., Alhosaini, K.A., Khan, M.S., Kumer, A., & Tabrez, S. (2025). Breast Cancer: Molecular Pathogenesis and Targeted Therapy: MedComm 6, e70404.

Annotation - This review delineates the molecular landscape of breast cancer (BC), tracing its progression from cellular initiation to invasive malignancy. Driven by environmental triggers and a synergy of genetic alterations—specifically, gain-of-function in oncogenes (HER2, PIK3CA) and loss-of-function in tumor suppressors (TP53, BRCA1/2)—BC pathogenesis involves the profound dysregulation of signaling cascades, including PI3K/Akt/mTOR and Wnt/β-catenin. The study highlights the "ADC Revolution" by evaluating next-generation conjugates such as Trastuzumab deruxtecan. By integrating insights into intratumoral heterogeneity and liquid biopsy for resistance detection, the authors emphasize a transition toward precision oncology, supported by AI-driven discovery and patient-derived organoids to improve outcomes in aggressive subtypes.

Schröder, C.P., van Leeuwen-Stok, E., Cardoso, F., Linderholm, B., Poncet, C., Wolff, A.C., Bjelic-Radisic, V., Werutsky, G., Abreu, M.H., Bozovic-Spasojevic, I., et al. (2023). Quality of Life in Male Breast Cancer: Prospective Study of the International Male Breast Cancer Program. The Oncologist 28, e877–e883.

Annotation - This prospective study investigates the health-related quality of life (QoL) and symptom burden in men diagnosed with breast cancer, addressing a significant gap in oncological research. Utilizing data from the International Male Breast Cancer Program, the researchers found that male patients generally reported high global health status and functioning scores at the time of diagnosis, often surpassing historical female reference data. While symptoms like fatigue, insomnia, and pain were present, they were less burdensome than those typically experienced by women. The findings emphasize that while emotional and social functioning remain stable, sexual activity is negatively impacted by advanced disease and older age.

Ter-Zakarian A, Agelidis A, Jaloudi M. (2025). Male Breast Cancer: Evaluating the Current Landscape of Diagnosis and Treatment. *Breast Cancer (Dove Med Press)*. 567–572.

Annotation - provides a comprehensive analysis of the current landscape of male breast cancer (MBC), systematically examines the epidemiology and risk factors, noting that men are typically diagnosed at an older age and more advanced stages compared to women, and highlights critical genetic predispositions, specifically the high relative risk associated with BRCA2 mutations, and hormonal factors like hyperestrogenism.