



Male breast cancer: a review of literature

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ARTICLE INFO

Article type

Review article

Article history

Received: 28 Nov 2015

Revised: 16 Apr 2016

Accepted: 28 Apr 2016

Keywords

Breast cancer

Male

Treatment

ABSTRACT

Studies have devoted relatively scant attention to male breast cancer compared with female breast cancer. Nevertheless, the incidence of male breast cancer has increased considerably in parallel manner with women. There is not comprehensive knowledge regarding the etiology of breast cancer in men. The environmental agents and genetic factors are proposed as the influential parameters in the pathogenesis of breast cancer. Invasive ductal carcinoma is the most frequent subtype of breast cancer in men and a palpable mass is the most common presentation. Breast masses might be identified at advanced stages of the disease, if undiagnosed, due to the lower prevalence and lack of awareness in men compared to women. There is not any large sample size trial or retrospective study regarding any specific treatment strategy; the routine treatments are based on existing data. In this review, we studied the risk factors, biological characteristics, and therapeutic strategies of breast cancer in men.

Please cite this paper as:

Shahidsales S, Fazl Ersi M. Male breast cancer: a review of literature. *Rev Clin Med.* 2017;4(2):69-72.

Introduction

Breast cancer is one of the most prevalent malignancies with a high annual mortality rate in men and women (1). Despite the introduction of various treatment strategies, breast cancer still poses a threat to human life (2). Male breast cancer is a rare malignancy with somewhat similar clinical features to breast cancer in females (3). Biological properties of male breast cancer are reported to be mostly similar to postmenopausal women (4).

The occurrence of breast cancer exerts several negative impacts on men similar to women including psychological changes such as body image disruption, increased nervousness, and depression (5). Studies have devoted relatively scant attention to male breast cancer compared with breast cancer in women. The purpose of this review is to present the risk factors, biological characteristics, and the treatment strategies of male

breast cancer.

Literature review

Epidemiology and risk factors

Male breast cancer accounts for about 1% of all cases of breast cancer. Approximately 1.5% to 2.5% of all types of male cancers are allocated to breast cancer (6). Breast cancer occurs at the mean age of 67 years in men, which is about 5 years higher than the average age of breast cancer diagnosis in female patients (7). The incidence of male breast cancer shows an increase in advanced ages and remains steady until it reaches a plateau around age 80 (8). Male breast cancer has increased in recent years similar to women with an increased incidence of 26% over the past 25 years (7). Male breast cancer has similar risk factors to those for postmenopausal women with breast cancer (4). Similarly, a history of breast cancer in

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a male first-degree relative is associated with an increased risk of breast cancer in men. Positive family history of breast cancer is observed in 7% of male population, while 15% to 20% of men with breast cancer have a positive family history (7). Mutations in BRCA gene increase the risk of male breast cancer and BRCA2 mutation carries a higher risk of breast cancer compared to BRCA1 mutation (9-15).

Conditions such as increasing estrogen to androgen ratio have linked to the higher risk of male breast cancer. Klinefelter syndrome (16,17), administration of estrogen or progesterone, obesity (18,19), orchitis/epididymitis (19), finasteride (20), and prostate cancer treated with estrogens have been implicated as potential risk factors of breast cancer (21). Moreover, it has been proposed that individuals with the history of liver disease are at higher risk of breast cancer as the result of the liver role in steroid and estrogen metabolism (22). Most studies did not find any association between alcohol use and male breast cancer. However, various investigations have been conducted regarding the effect of environmental factors on the incidence of breast cancer (23). According to one investigation, various factors might be related to male breast cancer including high workplace temperature, presence of pollutants, aromatic hydrocarbons, and ionizing radiation. The impact of electromagnetic fields is also evaluated in another study, but the relation is still not clear (23).

Clinical symptoms and diagnostic methods

As opposed to increase the knowledge of women about breast cancer and available recommendations, there is not sufficient knowledge about breast cancer in men. Because of the specific anatomy of male breast, cancer could be easily diagnosed in early stage of the disease. However, male breast cancer is typically diagnosed at advanced stages, most likely due to the lack of awareness. A palpable breast mass under the areola without corresponding pain is a common presentation of male breast cancer. Skin changes, including nipple retraction, ulceration, or fixation of the mass to the surrounding skin or underlying tissues may be considered as possible presentation of male breast cancer. Axillary lymph nodes are typically palpable in advanced stages (24).

The differential diagnosis of a breast mass in a man includes gynecomastia, pseudogynecomastia, infections, lipoma, fibromatosis, and metastatic diseases (25).

Although mammography is an accepted screening strategy in women, there are few studies regarding the efficacy of mammography in male breast cancer. According to studies, mammogra-

phy and other imaging techniques are routinely applied in men, especially in younger individuals with suspected breast cancer; mainly because of the lower incidence rate of breast cancer in men compared with women and high sensitivity of meticulous physical examination in detecting breast tumors in men. Breast mass can be often diagnosed through an accurate physical examination, thus mammography is suggested only in whom the physical examination fails to detect breast tumor (26).

Any suspicious mass should be confirmed by biopsy and evaluated for hormonal receptors including Estrogen Receptor (ER) and/or Progesterone Receptor (PR), and human epidermal growth factor receptor 2 (HER2 status). Fine needle aspiration (FNA) could provide adequate samples in many cases; however, core needle biopsy offers a more definitive histologic diagnosis, and can usually distinguish between invasive and in situ carcinomas. If inadequate tissue is obtained for diagnosis, an open biopsy should be performed (27,28).

Staging work-up

Diagnostic evaluation and staging system used for breast cancers are similar in males and females. Breast cancer staging is defined according to the tumor size, nodal involvement, and metastasis (TNM). The same as female patients, stage, tumor size, and axillary lymph node involvements are the most important prognostic factors in male breast cancer.

Pathological and biological characteristics

The most common pathological subtype of male breast cancer is invasive ductal carcinoma, similar to females. Invasive lobular carcinoma has a very low incidence in men (7,29). The most common subtype is hormone receptor-positive subtype with approximately 20% to 40% of HER-2 positive (30-32).

Treatment

The surgical approach to breast cancer is similar in both genders, depending on the extent of the tumor at the time of presentation.

Early-stage disease

Generally, men with early-stage of breast cancer (T1-T2, N0-N1) undergo a modified radical mastectomy, axillary lymph node dissection, or sentinel lymph node biopsy (SLNB) (33), and breast-conserving surgery is an alternative treatment in men who refused mastectomy (34). In a review of data obtained by the Surveillance, Epidemiology, and End Results (SEER) Program, 1541

cases of male breast cancers were identified, and almost 20 percent were treated with breast-conservative surgery (31). Adjuvant radiation therapy (RT) should be performed in men undergoing breast-conserving surgery.

Locally advanced disease

Male with locally advanced breast cancer (T3N0 or stage III of the disease), or inflammatory breast cancer are treated the same as females. In this setting, neoadjuvant chemotherapy is a preferred approach because it is associated with higher rates of clinical and pathological responses, without compromising survival outcomes (32).

Management of the regional lymph nodes

Evaluation of the regional lymph nodes is essential in surgical management of breast cancer. Sentinel lymph node biopsy is acceptable in clinically node-negative male patients (35). In the presence of negative SLNB results, patients will not need additional surgical treatment. Moreover, axillary lymph node dissection is recommended for positive SLNB results.

Adjuvant therapy

Adjuvant therapy includes radiotherapy (RT), endocrine therapy, and chemotherapy.

Radiotherapy

Radiotherapy is used to treat breast cancer in men based on the same formal guidelines in women. Post-operative radiotherapy is recommended in patients with tumor size larger than 5 cm, more than four positive axillary lymph nodes, 1 to 3 positive nodes with extracapsular extension, or positive surgical margins, and in men undergoing breast-conserving surgery (36).

Systemic treatment

There is not enough data regarding the systemic treatment in men. Systemic chemotherapy is used to treat breast cancer in the same way as treated in women (33). Several factors affect the prognosis including hormone receptor status and P53 mutations (37). Bone is the most common site of the metastasis in hormone-receptor positive patients, while metastatic breast cancers spread to the brain in HER2-positive patients (38).

According to the various studies, endocrine therapy exerts beneficial effects in men (39). Tamoxifen is a preferred available agent compared with aromatase inhibitors (AIs). There are not adequate studies to support the use of AIs in the treatment of male breast cancer. Administration of tamoxifen at a dosage of 20 mg for five years is proposed as the standard adjuvant treatment. There is not any

documented finding regarding the efficacy of trastuzumab administration in HER-2 positive men. Metastatic or advanced breast cancers are treated in the same way as in women with metastatic breast cancers. Tamoxifen is also the preferred agent in this setting (33). Genetic testing should be offered to all male patients with breast cancer because of the increased risk of BRCA mutations, particularly in patients with a positive family history of ovarian or breast cancers.

Metastatic breast cancer

Despite the treatment of early-stage breast cancer, some patients will develop distant metastasis (39). Metastatic breast cancer is defined when tumoral cells have spread beyond the breast to distant locations. Metastatic breast cancer is primarily treated by palliative strategies. Overall, 5-year survival rate of metastatic cancers was reported approximately 24% (40). Chemotherapy or hormonal therapies (in hormone-positive breast cancer) are the initial treatments in patients with metastatic breast cancer. Radiotherapy has a limited role in metastatic diseases that can be used in palliative setting

Conclusion

The etiology of male breast cancer and identification of the most effective therapeutic strategy are still under consideration. Further investigations are required to clarify the exact biological properties, efficacy of various treatments, and the quality of life in men with breast cancer.

Conflict of Interest

The authors declare no conflict of interest.

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