Male breast cancer: Risk factors, diagnosis, and management (Review)

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Received July 8, 2010; Accepted August 23, 2010

DOI: 10.3892/or_00000962

Abstract. Male breast cancer (MBC) is extremely rare, with an incidence in the general US population of <1%. It tends to be diagnosed at later stages than breast cancer in females, likely because of low awareness on the part of the patient and low suspicion by the physician. Risk factors include genetic predisposition, alterations to the estrogen-testosterone ratio, radiation exposure, and occupational hazards. Because of the rarity of MBC, mammography in men is more often utilized as a diagnostic tool to evaluate breast symptoms rather than as a tool for widespread screening. While clinical breast examinations are effective at evaluating breast symptoms, mammography also may be beneficial in separating malignant from benign breast disease. This study reviews MBC and its risk factors, recommendations for screening and diagnosis, the roles of mammography and genetic testing in surveillance, and management of patients with MBC. Heightened awareness of the increased risk in certain men by both physicians and patients, and adherence to guidelines recommended for the surveillance of men at increased risk, may result in earlier detection.

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Key words: male breast cancer, mammography, *BRCA*, genetic testing

1. Introduction and background

Each year, far fewer men than women are diagnosed with breast cancer. In the United States in 2009, ~190,000 women were expected to be diagnosed with breast cancer, while only ~1,900 men were expected to receive this diagnosis (1). Despite the lower incidence of male breast cancer (MBC), its case-fatality rate is similar to that of female breast cancer (FBC) (2). The rarity of MBC has resulted in comparatively few clinical studies assessing the risk factors, detection methods, and treatment of the disease (2,3). Instead, diagnosis and management of patients with MBC has been derived from studies on FBC.

Male breast tissue is predominantly made up of rudimentary ductal elements, surrounded by stroma, adipose, and subcutaneous tissue (4,5). Lobular tissue, which in women is responsible for lactation, is not normally present unless the male has been exposed to increased concentrations of estrogen (4,5). Accordingly, 85-90% of MBC is invasive ductal carcinoma (3,4), while lobular carcinoma is extremely rare (3,6). Ductal carcinoma *in situ* (DCIS) is the most common type of *in situ* (noninvasive) tumor in men (7). Approximately 65-90% of MBC tumors are both estrogen- and progesterone-receptor positive, similar to the proportion of estrogen- and progesterone-receptor positive breast tumors in post-menopausal women (3,4,8). MBC tumors are ~3 times less likely to be HER2-positive than FBC tumors (5 vs. 15%) (9,10). In about half of MBC diagnoses, the cancer has metastasized to the axillary lymph nodes (3,11).

The incidence of MBC in the general population is approximately 1 in 100,000 (11), and MBC accounts for <1% of all cancers in males (7). MBC most commonly presents as a painless unilateral breast mass or thickening, sometimes accompanied by nipple discharge, retraction, or skin ulceration (3,4,5,11). The peak incidence of MBC occurs between the ages of 68-71 years (4,5,7,11). More than 50% of male breast tumors have advanced to stage II or beyond by the time of diagnosis, compared to ~35% of female breast tumors (4,12). The later stage at diagnosis implies a delay in diagnosis of MBC that has been blamed on its rarity, and hence low index of suspicion of MBC by both physicians and patients (3,4). The lack of routine screening for MBC also likely contributes

to the observed delay in diagnosis. The five-year survival rates for men with stages I-IV breast tumors are 96, 84, 52, and 24%, respectively; the rates do not differ significantly from five-year survival rates for FBC (12). Overall survival rate in men with breast cancer tends to be lower than that for females with breast cancer, likely due to the comorbidities associated with the older age at which MBC is diagnosed (9).

This study reviews MBC and its risk factors, recommendations for screening and diagnosis, the roles of mammography and genetic testing in surveillance, and management of patients with MBC.

2. Risk factors for MBC

BRCA1 and BRCA2. The *BRCA1* and *BRCA2* protein products play a key role in DNA repair and cell cycle checkpoint control (13,14). They are classified as tumor-suppressor genes; i.e., they maintain genomic stability and control of cell proliferation (13). Mutations in the *BRCA1* or *BRCA2* genes result in the cells inability to repair DNA damage, allowing for the accumulation of genetic instabilities that can alter cell-cycle checkpoint control (13,14). Dysfunctional checkpoint control enables cells to proliferate, resulting in tumor growth (13). Thus, carriers of *BRCA* mutations are at an increased risk for tumor development. Accordingly, *BRCA* mutation carriers show higher risk for breast (in both females and males), ovarian, prostate, colorectal, and pancreatic cancers (15).

More than 1000 mutations in both *BRCA1* and *BRCA2* have been described (16). The genes are inherited in an autosomal dominant pattern; i.e., the male or female offspring of a mutation carrier have a 50% chance of inheriting the mutation (17). Studies examining the prevalence of *BRCA* mutations in the general population have reported ranges of 0.06-0.32% for *BRCA1*, and 0.12-0.69% for *BRCA2* (18-20). People of Ashkenazi Jewish descent are more likely to carry certain *BRCA* mutations. Approximately 2.5% of Ashkenazi Jewish individuals carry one or more of three specific *BRCA* mutations, increasing the occurrence of hereditary forms of breast and other cancers in this population (18).

The strongest risk factor for MBC is the presence of an inherited *BRCA2* mutation. The lifetime risk for breast cancer in a male *BRCA2* mutation carrier is ~7%, 80-100 times higher than for the general population (15,16,21). It is estimated that 4-40% of MBC patients carry a mutation in *BRCA2* (12,22-24). However, a precise estimate is limited because few studies have included populations of males who were not already diagnosed with breast cancer. The association between *BRCA1* mutations and MBC is not as strong as that seen for *BRCA2* mutations. The lifetime risk for breast cancer in a male *BRCA1* mutation carrier is just over 1%, and it is estimated that a *BRCA1* mutation is present in up to 4% of MBC cases (13,25,26).

Mutations in several other genes, including those that regulate cell cycle checkpoints and estrogen/androgen activity, increase risk for MBC, although none currently confer risk as high as that associated with *BRCA2* mutations (9).

Estrogen exposure and androgen insufficiency. Alterations to the estrogen-testosterone ratio in males is among the risk factors for developing breast cancer (3,4). The hormonal condition most strongly associated with breast cancer is Klinefelter syndrome, characterized by the addition of at least one X chromosome to the normal XY complement (3,4). Males with Klinefelter syndrome have testicular dysgenesis, gynecomastia (the benign enlargement of the male breast), low testosterone concentrations, and increased gonadotropins (4,27), leading to a 50-fold increase in risk for breast cancer (27). It is thought that males with Klinefelter syndrome account for 3% of all MBC cases (3,27). Other testicular abnormalities that result in testosterone deficiency, including undescended testes, congenital inguinal hernia, injury, orchitis, and orchidectomy, are associated with an increased risk for MBC (3,4,28).

Obesity, which increases the estrogen-testosterone ratio, is a risk factor for MBC. Men with a body-mass index of greater than 30 have an almost doubled risk (4,29). Increased estrogen levels are also frequently seen in males with liver cirrhosis, increasing MBC risk 9- to 13-fold (7,30). Bilateral breast cancers have been reported in men exposed to exogenous estrogens, such as those treated for prostate cancer and transsexuals taking estrogen (4). Although decreased levels of testosterone and increased levels of estrogen appear to increase the risk for MBC, no studies have shown significantly lower levels of testosterone or consistently higher levels of estrogen in males with breast cancer (4).

Radiation exposure. Medical procedures requiring radiation include radiography, fluoroscopy, computed tomography scans, interventional radiology, and bone densitometry. Radiation doses from single exposures are low, but for those who receive repeated examinations over time, or who are treated with therapeutic doses, cumulative radiation exposure can reach levels beyond what is considered safe (31). Exposure to therapeutic ionizing radiation is associated with an increased risk for breast cancer in women, and a small number of studies suggest a similar situation for men (4,28). MBC has occurred following treatment of unilateral gynecomastia and thymic enlargement with radiotherapy (32). It is estimated that the treatment, no longer used, increased risk for MBC by almost two-fold (32). In men who receive anti-androgenic factors to treat prostate cancer, gynecomastia commonly occurs and is treated with low-dose radiotherapy (4,33). However, there are no data on long-term risk for MBC in these patients (4). Accidental exposure to radiation has also been linked to male cancers. In a large study of male Japanese atomic bomb survivors, a dose-response relationship was observed between radiation exposure and risk for MBC, with risk increasing eight-fold per sievert of radiation exposure (28,34).

Occupational risks. Men who work in high-temperature environments, such as blast furnaces, steel works, and rolling mills have a higher risk for breast cancer, probably due to testicular failure resulting from long-term exposure to high ambient temperatures (4,29). In a 1988 Swedish study, those who worked in the soap and perfume industry showed an almost eight-fold increase in risk for MBC, likely because during the 1950s and 1960s this industry made estrogen-containing cosmetic creams, increasing workers' exposure to exogenous estrogens (35). Occupational carcinogen exposure,

Table I. Risk factors for MBC (3,4,7,13-41).

Known presence of *BRCA* mutation
History of *BRCA*-suggestive cancer, either in self or family
Estrogen exposure/androgen insufficiency
Klinefelter syndrome
Testicular abnormality
Obesity
Liver cirrhosis
Exogenous estrogen therapy
Radiation exposure
Occupational exposure
High ambient temperature
Estrogen exposure
Carcinogen exposure

Table II. Screening and surveillance recommendations for men at increased risk[b] for developing breast cancer.[a]

Monthly breast self-examination
Semi-annual clinical breast examination
Baseline mammography followed by annual mammography if gynecomastia and/or breast density seen on baseline
Consider genetic testing, inform family members of risk and genetic testing options

[a]Adapted from National Comprehensive Cancer Network, United States Preventive Services Task Force, American Society of Clinical Oncology, and GeneTests recommendations (18,42,46-48). [b]The increased risk category includes men with a strong family history of breast cancer (both FBC and MBC), a genetic predisposition, and prior personal history of MBC.

such as that found in gasoline and exhaust fumes, has also been implicated in increasing risk for breast cancer (4,36).

Other lifestyle factors. Lifestyle factors such as alcohol intake, smoking, and physical activity level have been investigated as risk factors for MBC; none has consistently been associated with higher risk. Although one small study reported that excessive alcohol consumption was linked to MBC (37), other studies have failed to demonstrate the same (29,38,39). The link between smoking and MBC has also not been clearly demonstrated (29,40). Others have investigated level of exercise and physical activity as a risk factor, but again, no clear association has been established (29,40,41). Risk factors for MBC are summarized in Table I.

3. Screening and diagnosis of MBC

The rarity of MBC has precluded the large clinical trials that are often necessary for formal recommendations and guidelines on screening and diagnosis. Thus, extrapolation from FBC studies, along with retrospective analyses of smaller MBC studies, has formed the basis for the few and very specific recommendations that exist for MBC.

Screening recommendations. Recommendations for FBC screening have been in place for many years, and are updated regularly. They include combinations of mammography, clinical breast examination, and breast self-examination (42-44). The low incidence of MBC in the general population (approximately 1 in 100,000) renders mammographic screening of all men impractical (7,28). Thus, there are no guidelines or formal recommendations for screening mammography, nor are there recommendations for clinical breast examination or breast self-examination in asymptomatic men with no other risk factors.

For individuals at increased risk for developing breast cancer, there are clear surveillance and screening guidelines. These were developed based on large studies of FBC, but also apply to men considered to be at increased risk for MBC. For both men and women, the 'increased risk' category includes those with a strong family history of breast cancer (both FBC and MBC), a genetic predisposition (mutations identified that are known to increase risk of breast cancer, such as *BRCA1* and *BRCA2*), and prior personal history of breast cancer (particularly MBC) (42,45). Other risk factors in men, including increased estrogen exposure or androgen insufficiency, radiation exposure, and occupational exposure, are not included in formal guidelines, likely because of the paucity of large risk factor studies that are often needed for guideline development.

For men in the increased risk category, monthly breast self-examinations, semi-annual clinical breast examinations, and baseline mammography followed by annual mammography if gynecomastia and/or breast density are seen on baseline are recommended (18,46). Guidelines also recommend that both men and women in the increased risk category be tested for genetic mutations (if mutation status is unknown), be advised of the risk to other relatives, and consider genetic testing for at-risk relatives (46-48). Guidelines for surveillance and screening of men at increased risk are outlined in Table II.

Mammography. Although mammography is recommended for the surveillance and management of males at increased risk for MBC (46), its role in males with no apparent risk factors is less clear. The majority of breast symptoms in males are caused by benign abnormalities such as gynecomastia (49). The diagnostic challenge facing physicians is to correctly separate the small number of patients with malignant disease from the greater number with benign disease (50). This task can be more difficult when there is no family history of breast cancer and no other risk factors for MBC, such as hormonal or occupational exposure. Several retrospective studies have found that a thorough clinical evaluation, including physical examination and fine-needle aspiration or core biopsy, is effective at distinguishing breast cancer from benign disease, and that mammographic data add little diagnostic information (49,51-53). Others argue that mammography adds accuracy to the evaluation of breast symptoms (50).

In one study, the sensitivity and specificity of mammography was 92 and 90%, respectively; i.e., mammography detected malignancy in 92% of known malignant cases, and ruled out malignancy in 90% of known benign cases (50). Mammography demonstrates considerable efficacy in distinguishing breast cancer from gynecomastia, and also appears to reduce the number of false-positive biopsies that would be generated by clinical examination alone (54,55). In some cases, gynecomastia can partially or completely obscure the detection of an underlying malignancy by clinical examination (28,56). Algorithms for deciding when mammography is indicated in males with breast symptoms but with no apparent risk factors for MBC have been suggested, although they have not been validated (5,55,57).

BRCA genetic testing. For both men and women who are diagnosed with breast cancer and appear to have a strong family history of cancers that are consistent with *BRCA* mutations, such as breast (especially MBC), ovarian, prostate, and pancreatic cancers, a genetic consultation, including genetic testing when appropriate, is recommended (18,46-48). Consultations are conducted by clinical geneticists and/or genetic counselors. A clinical geneticist provides clinicians and patients with risk assessment, diagnosis, and recommendations for disease management and prevention. Genetic risk assessment is based on family history and pedigree analysis, physical examination, and ordering and interpretation of laboratory diagnostics such as genetic tests. Genetic counselors will also assess family history and any known mutations in the family to provide education, support, and communication of cancer risk to patients and family members, and will guide patients and family members through the genetic testing process. Genetic testing for BRCA mutations is commercially available, and can help guide surveillance and prevention strategies tailored to individual risk (17).

When there is already an identified *BRCA* mutation in a family, it is recommended that adult relatives be tested for that same mutation (18). More extensive mutation analysis (testing for more than one mutation or sequence analysis) may be recommended in certain cases, such as in individuals of Ashkenazi Jewish heritage and when *BRCA* mutations may be present in both maternal and paternal lines (18). Males found to carry a mutation should be placed in the increased risk category and should adhere to the surveillance program recommended for those at increased risk (46).

In families for which there is no identified *BRCA* mutation but that nonetheless display cancers indicative of *BRCA* mutations, genetic testing is recommended (46). Testing should ideally occur first in the individual who has already had cancer indicative of a *BRCA* mutation (18). That individual will likely undergo comprehensive testing that includes sequence and large rearrangement analysis of both *BRCA1* and *BRCA2*. This method may identify the specific inherited mutation that other family members carry, simplifying the subsequent testing process in these individuals (18). For male patients diagnosed with MBC but having no family history of *BRCA*-related cancers, comprehensive testing is recommended (18).

Not surprisingly, *BRCA* mutations are found more often in men with a first-degree relative diagnosed with breast cancer (23). This highlights the importance of attention to family history by both physicians and patients, and of communication among family members. The decision to undergo genetic testing has implications for both the individual being tested and for other family members (17). The identification of a mutation in an individual automatically implicates one of the parents as the transmitter of the mutation, and identifies the individual's siblings as having a 50% chance of also carrying the mutation (17). The individual receiving genetic test results has the onus of delivering cancer risk information to the rest of the family (17). In some families with a cancer history, male members are less likely to be informed of test results received by female relatives (58-60), and are less likely to be included in family conversations about familial cancer risk (61,62). Counseling by a genetics professional is recommended to help families communicate and understand individual risk (17).

4. Management of MBC

Management options for MBC patients are based mainly on information from the treatment of FBC (3,28). Radical mastectomy, for many years the standard treatment for localized MBC, has now been replaced by less invasive procedures like modified radical or simple mastectomy (3,4). Axillary node dissection may be performed even though it is associated with other complications such as lymphedema and parasthesia (9). Sentinel-node biopsy is now accepted as a reliable method to establish axillary node status for invasive MBC, avoiding complications associated with axillary node dissection (3,63,64). More conservative approaches, such as lumpectomy, have previously been shown to result in high rates of recurrence (65); however, others have found that breast-conserving surgery should be considered as an option (66).

Postoperative radiotherapy is often delivered as it seems to prevent local recurrences, although it is unknown whether radiotherapy affects survival rates in MBC (3,4,7,11). Radiotherapy is favored for histological findings such as nodal involvement, multifocality, high proliferation, or high grade (9). There is a general trend toward limiting radiotherapy to high-risk patients (3).

Most cases of MBC respond favorably to hormonal manipulation since the majority are estrogen receptor-positive. The anti-estrogen tamoxifen improves survival rates in estrogen receptor-positive FBC. Although no clinical trials have assessed the use of tamoxifen in MBC, men who have been treated with it show improved disease-free and overall survival rates, with the five-year disease-free rate improving from 28 to 56%, and the five-year overall survival rate improving from 44 to 61% (4,7,64,67). For this reason, tamoxifen has an important role in the treatment of most MBC cases (7). There is insufficient data on the use of Aromatase inhibitors to treat MBC (7). Orchidectomy, adrenalectomy, and hypophysectomy, once used for hormonal manipulation, are no longer used due to the associated severe side effects (68).

Chemotherapy appears to benefit survival and prevent recurrence, although data are most established for node-positive men (3,4,69,70). It has been suggested that chemotherapy be used in patients with stage II or greater

disease (7,68). A 2004 retrospective study showed that additional adjuvant therapy in the form of radiation, hormones, and chemotherapy, either alone or in combination, more than doubled the survival rate in men with breast cancer (3,71).

5. Conclusions

MBC is rare, but heightened awareness of the increased risk in certain men by both physicians and patients may result in earlier detection. Guidelines for surveillance in men at increased risk suggest a management course similar to that recommended for women at increased risk, and include semi-annual clinical breast examinations, monthly breast self-examinations, baseline mammography and annual follow-up mammography when indicated, and consideration of genetic testing when appropriate. The utility of mammography for evaluation of breast symptoms in the absence of other risk factors for MBC is not entirely clear, but evidence suggests that it may increase diagnostic accuracy.

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