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Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship

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Background: The causes, optimal treatments, and medical/psychosocial sequelae of breast cancer in men are poorly understood.

Design: A systematic review of the English language literature was conducted to identify studies relevant to male breast cancer between 1987 and 2012 and including at least 20 patients. Searches were carried out on PubMed using the title terms 'male breast cancer' or 'male breast carcinoma'.

Results: Relevant published data regarding risk factors, biological characteristics, presentation and prognosis, appropriate evaluation and treatment, and survivorship issues in male breast cancer patients are presented. BRCA2 mutations, age, conditions that alter the estrogen/androgen ratio, and radiation are proven risk factors. Disease biology is distinct in men, but diagnostic approaches and treatments for men are generally extrapolated from those in women due to inadequate research in men. Survivorship issues in men may include sexual and hormonal side-effects of endocrine therapies as well as unique psychosocial impacts of the disease.

Conclusion: Further research is needed to address gaps in knowledge pertaining to care of male breast cancer patients and survivors.

Key words: breast neoplasms, drug therapy, etiology, male, survivors

introduction

Researchers have focused relatively little attention on male breast cancer compared with female breast cancer. While only 0.5%–1% of all breast cancers in the United States occur in men, approximately 2000 men are diagnosed with breast cancer annually, and the incidence appears to be slowly rising [1–5]. Men are approximately as likely to be diagnosed with breast cancer as to develop chronic myelogenous leukemia. Because robust clinical evidence is lacking, treatment standards for men have generally been extrapolated from the enormous literature and clinical experience in women. However, these data may not be entirely applicable to men. The male

hormonal milieu may be a unique and powerful determinant of risk, prognosis, and treatment outcome. Moreover, gender differences may affect patient preferences, toxic effects from therapies, and survivorship priorities. The purpose of this review is to examine systematically all recent published data regarding risk factors, biological characteristics, presentation and prognosis, appropriate evaluation and treatment, and survivorship issues in male breast cancer patients.

methodology

A systematic review of the English language literature was conducted to identify studies relevant to male breast cancer between 1987 and 2012 and including at least 20 patients. Searches were carried out on PubMed using the title terms 'male breast cancer' or 'male breast carcinoma'. Of 723 articles generated by these search terms, 340 were case reports or case series that included fewer than 20 patients, 82 were reviews or editorials,

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41 were not relevant (e.g. had studied male partners of female breast cancer patients), 34 could not be obtained online through Harvard ECommons journal access, and 1 was retracted after publication.

risk factors

Known risk factors for breast cancer in men are listed in Table 1. It is well established that incidence rates rise steadily with age. In the United States, men are 5 to 10 years older than women on average at the time of diagnosis, but in other parts of the world such as the Middle East and South Asia, the age gap is smaller [6, 7].

Genetic contributors to risk in men are similar, but not identical, to those in women. Family history is relevant for both sexes [8–14], and BRCA2 mutations and rearrangements play a particularly prominent role in male breast cancer [15–28]. Five percent to 10% of men with BRCA2 mutations (and a smaller proportion of those with BRCA1 mutations) eventually develop breast cancer [29, 30]. Deleterious BRCA2 mutations are found in 4%–14% of men with breast cancer in the United States or UK [31–33]. However, one study of 102 Italian male breast cancer patients found no BRCA1 or BRCA2 rearrangements [34]. Data are mixed regarding the relevance of other germ-line mutations such as those in PALB2, the androgen receptor (AR), CYP17, and CHEK2 [35–44]. Certain

other mutations that increase risk of female breast cancer (e.g. BRIP1, RAD51C) have not been found to increase risk of male breast cancer [45, 46], and polymorphisms in the vitamin D receptor do not appear to be associated with risk based on one study [47]. Conditions that alter the ratio of estrogen to androgen have been linked to breast cancer risk in men. Klinefelter's syndrome [48, 49], exogenous estrogen or testosterone use [50], obesity [9, 10, 49, 51–53], orchitis/epididymitis [49], finasteride [54, 55], and a history of prostate cancer treated with estrogens have been implicated [56]. Exercise appears to reduce risk [8], and one small study suggested that tobacco use may also be protective [57], but larger studies have not confirmed this finding [8, 53]. Most studies have not found an association between alcohol intake and male breast cancer [8, 49, 53, 58]. In Sub-Saharan Africa, infectious hepatotoxic disease may compound genetic risks, contributing to a high incidence of male breast cancer [59–61]. Unlike in women, white race does not appear to be a risk factor [62, 63].

Epidemiological studies have evaluated occupational exposures including to electromagnetic fields [64, 65], heat [66], and polycyclic aromatic hydrocarbons and other chemicals [67–69] as possible contributors to risk of male breast cancer, but data have been mixed and inconclusive [59, 70, 71].

biological characteristics

The vast majority of male breast cancers are hormonally sensitive [62, 72–83]. In the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2005, 92% of the 5494 male breast cancers but only 78% of the 838 805 female breast cancers were estrogen receptor (ER)-positive [62]. As in women, the majority of men's cancers are invasive ductal carcinomas [61, 79, 84–88]. Papillary carcinomas are comparatively more common, and lobular carcinomas are rarer in men [89].

Missing and conflicting data from retrospective registry studies limit definitive conclusions about grade and HER2 status of male breast cancers. In a SEER database analysis encompassing breast cancers between 1973 and 2000, HER2 data were not available, but 39% of the 1180 male tumors with known grade were grade 3, comparable with the proportion in postmenopausal women, but less than that in premenopausal women [90]. In contrast, a much smaller study of 41 male breast cancers found that 73% were grade 3 and 45% were HER2-positive [91]. HER2 overexpression rates range from 2% to 42% in other studies [72, 74, 78, 92–99].

Small studies have identified several other biological features that may be active in driving breast cancer growth in men. One study suggested that male breast cancers were more likely to be p53-negative, p21-positive, and aneuploid [100], but others have shown rates of p53 mutation that are comparable with those in women [101, 102]. It has been hypothesized that kinase inhibitor proteins may play a unique role in male breast cancer [103], and that androgen pathways may be more active than in female breast cancers [104], but data are preliminary. Case series have found 34%–95% AR positivity in male breast cancers [105–108]. The prolactin receptor has also been

Table 1. Risk factors for breast cancer in men

| |
|--|
| Age [80, 127, 135, 220–222] |
| Genetic factors |
| Well-established |
| Family history [8–14] |
| BRCA2 >> BRCA1 [15–33] |
| Possible |
| PALB2 [36, 39, 42, 44] |
| Androgen receptor [40, 43] |
| CYP17 [41] |
| CHEK2 [35, 37, 38] |
| Conditions associated with an abnormal estrogen-to-androgen ratio |
| Klinefelter's syndrome [48, 49] |
| Exogenous estrogen or testosterone use [50, 56] |
| Obesity [9, 10, 49, 51–53] |
| Orchitis/epididymitis [49] |
| Finasteride [54, 55] |
| Lifestyle |
| Lack of exercise [8] |
| Exposures |
| Well-established |
| Radiation [223, 224] |
| Possible |
| Electromagnetic fields [64, 65] |
| Heat [66] |
| Volatile organic compounds (e.g. tetrachloroethylene, perchloroethylene, trichloroethylene, dichloroethylene, and benzene) chemicals [67–69] |
| Miscellaneous possible risk factors |
| Birth order (possible higher risk in first borns) [225] |
| Bone fracture after age 45 [8] |

implicated in male breast carcinogenesis in one small study [109].

As in female breast cancer, structural genomic rearrangements appear to be common in male breast cancer [110, 111]. One comparative genomic hybridization study identified similar patterns of chromosomal aberrations in male and female sporadic and BRCA2-associated cancers [112]. In contrast, another study of select breast cancer-related genes found more copy number gain of certain genes (EGFR and CCND1) and less copy number gain of others (EMSY and CPD) [113], as well as less hypermethylation of ESR1, BRCA1, and BRCA2 [114], in male breast cancers than in female breast cancers. Likewise, contrasting comparative genomic hybridization in fresh frozen male breast tumors with a publicly available dataset from female breast tumors, male tumors were more likely to have genomic gains and less likely to have losses of genomic material and high-level amplifications [115]. Hierarchical clustering of male tumors based on copy number alterations identified in female tumors revealed two male breast cancer subgroups. Subsequently, analysis of mRNA expression in these tumors (plus 10 additional samples) suggested that both subgroups (termed 'luminal M1' and 'luminal M2') not only differ from each other in tumor characteristics and outcome, but also are different from known female breast cancer subgroups [116]. MicroRNA expression signatures also appeared to differ between male and female breast cancers in a US study [117]. In another small study, gene expression profile analysis revealed that nearly 1000 genes (including some associated with the AR) were differentially expressed between female and male breast cancers in Italy [118]. It is possible that gender-related biological differences have clinical implications for breast cancer patients.

diagnosis

presentation and prognosis

Perhaps due to poor awareness of the disease and diagnostic delays, most (but not all) [119] studies suggest that men are diagnosed with higher stage tumors and have a poorer prognosis overall [89, 120–125]. One study found that only 29% of 100 Croatian male breast cancer patients were diagnosed within 3 months of symptom onset, far fewer than the 58% of 500 Croatian female breast cancer patients who were diagnosed within the same time frame [126]. A Spanish study found that the average delay between symptom onset and diagnosis was >10 months, and that those who had shorter delays were more likely to have lower stage disease [79]. When matched by stage and age, men appear to have a comparable or better prognosis than women [77, 127–129].

Sociodemographic predictors of prognosis are evident in male breast cancer patients. Black men and men who live in non-metropolitan areas seem to fare poorly, likely at least in part due to disparities in treatment [130–133]. One Israeli study suggested that Sephardic Jewish patients have poorer outcomes than Ashkenazi Jewish patients, but it is uncertain whether this is related to genetic or social factors [134]. Younger age does not appear to correlate with worse prognosis in men [89, 135–138]. Breast cancer-related death was found to

be more common in unmarried than in married men in a large SEER study [132].

In men, breast cancer often presents as a painless subareolar lump [139–144]. Compared with female tumors, these are more likely to be node-positive, and lymphovascular invasion and nipple involvement may be more common [145, 146]. As in women, lymph node status is tightly linked to breast cancer outcomes in men [72, 104, 147–165]. When male cancers are diagnosed early enough that only ductal carcinoma *in situ* is present (often detected due to bloody nipple discharge), these are usually only low or intermediate grade [166], and distant recurrences are very infrequent [167]. A SEER database study found that 9% of all male breast cancers are diagnosed while still *in situ*, and that *in situ* carcinoma incidence is rising in men despite the absence of screening mammography [168].

As in women, grade is a powerful prognostic factor [158, 162, 169, 170]. One case series including 27 Italian men with breast cancer found that the median survival was 72 months in those with grade 2 tumors and 33 months in those with grade 3 tumors [171]. In 43 Canadian patients, 5-year survival was 58% in those with grade 2 tumors and 45% in those with grade 3 tumors [146].

It has not yet been definitively ascertained whether other biologic markers are equally prognostic in men and women. In men, some small studies have shown no correlation between HER2 status and survival [172–175], but others have demonstrated that HER2 positivity predicted a shorter disease-free or overall survival [145, 159, 176–178]. Progesterone receptor status has not been proven to influence prognosis in men to date [177, 179]. Likewise, the prognostic importance of lymphovascular invasion in men is uncertain [180]. However, small studies have preliminarily found that higher risk disease is associated with the following: loss of BRCA1 in sporadic tumors [181]; high levels of MIB-1 [182]; p53 expression [176, 177]; loss of p27 [182]; overexpression of p21 [183], p57 [183], and proliferating cell nuclear antigen [183]; and AR expression [184]. In contrast, some studies have found that AR positivity correlates with favorable outcomes [97], and others have not identified any association between AR and outcome [106]. Overexpression of cyclin D1 and c-myc may correlate with better outcomes [183]. Two small tissue microarray and immunohistochemistry studies also suggested that intratumoral aromatase expression was associated with lower grade and better overall survival in male cancers, but COX2 and survivin expression were not [185, 186]. Another study recently showed that the presence of a fibrotic focus and overexpression of hypoxia-inducible factor-1 alpha in a breast tumor was associated with worse prognosis in men [187]. One recent study identified more high-grade, progesterone-receptor-negative, HER2-positive disease in male patients who carried BRCA2 mutations [188], and earlier research found poorer prognosis in men with BRCA2-associated tumors [184].

diagnostic testing

Data are very limited regarding appropriate diagnostic tests for men with breast abnormalities. In a series of 20 male patients who presented with a breast complaint that was later

diagnosed as breast cancer, 13 underwent mammography, of whom 6 had an ill-defined mass, 5 had a speculated mass, and 2 had a well-defined mass visualized [189]. In that series, a mass was also visualized in 13 of the 14 men who underwent ultrasound, demonstrating that ultrasound may also be a valuable imaging modality in male patients. Another small study suggests that fine-needle aspiration can be used in a male patient to differentiate malignant from non-malignant breast disease [190]. The utility of magnetic resonance imaging is unknown in men.

treatment

local therapy

Surgical options for men with early-stage breast cancer include breast-conserving therapy and mastectomy [191]. Today, most patients undergo modified radical mastectomy [191–193]. It is generally assumed that the cosmetic sequelae of mastectomy are not problematic for men, but lumpectomy may be preferable for some, in part because it is a considerably less morbid surgery. Older patients may be more likely to opt for lumpectomy with or without radiation, though this has not been studied.

Several small studies have demonstrated feasibility of sentinel node biopsy in men [194–196]. One found that male patients who had cancer in a sentinel node were more likely to have additional cancer-containing axillary nodes than female patients with cancer in a sentinel node (63% versus 21%, $P = 0.01$) [195]. Another study reported no axillary recurrences at 28 months' median follow-up after the use of a sentinel lymph node biopsy strategy for 78 male patients [196].

Post-surgical radiation criteria are generally extrapolated from data in women [197, 198]. One study of 31 male patients found that there was only one local relapse when criteria for post-mastectomy radiation in women were applied to this group, with 16 men receiving adjuvant radiation [199]. Men with tumors >5 cm or with four or more lymph nodes involved usually receive post-mastectomy radiation. Some men with one to three lymph nodes involved, with extensive lymphovascular invasion in the breast, or with close surgical margins will also be recommended to receive post-mastectomy radiation, though this decision-making is complex in the absence of data specific to men. In 55 Turkish patients, controlling for other disease and treatment factors, receipt of radiotherapy was found to prolong disease-free survival [161]. A case series of 75 men treated with curative intent in Ontario found significantly improved local recurrence free survival in the 46 who received post-mastectomy radiation, but their overall survival was not different [200]. Two other smaller case series in Turkey also found no survival benefit with postmastectomy radiation [201, 202]. However, there were too few patients in any of these studies to adequately control for the strong possibility that men with higher risk tumors received the radiation, biasing toward no detection of benefit.

systemic therapy

There are limited data regarding systemic therapy in men [123, 203, 204]. One American single-institution retrospective cohort

study of 135 men treated between 1944 and 2001 revealed a nonsignificant trend in men with node-positive disease toward better outcomes with the use of adjuvant chemotherapy (mostly anthracycline-based in this retrospective cohort) [205]. A Turkish study of 121 male breast cancer patients treated between 1972 and 1994 also found improved survival in those who received adjuvant chemotherapy [123]. Definitive conclusions cannot be drawn from either study. There are no data on the efficacy of trastuzumab for HER2-positive disease in men, though many providers follow the same approach that is used in women.

Several small retrospective studies have suggested a benefit from endocrine therapy [206, 207]. Standard adjuvant endocrine therapy for men entails 20 mg of oral tamoxifen daily for 5 years. In the 1944–2001 American cohort, the 38 men who received adjuvant endocrine therapy (92% tamoxifen) had superior recurrence-free (HR 0.49, 95% CI 0.27–0.90) and overall (HR 0.45, 95% CI 0.25–0.84) survivals compared with those who did not receive endocrine therapy, with the apparent benefit of adjuvant endocrine therapy approximating that in women [205]. Likewise, in a Chinese retrospective single-institution study of 72 male patients over 40 years, multivariate regression found that receipt of endocrine therapy was associated with better survival [165]. In contrast, a Veterans Administration study of 65 male breast cancer patients found no benefit from tamoxifen for ER-positive tumors [177].

Treatment for metastatic disease in men has been primarily evaluated in case reports and small case series. In a Spanish series of 50 men with breast cancer, 10 of whom were treated with endocrine therapy for metastatic disease (either orchiectomy, estrogen, or tamoxifen), 2 of the 10 had complete responses, 1 of which lasted 60 months [208]. In men with metastatic disease or men who have a contraindication to tamoxifen, an aromatase inhibitor is often used, though data supporting this approach are extremely limited, particularly in the adjuvant setting. It is uncertain whether a gonadotropin-releasing hormone agonist (GnRH-a) or orchiectomy is needed when an aromatase inhibitor is prescribed to a man in order to achieve complete estrogenic suppression. Only case reports have documented control of advanced disease with other hormonal agents (e.g. megestrol, fulvestrant). To our knowledge, anti-androgen therapy has not yet been explored as a treatment for male breast cancer.

survivorship issues

Men often experience bothersome symptoms from endocrine therapy, and approximately one in four discontinue treatment early due to hot flashes or sexual dysfunction [209–211]. No interventions have been developed to ameliorate these symptoms in male breast cancer patients specifically.

Little is known about short- or long-term toxic effects of chemotherapy and local treatments in men, nor about psychological sequelae of the disease in this population. Although no studies have evaluated cardiac toxic effects in men specifically, it is possible that these are more common in men with breast cancer than in their female counterparts as a result

of advanced age and higher baseline cardiovascular risks. A recent comparison of Behavioral Risk Factor Surveillance System telephone survey data between 198 men without cancer and 66 men with a history of breast cancer (on average 12 years post-diagnosis) found poorer physical and mental health in the breast cancer survivors. Obesity, diabetes, and activity limitations due to a physical, mental, or emotional problem were more common in the men with a history of cancer [212]. Another recent study reported that 84 male survivors of breast cancer had better health-related quality of life than 20 589 female survivors when confounders were controlled for, but worse health-related quality of life (particularly in role functioning) compared with historic data in the men in the general population [213]. Breast cancer may be socially isolating for men, who may feel stigmatized by their diagnosis because it is so strongly associated with women. That said, it is unknown if men with breast cancer have greater difficulties with adjustment than men with other prognosis-matched cancers.

Optimal surveillance strategies are uncertain in male breast cancer survivors. Although the risk of a new breast cancer is <5% in a male breast cancer survivor, some men will opt for annual mammography of remaining breast tissue. A multicenter international study that pooled data from 13 cancer registries found that 12.5% of 3409 male breast cancer survivors went on to develop a different (non-breast) cancer, and that risk of new primary cancers was elevated in the small intestine, rectum, pancreas, skin (non-melanoma), prostate, and lymphatics/blood [214]. Other more recent studies have confirmed an increased risk of other cancers in male breast cancer survivors [215].

Genetic counseling should be offered to most male breast cancer patients based on their increased risk of BRCA mutations, particularly in the context of a family history of breast or ovarian cancer [36]. Instruments such as BRCAPro have been validated for use in male breast cancer patients [216]. However, the clinical importance of BRCA testing may be greater for female family members than for the male proband. In the absence of BRCA testing, it is known that breast cancer risks in family members of male breast cancer patients are elevated [217], particularly if other family members have been diagnosed with prostate cancer [218] or other BRCA-related cancers [219].

conclusion

Many questions remain regarding the causes, consequences, and optimal care of breast cancer in men. More work is required to further elucidate biological underpinnings, risks and benefits of specific treatments, and quality of life in men with breast cancer. The European Organization for Research and Treatment of Cancer is planning a prospective registry that will collect tissue specimens and diagnostic and treatment information in order to answer critical clinical questions in male breast cancer. We have reason for optimism that future research efforts will facilitate the development of interventions that improve the prognosis of individuals in this unique and understudied population.

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Aromatase inhibitor-induced arthralgia: a review

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Though aromatase inhibitors (AIs) are an essential part of estrogen receptor-positive (ER+) breast cancer therapy, many patients discontinue the medicine before their adjuvant therapy is completed because of the arthralgia which often accompanies the medicine. Up to half of women on AI therapy experience joint pain, and up to 20% will become non-compliant with the medicine because of the joint pain. Yet, very little is known about what causes AI-induced arthralgia (AIA), and there is no established, effective treatment for this difficult problem. It compromises survivors' quality of life and leads to non-compliance. This paper will discuss AIA in depth, including potential etiologies, clinical significance, risk factors, and possible management solutions. Of note, this article presents one of the first proposed algorithms which clearly lays out a treatment plan for AIA, incorporating a variety of interventions which have been proven by the available literature.

Key words: aromatase inhibitors, arthralgia, breast cancer, survivorship

introduction

The emerging field of breast cancer survivorship is becoming increasingly relevant as therapies for breast cancer continually improve and survival rates surge. In the United States, there are estimated to be over 2.97 million breast cancer survivors, and this number is expected to climb to 3.79 million by January 2022 [1]. According to SEER data, the 5-year relative survival for breast cancer patients, compared with the rest of the population, is 89%. Furthermore, even those with metastatic disease have a 23% 5-year survival on average [2]. Clearly, our breast cancer patients are living longer than they were previously, and a special set of needs arises for them in relation to the side-effects of therapy.

In this review, I will focus on the arthralgia related to aromatase inhibitor (AI) therapy, as this is an extremely common problem among breast cancer patients which negatively impacts day-to-day well-being. Because AI therapy is often continued for up to 5 years, arthralgia may be a very plaguing problem for women, sometimes resulting in non-compliance with AI therapy. This is a significant public health issue because we know that AIs are the most effective

hormonal therapy available for post-menopausal women; AIs offer improved disease-free survival and decreased rates of contralateral breast cancer when compared with adjuvant tamoxifen [3–5].

definition

In order to discuss the issue of AI-induced arthralgia (AIA), it is first important to clearly define the term. In fact, the current ambiguity surrounding the syndrome has presented a problem in the literature. In the absence of a clear definition of the problem, various clinical trials have reported a wide range of AIA incidence, likely because they are each defining AIA differently. Also, some physicians may not recognize more subtle manifestations of this side-effect because no objective diagnostic criteria exist. Generally, AIA presents with symmetrical joint pains, most commonly affecting the wrists, hands, and knees [6]. Carpal tunnel syndrome and trigger finger may be common complaints as well. Retrospective data from both the arimidex, tamoxifen, alone or in combination (ATAC) trial and the Intergroup Exemestane Study (IES) showed significantly higher rates of carpal tunnel syndrome with AI use when compared with tamoxifen [7, 8]. Other symptoms may include morning stiffness, myalgia, and decreased grip strength. The median time to onset of symptoms is 1.6 months, though it can range from a couple of weeks to more than 10 months. Symptoms tend to peak at ~6 months [9].

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