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Male breast cancer: Medical and psychological management in comparison to female breast cancer. A review

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ABSTRACT

Background: Male breast cancer (MBC) is a rare illness and its management is largely based on published data from female breast cancer (FBC). The objective of this review was to evaluate the literature to determine if MBC is adequately understood, studied and treated, both medically and psychologically, despite its rarity.

Methods: A literature search was conducted, using PubMed, ProQuest, EBSCOHOST, and PsycINFO, for all articles containing the term "male breast cancer" or "male breast carcinoma" and published in English up to October 2015. Additional references were obtained from secondary search engines like Google Scholar and the citation lists of sourced articles.

Results: Published literature and public and healthcare awareness of MBC are far more limited than for FBC. Combined with misperception of breast cancer as a 'female illness', this may contribute to delayed diagnosis, worse prognosis, stigma and limited psychosocial support for male patients. Inconsistent use of medical treatment modalities, fewer treatment benefits, sparse safety data and a paucity of psychosocial research and services, as compared to FBC, may further contribute to poorer outcomes in MBC. Differences in etiological, diagnostic and treatment data between MBC and FBC also challenge the applicability of FBC management strategies to MBC.

Conclusion: MBC is a distinct condition that is much less understood, significantly understudied, and possibly undertreated, than FBC. Prospective research is essential to establish MBC-specific standards of care and guide medical and psychological interventions. Public and health professional education is also needed to raise awareness of MBC, reduce stigma and facilitate early detection.

1. Introduction

Male breast cancer (MBC) is a rare disease, comprising only 0.1% of all cancers in males [1], while female breast cancer (FBC) comprises 25% of all cancers in females [2]. While global incidence of FBC has risen over the years, that of MBC has remained relatively stable [3,4]. Incidence of FBC and MBC is positively correlated, suggesting some overlap in vulnerability factors [4,5]. However, the disparity in their incidence rates also points to heterogeneity in other risk factors and pathogenesis that may be sex-dependent [4].

Others characteristics of MBC and FBC also have both similarities and differences (see Table 1). MBC tends to be diagnosed in later life and is considered similar to late-onset (post-menopausal) FBC, which is thought to be influenced by hormonal, environmental and/or lifestyle exposures over the lifetime [5–7]. Symptoms common to both MBC and FBC include inverted nipple, nipple discharge, skin thickening, changes in breast symmetry, or most commonly, discrete mass [3,8,9]. Invasive ductal carcinoma is the most common histologic type of cancer for both MBC and FBC [1,8,10,11]. However, compared to FBC, MBC has more estrogen and progesterone receptor positive (ER+ and PR+) tumors [1,6,11,12], is mostly diagnosed at later stage with larger tumors and more lymph node metastases [7,10,13], and has poorer outcomes [1,10]. Tumor location is also most commonly central (subareolar) for MBC, versus upper outer quadrant for FBC [8,9]. In addition, the rise in incidence rates with age, while steady for MBC, is more rapid for FBC in the early-onset period, and slower in the late-onset period [6,11]. Finally, the improvement in survival rates over time has been smaller for MBC than for FBC [7].

Due to the rarity of MBC, the body of literature on its pathophysiology, treatment and psychological impact is far smaller than for FBC. This has significant implications for comprehension of risk

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Table 1
Similarities and differences in characteristics of FBC and MBC [1–13].

	Female breast cancer	Male breast cancer
Frequency among cancers	25% of all cancers in females 99% of all breast cancers	0.1% of all cancers in males 0.6–1% of all breast cancers
Change in global incidence rate (1958–2002, averaged)	Rise from 42 to 96 per 100,000 woman-years	Change from 0.3 to 1.1 per 100,000 man-years
Onset and peaks	Early onset (< age 50) and late onset (> age 50) Two peaks: Early 50s and early 70s	Late onset (> age 50) Single peak: Early 70s
Rise in incidence with age	Faster rise prior to age 50, slower rise after age 50	Steady, linear incline
Most common physical symptom	Discrete mass: 70–90%	Discrete mass: 70–90%
Status at diagnosis	Stage III–IV: 15–35% Tumor size > 2.0 cm: 25–40% Positive lymph node status: 20–35%	Stage III–IV: 20–45% Tumor size > 2.0 cm: 30–45% Positive lymph node status: 25–45%
Receptor positive tumors	ER+: 40–75% PR+: 50–75%	ER+: 60–95% PR+: 55–95%
Tumor location	Mostly upper outer quadrant	Mostly central (subareolar)
Most common histologic type	Invasive ductal carcinoma: 70–90%	Invasive ductal carcinoma: 75–95%
Change in hazard ratio (risk of mortality) over time (1976–2005)	Reduced by 40–45%	Reduced by 25–30%

Abbreviations: ER+ = estrogen receptor positive; FBC = female breast cancer; MBC = male breast cancer; PR+ = progesterone receptor positive.

factors and development of appropriate prevention and intervention initiatives for MBC. The purpose of this narrative review was to examine the published literature on MBC to determine if it is adequately understood, studied and treated, despite its rarity.

2. Methods

A search of the literature was conducted, using PubMed, ProQuest, EBSCOHOST, and PsycINFO, for all articles containing the term “male breast cancer” or “male breast carcinoma” and published in English up to October 2015. Supplementary search terms included “incidence”, “risk factors”, “screening”, “diagnosis”, “treatment”, “psychological impact”, “stigma”, and “functioning”, among others. Additional references were obtained from secondary search engines like Google Scholar and the citation lists of sourced articles. Of the 5429 publications found, 97 articles (guidelines, reviews, meta-analyses, controlled/uncontrolled trials, qualitative studies, case reports) were included in this review based on the significance of their findings and relevance of their information to the key topics described above. Articles were excluded if they failed to meet these criteria, or merely duplicated findings in more prominent publications without any new or supplementary information. The literature search and article review and selection were conducted by the author. The resulting data are examined and discussed below.

3. Results

3.1. Risk factors

Risk factors for breast cancer (BC) are demographic, genetic, hormonal and environmental in nature and are well researched in FBC. The limited data on risks for MBC come primarily from retrospective studies and often differ from findings in FBC (see Table 2).

3.1.1. Demographics

As in FBC, risk factors for MBC include older age, body mass index, obesity and family history of BC [1,5,10]. About 15–20% of MBC patients have a family history of BC or ovarian cancer [11,14], and such history (particularly of FBC) in first-degree relatives increases risk of MBC by 2–3 times [1,14]. In addition, evidence for early birth order as a risk factor is inconclusive in both FBC and MBC [5,10]. However, while Caucasian race confers greater risk than Afro-Caribbean race for FBC, the reverse is true in MBC [1,6,11]. As a result, the global male to female BC ratio is higher among Afro-Caribbeans [6,13] than among Caucasians [6]. Further, early puberty and never having borne children are risks for FBC [5,10], but data are mixed for age at puberty as a vulnerability factor for MBC, though childless males do appear to be at greater risk for an as yet unelucidated reason [15,16]. There is also inconsistent evidence for diabetes as a risk factor for MBC, unlike in FBC [14,15].

3.1.2. Genetics

Genetic vulnerability is a shared risk for FBC and MBC, but the genes relevant to each vary considerably [17]. The high penetrance BRCA mutations are significant to both conditions, but whereas risk of FBC increases by 55–65% with BRCA1 and 45% with BRCA2 [18,19], risk of MBC is increased by only 1–5% with BRCA1 and 5–10% with BRCA2 [10,14]. HER2 gene overexpression is also much more variable in MBC (1–42%) than in FBC (15–40%) [10,12]. Both FBC and MBC have reasonable data for the influence of moderate penetrance mutations like PTEN, PALB2 and CHEK2 [5,10,14,17,20]. However, evidence is mixed for association of MBC with other moderate penetrance mutations such as AR, CYP17, BRIP1 and RAD51C [10,14,21,22], which are linked more to FBC [10,14,17].

3.1.3. Hormonal exposures

Higher circulating concentrations of estrogens and androgens are associated with greater risk of FBC [23,24], while higher levels of estrogens (but not androgens) increase risk of MBC [15,25]. Conditions associated with alterations in the estrogen to androgen ratio have also been found to increase risk of MBC. These include Klinefelter's syndrome, obesity and orchitis/epididymitis [1,10,14], as well as estrogen therapy for prostate cancer, use of anti-androgen drugs to treat enlarged prostate or male pattern baldness, and use of estrogen or testosterone supplements (e.g. by transgendered persons or for sexual dysfunction) [1,5,10]. However, there is mixed evidence for gynecomastia and liver disease as risk factors for MBC [1,14,15,26].

Table 2
Similarities and differences in risk and protective factors for FBC and MBC [1–27].

	Female Breast Cancer	Male Breast Cancer
Risk level		
Strong risk	Family history of BC BRCA1 and BRCA2 mutations High circulating levels of estrogens and androgens (for late-onset FBC)	Family history of BC BRCA2 mutation > BRCA1 mutation High circulating levels of estrogens Klinefelter's syndrome Orchitis/epididymitis Estrogen or testosterone intake Radiation exposure
Medium risk	Older age Caucasian race Body mass index (low for early-onset FBC, high for late-onset FBC) Obesity Early puberty Never borne children Diabetes Gene mutations: HER2, CHEK2, PTEN, PALB2, AR, CYP17, BRIP1, RAD51C Use of hormonal supplements (oral contraceptives, hormone replacement therapy) Alcohol Radiation exposure Occupational exposure (heat, endocrine-disrupting chemicals)	Older age Afro-Caribbean race High body mass index Obesity Gene mutations: CHEK2, PTEN, PALB2
Inconclusive evidence of risk	Early birth order Electromagnetic exposure	Early birth order Age at puberty Childlessness Diabetes Gene mutations: HER2, AR, CYP17, BRIP1, RAD51C Gynecomastia Liver disease Alcohol Occupational exposures (electromagnetic fields, heat, endocrine-disrupting chemicals)
Protective effect		
Good evidence of protection	Exercise	
Uncertain evidence of protection		Exercise Tobacco

Abbreviations: BC=breast cancer; FBC=female breast cancer; MBC=male breast cancer.

3.1.4. Environmental exposures

For both FBC and MBC, radiation exposure is a risk factor, but electromagnetic exposure is not [1,5,10]. However, while alcohol use and occupational exposure to endocrine-disrupting chemicals (found in the chemical manufacturing and motor vehicle industries) have been found to increase risk of FBC [5,27], the data are inconclusive in MBC [1,5,10]. Evidence is also mixed in MBC for the protective effects of exercise (again contrary to positive findings in FBC) [5,10,11], and, more controversially, of tobacco [10,11].

3.2. Management

Management of BC, in general, involves screening, diagnosis, medical treatment and psychological support. In contrast to FBC, where these are well studied, particularly through randomized controlled trials (RCTs), there is a paucity of research on appropriate tests and interventions for MBC. As a result, its management is based primarily on findings in FBC research [1,10,11]. Despite this, available evidence (though sparse) from prospective surveys, retrospective and qualitative studies, and case reports, shows that strategies used in MBC have many differences from the standards applied in FBC (see Tables 3 and 4).

3.2.1. Awareness and screening

Public awareness of MBC is very limited, in contrast to FBC [14,28]. Historic and persistent advocacy by women's groups to increase public awareness and research into the etiology, early detection, treatment and prevention of FBC has led to international awareness and a high public health profile for the disease [9,14,20,28]. Similar activism for MBC does not yet exist and public education about MBC is scant [20,29], leading to limited awareness of the signs, symptoms and risk factors for MBC among both the general public and health professionals [14,20]. Similarly, breast self-exams (BSEs), clinical breast exams and mammography are standard components of screening and early detection programs for women, with genetic testing added for high-risk females, such as those with a family history of BC [14]. However, such programs are non-existent for males [14]. Retrospective analyses have shown that while a good proportion of FBC is detected by screening mammography at early stage, MBC tends to be detected only symptomatically, often at later stage [30,31]. In addition, patient and clinician ignorance of the physical symptoms of MBC may contribute to an up to 2-year delay between symptom presentation and diagnosis [32–34], and advanced stage of disease at treatment [9].

Physician and patient recognition of the health implications of a family history of BC is essential to appropriate patient management. However, observational studies have noted that family history of medical illness is only discussed in 51% of new patient visits and 22% of return visits in community practices [35] and that only 50% of family physicians specifically ask about family history of BC [36]. Ignorance of the possible consequences for males of a family history of BC may lead to less disclosure by male patients about

Table 3
Similarities and differences in general management of FBC and MBC [28–96].

	Female breast cancer	Male breast cancer
Awareness and screening	High public health profile Good public awareness of signs and symptoms Common screening programs: Annual clinical breast exam, monthly BSEs, annual mammography for all women from age 50 (starting much earlier for women with family history of BC), genetic testing for women with family history of FBC	Low public health profile Poor public awareness of signs and symptoms No common screening programs
Diagnosis	Clinical breast exam, imaging and biopsy are standard practice	Clinical breast exam is customary, but imaging and biopsy are not always done
Treatment: Surgery	BCS more performed: 45–80% Mastectomy less performed: 20–55%	BCS less performed: 0–15% Mastectomy more performed: 75–100%
Treatment: Radiotherapy	More frequently used: 35–60%	Less frequently used: 20–45%
Treatment: Chemotherapy	More utilized: 20–55%	Less utilized: 15–45%
Treatment: Endocrine therapy	More often administered: 50–80% Tamoxifen: 55–65% AIs: 35–45%	Less often administered: 35–75% Tamoxifen: 65–100% AIs: 15–30%
Psychological/supportive interventions	Commonly available: Patient/couple/family education and support groups, exercise and nutrition programs, information on and treatment for psychological symptoms, information on hair loss, cosmetology and mastectomy products and services	No standard availability

Abbreviations: AI=aromatase inhibitor; BC=breast cancer; BCS=breast conserving surgery; BSE=breast self-exam; FBC=female breast cancer; MBC=male breast cancer.

such history and/or to fewer referrals by physicians for secondary assessment [32]. Qualitative studies have found that a large majority of MBC patients were shocked by the diagnosis and/or did not know that men could develop the disease, despite having a family history of FBC [3,32,37]. Male patients have also reported having to insist on exploratory tests from physicians who did not consider their symptoms serious [32]. A prospective survey further found that similar proportions of men and women with family history of BC knew about genetic testing, but although 13% of those with FBC family history discussed it with a physician and 3% underwent genetic testing, none with MBC family history did either [38]. Another prospective survey noted that 25% of MBC patients were not referred for genetic testing despite increased risk of BRCA mutations in this population [39].

3.2.2. Diagnosis

Clinical breast exam followed by imaging (mammogram, ultrasound) and biopsy is the recommended standard for diagnosis in both MBC and FBC [1]. Similar to findings in FBC, mammography has 70–90% sensitivity and 85–90% specificity in detecting malignant masses and lymph node involvement in MBC, while sonography has 50–100% sensitivity and 80–100% specificity for the same [40–43]. There are no data on the utility of MRI for diagnosing MBC [1,10], possibly because the majority of MBC presents as palpable mass [1]. For biopsy, fine needle aspiration (FNA) has close to 100% sensitivity and specificity in MBC, as in FBC [44,45]. Core needle biopsy, which has almost 100% accuracy, is recommended when FNA is inconclusive or inadequate [42,46].

Despite these findings and likely due to healthcare unfamiliarity with MBC management, imaging and/or biopsy are not

Table 4
Similarities and differences in common side effects of treatment reported by FBC and MBC patients [48–86].

	Female breast cancer	Male breast cancer
Surgery	Pain, breast and arm edema, breast tissue fibrosis, decreased range of motion	Breast and arm edema, breast tissue fibrosis, decreased range of motion
Radiotherapy	Fatigue, skin reactions, breast fibrosis or shrinking, darkening and sun-sensitivity of treated skin, lymphedema, pain, sleep difficulties, cognitive deficits, depression and anxiety, sexual dysfunction, infertility, swollen arm, heart palpitations, shortness of breath, cough, nausea, loss of appetite, hot flashes/sweating, weight gain/loss, cardiovascular and pulmonary morbidity, secondary pulmonary or esophageal cancers	No published data
Chemotherapy	Amenorrhea, irregular bleeding, fatigue, nausea, vomiting, hair loss, loss of appetite, constipation, diarrhea, cognitive deficits, shortness of breath, hot flashes/sweating, sleep difficulties, depression, weight gain, sore mouth, urinary incontinence, vaginal dryness, sexual dysfunction	No published data
Endocrine therapy	Tamoxifen: Hot flashes/sweating, muscular problems, fatigue, sleep difficulties, depression, urinary tract problems, fluid retention, vaginal dryness, sexual dysfunction, anxiety. Also, higher risk for endometrial cancer or venous thrombosis compared to AIs AIs: Muscular problems, hot flashes/sweating, fatigue, vaginal dryness, sleep difficulties, depression, anxiety, sexual dysfunction, urinary tract problems. Also, higher risk of cardiovascular morbidity and bone fractures and trend towards higher mortality than with tamoxifen	Tamoxifen: Sexual dysfunction (more frequent than in FBC), weight gain, hot flashes (less frequent than in FBC), cognitive deficits, thromboembolic events, mood changes and depression, fatigue, sleep difficulties, gastrointestinal symptoms, bone pain, leg cramps, rash AIs: Hot flashes/sweating, sexual dysfunction, peripheral edema, depression. Also, higher risk of mortality compared to tamoxifen

Abbreviations: AI=aromatase inhibitor; FBC=female breast cancer; MBC=male breast cancer.

customary in MBC diagnostic processes in many clinical centers and many patients undergo surgical treatment without receiving either [8,43]. In retrospective studies, only 23% of MBC patients had pre-surgical imaging [43], and among those who did undergo diagnostic imaging, 24% were not biopsied prior to mastectomy even when imaging results were not suspicious [42]. Failure of clinicians to appreciate the influence of male-specific biological conditions or characteristics on imaging presentation may also affect results interpretation and secondary testing decisions [8]. For example, gynecomastia and MBC (which co-occur in up to 40% of MBC patients) can appear similar in imaging; MBC is usually eccentric to the nipple, whereas gynecomastia is concentric, but both are subareolar, and MBC often presents as central mass, like gynecomastia [8,43]. In such cases, and in the absence of additional signs of malignancy (e.g. skin thickening), MBC may be missed unless clinical evaluation also involves biopsy [8]. As well, mammogram-detected calcifications (scattered and punctuate) and mammogram- or ultrasound-detected well-defined mass, which are usually associated with benign lesion in females, are sometimes associated with malignancy in males and should be assessed further [8,43]. Presence of ultrasound-detected cystic lesions points to the likelihood of papillary lesions and the need for biopsy in both FBC and MBC [8,47]. However, benign nodular breast lesions, common and generally non-significant in females, are rarer in males and are usually associated with MBC, necessitating additional investigation when found [8].

3.2.3. Treatment

As in FBC, surgery, radiotherapy, chemotherapy and endocrine (anti-hormonal) therapy are among treatment options for MBC [48–51]. Surgical strategies for removal of primary tumor consist of total simple mastectomy (TSM), radical mastectomy, modified radical mastectomy (MRM) and breast conserving surgery (BCS, also called lumpectomy or partial mastectomy) [10,11]. MRM is the main surgical choice in MBC, while BCS is usually performed more than mastectomy in FBC [12,30,51–54]. Reconstructive surgery is rarer in MBC than in FBC, and focuses on adequate skin coverage rather than esthetics due to the extensive resection and primary skin closure difficulties associated with later stage presentations [1]. BCS use in MBC has been limited by the comparatively little breast tissue in males, central tumor location, later stage at diagnosis, and concerns about local recurrence of disease with insufficient tissue removal [1,11,52]. However, due to its greater cosmetic, functional and psychological benefits versus mastectomy in FBC [52,54], its greater application in MBC has been proposed [52]. In support of this, while some retrospective studies in MBC did find more local recurrence with BCS than mastectomy [1], others did not [52], and comparable survival rates between TSM, MRM and BCS have also been reported [51,52]. Surgical side effects, which can influence surgical choices but have been investigated primarily in FBC [52,54], were also noted in a single available retrospective report in MBC to be lower overall with BCS than with MRM or TSM [52].

Post-surgery radiotherapy usually involves radiation of the chest wall and draining lymphatic basin to reduce local recurrence of disease, though the optimal regimen lacks consensus [20]. It is administered less frequently in MBC than in FBC [10,30,31,53], even among stage-matched patients [26,52,55]. Some have argued for its greater use in MBC, since less male breast tissue volume can challenge achievement of comfortable clearance margins after resection [1,55,56], but available data are conflicting. Retrospective studies have noted that although adjuvant radiotherapy decreased local recurrence in MBC [51,55–57], it did not improve overall survival rates, except in some later stage patients [51,56,58]. In contrast, it is associated with both reduced local recurrence and higher survival rates in FBC [59,60]. Additionally, while radiation toxicity has been little investigated in MBC, though well documented in FBC [59–61], the risk of significant cardiovascular and pulmonary side effects may particularly limit its utility in older male patients, who are more vulnerable to such events [1].

Chemotherapy consists of intravenous administration of a range of cytotoxic drugs, mainly anthracyclines and taxanes, to kill cancer cells [20]. It is usually recommended for male patients with intermediate to high grade tumors, ER-negative tumors and/or lymph node involvement [1,11]. Similar to radiation, however, chemotherapy is less utilized in MBC than in FBC in clinical practice, even for age- and stage-matched patients [1,30,31,53,62]. Although it has shown substantive benefit in reducing mortality in FBC [63,64], its evidence in MBC is mixed, with some retrospective studies reporting improved survival rates [10,12,48,62], whereas others did not [10,55,65]. Chemotherapy side effects have been well explored in FBC [66,67], and are considered in treatment planning for female patients [68], but there are little published data on adverse effects experienced by MBC patients or interventions for those [10].

Endocrine therapy, in which anti-estrogen drugs play key roles, is a highly effective treatment for FBC [69,70]. It is also recommended for male patients due to the higher rate of ER+/PR+ disease in MBC than FBC [1,20]. Despite this, it, too, is prescribed at a lower rate in MBC than in FBC in clinical care [49,53,62]. Tamoxifen, a selective ER modulator, is the first choice anti-hormonal treatment for early and advanced stage ER+ BC (more so in MBC than FBC) [12,30,49,53], but is administered for far shorter duration in MBC (up to 3 years) [34,48,71,72] than the 5-year minimum standard in FBC [34,71]. Though it has strong evidence for reducing recurrence and mortality in FBC [69,70], data in MBC are less consistent, with some retrospective studies noting improved survival rates [1,10,55], while others did not [31,55,65,73]. Further, while incidence of tamoxifen adverse effects is similar in MBC and FBC [72], male patients have reported a wider range and greater severity of symptoms than females [74–76]. Tamoxifen discontinuation due to side effects occurs in over a third of male [72,75–77] and female patients [76–78], and is associated with worse prognosis [10,74] and lower survival [76,77] in both groups. However, while these side effects are commonly considered in treatment plans in FBC [79], with interventions to alleviate them [10], this is not paralleled in MBC [10].

Aromatase inhibitors (AIs), which block aromatase, the enzyme that converts androgens to estrogen, have shown superior efficacy to tamoxifen in reducing disease recurrence (though not overall survival) in both early and advanced stage FBC [69,70]. They are much less used in MBC compared to FBC [12,30,49,53], due to concern that they do not block estrogen synthesis in the testes, where 20% of endogenous estrogen in males is produced [1]. They are not recommended for early stage MBC [1]. In metastatic MBC, a few available case reports showed inconclusive data for benefit with AIs [1,20], but a pooled analysis of small case studies that combined AIs with gonadotropin-releasing hormone (GnRH) analogues (which desensitize pituitary receptors and reduce androgen production) did report notably better clinical benefit than AIs alone, though survival rates were no different [80]. AIs are associated with side effects in up to 40% of both male and female patients [72,79], and the severity of some of these, such as increased risk of mortality compared to tamoxifen [79,81], may also contribute to their limited use in MBC.

Other endocrine therapy agents common to FBC are even less applied in MBC. Trastuzumab, an HER2+downregulator, is effective in reducing recurrence and mortality in HER2+FBC [82,83]. There are only sparse case reports of trastuzumab in MBC since HER2+overexpression is less common in male patients, but similar positive outcomes to those in FBC were found [1,83]. Fulvestrant, a selective ER downregulator, is used to slow disease

progression and improve survival in FBC that has metastasized or recurred following tamoxifen or AI therapy [70,82,84]. It, too, has only case studies in comparably resistant metastatic MBC [10,20], but a pooled analysis of this data also noted positive results similar to those in FBC [85].

Besides the differences in treatment application described above, treatment information provided to FBC and MBC patients also varies. Women commonly receive verbal and written advice about treatment processes and side effects, e.g. surgical wounds, menopause-type effects [86]. Men rarely receive such advice or MBC-relevant details [3,28,29], and written information offered is usually the same female-centric material provided to FBC patients [3,32,86].

3.2.4. Psychological impact and intervention

There is considerable research in FBC on the short- and long-term psychosocial and behavioral impacts of diagnosis and treatment, which include depression and anxiety, altered body image, impaired daily functioning, and lower quality of life [28,60,61,66,67]. Threat to female gender identity, since the breast is part of both female anatomy and female embodiment, has also been recognized [87], with worse psychological outcomes noted in mastectomy versus BCS patients [54]. Psychological and functional management and support are key components of treatment for FBC patients [66,67], including for their romantic partners [88,89], and related interventions have been well investigated in these populations [90]. Social support is also widely available for female patients, who are encouraged to disclose their diagnosis and seek such support within and outside their intimate circle [28,91].

In contrast, psychological studies are limited in MBC, and psychosocial adjustment is rarely considered in MBC patient care. For example, although mastectomy occurs far more often in MBC than in FBC [12,54], clinicians generally assume that males are not bothered by the esthetic results of mastectomy, as females are [10,32]. Yet, available qualitative data indicate that psychological ill-effects from diagnosis and treatment are as common in MBC as in FBC. Prominent among these for males are stigma, embarrassment and sense of isolation, due to public (and patient) misperception of BC as a disease experienced only by women [3,29,91,92], other patient misconceptions, such as that ER+ disease means that they are more 'feminine' than other men, or that anti-estrogen therapy will be feminizing [14,29], little availability of peer support from other MBC patients due to its rarity [9,14,29,86,87], and lack of MBC-specific information (even though $>50\%$ of patients have expressed a desire for it) [3,92]. Self-perceived 'female illness' and physical changes due to treatment (e.g. hair loss from chemotherapy; surgery-related scarring, deformity, loss of arm strength and reduced range of motion) have also been associated with emasculation (threat to sense of masculinity), challenges to male embodiment, altered body image, and perceived decrease in personal attractiveness and desirability [3,9,14,29,32,87,91,92]. Depression, anxiety, cancer-related distress (including fear of disease recurrence or death), loss of self-confidence and diminished sense of control have also been reported [9,39,91,92]. Yet, there are no published studies on interventions for psychological distress in MBC.

There are also sparse data on quality of life and daily functioning among MBC patients. In one prospective study, male patients reported better quality of life than female patients, but worse quality of life and more difficulties with physical and role functioning and mental health than healthy male controls [93]. Another prospective survey found that, even an average of 12 years after diagnosis, MBC patients were more likely than controls to report significant medical co-morbidities such as endocrine, cardiovascular, pulmonary and rheumatic disorders, as well as lower life satisfaction, worse mental health, and more functional limitations [28]. FBC patients' mental health and overall functioning are close to normal at a similar post-diagnosis time point [94,95], suggesting that MBC patients may be at higher risk of negative long-term effects from illness and treatment [28]. However, published research on interventions to enhance quality of life and functioning in MBC is lacking.

Qualitative data also indicate that social and emotional supports are much less available in MBC than in FBC [3,29,86]. Male patients receive support mainly from romantic partners and female friends [3,32]. They tend to conceal their diagnosis beyond their intimate circle to avoid stigma and embarrassment [28,87], but while this may help with interim coping [29,91], it may also increase anxiety and distress longer-term [92]. Within the medical system, males receive less support from health professionals even when both MBC and FBC patients are treated at the same clinic [29,32]. Organized support groups for MBC patients are also sparse, adding to their isolation [87]. They are sometimes offered access to FBC support groups but are often reluctant to participate [3,9,86], possibly due to embarrassment and the low likelihood of there being other male attendees, which may exacerbate their concerns about feminization [9,87]. Though male patients would prefer male-only support groups [3,92,96], the rarity of MBC may make it difficult for clinics to gather adequate patient numbers for traditional face-to-face formats. Other group formats may offer more viability; the only published report of a psychosocial intervention in MBC evaluated a telephone-based support group for geographically distant patients, with positive results [96]. Participants found the group helpful for information sharing, obtaining peer support, and reducing isolation, and there was no drop-out (unusual for any support group), supporting the utility of this novel group format and perhaps indicating participants' strong desire for social support [96]. Partners of MBC patients have also expressed a need for counseling and guidance [32], but research on or availability of couples therapy or family support in MBC is also scarce [29].

4. Discussion

Biology, genetics and pathogenesis of BC differ between male and female patients, but the rarity of MBC makes it difficult to conduct prospective RCTs, and the only available phenomenological or treatment data with male patients are from small-sample retrospective and qualitative studies and case series [10,28,49]. Limited public and medical awareness of MBC may also contribute to the sparse research. As a result, when compared to FBC, it is significantly understudied [49,65] and lacks standards of care [12]. Its treatment is instead extrapolated from the extensive literature in FBC [1,10,11], where clinical practice guidelines for the management of FBC are theoretically also guides for managing MBC. However, these guidelines make little direct reference to MBC, and across guidelines, the few MBC-specific recommendations offered are not always the same [97–102] (see Table 5). Adoption of guideline recommendations into clinical care, while fairly quick in FBC, is also much slower in MBC [7]. Together, these may contribute to the observed variance between recommended management of MBC and actual practice (see the Results section). However, as data on MBC expand, its distinctiveness as a disease and its need for customized clinical guidelines are becoming more evident [11,49].

The low incidence of MBC also makes epidemiological research (familial, genetic, environmental) a challenge [14,49]. Nonetheless, available data on differences in risk factors between MBC and FBC, such as race [1,11], gene mutations [10,14] and alcohol use [5,10], underscore their biological differences and the need for more investigation of such factors. For example, in retrospective studies,

Table 5
Comparison of recommendations for management of MBC in FBC clinical guidelines [97–102].

	NCCN	ESMO	NICE
Awareness and screening	Clinical breast exam recommended annually for men with BRCA gene mutations, starting at age 35 BSE training and monthly BSEs recommended for men with BRCA gene mutations, starting at age 35 Regular mammography not recommended due to limited evidence for benefit of imaging in screening for MBC Genetic assessment recommended for all MBC patients or those with history of MBC, particularly for BRCA gene mutations Education on the signs and symptoms of MBC and other cancers, especially those related to BRCA gene mutations, recommended for BRCA carriers	No specific recommendation	No specific recommendation
Diagnosis	No specific recommendation	No specific recommendation	No specific recommendation
Treatment: Surgery	No specific recommendation except for a general statement that MBC should be treated similarly to post-menopausal FBC	No specific recommendation	No specific recommendation
Treatment: Radiotherapy	No specific recommendation except for a general statement that MBC should be treated similarly to post-menopausal FBC	No specific recommendation	No specific recommendation
Treatment: Chemotherapy	No specific recommendation except for a general statement that MBC should be treated similarly to post-menopausal FBC	Chemotherapy for early MBC recommended to follow the same treatment guidelines as for luminal-like (ER+) FBC	No specific recommendation
Treatment: Endocrine therapy	No specific recommendation except for a general statement that MBC should be treated similarly to post-menopausal FBC. Also noted: AIs would only be effective if used in combination with testicular steroidogenesis suppressants	Tamoxifen recommended as the standard systemic adjuvant therapy in early MBC, since most MBC is ER+ AI monotherapy not recommended in early MBC due to limited efficacy Endocrine therapy recommended as preferred option for ER+ advanced MBC, which form most cases, except when endocrine resistance or rapidly progressive disease requiring quick response are present Tamoxifen recommended as preferred endocrine therapy agent for ER+ advanced MBC For advanced MBC requiring AIs (e.g. tamoxifen contraindication or intolerance), AIs recommended in combination with LHRH agonists or orchiectomy. AI monotherapy also suggested with close monitoring. Need for clinical trials with AIs in advanced MBC noted	Tamoxifen recommended as first-line treatment for ER+ advanced MBC No specific recommendation for AIs, but need stated for more studies with AIs or AIs+GNRH agonists in advanced MBC
Psychological intervention	No specific recommendation	No specific recommendation	No specific recommendation

Abbreviations: AI=aromatase inhibitor; BSE=breast self-exam; ER+=estrogen receptor positive; ESMO=European Society for Medical Oncology; FBC=female breast cancer; GNRH=gonadotropin releasing hormone; LHRH=luteinizing hormone releasing hormone; MBC=male breast cancer; NCCN=National Comprehensive Cancer Network; NICE=National Institute for Health and Care Excellence.

25–100% of MBC patients with BRCA mutations did not have a family history of BC [14], in contrast to the more prominent familial links found among FBC patients with BRCA mutations [18]. This suggests that other genes may be more relevant to MBC. Numerous disparities have also been noted between FBC and MBC in gene transcriptome and cancer genome [103,104], and in epigenetic distinctions in DNA methylation and miRNA expression profiles [17], further indicating that they are discrete illnesses with fundamental biological differences that may affect treatment response [4,10]. However, while such aspects have been well examined in FBC [105,106], there has been little exploration of MBC-specific gene mutations and epigenetic alterations [10,17], or of secondary risks linked to FBC, such as age at puberty and diabetes [5,15], among male patients. Many other risk factors unique to MBC likely still remain to be identified. This knowledge gap is a major barrier to better understanding of and intervention in MBC, and highlights the need for more research in this area.

The general public and health professionals are both largely ignorant about known risk factors for and clinical characteristics of MBC [29,32,107]. This can hinder early intervention and prophylaxis. Delayed diagnosis, and older age, later stage and more medical co-morbidities (e.g. cardiovascular disease, second primary cancers) at diagnosis, are recognized contributors to the worse outcomes seen in MBC, compared to FBC [49,62,65,108,109]. In turn, delayed diagnosis and advanced stage at diagnosis have been at least partly attributed to the paucity of public (and healthcare) education campaigns on, and screening programs for, MBC [11,110]. Male patients' tendency to limit disclosure of diagnosis may further contribute to public unawareness of the disease and its symptoms [88]. Timely intervention may also be

challenged by clinician unfamiliarity with the diagnostic complexities of MBC. For example, failure of radiologists to appreciate the distinctions between FBC and MBC presentations in imaging may result in misdiagnosis of malignant MBC lesions as benign [8,43], and delayed treatment. To improve early detection of MBC, public and health professional education and routine screening for high-risk males [14,92], as well as incorporation of MBC education and BSEs into standard health investigations for all males [87,107], are highly needed. Genetic counseling and testing should also be discussed with all males with first-degree (or multiple) relatives with history of MBC, FBC or ovarian cancer [10,38]. Physician education should include the complex implications of positive genetic tests, to ensure appropriate patient and family counseling; for example, high penetrance genes tend to receive most attention, but the presence of low penetrance genes is also noteworthy, as their combined, rather than individual, contribution also increases risk of BC [17]. Physician education should also address the ethics of genetic testing, such as when patients' right to know versus right to ignore may affect their psychological care [111].

MBC and FBC treatment utilize the same modalities, but can vary greatly in benefits seen. Retrospective data show that in BC patients receiving the same adjuvant treatment, survival rates for females were 10–16% higher than for males [7,49,65]. This suggests that MBC may be undertreated [65], and the inconsistent application of treatment modalities in MBC [e,g. 3,29,30] may be contributory. Indeed, some retrospective studies have found that male patients did not receive equal treatment to females [12,53,71]. Others have noted that with equal treatment [12,112,113], or when matched for age and stage [91,113–115], MBC and FBC survival rates are similar. However, given the sparse and sometimes inconclusive data on the benefits of current treatment forms in MBC (e.g. chemotherapy, endocrine therapy) [10,55], prospective research is urgently needed to clarify their utility in the disease. Such data, including active head-to-head comparisons of modalities, are standard in FBC [97,99–102], but are lacking in MBC. Available retrospective comparisons in MBC have reported better functionality after BCS than mastectomy [52], greater benefit with chemotherapy than endocrine therapy [12,65], superiority of tamoxifen-radiation combination to radiation alone, but not tamoxifen alone [55] and lower risk of mortality with tamoxifen than AIs [81]. Prospective, randomized treatment comparisons, addressing both short- and long-term benefits, could significantly enhance treatment selection and outcomes in MBC. Longitudinal data on treatment toxicity, which are well tracked in FBC [68,79] but are sparse in MBC, thus far [10], would also be very useful for treatment planning. MBC-specific information material on treatment processes and effects (benefits and side effects) also requires development [3,32,92]; its current scarcity, in contrast to the high availability of FBC-specific material [86], further underscores the marginalization and unequal clinical experience of male patients versus females [17,28]. Health professionals who receive education about MBC could become additional sources of reliable information for male patients [32,92].

The appropriateness of FBC-derived treatment for MBC is also under debate. Pre-clinical animal studies on the pathogenesis and treatment of BC, which correspondingly inform research and treatment in FBC, involve only female mammals [116,117], and thus, may have less translational value for MBC. Sex differences between MBC and FBC in risk factors, tumor biology and treatment response [49], and in hormonal influences on risk, prognosis, outcomes and side effects experienced [10], further challenge the applicability of FBC treatment standards to MBC [10,49]. For example, it has been suggested that hormone receptor positivity may not be as favorable a prognostic indicator in MBC as it is in FBC [65,73,118] – thus, ER+ or PR+ tumors in MBC may indicate more severe or treatment-resistant illness and may require different treatment strategies to optimize outcomes than those used in FBC. Supporting this theory are the mixed results with tamoxifen and AIs in MBC [1,20,55,108], in contrast to their consistent benefits in FBC [20,115] and despite the higher rate of ER+/PR+ disease in MBC than FBC [1,20], which question the utility of endocrine therapy in MBC [119]. Combined, the above findings further substantiate that MBC is a unique condition, distinct from FBC [10,11,49], and emphasize the need for research on MBC-specific risks, biology, treatments and standards of care. Two recent international collaborations, the Male Breast Cancer Study Consortium led by the Leeds Institute for Molecular Medicine (LIMM) [120] and the International Male Breast Cancer Program led by the European Organisation for Research and Treatment of Cancer (EORTC) [11,121] are attempting to fill this need. Both are gathering retrospective MBC patient data and tumor specimens from other research groups for meta-analyses of clinical/biological characteristics and treatment outcomes, and for identification of new prognostic and predictive biomarkers of treatment response [120,121]. The EORTC study is also recruiting MBC patients prospectively for an international registry and will assess clinical data, patterns of care and outcomes; quality of life will also be measured in a sub-study [11,121]. It is also planning a RCT and will gauge the feasibility of global recruitment, to surmount the enrollment challenges faced by prior attempts at MBC clinical trials [11]. In addition, the LIMM and EORTC collections will enable comparative assessments of MBC and matched FBC, which are difficult for individual centers to conduct due to their much smaller datasets for MBC than FBC [12,120]. The results of both these projects are expected to greatly enhance understanding of MBC and to support the development of evidence-based, consensus-driven guidelines for its management [12,120].

Psychological support for male patients is another aspect of MBC management that requires improvement. Though psychological data in MBC are much more limited than in FBC [28,29], profound impacts have been noted in both sexes [9,29,66,67]. These may be exacerbated in MBC patients by the scarcity of psychoeducation or psychotherapy referrals or services for them and their families and the low social support they receive from clinicians [9,20,29,32], versus the high availability of the same in FBC [29,32,88–90]. Their sense of isolation may also be intensified by the separate entrances/exits and waiting rooms for MBC and FBC patients that have been reported at some clinics [29]. Collectively, these healthcare practices strongly imply a broad-scale health system assumption that males are unaffected by MBC diagnosis or treatment [10,32]. They also make health professionals complicit in the marginalization of male patients and reinforcement of MBC stigma [29]. Public and health professional education on the psychosocial and behavioral impact of MBC and clinician training in counseling and support for male patients and their families are essential to remedying this [32]; clinician support, in particular, has been linked to better health outcomes and well-being in patient populations [122]. Psychological assessment after diagnosis and at all clinical visits should also be routine for all BC patients, to enable early, targeted therapy and support [86,92]. However, assuming that FBC-derived interventions will be effective in MBC only further devalues the male experience and helps to maintain stigma [29]. Thus, investigations of psychological interventions specifically in MBC samples are needed. Tech-based interventions may be worth exploring to mitigate the enrollment difficulties associated with MBC and for a practical service option [28,96].

An obstacle to early medical or psychological intervention for male patients with cancer (including those with MBC) is that compared to women, they are less informed about health issues, tend to delay seeking medical care even when physical symptoms are evident, and are also more reluctant to pursue psychological

support [123,124]. Adherence to traditional concepts of masculinity, i.e. that men are self-reliant, strong, and endure physical or emotional discomfort without complaint, plays a significant role in this [123,124]. Indeed, cultural perceptions of both masculinity and male gender identity are reported to inhibit male cancer patients' seeking or receiving support from family or peers, or offering it in turn, or even being fully open about their experience with other male patients [125,126]. Communication skills training and use of humor are male gender identity congruent strategies that have been used in other male cancers to promote disclosure, support-seeking and coping [127,128]. They may be of use in MBC, as well.

Challenges to gender identity and sexuality are psychological impacts common to both MBC and FBC [29,87], but male patients may experience these more profoundly. The lived experience of MBC is more affected by the issue of gender than any other illness common to both sexes, and threat to perceived masculinity is at its core [29]. MBC patients face singular difficulties rarely encountered with other diseases [29], such as concerns about both emasculation (from having a 'female illness') and feminization (from ER+ disease and anti-estrogen therapy) [14,29,92]. A major contributor to these concerns is the public, and often medical, view of BC as a female gendered disease [3,29]. Such a view is perhaps unsurprising; BC research, fundraising and public awareness programs are female-focused, and pink, the symbolic color of BC campaigns, is culturally linked to femininity [87,96]. The female breast is also sexualized in popular culture, while the male breast has merely anatomical connotations [32]. Even the word 'breast' (and thereby, any disease of the breast) is gendered in popular usage as a default reference to females, while 'chest' is used to describe parallel male anatomy. Jointly, these aspects may contribute significantly to unawareness of MBC and the general misperception (even among clinicians) that BC is a female-specific disease [29,87,96], as well as to the stigma, isolation and exclusion male patients experience [29,96]. They may also contribute to delays in help-seeking and diagnosis via adverse influence on patient and clinician behavior [29,32].

Given the gendered perception of BC, it is perhaps unsurprising that MBC has a considerable negative effect on male gender identity. Gender studies propose that gender and gender identity (and femininity and masculinity) are culturally defined, relational and contextual constructs that are attached to representations of biological sex and are integral to societally-determined gendered transactions [129–132]. Gender influences males' perception and use of their bodies, and their health risk patterns, health behaviors and psychological reactions to illness [124]. Gender identity for both sexes is affirmed through sexuality and, especially for males, through sexual performance [133]. In the context of BC, the female breast has deep symbolic and sensory significance for women for expression of femininity and sexuality [134], and thus, female embodiment [87]. The male breast may not have identical meaning for men, but forms an anatomical part of male body image and self-perception [29], which are linked to male physicality and sense of masculinity [87]. Phenomena that negatively affect perceived femininity/masculinity, embodiment and sexuality can thus also impact gender identity, e.g. sexual dysfunction [29,135], altered chest anatomy [29,87] or experience of specific diseases like BC [3,87,92]. For MBC patients, embedded notions of gender, gender identity and perceived masculinity are also challenged by the stigma of the disease [29]. The overall result is worsened psychosocial functioning and adjustment to illness in MBC [32]. However, the roles gender and related issues play in psychological health are often ignored in patient care, especially for males [29]. For example, while the impact of disease and treatment on self-image and gender identity is commonly discussed with FBC patients, along with alleviations like breast reconstruction and aids for sexual dysfunction [1,68,79], these are rarely addressed with MBC patients [10,87]. Clinicians could facilitate male patients' psychosocial adjustment through open dialog on the effect of MBC on gender identity and perceived masculinity, and by helping them to reassess or renegotiate their masculinities by accepting their altered body/body image and ignoring or countering public misperceptions about MBC (such as via wide disclosure of their diagnosis) [29].

5. Conclusion

MBC is a rare illness that, compared to FBC, is much less understood, considerably understudied and possibly also undertreated (particularly in the psychological sphere). Sex differences in hormonal milieu, risk factors, disease biology and treatment outcomes support a reconceptualization of MBC from simply a version of FBC to a distinct condition that requires customized management [10,11,49]. Evidence-based standards of care for MBC are much needed to guide comprehensive and appropriate medical and psychological treatment and improve prognosis. Public and health professional education on MBC is also essential to reduce stigma, counter gendered misperceptions of BC, facilitate early diagnosis, and increase psychosocial support for male patients.

Consent

Not applicable.

Conflict of interest statement

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