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The incidence of male breast cancer: from fiction to reality – correspondence

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Dear Editor,

Male breast cancer (MBC) is uncommon, accounting for roughly 1% of all male malignancies and 1% of all breast cancers (BCs) worldwide[1–4]. MBC accounts for just under 0.2% of cancer-related mortality in men. Due to the low incidence of MBC, BC literature, research, clinical trials, and the advancement of novel treatments primarily focus on female BC. Male and female BC have been described to have distinct molecular and clinicopathologic characteristics[5–9]. According to statistical projections, ~2670 novel incidences of BC were anticipated to be detected among the male population in the United States during the year 2019, with a projected 500 fatalities resulting from this disease[10]. The incidence rate of BC in males is ~1 in 1000, whereas in females, it is roughly 1 in 8, resulting in a significantly higher risk for women. The overall BC rates in men and women increase progressively with age. Nevertheless, the mean age of initial diagnosis of BC in men is comparatively higher, with an average of 67 years, in contrast to women diagnosed at an average age of 62 years[11]. Significant gaps in understanding exist regarding the most effective approach to managing BC in male patients. Thus far, the methodologies employed in managing MBC have been primarily derived from studies on female BC patients[12]. Clinical trials that are currently in progress or have been planned, with an emphasis on MBC treatment, can influence the standard of care in the future. However, these trials are still in progress and will require several years. The current guideline issued by the American Society of Clinical Oncology (ASCO) provides recommendations about various crucial facets of MBC management[13]. In this correspondence article, we discuss the background, risk factors, and potential future treatments for treating MBC. We have tried to shed light on the importance of MBC and why it calls for a detailed discussion and research on this topic.

Despite the rising incidence, MBC remains a rare ailment, which hinders the conduct of extensive clinical trials essential for determining the most effective approach to its management. Risk factors for MBC may include hormonal imbalances, such as an excess of estrogen or a lack of androgens, Klinefelter syndrome, or a family history of BC. There is a tendency for males to receive a diagnosis at a more advanced age than females, with a higher incidence of disease progression. MBCs exhibit a higher tendency to express estrogen and progesterone receptors while demonstrating a lower likelihood of overexpressing Her2-neu than BCs found in females[3]. Research supports the hypothesis that higher MBC risk is caused by pathogenic mutations in ATM, BRCA2, and PALB2 but not by pathogenic variations in BRCA1 (Fig. 1)[14]. It has been observed that 20% of MBC cases have a first-degree relative who has also been diagnosed with the disease. Susceptibility to a particular disease can arise due to infrequent mutations in genes with high penetrances, such as BRCA1 and BRCA2, which confer a substantial risk, or due to more common mutations with low penetrance that result in a modest increase in risk. Autosomal dominant inheritance is believed to cause 5–10% of female BCs, with BRCA1 and BRCA2 mutations implicated in particular[15]. The anticipated range for the corresponding proportion among males is between 4 and 40%[16]. An exciting study claims that males who have survived breast cancer are at an increased risk of developing cancers in the colorectal, pancreatic, and thyroid regions. The provided estimations could potentially aid in the clinical management of patients and facilitate informed decisions regarding genetic testing[17].

The incidence of MBC is significantly higher in families with BRCA2 mutations than in those with BRCA1 mutations. The absence of BRCA1 mutations was observed in a cohort of 54 male BC patients from Southern California, while a BRCA2 mutation was detected in 4% of the patients[18]. A study conducted in the United Kingdom involved 94 patients, and it was found that there were no germline BRCA1 mutations. However, five patients, which accounted for 6% of the total, had BRCA2 mutations. Additionally, 20% of these patients reported having a first-degree relative with BC[19]. No correlation was observed between the location of mutations within the BRCA2 gene and the risk of BC in either of the studies. A study examined a cohort

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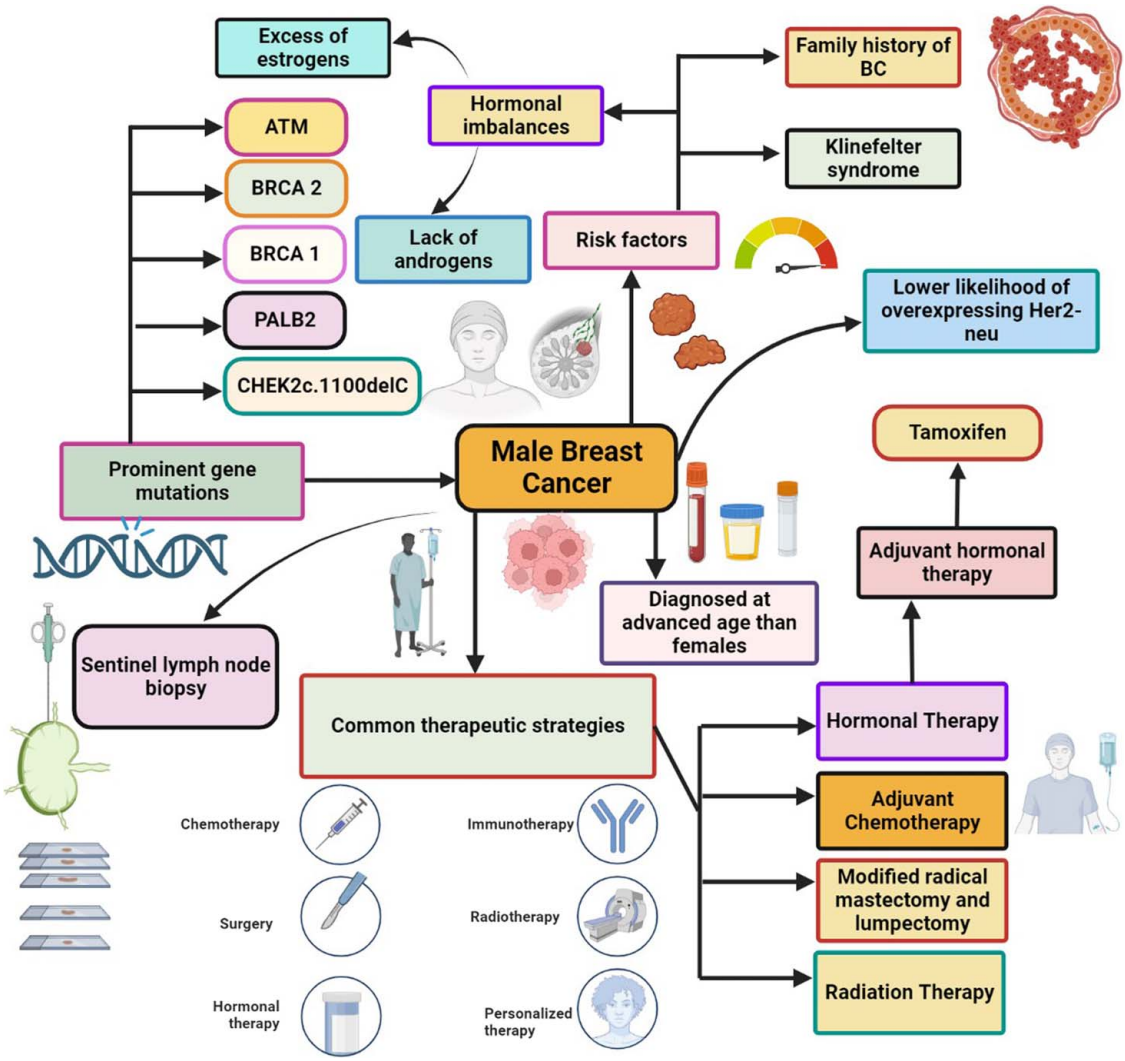

Figure 1. This figure provides a complete overview of the characteristics and background of male breast cancer, including an idea of the risk factors, genetic mutations, and therapeutic strategies.

of 76 male BC patients referred for commercial gene testing. The results indicated eight individuals harbored deleterious BRCA1 mutations, while 14 carried BRCA2 mutations. These findings suggest that the prevalence of BRCA1 mutations in MBC patients may be higher than earlier estimated[20]. The study found that the median age of diagnosis for males with BRCA1 mutations was 52 years, while those with BRCA2 mutations had a median age of diagnosis of 59 years. In contrast, men without mutations had a median age of diagnosis of 59 years[2].

In the context of MBC, the utilization of sentinel lymph node biopsy has been demonstrated to be a dependable method for detecting nodal metastases[21,22]. Hormonal therapy is considered the most effective treatment for hormone receptor-positive MBC. Tamoxifen is the recommended adjuvant hormone therapy for 5 years. Tamoxifen is linked with a reduction in the likelihood of recurrence, with a rate of 51%, comparable to that of female BC treatment[23]. Approximately 80% of the estrogen in males is synthesized through the aromatase pathway, while the remaining 20% is produced by the testes[24]. Nonetheless, limited research has been conducted on using adjuvant aromatase inhibitors (AIs) in male patients. Eggermann and colleagues compared adjuvant tamoxifen and AIs. Their report showed a statistically significant decline in mortality risk and overall survival in the AI cohort[25]. Adjuvant chemotherapy is typically advised for high-risk patients with young age, high tumor grade, and/or axillary nodal involvement. The administration of adjuvant chemotherapy resulted in decreased time to recurrence and an enhancement in overall survival, albeit not reaching statistical significance[23]. There is currently a lack of available data regarding the adjuvant application of trastuzumab in MBC. Only one case report has been published, which offers speculation regarding its effectiveness in treating this type of disease[26]. Given the absence of a biological rationale for the differential efficacy of trastuzumab in MBC versus female BC patients, it may be appropriate to contemplate using this therapeutic agent and pertuzumab in individuals with HER-2-positive MBC. Tamoxifen is widely considered the primary treatment option for male patients. A study reports that the 5-year overall survival rates for patients with female BC and MBC who received tamoxifen treatment were similar, with rates of 85.1 and 89.2%, respectively[27].

Additional therapeutic options include the utilization of Luteinizing hormone-releasing hormone agonists and orchiectomy. Hormonal therapy is correlated with a plethora of adverse effects in male individuals. Hot flashes are the most frequently occurring adverse event associated with tamoxifen. Symptoms such as reduced sexual desire, increased body weight, and general discomfort have been reported. Rash and erectile dysfunction are infrequent occurrences. According to a study[28], infrequent occurrences of hepatic dysfunction, pulmonary embolism, thrombophlebitis, myalgia, depression, visual impairment, and diarrhea have been reported. The literature has documented adverse effects associated with the use of AI. Specifically, anastrozole has been linked to decreased libido, leg swelling, and depression, while letrozole has been associated with edema and hot flashes[29]. Chemotherapy has been proposed as a viable option for second or third-line therapy in cases of metastatic MBC following a relapse of hormonal therapy in patients with estrogen receptor-negative status[30,31].

The surgical technique of modified radical mastectomy is commonly employed in around 70% of patients as the preferred approach for managing MBCs. The less preferred methods include radical mastectomy, particularly in elderly patients, total mastectomy, and lumpectomy with or without radiation[32]. A study by Sarmiento *et al*. evaluated a significant population-based cohort of 16 498 MBCs from the National Cancer Database. The study demonstrated that treatments, specifically surgery, were associated with enhanced survival outcomes. The study found that reduced survival was linked to advanced age, black ethnicity, government-provided insurance, a greater presence of comorbidities, and higher tumor stages[33]. Yadav *et al*. established the correlation between unfavorable prognosis and advanced age, black ethnicity, comorbidities, high grade and stages, and inadequate healthcare accessibility. A negative correlation with mastectomy was reported, in contrast to the findings of Sarmiento's study. According to Yadav and colleagues' research, a more significant proportion of male patients received total mastectomy instead of breast-conserving treatment, typically the preferred surgical option for female patients. The study demonstrated a correlation between radical mastectomy and unfavorable clinical results, which may be attributed to a selection bias resulting from the larger tumor size and/or node involvement associated with higher stages in this group[34,35].

Although MBC is a rare and frequently disregarded condition, knowledge of the biological distinctions between male and female BC is advancing. These distinctions suggest that MBC should be considered a separate illness from female BC. MBC patients present a clinically complex situation with numerous unresolved issues. In order to find better treatment options, studies in this field focus on analyzing the biological foundations of this subtype of malignancies. Understanding germline mutations like BRCA2 that are more common in MBC may aid in discovering advanced therapeutic options like PARP inhibitors. Androgen receptor (AR)-targeted drugs may be an effective treatment option, either as monotherapy or in combination with other therapies, given the near-universal expression of the AR in male BC cancers and its relatively benign toxicity profile. Seviteronel's initial action on MBC emphasizes targeting the sex-steroid biosynthesis pathway and AR activation as a potentially effective treatment strategy[7]. Hence, additional research endeavors tailored towards MBC are imperative to elucidate the most effective approach to its management. Recent findings suggest that epigenetic modifications occurring at the somatic level may have implications for developing personalized therapies for distinct subgroups of MBC. It is hoped that a collaborative multinational approach will enable the implementation of MBC-specific prospective trials shortly.

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