Perspective

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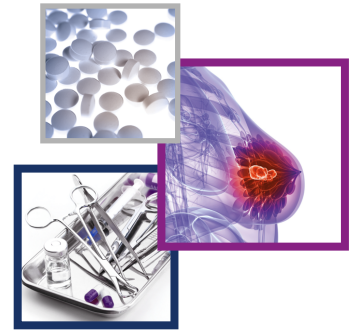
Breast Cancer Management



Male breast cancer: a neglected disease

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Practice points

- Obesity is a risk factor for male breast cancer (MBC), as is a sedentary lifestyle.
- After careful matching, men have a worse prognosis than women with breast cancer.
- Most MBC are ER+ve and of luminal A type.
- Five single nucleotide polymorphisms are significantly associated with MBC risk with two located in the 8q24.21 region.
- Nipple preserving surgery is increasing but could be greatly facilitated with use of neoadjuvant endocrine therapy.
- Only the establishment of collaborative research groups will result in better understanding and real advances in treatment for MBC.

Male breast cancer (MBC) is rare, tending to afflict sedentary men, with adolescent obesity being a risk factor. Men fare worse compared with matched females with breast cancer. The preponderance of ER+ve disease affects the molecular profile: most cases have luminal A tumors. Through male ignorance and risk-taking, delay is frequent and this lacuna needs addressing with health education. The major gene mutation responsible for MBC is *BRCA2*. Five single nucleotide polymorphisms (SNPs) are significantly and uniquely associated with MBC risk with two located in the 8q24.21 regions. Mastectomy is being gradually replaced by nipple-preserving surgery and radiotherapy but this trend could be expedited with neoadjuvant endocrine therapy. Significant advances will occur only after expansion of collaborative groups and this is a matter of pressing importance.

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Because of its rarity, male breast cancer (MBC) has been under-investigated. Therefore, treatments have been derived from the cornucopia of randomized trials conducted on its big sister, female breast cancer (FBC). Although this approach has been of some value, it is missing some of the important gender differences which merit more study and exploitation [1]. The best way forward is through collaborative national and international groups enabling the achievement of a critical mass of cases for study and whenever possible, entry to randomized controlled trials (RCTs) [2,3].

Important differences between MBC and FBC will be discussed in this Perspective and potential questions that could be answered by RCTs will be described, predicated upon the establishment of more collaborative groups so that the treatment of MBC can be derived from a rational evidence base.

Epidemiology

Age-adjusted incidence rates for breast cancer show an important difference between the male and female disease. Using the Surveillance, Epidemiology and End Results database Anderson *et al.* reported that for men the age-specific incidence rate curve had a constant slope, whereas women manifested Clemmeson's hook with a rapid increase up to age 50 years followed by a reduced rate in the postmenopausal [4]. From this finding they concluded that MBC was more akin to postmenopausal breast cancer.

Because some occupations were associated with exposure to potential carcinogens, several studies have analyzed this aspect though older studies may not be relevant to present day work patterns. As an example, the high ambient

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Table 1. Comparative molecular profiles of male breast cancer and female breast cancer.

Study (year)	N	Luminal A ER+ HER2-	Luminal B ER+ HER2+	HER2 ER- HER2+	Basal ER- HER2+	Ref.
Shabaan *et al*. (2012)	♂ 203 ♀ 220	199 (98%) 197 (90%)	0 14 (6%)	0 4 (2%)	4 (2%) 5 (2%)	[15]
Kornegoor *et al*. (2012)	♂ 130	98 (75%)	27 (21%)	0	5 (4%)	[16]
Nilsson *et al*. (2013)	♂183	160 (87%)	21 (11%)	0	2 (1%)	[17]
Schildhaus *et al*. (2013)	♂ 96	56 (58%)	37 (39%)	0	3 (3%)	[18]
Abreu *et al*. (2016)	♂ 111	99 (89%)	8 (7%)	1 (1%)	3 (3%)	[19]
Inwald *et al*. (2015)	♀ 4344	2102 (48%)	1078 (25%)	774 (18%)	390 (9%)	[14]
Total	♂ 723 ♀ 4564	612 (85%) 2299 (50%)	93 (13%) 1092 (24%)	1 (<1%) 778 (17%)	17 (2%) 395 (9%)	

working temperature in steel mills has been associated with an increased risk of MBC as a result of testicular malfunction [5]. Because of technological advances in the western world such occupations are now rare.

In the Nordic Occupational Cancer Study, the relationship between MBC and occupational agents, including solvents, metals and exhaust gases, was examined in 1469 Scandinavian MBC cases and 7345 controls [6]. There was a significant reduction in risk among men with higher physical workload (odds ratio [OR]: 0.78). Furthermore, this benefit increased with greater level of exposure. There were increases in risk associated with exposure to trichloroethylene, welding fumes, lead, iron and wood dust and decreases for work with asbestos, silica dust and perchloroethylene but these were all non-significant and inconsistent.

In contrast, the Centre for Research in Epidemiology and Population Health Objectives (Inserm, Paris, France) reported a case–control study of 104 MBC and 1901 controls in which exposure to organic solvents was associated with significantly increased risk [7]. They reported that a cumulative exposure to trichloroethylene >23.9 parts per million (ppm) years was associated with a doubling of risk, but only when exposures ≥10 years before diagnosis were taken into account. Reduced use of fossil fuels to mitigate the greenhouse effect may reduce the incidence of MBC.

Further support for the protective effect of higher physical workloads has come from the Canadian Occupational Disease Surveillance System which conducted a cohort study between 1983 and 2016 in which there were 17,865 FBC and 492 MBC cases [8]. Elevated risks were found in those with relatively nonphysical jobs: management, administration/clerical and teaching.

Obesity is an established risk factor for both MBC and postmenopausal FBC but there are gender differences [9,10]. Keinan-Boker *et al.* investigated the association between BMI in adolescence and MBC risk in a large cohort study of 1,382,093 Jewish 16- to 19-year-old males [11]. All had undergone anthropometry, a general intelligence test and other examinations between 1967–2011. There were 97 MBC cases included in the analyses. When compared with adolescents with a body mass index (BMI) in the normal range, there was a significantly increased risk of MBC in the overweight (BMI <30.0 kg/m^2). High general intelligence test scores or European origin were independently associated with a significantly increased risk of MBC. Possibly this was a surrogate for the relative lack of physical activity in the jobs that such individuals obtained.

Molecular profile

The molecular profile of MBC differs significantly from that of FBC in that tumors are predominantly hormone-sensitive: an analysis of 1984 MBC revealed that >80% were estrogen receptor (ER) positive and >70% were progesterone receptor (PR) positive [12]. Approximately 66% of FBC are ER+ve [13]. This difference has a significant effect on the distribution of the four major molecular groups: luminal A (ER+ve, PR+ve, HER2-ve, Ki67 low), luminal B (ER+ve, PR-ve. HER2-ve, Ki67 high), HER2 (ER-ve, PR-ve. HER2+ve) and basal, (ER-ve, PR-ve, HER2-ve). A comparison of the gender profiles in Table 1 is derived from six large studies [15–19]. Luminal A was the most frequent phenotype in both MBC and FBC, Luminal B was less common and both HER2 and Basal subtypes were rare in males. After hierarchical clustering it emerged that in females ERα clustered with PR whereas in males ERα is associated with ERβ and androgen receptors [14].

Table 2. Median delay before consultation in male breast cancer.

Study (year)	Number	Country	Delay in months (median)	Ref.
Goss *et al.* (1999)	203	Canada	4	[27]
Ben Dhiab *et al.* (2005)	123	Tunisia	8	[28]
Liukkonen *et al.* (2010)	58	Finland	6	[30]
Cutuli *et al.* (2010)	489	France	3	[31]
Bourhafour *et al.* (2011)	127	Morocco	28	[29]

Prognosis

There has long been uncertainty as to whether MBC was a, more or less, aggressive disease than FBC because most results were derived from relatively small cohorts of men. Recently large-scale studies have been conducted. Wang *et al.* reported a nationwide, registry-based cohort study derived from the National Cancer Database [20]. The analysis included 16,025 males and 1,800,708 females with breast cancer diagnosed between 1998 and 2007. Variables including age, race/ethnicity, clinical prognostic factors, local/systemic therapy and access-to-care factors were entered into nested, age-adjusted, Cox proportional hazards regression models. What emerged was a higher mortality rate in all stages of breast cancer in males.

Overall survival was 46% in males compared with 60% in females. In males both clinical factors and under-treatment were associated with a 63% increase in mortality. Liu *et al.* conducted a similar but more recent analysis of 2054 MBC and 287,619 FBC treated from 2005 to 2010 [21]. There was a significantly worse outcome for males with 5-year overall survival of 89% for females and 83% in males. This suggests a difference in the biology of the disease in women and men.

In part, however, there is a behavioral aspect: poor prognosis as manifested by delay in presentation. Most men do not feel that they are at risk of breast cancer and ignore signs and symptoms for which females would seek urgent medical help. This behavior applies to many aspects of male health: men are less likely to achieve good dental care [22], attend for health checks [23], more likely to take illegal drugs, drive while under the influence [24] and fail to wear seat belts [25].

In the first large series of 146 MBC cases from the Memorial Hospital in New York (NY, USA) symptom duration was between 2 days and 44 years: only 22% presented within 3 months [26]. Results of the larger more recent series reporting delay are summarized in Table 2 [27–31] and the delay of 3–28 months suggests that a more comprehensive approach to early detection of various malignancies is needed for men. MBC is a very small component of the cancers that can afflict males, but its possibility could be raised by an educational policy urging that new lumps (anywhere) are usually going to be benign but specialist help is required to confirm this. In the case of the male breast the likely explanation of a breast lump is benign gynecomastia confirmed by clinical examination and breast ultrasound.

Sociodemographic status is another adverse prognostic factor. Restrepo *et al.* analyzed data from 10,258 men with stage I–III breast cancer diagnosed between 2004 and 2010, registered with the US National Cancer Database [32]. They reported that black men had a 19% higher death rate when compared with white men. Furthermore, government insurance rather than private insurance was associated with a 57% increase in mortality. These worrying findings were further underlined by a 35% increase in deaths among the poorer cases (income <US$30,000) compared with richer men (income >US$46,000). At last, those managed in academic centers had a better survival than those treated in community hospitals. It is to be hoped that within the UK National Health Service, where treatment is not dependent upon the patient's ability to pay that some of these egregious socio-economic differences will be minimized.

Genetics

Of the two major breast cancer susceptibility genes *BRCA1* and *BRCA2* [33,34] the former is the major genetic driver of familial FBC. Surprisingly however, when Stratton *et al.* analyzed 22 families with at least one affected male, they found no linkage between *BRCA1* and MBC [35]. Subsequent studies of MBC have shown the predominance of *BRCA2* mutations [36–40]. Overall, mutations were found in 11% of MBC cases with 10% involving *BRCA2* and only 1% *BRCA1*. The Breast Cancer Linkage Consortium study comprised 164 families with breast/ovarian cancer and germline *BRCA2* mutations and for male carriers the estimated cumulative risk of MBC was 7% by the age of 80 years [41].

Silvestri *et al.* performed whole-exome sequencing together with targeted gene sequencing in 48 *BRCA1/2* mutation–negative men with breast cancer [42]. The c.1984A>T nonsense mutation of *PALB2* was present in one case. In those families with multiple MBC or FBC, but no *BRCA* mutation, testing for *PALB2* may be of value. Pritzlaff *et al.* used germline multigene panel testing in 715 previously untested MBC patients and reported that 129 (18.%) had mutations in 16 breast cancer susceptibility genes [43]. Pathogenic variants in *BRCA2*, *CHEK2* and *PALB2* led to significant increase in risk of MBC, indicating the potential value of multigene panel testing in all cases.

Or *et al.* carried out a genome-wide association study in 823 MBC with 2795 controls and as subsequent validation examined 438 independent cases and 474 controls [44]. They reported a SNP in *RAD51B* at 14q24 which was significantly associated with risk of MBC (OR = 1.57). Additionally, they confirmed the association of a SNP within *TOX3* with increased MBC risk (OR = 1.50). Silvestri *et al.* investigated SNPs in the 8q24.21 multicancer susceptibility region in a case–control study on 386 MBC cases and 1105 healthy male controls [45]. They also examined other known breast cancer associated loci in the genome using the Sequenom iPLEX platform with 29 susceptibility SNPs *in toto*. Five SNPs emerged as being significantly associated with MBC risk: rs1562430 and rs445114 located in the 8q24.21 region and rs1011970 in 9p21.3, rs614367 in 11q13.3 and rs1314913 in 14q24.1.

Men with ER+ve cancers were more likely to be of rs614367/11q13.3 risk genotype whereas the rs1011970/9p21.3 genotype was associated with HER2+ tumors. This work confirmed the 8q24.21 region is associated with MBC risk as do the SNPs rs1562430/8q24.21 and rs1314913/14q24.1. It is also possible that the latter may modify risk male mutation carriers.

Treatment

A recent report of 10,873 MBC cases with stage I/II/III to stage III disease diagnosed between 2004 and 2014 and registered in the National Cancer Database gives an overview of treatment modalities and their change with time [46]. The median age at diagnosis was 64 years. Mastectomy was no longer the sole surgical offer and breast-conserving therapy was carried out for 24% of patients, with the majority (70%) receiving postoperative radiotherapy. Paradoxically for a hormone sensitive disease, 44% received chemotherapy and only 62% of patients with ER+ve disease were given endocrine therapy. For those with node negative ER+ve disease 35% had Oncotype DX testing. During the years of the study, rates of total mastectomy increased as did contralateral prophylactic mastectomy. Poorer prognosis was associated with older age, black race, higher Charlson Comorbidity Index, high tumor grade and stage of disease. Additionally, having a total mastectomy carried a worse prognosis. Good prognostic factors included living in a higher income area, having PR+ve tumors and receipt of a PR+ve cancer and receiving chemotherapy, radiotherapy and endocrine treatment.

Breast-conserving surgery

In the context of MBC, breast-conserving surgery means nipple-preserving surgery. What has been lacking in MBC has been any structured attempt to increase the possibility of nipple-preserving surgery by using neoadjuvant systemic therapy. Since the majority of MBC lesions are ER+ve and relatively large this provides a good target for endocrine treatment rather than chemotherapy but no prospective studies of endocrine neoadjuvant therapy for MBC have been reported. Part of the problem is the choice of hormonal therapy. For FBC, RCTs have shown that aromatase inhibitors (AIs) are superior to tamoxifen as adjuvant therapy in postmenopausal women with ER+ve disease [47]. MBC has been likened to postmenopausal FBC and predictably adjuvant AIs were used for MBC [48]. When, however, Harlan *et al.* analyzed outcomes in 512 MBC cases from the Surveillance, Epidemiology and End Results database although there was a significant reduction in cancer mortality among those given tamoxifen compared with no systemic therapy, adjuvant AIs did not reduce deaths [49].

Eggermann *et al.* studied 257 MBC patients with ER+ve disease and 2785 FBC cases matched for age, tumor stage, tumor grade, nodal status, HER2 status and receipt of chemotherapy [50]. Tamoxifen was given to 316 women and 158 men and AIs to 60 and 30, respectively. Although tamoxifen-treated patients of both genders had similar 5-year survival, FBC patients given AIs had significantly better 5-year overall survival compared with AI-treated males, 85% versus 73% (p = 028). One possible reason is that testicular production of estrogen (approximately 20%) is unaffected by AIs [51]. This suggests that tamoxifen rather than an AI should be used as neoadjuvant endocrine therapy for MBC.

There is however a potential problem with tamoxifen compliance in males. In a series of 24 MBC cases, 15 (63%) complained of one or more side effect including reduced libido (7) weight gain (6), hot flushes (5) and altered mood (5) [52]. One developed deep vein thrombosis and five (21%) stopped tamoxifen within 1 year compared with a discontinuation rate of 10% in FBC [53]. The Ottawa Hospital Cancer Centre (ON, Canada) reported similar findings: 50% suffering side effects and 24% stopped tamoxifen, one having had a pulmonary embolism [54].

Noncompliance can cost lives. In a cohort of 116 MBC patients with ER+ve disease, advised 5 years of tamoxifen, after 1 year only 65% were still taking the agent , 46% after 2 years, 29% at 3 years, 26% at 4 years and only 18% in the final year [55]. The 10-year disease-free survival was 96% in the compliant versus 42% in the noncompliers.

The situation is further complicated by the variation in the metabolism of tamoxifen by different patients. In a study of 53 MBC, treated with adjuvant tamoxifen, Abreu *et al.* carried out *CYP2D6*4* genotyping on either tumor or blood and reported two metabolic activity types [56]. There were 36 (68%) who did not possess the A allele (*CYP2D6*4 A-*) and 17 (32%) with the A allele in homozygous or heterozygous form (*CYP2D6*4 A+*). The latter group were poorer tamoxifen metabolizers, which was associated with a higher recurrence risk. The 10-year disease-free survival for A- was 63% compared with 91% for A+ cases.

If tamoxifen is used as neoadjuvant treatment for shorter durations, noncompliance will probably be less of a problem while there are other potential approaches such as GnRH analogs which temporarily inhibit testicular function, but this may not be acceptable to many men with MBC. When the surgical treatment for advanced or metastatic MBC was orchidectomy this was rejected by >50% of patients [57].

Future perspective

Achieving the balance between efficacy and toxicity will require international cooperation to run RCTs of neoadjuvant endocrine therapy for MBC, possibly in association with a CDK inhibitor such a palbociclib [58]. Only with better understanding of the disease will there be significant improvements in treatment and outcome. International collaboration is underway but more centers need to participate in appropriately powered studies, including quality of life metrics, in order to achieve an evidence base for rational treatment of MBC [12,59,60].

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•• **Evidence of the value of collaboration.**