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BRIEF REVIEW
ΒΡΑΧΕΙΑ ΑΝΑΣΚΟΠΗΣΗ

# Male breast cancer

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2012, 29(6):695–701

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*Περίληψη στο τέλος του άρθρου*

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## 1. INTRODUCTION

Breast cancer in men is rare, accounting for only 0.6% to 1% of all breast cancers and <0.1% of all male cancers.[1,2] As a result, there have been very few clinical and epidemiological studies relating to this malignancy. Male breast cancer (MBC) has important differences from the female counterpart. Specifically, MBC has a different hormonal receptor status with higher expression of estrogen receptor (ER) and progesterone receptor (PR), and histological variations, showing a predominance of invasive ductal carcinoma.[3,4]

## 2. EPIDEMIOLOGY AND RISK FACTORS

### 2.1. Age at diagnosis

Various studies estimate the age at diagnosis of breast cancer in males to be later in life than in females. Examination of the trends in incidence and age at diagnosis reveals that the incidence rate for MBC increases with age in a linear fashion, peaking at the age of 71 years. In contrast, the age-specific rates for female breast cancer (FBC) increase rapidly until the age of 50, following which they continue to increase at a slower rate in older women.[5] MBC thus has a unimodal age-frequency distribution, in contrast to FBC, which demonstrates a bimodal age-frequency distribution, with early-onset and late-onset peak incidences at 52 and 71 years respectively.[1,3] The bimodal nature of FBC is believed to be related to changes in estrogen exposure.[3]

### 2.2. Race

The incidence of MBC is higher among Afro-Caribbean men.[3] In addition, and in contrast to Caucasian men, Afro-Caribbean men with breast cancer tend to have an early-onset peak incidence at 56 years and present with a higher tumor grade, negative hormone receptor expression and a more advanced stage at diagnosis. This is thought to be due in part to reduced access to health care and socio-cultural factors.[3,6]

### 2.3. Genetics

A family history of breast cancer confers a relative risk of 2.5 with 20% of cases having a first-degree relative with the disease.[7] The risk association of MBC mirrors FBC and is around 5–10%.[8,9] The BRCA2 mutation appears to have a more greatly enhanced role in MBC than in FBC in terms of risk of cancer development at a young age.[10,11]

### 2.4. Endocrine risk factors

*2.4.1. Exogenous exposure.* There is no doubt that exogenous estrogen increases the risk of breast cancer in males, with cases of breast cancer reported in men with estrogens treated for prostate cancer.[12] In addition, transsexual men taking estrogens have been shown to be at increased risk of developing this tumor.[13]

*2.4.2. Endogenous exposure.* The incidence of MBC is also

increased in conditions that elevate the endogenous exposure to estrogen or decrease androgen exposure. The risk of breast cancer in individuals with Klinefelter's syndrome is 20 to 50 times higher than in XY men and the mortality rate in men with Klinefelter's syndrome is similar to that in women.[14,15] Obesity also increases the risk of MBC. In these cases, the increased levels of circulating estrogens are believed to be responsible for the observed doubling of risk.[16,17] Other causes of testicular abnormality that are implicated in endocrine-related MBC include mumps, undecended testes and congenital inguinal hernia resulting in unilateral or bilateral orchidectomy.[18] Liver cirrhosis has been found to be associated with MBC due to its effect on circulating androgens.[19]

## 3. LIFESTYLE AND ENVIRONMENTAL RISK FACTORS

### 3.1. Lifestyle

In terms of lifestyle factors, body mass index (BMI) is significantly associated with MBC.[17] Several studies have suggested that excessive alcohol consumption may raise MBC risk, with an increase of 16% per 10 g daily alcohol intake.[20,21]

### 3.2. Environmental risk factors

In male atomic bomb survivors the risk per sievert was increased by a factor of 8.[22] A higher frequency of breast cancer is reported in men who work in hot environments, such as blast furnaces, steel works, and rolling mills, and there is evidence implicating occupational exposure to petrol and exhaust fumes as a risk factor.[23]

## 4. CLINICAL PRESENTATION

### 4.1. Symptoms

The most common symptom is a lump, which is the presenting feature in 75% of cases. Pain is associated with a lump in only 5%. In contrast to FBC, nipple involvement usually occurs early in the course of the disease, presenting with ulceration, retraction or discharge. Occult disease presenting with axillary lymphadenopathy alone is rare.[16]

## 5. MANAGEMENT OF MALE BREAST CANCER

### 5.1. Assessment

The rarity of MBC together with the low index of suspicion often results in a significant delay in presentation and subsequent diagnosis. This delay, coupled with the scarcity of breast tissue in men, results in more than 40% of cases presenting with stage III/IV disease,[4] and at diagnosis 7% of men have evidence of distant metastatic disease, compared with 5.6% of women. The size of the tumor is also different, with only 10% of men presenting with a tumor size of <1 cm compared with 20% of women.[1]

Triple assessment forms the cornerstone for detecting MBC. During clinical examination the axilla must be carefully examined, as cases of occult MBC presenting solely with axillary node metastases have been reported.[24] Mammography, with a sensitivity of 92% and a specificity of 90% in MBC,[25] is valuable in the diagnostic workup as it helps to identify the cases which need further cytological evaluation. Typical features of a malignant lesion include a mass which is often, but not always, spiculate. The mass tends to be eccentric to the nipple, in contrast to gynecomastia which tends to be concentric to the nipple.[26] Calcifications are less common than in women, but when present calcifications that would be accepted as benign in women can indicate malignant disease in men.[27]

Ultrasound (US) scanning typically reveals a hypoechoic mass with irregular or indistinct margins. Color flow doppler may reveal vascular flow within the peripheries of the lesion with scanty vessels. Cysts are rare in male breast tissue; thus, all cysts should be thoroughly evaluated for complexity as neoplastic papillary lesions are frequently manifested as complex cystic lesions.[28] As in FBC, US also plays a role in staging the axillary spread, accompanied by cytological assessment where indicated. As the vast majority of MBC lesions are palpable the role of magnetic resonance imaging (MRI) is not established. Cytology remains the primary pathological sampling technique because of its versatility and reliability. Several studies comparing fine-needle aspiration (FNA) findings from breast lesions with subsequent core or excision biopsy results have revealed sensitivity and specificity approaching 100%, respectively.[29,30] When the FNA is inadequate or equivocal, a core biopsy is indicated.[31]

### 5.2. Histopathology

Since male breast tissue is rudimentary, it does not usually differentiate and undergo lobule formation unless exposed to increased concentrations of endogenous or exogenous estrogen. Thus the predominant histological type of disease is invasive ductal carcinoma, which accounts for more than 90% of cases, the corresponding percentage in women being 80%. Much rarer tumor types include invasive papilloma and medullary lesions. In terms of tumor grade, at diagnosis, 15% are grade I, 55% grade II and 30%

grade III. Lobular carcinoma is very rare and accounts for only 1% of cases of MBC, in comparison to 12% of FBC.[1]

## 5.3. Surgery

*5.3.1. Breast.* The vast majority of cases continue to be treated with complete resection of the breast tissue. As with FBC, the extent of surgery has become less aggressive over the years, from radical mastectomy to modified radical mastectomy and currently simple mastectomy, with no effect on survival or local recurrence rates.[32] The role of breast conservation surgery in MBC is less clear. The relatively larger tumor size, retro-areolar location, paucity of breast tissue and higher rate of chest wall infiltration are factors which may render breast conservation technically less appropriate. In a Canadian study of 229 patients with MBC, those who underwent breast conservation surgery had a higher local recurrence rate than those who underwent mastectomy.[33] In a French study of 31 cases of ductal carcinoma *in situ* (DCIS), the local recurrence rate was significantly higher after lumpectomy than mastectomy.[34] Conversely, a study from the Brigham and Women's Hospital in Boston demonstrated no evidence of local recurrence at 67 months in any of 7 men with breast cancer treated by lumpectomy. The authors suggest that men without overt nipple-areolar involvement can safely undergo wide excision to clear the margins, with reasonable local recurrence rates and acceptable cosmetic results. Breast conservation surgery may thus be a feasible and oncologically sound approach for carefully selected patients.

*5.3.2. Axilla.* Axillary dissection was standard care for many years, but it was associated with well-documented morbidity such as lymphedema, paresthesiae, persistent pain and reduced shoulder mobility. The first case of sentinel lymph node biopsy in men was published in 1999,[35] since when there has been a growing interest in this technique in MBC. As men tend to present with breast cancer at a more advanced stage, there has been some concern that this may have an adverse impact on the false negative rate when using the sentinel lymph node biopsy technique.[36] Subsequent studies in women, however, have shown that though the false negative rate increases with the primary tumor size, this increase is not statistically significant.[37] Thus, sentinel lymph node biopsy should be considered as the initial axillary staging procedure in clinically node negative cases.

*5.3.3. Reconstruction.* The common rationale for breast reconstruction in males following breast cancer surgery is to provide adequate skin coverage. This is often needed, as 40% of cases present with stage III or IV disease making primary skin closure challenging.[4] The utilization of a variety of fasciocutaneous and myocutaneous flaps has been proposed.[38] In the simplest cases, Di Benedetto recommends the use of thoracic flaps, based on the superficial thoracic artery, or thoraco-epigastric fasciocutaneous flaps, based on the intercostal perforators. The latter are easy to harvest and offer a good and stable covering of the lost tissue area with very rapid postoperative recovery. When very large and deep excisions are required, myocutaneous flaps, such as latissimus dorsi flaps or transverse rectus abdominis muscle flaps are preferred as these provide an appropriate thickness for the newly reconstructed thoracic wall. Other less well-known flaps have also been described, including the use of a deltopectoral flap or a transverse thoracoepigastric flap.[39,40] Spear and colleagues recommend the use of the transverse rectus abdominus myocutaneous (TRAM) flap as this not only affords adequate cover of the post mastectomy defect, but also has the added advantage of providing hair bearing skin similar to that of the male chest.[41]

## 5.4. Radiotherapy

In FBC post mastectomy radiation to the chest wall and axillary lymph nodes is used to decrease loco-regional recurrence and to improve survival.[42] Data on the rate of post surgery local recurrence in MBC are limited and very variable.[43,44] This, together with the fact that the lack of breast tissue does not allow for a large surgical margin, has been the rationale for the frequent use of post mastectomy radiation for all stages of MBC. The dose delivered to the chest wall is usually 45–65 Gy, with 45–54 Gy administered to the supraclavicular, axillary and internal mammary lymph nodes as appropriate. Some patients receive a boost to the scar. The regime duration tends to involve daily sessions lasting 3–6 weeks. One study demonstrated that the addition of radiation decreased the incidence of local recurrence in MBC,[7] but a study from Johns Hopkins suggested that post mastectomy radiation should be reserved for high-risk disease alone, as is the case in FBC.[45] Although breast conservation surgery is relatively infrequent in MBC, when employed it is followed by adjuvant radiotherapy in an attempt to reduce the local recurrence rate. Typically, the radiation technique used is whole breast irradiation for a dose of 45 Gy, while the tumor bed receives a total dose of 60 Gy, similar to the technique used in women with breast carcinoma.[46]

## 5.5. Chemotherapy

As with radiation therapy, the role of chemotherapy in

the treatment of MBC suffers from a paucity of robust data, as a result of which there may be a risk of undertreating MBC. In a study from the US National Cancer Database, only 27% of men were treated with adjuvant chemotherapy, compared with 41% of age- and stage-matched women with breast cancer.[47] Several small retrospective studies of MBC have suggested that the use of adjuvant chemotherapy is associated with a reduced risk of relapse.[48,49] The chemotherapy regimes frequently used include cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or anthracycline-based regimes, often 5-fluorouracil, adriamycin, cyclophosphamide (FAC). Taxanes have been used with anthracyclines but the data are too limited to allow any conclusion to be drawn regarding possible greater efficacy.[50] It is very unlikely that adequately powered randomized studies will ever be performed to evaluate the role of chemotherapy in treating MBC, but drawing on the experience of the use of chemotherapy for breast cancer in women, supported by some of the small studies outlined above, it would be seemed reasonable to recommend the use of chemotherapy for men with intermediate or high grade disease, particularly those with ER negative tumors.

*5.5.1. Trastuzumab.* The HER2 receptor appears to be less frequently overexpressed in MBC than in FBC.[51] Although there are no male specific data, given the benefits that trastuzumab therapy provides to women with HER2 positive breast cancer, it would be prudent to consider its use in men with high risk HER2 positive disease.

### 5.6. Endocrine therapy

Since MBC is ER positive in approximately 90% of cases, adjuvant hormonal therapy in men has become an integral part of treatment. Tamoxifen is generally accepted as the standard of care for adjuvant hormonal therapy in MBC,[33] but there appears to be a high rate of tamoxifen related side effects among male patients, leading to a higher rate of discontinuation than expected. In the largest retrospective study of its kind, researchers from MD Anderson found that the most common significant side effects included sexual dysfunction, weight gain, hot flushes, thromboembolic events and neurocognitive deficits. As a result, 20% of men discontinued tamoxifen during the treatment period.[52] Newer generation aromatase inhibitors (anastrozole, letrozole, and exemestane) act by inhibiting aromatase, the enzyme that produces estrogen via peripheral aromatization of the circulating androgens. In men, 80% of circulating estrogens arise from peripheral aromatization while the remaining 20% are derived from the testicular production of estrogen, which is independent of aromatase.[53] This potentially limits the efficacy of the aromatase inhibitors. There is minimal documentation of the use in men of the pure anti-estrogen fulvestrant, which unlike tamoxifen has no agonist estrogenic activity.[16] Overall, however, in the absence of large scale studies, tamoxifen remains the first line hormone therapy.

## 6. METASTATIC DISEASE

In the past, the management of metastatic MBC consisted of surgery to produce hormonal status modifications, such as orchidectomy, adrenalectomy or hypophysectomy. Although traumatic, these interventions did produce a positive response in 55–80% of cases, depending on the procedure.[54] Indeed, gonadal ablation remains an effective therapeutic intervention in metastatic MBC. Nowadays, medical hormonal manipulation with tamoxifen has replaced surgery, with equal success. There have even been reports of complete response to LH-RH analogues, with or without antiandrogens.[55] Other possibilities include androgens, progestins, corticosteroids and high doses of estrogens. These have been shown to have a response rate of up to 75%.[49] Third generation aromatase inhibitors have also been used with case reports suggesting the beneficial role of letrozole in metastatic MBC.[53] As most men will respond to hormonal manipulation, systemic chemotherapy is often reserved as a second line treatment strategy in metastatic MBC. Chemotherapy can provide a palliative role in cases of hormone-refractory MBC. Response rates reported ranges from as low as 13% for the single agent fluorouracil to as high as 67% for a combination regime including fluorouracil, doxorubicin, and cyclophosphamide (FAC).[54]

## 7. PROGNOSIS

The age-adjusted incidence of MBC is increasing. The rate of increase in incidence does not appear to slow after the age of 50 years as is observed in women, probably due to the lack of, or a more gradual change in, the hormonal milieu than occurs in women at menopause.[1,56] Overall, mortality from breast cancer has improved over time for the last three decades. One study showed that approximately 40% of men with breast cancer die from causes unrelated to their breast cancer.[1]

### 7.1. Survival

Various studies put the overall 5 and 10 year survival rates in MBC at 63% and 41%, respectively, ranging from a 78% 5-year survival for stage I disease to a 19% rate for

stage IV disease. The overall 5-year survival rates were found to be lower stage-by-stage for men than women with breast carcinoma. Comparing men with women the relative 5-year survival is nearly the same, at 96% versus 99% for stage I disease, 84% in both for stage II disease, 52% versus 55% for stage III and 24% versus 18% for stage IV disease.[1]

### 7.2. Factors affecting prognosis

Patients' age greater than 65 years, larger tumor size, lymph node involvement and a high tumor grade have all been found independently associated with a higher risk of death.[1] Conversely ER and PR positivity is associated with a significantly reduced risk of death.

*7.2.1. Ethnicity*. Although Afro-Caribbean men have a higher incidence of breast cancer than Caucasian men, their survival is similar. Compared to men of other ethnic groups, however (Asian, Pacific, Hispanic), both had substantially decreased survival rates: The overall 5-year survival rate is 66% for Caucasian men, 57% for Afro-Caribbean men and 75% for men of other ethnic groups. Although these data suggest ethnic differences in survival rates these differences may be due to other factors reflected in the race or ethnicity, rather than to genetics *per se*. They may reflect a "healthy immigrant" effect; for example, men who immigrate to the United States may be in better overall health and better able to survive breast carcinoma.[57]

## 8. SUMMARY

Overall, much of the rationale behind the management of MBC has been derived from extrapolation from studies involving FBC, with reasonable success. Further male specific studies would be welcome, but may be difficult to organize given the relative rarity of this disease.


## ΠΕΡΙΛΗΨΗ

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Ο καρκίνος του μαστού στους άνδρες αποτελεί μια σπάνια πάθηση, καθ' ότι αποτελεί μόνο το 0,6–1% του συνολικού αριθμού των περιπτώσεων καρκίνου του μαστού και <1% των καρκίνων στους άνδρες. Παρ' ότι έχει πολλά κοινά σημεία με τον αντίστοιχο καρκίνο στις γυναίκες, υπάρχουν σημαντικές διαφορές τόσο στην εμφάνιση και στη διάγνωση όσο και στη βιολογία και στην αντιμετώπιση της νόσου. Οι διαφορές αυτές σχετίζονται με τους ορμονικούς υποδοχείς, το στάδιο στο οποίο γίνεται συνήθως η διάγνωση, τον ιστολογικό τύπο του καρκίνου, την ηλικία εμφάνισής του κ.λπ. Σε γενικές γραμμές, η αντιμετώπιση και η θεραπεία του ανδρικού καρκίνου του μαστού, κυρίως λόγω της σπανιότητάς του, που έχει ως αποτέλεσμα την έλλειψη μελετών μεγάλων σειρών ασθενών, ακολουθεί τη λογική αυτής του γυναικείου καρκίνου του μαστού. Προκειμένου να καθιερωθούν συγκεκριμένα πρωτόκολλα για τον ανδρικό καρκίνο του μαστού, θα πρέπει να διεξαχθούν νέες μελέτες οι οποίες θα περιλαμβάνουν μεγαλύτερο αριθμό ασθενών.


**Λέξεις ευρετηρίου:** Ανδρικός, Καρκίνος, Μαστός

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