Male breast cancer (MBC) – A Review

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ABSTRACT: Males account for 1% of all cases of breast cancer. With the aging of the world’s population, the disease has exhibited a rise in incidence in recent decades. Male breasts are smaller than female breasts, making the disease easier to spot, but patients often do not report their cases in time due to a lack of awareness. The stage-to-stage prognosis of male breast cancer is comparable to that of their female counterparts. Due to the relative rarity of the disease and poor patient enrollment in large randomized studies, the optimal management of male breast cancer remains uncertain. This article presents a narrative review of male breast cancer in light of recent literature, with an emphasis on epidemiology, clinical features, and current management.

KEYWORDS: androgen receptors, BRCA1, BRCA2, chemotherapy, male breast cancer, mastectomy, tamoxifen

ABBREVIATIONS

AIs – aromatase inhibitors
ALN – axillary lymph nodes
AR – androgen receptor
BCS – breast-conserving surgeries
CAG – polymorphic polyglutamine
CI – confidence interval
DCIS – ductal carcinoma in situ
DNA – deoxyribonucleic acid
EGFR – epidermal growth factor receptor
ER – estrogen receptor
FBC – female breast cancer
FSH – follicle-stimulating hormone
GGC – polyglycine tract
GnRH – gonadotropin-releasing hormone
HR – hazard ratio
MBC – male breast cancer
MGPT – multi-gene panel testing
MRM – modified radical mastectomy
MSBE – male self-breast examination
OBC – occult breast cancer
OR – odds ratio
PTEN – phosphatase and tensin homolog
SLNBX – sentinel lymph node biopsy
TNM – tumor, node, and metastasis
WBRT – whole breast radiation

INTRODUCTION

Male breast cancer (MBC) is considered a relatively uncommon disorder, but its incidence has exhibited a substantial increase in recent decades [1, 2]. In terms of diagnosis, staging, and treatment, the condition is comparable to female breast cancer (FBC). Male breasts are smaller and any abnormality is liable to be detected early, in theory. However, the lack of awareness about the disease and the absence of screening protocols leads to delayed reporting of patients [1–3]. There are numerous risk factors and the disease might present itself in unexpected ways. This article has been compiled to present a narrative review of MBC in light of the recent literature.

MATERIALS AND METHODS

By utilizing the search terms “male breast cancer”, English-language articles published on the subject between 1992 and 2022 were derived from the databases PubMed, Google Scholar, and ResearchGate. Demographic information, pathophysiology, clinical characteristics, risk factors, staging, complications, and therapy were analyzed from these articles.

EPIDEMIOLOGY

Although there is a great deal of epidemiologic information on female breast cancer, the etiology of MBC is still mostly unknown and the data applied to men is generally extrapolated from the results of studies conducted on women.

This variation is explained [4] by the rarity of MBC, which results in limitations:

1. applying epidemiologic methodology to studies and
2. attaining a sample size appropriate for observing an association between the risk factor and the disease.

Furthermore, MBC tumors are small and leave little tissue for research purposes after the requisite pathology workup for molecular and genetic studies. New research suggests that, with the likely contribution of hereditary and hormonal factors, the analytical epidemiology of male breast cancer is often comparable to that of female breast cancer. However, many aspects of the etiology and treatment of MBC do not fit the simplistic model that men usually have endocrine-sensitive tumors which behave like those in postmenopausal women [4].

GENETIC FACTORS

A family history of breast cancer has been discovered to increase the risk of MBC, much like in FBC. Friedman et al. found that 17% of MBC cases from Southern Carolina had at least one first-degree relative with breast and/or ovarian cancer [5]. Similarly, Hill et al. [6] found that 15% had a first-degree relative who had previously...
experienced breast cancer. It was found in that study that the presence of a family history had no statistically significant correlation with the patient's age at presentation, the length of their symptoms, their disease stage at presentation, or their overall survival. Over the past ten years, numerous other population-based investigations have found that roughly 20% of male patients had a female relative who had experienced breast cancer [7, 8]. In general, a recent literature review revealed that a first-degree relative's positive family history of either MBC or FBC is linked to a 2- to 3-fold increase in MBC risk. In a recent unmatched study, Calip et al. [9] tried to define the association between MBC and family history of breast cancer in patients without mutations in BRCA1 or BRCA2. They found that breast cancer in a first- or second-degree relative was associated with four-fold higher odds of MBC (OR 4.7; 95% CI 4.1, 5.3) and that a history of breast cancer in two or more first-degree relatives had the strongest associations (OR 7.8; 95% CI 5.2, 11.6). Similarly, there was strong association for probands and first-degree relatives diagnosed at age 45 or younger (OR 6.9; 95% CI 3.9, 12.4) and for a family history of MBC (OR 17.9; 95% CI 7.6, 42.1). The study drew the conclusion that MBC patients without mutations in BRCA1/2 have significantly higher odds of a family history of breast cancer, suggesting the existence of unidentified MBC susceptibility alleles.

In contrast to women, where the estimates reach up to 86%, a number of studies have shown that 4% to 40% of MBC can be attributable to hereditary mutations [10, 11]. BRCA2, the AR gene, cytochrome P45017 (CYP17), Klinefelter syndrome (XXY karyotype), the PTEN tumor suppressor gene linked to Cowden syndrome, and the CHEK2 gene are among the genes that have been linked to the etiology of MBC.

**BRCA2**

Located on chromosome 13q12–13, the BRCA2 gene has been linked to the majority of hereditary BCM cases [12]. The loss of RAD51’s intracellular localization and DNA-binding capabilities after BRCA2 inactivation is thought to be a significant event that contributes to genomic instability and cancer. The 999del5 mutation is the most prevalent documented change in the BRCA2 gene. A 40% involvement of the constitutional 999del5 mutation in MBC in Icelandic patients has been demonstrated [13]. Duplication at 9p23–24 is another significant BRCA2 mutation in MBC that has been mentioned in the literature. However, BRCA1 mutations are uncommon in MBC and the majority of investigations have not found any BRCA1 mutation carriers. Only a few studies have found BRCA1 mutations in MBC patients, such as a study by Ottini et al. in which 1 of 25 (4%) MBC cases from Florence, Italy were reported to have a BRCA1 mutation [14].

**Klinefelter Syndrome**

Klinefelter syndrome has been identified in 4–7.5% of MBC cases [15]. One in 1,000 males have the syndrome, which is defined by a rare chromosomal anomaly known as the 47 XXY karyotype. A high estrogen/androgen ratio, eunuchoid habitus, gynecomastia, small, hard testicles, and elevated FSH secretion are typical signs of this hereditary condition throughout puberty. However, there are also low levels of androstenedione and normal or slightly reduced levels of estrogens. Men with Klinefelter syndrome have a 49-fold higher risk of developing breast cancer, according to research. This higher risk is attributed to aberrant hormonal stimulation of cell proliferation in the mammary ductal epithelium [15]. Another explanation attributes the problem to the use of exogenous testosterone therapy, which causes peripheral adipose tissue to produce estrogens [16]. To identify the subsets of Klinefelter syndrome – individuals who are at a high risk of developing MBC – and to distinguish between potential predisposing factors, such as altered endogenous hormone levels, Brinton LA [16] has emphasized the need for additional well-designed epidemiologic research.

**Androgen Receptor Gene Mutation**

A decrease in the protective impact of androgens on breast cells caused by germline mutations in the androgen receptor (AR) gene has also been offered as a possible explanation for the emergence of MBC. The link between MBC and a germ line mutation in exon 3 encoding the DNA-binding domain of the AR has been observed in various studies [17–20]. Within the coding region of exon 1 of the AR gene are highly polymorphic polyglutamine (CAG) and polyglycine (GGC) tracts. Song et al. recently discovered that the CAG repeat length and AR expression are two distinct prognostic markers in MBC patients [19]. In addition, it has been suggested that the AR gene’s CAG repeat length could be a valuable genetic diagnostic indicator for identifying men who are more likely than women to develop breast cancer [20].

In a recent study by Ucak et al. [21], the relationship between AR expression and clinicopathological parameters was studied retrospectively in 35 patients who had received a histological diagnosis of MBC. However, the study failed to document any significant relationship between AR expression and cancer stage (p = 0.585), histologic grade (p = 0.685), lymph node status (p = 0.685), survival rate (p = 1.000), age (p = 1.000), lymphovascular invasion (p = 0.700), perineural invasion (p = 1.000), skin invasion (p = 1.000), nipple involvement (p = 1.000), ER positivity (p = 1.000), PR positivity (p = 0.218), Her2 expression (p = 0.523), DCIS presence (p = 1.000), Ki67 index (p = 0.685), Luminal A group (p = 0.700), Luminal B group (p = 0.691), or triple negative group (p = 1.000). In another recent study by Scatena et al. [22], AR expression ranged between 10% and 98% in 44 enrolled cases of MBC; the majority of cases expressed moderate to high levels. In ER+/PgR+ cases, AR levels positively correlated with the other steroid receptors, pointing to the importance of hormonal cross-talk. In the ER+/PgR+ group, on the other hand, AR status inversely correlated with histological grade and lymph node status, hinting at a potentially favorable biological role of AR in this subgroup.

**CYP17Gene**

Another gene that may be linked to breast cancer in men is CYP17. The cytochrome P450c17α enzyme, which is necessary for the production of estrogens and androgens, is encoded by this gene [23]. However, further proof is required to establish a link between CYP17 mutations and MBC, since certain recent studies have indicated that polymorphisms in these genes may not be associated with breast cancer risk [24].

**Cowden Syndrome**

Multiple hamartomas are characteristic of Cowden syndrome, an autosomal dominant cancer susceptibility disorder that is linked to germ line mutations in the PTEN tumor suppressor gene.
Fackenthal et al. postulated that PTEN gene mutation syndrome contributes to the formation and early incidence of MBC after examining two Cowden syndrome patients with MBC [25].

**CHEK2**

Cellular responses to DNA damage are mediated by the kinase CHEK2, which also functions as a cell cycle checkpoint. The kinase function of CHEK2 is eliminated by the protein truncating mutation 1100delC in exon 10. This mutation has also been linked to an increased risk of MBC [26], even though some investigations have been unable to show such a connection [27].

**EPIDEMIOLOGICAL RISK FACTORS**

In the literature, a number of epidemiologic risk factors have been linked to MBC, including dietary variables, testicular disorders, benign breast abnormalities, occupational exposures, and conditions linked to high estrogen levels [28–30].

**Elevated Estrogen Levels**

Since estrogen-related risk factors have been significantly linked to the etiology of FBC, elevated estrogen levels in different diseases have been examined. The following hyperestrogenic factors have been linked to MBC:

1. Obesity;
2. Trans-sexuality;
3. Prostate cancer after treatment;
4. Cirrhosis of the liver.

**Testicular Disorders**

A higher risk of MBC has been linked to a number of testicular anomalies, including cryptorchidism, post-mumps orchitis, testicular injury, post-orchidectomy, and congenital inguinal hernia. Deficient androgen production is frequently linked to testicular problems, which could raise the risk of MBC.

**Dietary Risk Factors**

Dietary variables such as meat consumption and alcoholism [31] have been receiving attention as possible risk factors for MBC in recent research. In a similar vein, there is conflicting data linking a diet high in fruits and vegetables to a reduced risk of breast cancer of either gender [32]. While some studies did not discover any statistically significant link, others revealed a preventive effect from eating fruits and vegetables [32, 33]. It has been discovered that chronic alcoholism increases MBC risk by two to six times [31].

**Occupational Exposures**

Tasks that expose workers to high temperatures, nighttime lighting, electromagnetic waves, chemicals (such as polycyclic aromatic hydrocarbons, nitrogen oxides, nitrosamines, and metal fumes), and fuels (such as gasoline and combustion engine products) have all been linked to MBC [34], but there is still no conclusive evidence to support these claims.

**HISTOPATHOLOGY AND IMMUNOHISTOCHEMISTRY**

Invasive ductal carcinoma is the most frequent kind of breast cancer in men, accounting for over 90% of all male breast cancer cases [35], whereas in women the frequency of ductal histology is 70% to 75%. Other less common variants include medullary, papilloma, and lobular carcinoma. Due to a lack of knowledge and the stigma associated with MBC, ductal carcinoma in situ (DCIS) in men is a rare disease, representing only 5% of MBC cases. As a result, patients’ diagnoses are delayed and their outcomes are worse. In regards to hormone expression in MBC, approximately 90% express the estrogen receptor (ER) and 81% express the progesterone receptor, which is higher than for the female patients. FOXP1 is a member of the winged-helix or forkhead transcription factor family, which is involved in cell proliferation and cancer transformation. In a retrospective study of the clinicopathological features of 73 cases of MBC in the Chinese population, AR and FOXP1 were found to be highly expressed in MBC [34].

Ge et al. [36] conducted a study with the aim of classifying the molecular subtypes of male breast cancer based on the expression profile of immunomarkers and of evaluating their association with the clinicopathological features and expression patterns of epidermal growth factor receptor (EGFR) and nuclear factor kappaB (NF-kappaB). They found that the luminal A (83%) and B (17%) subtypes were the major subtypes of male breast carcinoma. Basal-like and HER2+/ER- subtypes were not identified in this group. All carcinomas expressed ER and 67% of them were PR+. High nuclear grades were more common in the luminal B subtype (71%) than in the luminal A subtype (34%). The luminal B subtype carcinomas expressed EGFR (42%) and NF-kappaB (57%) more frequently than the luminal A subtype did (17% vs. 37%, respectively).

**CLINICAL FEATURES**

The most common method for detecting MBC is by inadvertently seeing a unilateral, painless bulge or thickening in the breast that resembles what happens in women [29, 35]. Pain, skin dimpling or puckering, nipple discharge, nipple retraction, and changes in the nipple or breast skin, such as ulceration, scaling, or redness, are other possible clinical characteristics. Men typically have smaller breasts than women, making masses easier to spot. It is crucial to ask questions about the patient’s work, previous medical history, family history of breast cancer, and whether or not he has ever been exposed to radiation or estrogen.

**EVALUATION**

As with FBC, the diagnosis of MBC is made by a triple assessment of (i) clinical assessment, (ii) imaging – mammography or ultrasonography – and (iii) core biopsy. Mammography has a sensitivity of 92% and a specificity of 90%, though it occasionally has limitations because male breasts differ in volume. For the most accurate diagnosis, ultrasound-guided core biopsy is preferred over fine-needle aspiration [35].

Recent studies have been conducted to assess the role of multi-gene panel testing (MGPT) in the evaluation of MBC. Pritzlaff et al. [37]...
subjected 715 cases of MBC to MGPT and their detection rate was 18.1% when testing for variants in 16 breast cancer susceptibility genes. They concluded that all MBC patients, regardless of age at diagnosis, history of multiple primary cancers, or family history of MBC, should be offered MGPT. Fostira et al. [38], however, after evaluating the clinical utility of MGPT by investigating MBC patients derived from a population with known founder effects, concluded that the tool may be of limited benefit for MBC patients and their families.

OCCULT BREAST CANCER (OBC)

The type of breast cancer known as OBC lacks any visible breast abnormalities (i.e., no primary cancer lesion is found in either breast on physical examination or in imaging studies such as ultrasound and mammography). OBC is quite uncommon in men and is histologically similar to metastatic breast cancer. The initial symptom in the majority of the cases documented in the literature is axillary lymph node metastases [39–41].

In 2018, Terada et al. [41] proposed that ectopic breast tissue seen in the axillary lymph nodes (ALNs) is the cause of OBC. They found a number of factors that support this notion. Firstly, recent developments in radiological imaging have led some experts to believe that a primary breast tumor is not just undetected, but completely nonexistent in OBC. Secondly, it has been noted that ectopic breasts present in ALNs might lead to proliferative breast lesions. Finally, according to immunohistochemistry, there is a variety of cellular subtypes in OBC, including common breast cancer, and the prognosis is comparable to that of stage II breast cancer. Mastectomy and whole breast radiation (WBRT), which are now administered to OBC patients, may not be necessary if the hypothesis of Terada et al. [41] is confirmed.

BILATERAL DISEASE

Bilateral MBC is very rare, accounting for only 1.5% to 2% of all MBCs [42–44]. The incidence of metachronous MBC is higher (two thirds) than that of synchronous MBC (one third).

DIFFERENTIAL DIAGNOSIS

The common differentials [45] that a clinician should be mindful of during the evaluation of MBC include:

1. Gynecomastia;
2. Fat necrosis;
3. Breast metastases;
4. Lymphomas;
5. Lipomas;
6. Sarcomas;
7. Abscesses.

STAGING

The staging protocol for MBC uses the tumor, node, and metastasis (TNM) staging approach; it is categorized similarly to that for FBC. Unfortunately, due to frequent delayed identification of male breast cancer, 40% of all cases are discovered to be in stage III or IV at the time of the initial diagnosis [45, 46].

MANAGEMENT

There are very few well-conducted randomized controlled trials for the treatment of MBC. The current treatment guidelines are therefore derived from research on female breast cancer [45, 46]. The therapeutic modalities are described below.

Surgical procedures

Surgical options should be individualized as per the extent of the disease, reconstruction considerations, psychological burden, and survival.

Modified radical mastectomy (MRM)

This is the mainstay of surgical management, as most MBCs present in the retroareolar location, have aggressive biology, and tend to present at a later stage. Nipple sparing is also difficult due to the location of the tumor.

Breast-conserving surgeries (BCS)

BCS such as lumpectomy are generally deemed feasible for a disease that is early-stage or distant from the nipple-areolar complex. This kind of surgical procedure has no impact on breast cancer-specific survival, according to Cloyd et al. [47]; however, they discovered that men with breast cancer are less likely than women to get adjuvant chemoradiation therapy after BCS or lymph node staging [48].

Management of axilla

Staging the axillary lymph nodes is an essential part of management. Sentinel lymph node biopsy (SLNBX) has been demonstrated to be a reliable and effective method of assessing whether the lymph nodes are clinically negative (non-palpable with normal size and appearance on imaging) [49]. If further analysis with fine-needle aspiration or biopsy reveals the presence of cancer in the clinically positive nodes, axillary dissection or down-staging with neoadjuvant therapy is carried out [50].

Radiation Therapy

All MBC patients should undergo evaluation by radiation oncologists, as recent studies suggest that adjuvant radiation is effective and thus recommended for Stage I–III MBC [51]. Gennari et al. [51] have recommended a more aggressive adjuvant radiation therapy
for MBC tumors greater than 1 cm or for any patient with positive lymph nodes, in light of the purported ease with which MBC spreads to the chest wall due to the smaller breast volume.

**HORMONAL THERAPY**

The majority of patients are candidates for hormone therapy due to the near universal expression (80%) of ER in MBC, though compliance is the biggest stumbling block. Tamoxifen (a competitive ER inhibitor that blocks estrogen signaling) is recommended for 5 years with the option of increasing the duration to 10 years. A German trial [52] conducted prospectively analyzed 448 ER-positive MBC cases with median follow-up of 39 months and found that the rate of death, disease-free survival, and recurrence were significantly worse in patients who did not receive adjuvant tamoxifen (22% vs. 14%). The recurrence rate and mortality in the group of patients without and with tamoxifen treatment were 18.2% and 11.2%, respectively. The most common site of metastases in that series was bone. After statistical adjustments for confounding factors, it was found that tamoxifen reduced the recurrence rate by 68% (hazard ratio, HR = 0.32; 95% confidence interval, CI: 0.14–0.74).

Aromatase inhibitors (AIs) target peripheral conversion of androgens into estrogen, have shown an inconsistent result in MBC, and are thus currently prescribed in the recurrence of metastatic lesions. The efficacy of anastrozole was found to be not very promising by Giordano et al. [53]. Zagouri et al., however, believe that AIs with or without gonadotropin-releasing hormone (GnRH) analogues may represent an effective and safe treatment option for hormone-receptor positive, pretreated, metastatic MBC patients [54].

**Health Education**

In order to report cases of MBC at the early stages of the disease and to reduce patient attrition before active management or during follow-up, there is a need to raise awareness of the condition [55].

Male self-breast examination (MSBE) needs to be encouraged among men who are at high risk for breast cancer, as it has been recommended to women and has provided major benefits.

**FUTURE DIRECTIONS**

Despite recent advancements and improvements in the medical sciences, MBC has a significantly lower survival benefit than FBC. Recent statistics reveal an almost 60% excess mortality rate when compared to women [56]. According to studies, variables including the prolonged use of FBC-based therapy and the underuse of adjuvant medications are causing an overall increase in MBC mortality [57].

Many well-organized clinical trials have recently started enrolling both genders, as strongly endorsed by the Food and Drug Administration. It is hoped that this fundamental change in approach will help reduce the current disparities in the quality of care [58], since men with breast cancer have been denied the opportunity to participate in clinical trials for decades.

**CONCLUSIONS**

MBC is a relatively uncommon disorder that accounts for less than 1% of all diagnosed breast cancers, but its incidence has shown an increase in recent decades. MBC is still poorly understood and has a significantly lower survival benefit, with about 60% excess mortality in comparison to female breast cancer. MBC diagnosis is challenging, not only because of the lack of screening, limited awareness, and education, but also because of the general inclination among men to delay care. Management is dictated by the studies carried out on the female population; they include surgery, radiotherapy, chemotherapy, and hormonal therapy. There is need for dedicated research to fully explain the various aspects related to this disease.

**REFERENCES**


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