



Contents lists available at ScienceDirect

Curr Probl Cancer

journal homepage: www.elsevier.com/locate/cpcancer



Special considerations in the evaluation and management of breast cancer in men¹



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ARTICLE INFO

Keywords:

Breast cancer in men
Estrogen receptor
BRCA2
Androgen receptor
Tamoxifen

ABSTRACT

Breast cancer in men is relatively uncommon but its incidence has been rising. Traditionally, the management of breast cancer in men is based on extrapolation from clinical trials of breast cancer in women, due to the much more extensive data available in women with this disease. There are, however, unique characteristics that distinguish breast cancer in men and these should be taken into consideration when managing this patient population. Breast cancer in men is more frequently estrogen receptor (ER) and progesterone receptor (PgR) positive, and less frequently HER2 amplified. Lobular carcinoma, which accounts for 10–15% of breast cancers in women, is exceptionally rare in men. Genetic risk factors, particularly *BRCA2* mutations, are increasingly recognized as a key risk factor for breast cancer in men and genetic testing is now routinely recommended for all men diagnosed with breast cancer. Tamoxifen remains the gold standard endocrine therapy for breast cancer in men, but other endocrine agents such as the aromatase inhibitors (AI) and fulvestrant are increasingly being used. While superior to tamoxifen in postmenopausal women, the use of AIs for adjuvant therapy in men with breast cancer may not be optimal since the physiology of

¹ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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hormonal regulation in men resembles that of premenopausal rather than postmenopausal women. Emerging areas of investigation include the role of genomic risk stratification to gain further insight into the biology of breast cancer in men, the study of the androgen receptor (AR) as a therapeutic target, and the role of gonadal suppression in the management of the disease. There is clearly a more concerted effort to study breast cancer in men as a unique disease in order to have a better understanding of its biology and we are likely to witness further advances that will help us better manage this unique disease situation.

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Introduction and epidemiology

The American Cancer Society estimates that approximately 2600 men would be diagnosed with breast cancer in the United States in 2016,¹ which accounts for 1% of all breast cancer cases (in both sexes), and no more than 0.03% of all new cancers in men.¹ Approximately 440 men would die from breast cancer in 2016, with a mortality rate of 17%, which is almost identical to the risk of mortality from breast cancer in women, and this accounts for 0.13% of all cancer deaths in men.¹

Because of its rarity, much of how we treat breast cancer in men is based on the more extensive data available on breast cancer in women. Data on breast cancer in men are predominantly derived from retrospective single institution studies, and prospective randomized therapeutic trials are lacking. It is important to note that, despite its rarity, it is clear that the incidence of breast cancer in men is rising^{1,2} in parallel to the increasing incidence of breast cancer in women, but at a smaller rate,² possibly related to the added contribution of mammography screening in women.

Risk factors

Most men diagnosed with breast cancer have no identifiable risk factors, but there is evidence that certain conditions of hormonal imbalance, either estrogen excess or androgen deficiency, may play an etiologic role. Conditions of estrogen excess include chronic liver disease,^{3,4} obesity,^{5,6} pharmacological estrogen therapy,⁷ and very rarely gonadal suppression in prostate cancer.⁸ In obese men, levels of endogenous estrogens may be increased with more conversion of androgens to estradiol and estrone in fat tissue,⁶ and exogenous estrogen use has been reported in connection with breast cancer rarely reported in male-to-female transsexuals.⁹

Conditions associated with lowered testosterone have been implicated in the etiology of breast cancer in men, including testicular conditions such as orchitis, undescended testes, orchiectomy, and Klinefelter syndrome.^{10,11} Occupational heat exposure, which may affect testicular function, has also been associated with increased risk of breast cancer in men, including in steel and blast furnace workers.¹²

Gynecomastia may be associated with breast cancer, and autopsy studies report that as many as 50% of all men with breast cancer may have associated gynecomastia present.¹³ A recent US Veterans population study confirmed the association of breast cancer in men with gynecomastia, Klinefelter syndrome, obesity, and orchitis, which lends further support to the role of hormonal factors in the etiology of breast cancer in men.¹⁴ Interestingly, that same study suggested that cholelithiasis might be a risk factor for the development of breast cancer in black men.

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