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Review

Male Breast Cancer: a Review of the Literature

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Although breast cancer is uncommon in men, it can cause significant morbidity and mortality. The current review was undertaken to determine whether strategies applied for the evaluation and treatment of breast cancer in females are appropriate in male breast cancer. Male breast cancer has biological differences compared with female breast cancer, including a high prevalence in certain parts of Africa, a higher incidence of oestrogen receptor positivity and more aggressive clinical behaviour. It responds to hormonal manipulation and chemotherapy, but optimal treatment regimens in males are unknown. Male breast cancer remains an uncommon disease. Most of our current knowledge regarding its biology, natural history and treatment strategies has been extrapolated from its female counterpart. Much research is needed to further characterise the molecular biological properties of male breast tumours and their prognostic significance, and to devise treatment strategies, including optimal chemotherapy regimens. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

BREAST CANCER is seen infrequently in men. Although breast cancer is the second most commonly diagnosed malignancy in the U.S.A. (excluding non-melanoma skin cancer), fewer than 1% of all cases of breast cancer occur in males. In the U.S.A., male breast cancer constitutes under 1% of all malignancies in men and is responsible for only 0.1% of male cancer deaths [1, 2]. In 1998, an estimated 1600 new cases of male breast cancer occurred among a total breast cancer incidence of 180 300, with 400 deaths [1].

The earliest reference to breast cancer is in the Edwin Smith Surgical Papyrus from Egypt, which dates from 3000–2500 BC and appears to have referred to a man [3]. The first clinical description of a case is attributed to John of Arderne in the 14th century. After that, breast cancer in males received no further mention until its reappearance in the literature in the late 19th and early 20th century.

Unlike female breast cancer, in which incidence rates are rising throughout the world [4–6], the comparative incidence of male breast cancer has remained relatively stable in most countries [7–9]. The prevalence of male breast cancer increases with age [7]. It is rare before the age of 30 years, and the average age at diagnosis is approximately 60 years, which is approximately 10 years older than in females with the disease [5, 9–14].

The incidence of male breast cancer varies by geographical location. It is higher in the U.S.A. and the U.K. than in Finland and Japan [13]. In many countries it parallels the much higher incidence in women, suggesting a similar aetiology, but with clinical progression that is enhanced by the sexual and reproductive function of women. In parts of Africa, the incidence of male breast cancer is relatively high. Egypt, for example, has an incidence rate 12 times that of the U.S.A. [15]. Some sub-Saharan countries have a high male breast cancer incidence that parallels their high female cervical cancer rate, suggesting the hypothesis of a relationship to a sexually transmitted disease in these countries [16]. In a report from Zambia, 15% of breast cancer cases were male [17]. Another plausible consideration for such elevated rates is the increased incidence of liver disease in these countries, with its associated high oestrogen levels.

Knowledge relevant to many aspects of the disease in men is still limited. Treatment strategies in men have been largely guided by the experience in women. We review the available literature.

AETIOLOGY

The aetiology of male breast cancer remains as poorly understood as that of female breast cancer [18], but an

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imbalance by various mechanisms in the oestrogen–testosterone ratio is probably implicated [19, 20]. Hormonal alterations due to testicular disease may be an important factor. There is an association with Klinefelter's syndrome, which may account for approximately 3% of male breast cancers. Also, males who have had mumps orchitis, undescended testes or testicular injury are at increased risk of breast cancer, perhaps due to androgen deficiency or excess oestrogens [21]. Cirrhosis of the liver, by virtue of increased oestrogen levels, may predispose to male breast cancer [22]. Exogenous oestrogens have occasionally been associated with causing male breast cancer. Cases of transsexuals developing breast cancer on exogenous oestrogens have been reported [23, 24], and some reports exist of breast cancer in men receiving oestrogens for prostate cancer [25, 26]. One study found that serum levels of oestradiol and oestrone were higher in male breast cancer patients, but did not relate the results to body weight [27]. Another study, however, did not find any differences between hormone levels of male breast cancer patients and matched controls [28]. Another risk factor, obesity, may act by affecting oestrogen levels by peripheral aromatisation of androgens. Thus, feminisation genetically or by environmental exposure appears to increase risk.

Environmental factors include increased risk for certain occupations, such as men employed in steel mills, blast furnaces and rolling mills, possibly due to chronic heat exposure, which can suppress testicular function [29]. Evidence also exists linking male breast cancer to radiation exposure [10]. It has been reported following repeated fluoroscopy [30], and in men who work in electromagnetic fields [31, 32].

Other elements that have been considered as aetiological factors include drugs, head trauma (by increasing prolactin production) [33], local chest trauma [34], smoking, history of rapid weight gain or amphetamine use. A family history of breast cancer, in man or woman, is certainly a risk factor [35]. The *BRCA2* gene shows evidence of linkage to breast cancer prone families in whom male breast cancer cases have occurred [36, 37], and *BRCA2* may prove a useful marker for identifying males who are at increased risk. *BRCA1*, unlike *BRCA2*, has shown no linkage to male breast cancer [38]. Sisters and daughters of male breast cancer patients have a 2- to 3-fold increased risk of developing breast cancer [39].

A meta-analysis of seven case-controlled studies revealed that the risk was significantly increased in males with the following characteristics: never married, benign breast disease, gynaecomastia, Jewish ancestry or history of breast cancer in first-degree relatives [20]. However, most individuals of either gender who develop breast cancer have no apparent risk factor for the disease, and the majority of male patients have no detectable hormonal imbalances [40, 41].

CLINICAL FEATURES

Because of the rarity of breast cancer in males, most reported series involve small numbers of patients. The statistical accuracy of clinical characteristics of male breast cancer is, therefore, not fully established. However, the mean age of presentation in most reported series spans 60–65 years, with a range from mid-20s to early 90s. This is approximately 10 years older than the corresponding mean age for breast cancer in women [9, 42, 43]. The presenting clinical finding in 75–90% of patients is a painless mass [10, 11, 44, 45], which is centrally located 70–90% of the time. The mean diameter of the mass is 3.0–3.5 cm, but can range from 0.5 to 12.5 cm. In collective reviews, the disease has a slight predilection for the left breast. Up to 20% of patients notice changes in the areola [45]. Serous discharge occurs in approximately 15% of patients [44], but bloody discharge is associated in 75% of cases with malignancies [46]. Nipple fixation or retraction, inversion, oedema or eczema can occur in 17–30% of patients [10, 44, 45]. Ulceration of the skin occurs in a significant proportion [10, 44]. Male breast cancer can present as Paget's disease in 5% of cases, with skin erythema, inflammatory changes, skin nodules or satellite lesions. Less commonly, patients have symptoms of breast tenderness, swelling, nipple itching, or symptoms of distant metastasis [45]. Axillary adenopathy suspicious for metastasis is clinically detected in 40–55% of patients at the time of presentation [47–49]. Bilateral male breast cancer ranges from 0 to 1.9% [12, 44].

The duration of symptoms before diagnosis is declining. Earlier series reported a mean of 14–21 months [50–52]; more recent series report a mean of 1–8 months [14, 44, 53]. This may be due to increased public awareness of breast cancer in men.

The effectiveness of tumour markers, such as CEA and CA15-3, has yet to be determined in the evaluation of male breast cancer. Mammography has been advocated for use in pre-operative evaluation of the opposite breast, although its use may be limited because of technical difficulties in obtaining an adequate study in men. Primary mammographic characteristics in males include a well-defined mass with spiculated margins, and less frequently, microcalcifications. Mammography is more useful in obese men with large breasts. In one group, mammography had a false negative rate of 8% [44]. In two recent series, mammography provided positive or suspicious findings in 80–90% of men with breast cancer [44, 54]. Also, galactograms can aid in the localisation of abnormal ductal tissue in patients with nipple discharge and no mass [55], but ultrasound has not been useful in diagnosing male breast cancer [56].

The use of fine needle aspiration has increased in recent series [57]. The cytological features of male breast cancer are similar to those described for female breast cancer [58]. In one series, fine needle aspiration was positive in 27 of 49 patients with operable breast cancer [54]. Generally, conventional cytological examination of the aspirate is adequate, but in some cases, monoclonal antibody analysis may be a useful adjunct [59]. In unconfirmed cases, surgical biopsy is carried out in order to arrive at a diagnosis [44].

PATHOLOGY

Virtually all known histological types of breast cancer have been identified in men. Infiltrating ductal carcinoma is the predominant subtype [60], comprising approximately 70% of cases [11, 44]. Approximately 15% of patients with localised disease have only ductal carcinoma *in situ* [44, 61]. Medullary, tubular, papillary, small cell and mucinous carcinoma constitute less than 15% of cases [11, 44]. Lobular carcinoma was long thought not to occur in men because of the absence of lobules in the rudimentary male breast, but at least 2 cases have been reported, including 1 in a patient with Klinefelter's syndrome [62, 63]. Inflammatory carcinoma has also been described [64]. The majority of male breast carcinomas in one series were of high histological grade [65], although in another series low and intermediate grade tumours predominated [66].

Various sarcomas have also been described, including cystosarcoma phylloides, haemangiopericytomas, liposarcomas and leiomyosarcomas [67]. Also, tumours metastatic to the breast have been noted. Prostate cancer is the most common solid tumour to metastasise to the breast [68–70]. Unlike in the female breast, cysts in the male breast are likely to be malignant [71].

Oestrogen receptors are positive in 65–85% [72–77]. The high oestrogen receptor positivity in male breast cancer may be due to low oestrogen levels leaving receptors available for binding, and is probably responsible for good hormonal response. Other receptors have also been identified. Fifty per cent of tumours are androgen receptor positive, and 50% are glucocorticoid receptor positive, although the clinical relevance of these findings remains to be determined [78]. Epidermal growth factor receptor was rare in one study [76], but was found in 76% of tumours analysed in another study [74]. Its prognostic significance in men is not known, unlike in women where it is an indicator of poor prognosis. The histopathological features including flow cytometry, DNA ploidy, S-phase fraction, thymidine labelling index, *HER-2* oncogene expression, nuclear grade and degree of nuclear differentiation have been studied, without clear evidence of their utility in predicting clinical behaviour [76, 79–81]. Chromosomal analysis has been useful to identify patients with Klinefelter's syndrome, and several cytogenetic abnormalities, including nullisomy of chromosomes 1, 8, and 12, monosomy of chromosome 7, and trisomy of chromosome 6, have been described [82–84].

PROGNOSTIC FACTORS

Stage and axillary node status are the most important prognostic indicators in male breast cancer. The TNM system is used for men, as well as women [85]. In non-disseminated cases, the size of the tumour (T status) and the axillary nodal status (N status) are the most important prognostic indicators. Prognosis declines as the tumour size increases, mainly because of the increased risk of axillary or distant metastasis. Five-year survival in one series was 77% for axillary node negative patients and 37.5% for node positive patients [86]. DNA ploidy, epidermal growth factor expression, *HER-2* oncogene expression and oestrogen receptor status have not been shown to be predictive of disease-free survival, although the S-phase fraction may have some significance, according to one study [87]. The c-erbB-2 oncoprotein is a potentially useful prognostic marker in female breast cancer [88]. Its overexpression has been demonstrated in 15–30% of patients with female breast cancer and is associated with shortened survival, particularly in node positive patients. Few data are available on c-erbB-2 expression in men. In a recent study the expression of the oncoprotein was lower (17%) in male patients than in female patients (33%) [89], and in another study, none of the male breast tumours studied expressed c-erbB-2 [90]. In another study, 7 of 16 male breast cancer patients were positive for c-erbB-2 expression with associated significantly shortened survival [66].

Mutations of the tumour suppressor gene *p53* have been found in 13–49% of women with breast cancer [91–93], and have been shown to have prognostic significance in patients with node negative disease [94, 95]. Little is known regarding *p53* gene alterations in male breast carcinomas, and so far no correlation between survival and p53 expression has been observed.

TREATMENT OF LOCAL DISEASE

Although radical mastectomy was the treatment of choice in earlier years, less invasive procedures, such as modified radical or simple mastectomy, are now more common. A number of series have not shown improvement in survival for men who underwent more radical procedures [96–98]. Axillary nodal dissection is indicated, as clinical assessment of the axilla is unreliable. Postoperative radiation therapy in some series has shown benefit in reducing locoregional recurrence, but no survival benefit is achieved [10, 11, 99]. In general, the guidelines used for adjuvant radiation in female breast cancer may be used, in particular for patients with large tumours or multiple positive nodes. It has also been suggested that since male breast cancers are predominantly central in location, adjuvant radiation if used should include the internal mammary nodes in addition to the routine fields used in women [99–101].

Based on the beneficial results of systemic adjuvant chemotherapy in women, it has also been advocated in men, although no controlled trials to confirm its value are available. The modality most commonly used for postoperative hormonal therapy has been tamoxifen, although orchidectomy has been reported in a few patients. In a recent series of 39 patients, adjuvant tamoxifen alone was administered to patients with stage II or operable stage III disease. The actuarial 5-year survival was 61% (range 42–80%) in the treated group as compared with 44% (range 35–57%) in historical controls ($P = 0.006$) [102]. Five-year disease-free survival rates were statistically significant at 55% (range 37–75%) for the treated patients versus 28% (range 17–33%) for the controls ($P = 0.005$). These results remain to be confirmed in a larger prospectively randomised trial. Tamoxifen's effectiveness for oestrogen receptor negative patients has not yet been evaluated. Reported side-effects include hair loss, rash, decreased libido, impotence, weight gain, hot flushes, mood alterations, insomnia and deep vein thrombosis.

Adjuvant combination chemotherapy has been administered to male patients with positive axillary nodes or stage II or greater disease in a number of series. In a series from the National Cancer Institute, 24 patients with stage II disease were treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF). The projected 5-year actuarial survival rate was greater than 80% (95% confidence interval 74–100%) [103], a substantial improvement over survival rates in other series. Another study of 11 patients with stage II or III disease, most of whom were treated with 5-Fluorouracil, Adriamycin, and Cyclophosphamide (FAC) reported a 63% disease-free survival rate and a 91% survival rate at 52 months [104]. However, because of the small sample size and the non-randomised nature of these series, no firm conclusions can yet be drawn regarding adjuvant therapy in male breast cancer.

TREATMENT OF METASTATIC DISEASE

Between 4 and 7% of men with breast cancer present with metastatic disease, and 18–54% of patients treated for localised disease will develop distant metastases. Sites of metastases in men are similar to those in women and include bone, lung, liver, brain and others. Also, up to 39% of treated patients will develop local recurrences. Median survival from the time of presentation with metastatic disease is approximately 26.5 months [14].

For patients with oestrogen receptor positive tumours, hormonal therapy is generally the initial treatment for

metastatic disease. Orchidectomy was the traditional hormonal therapy, with a response rate of 75–80% [105], and a reported response duration of 4–46 months. Other forms of ablative hormonal therapy include adrenalectomy with a response rate of 80% and a median duration of 15 months [106], and hypophysectomy with a response rate of 56% and a duration of 6–20 months [107]. Responses to hormonal therapy are more common and last longer in men than in women [108]. Because of poor patient acceptance of orchidectomy and high operative risk of adrenalectomy and hypophysectomy, additive hormonal therapy is now often used as the first-line therapy. Tamoxifen has a response rate of 80% in oestrogen receptor positive tumours [109]. Other hormonal agents used include ketoconazole, oestrogen, cyproterone acetate, corticosteroids, androgens, progestins, aminoglutethimide and buserelin with or without the anti-androgen flutamide [105, 110–114]. The duration of response to these agents varies from 3 to 12.5 months [111]. Patients who fail to respond initially, or respond to the first agent and relapse, may be effectively treated with a second hormonal agent [115].

Patients with oestrogen receptor negative tumours or disease-free survival of less than 1 year often fail to respond to hormonal therapy and may benefit from combination chemotherapy [115]. Approximately 35% of patients respond to combination chemotherapy, with doxorubicin-based regimens proven more effective, as in female breast cancer [116]. Although men appear to respond faster to chemotherapy, their duration of response may be shorter [105].

SURVIVAL OF MEN VERSUS WOMEN

The overall survival for male breast cancer patients, documented in various series, has ranged between 36 and 75% at 5 years [12, 117, 118]. In general, it has a less favourable outcome than breast cancer in women [54, 119]. A preponderance of stage III disease (22% in men versus 6% in women) and a higher incidence of lymph node positivity (60% in men versus 38% in women) have been linked to the poorer prognosis [44, 119, 120]. When age- and stage-matched breast cancer in men and women were compared, there was no difference in survival between the two groups [97, 121]. However, in men, the disease is usually more advanced, and skin infiltration and ulceration, with involvement of axillary nodes, is more common [121]. In addition, stage II male breast cancer tends to be T1N1 rather than T2N0, also contributing to a poorer prognosis [119].

The reasons for the worse prognosis of breast cancer in men are unclear. It has been attributed to the more advanced stage at presentation [44, 122] and a higher incidence of lymph node metastases [119, 120, 123]. These features would suggest a biologically aggressive tumour with a high grade, poor histological differentiation and negative hormone receptors. However, this is not the case. The histological grade tends to be lower in men than women. This is also accompanied by frequent oestrogen receptor and progesterone receptor positivity [124–126].

Another plausible explanation for the higher stage in men with breast carcinoma could be delayed presentation and larger tumour size. Again, these do not appear to be contributing factors [120]. Although routine mammography is not used as a screening procedure in men, the superficial and rudimentary male breast makes the diagnosis of palpable breast disease easier. Tumour size in men is smaller than palpable tumour masses detected in women in the pre-mammographic era. Men seek treatment earlier in the disease than women, with the average duration of symptoms being 5 months for men and 5.5 months for women [127]. However, even the smaller tumours in men show a higher propensity to metastasise [119, 120]. Men have a higher nodal positivity despite smaller primary tumour size [119, 120, 122, 127].

The aggressive behaviour of male breast cancer, despite a smaller tumour size, lower histological grade, and higher oestrogen receptor/ progesterone receptor content, may be the result of the anatomical differences between male and female breasts. The sparseness of breast tissue in men places even a small tumour close to the overlying skin and underlying pectoral fascia without the great bulk of intervening breast tissue in women. It has been shown that in men, the breast tissue close to the skin is drained by lymphatics into the subareolar lymphatic plexus and axilla [128, 129]. In contrast, in adult female breasts, the subareolar plexus plays a less prominent role in lymphatic drainage [130], and the main lymphatics run within the substance of the breast rather than on the superficial or deep surface. Several studies have shown that dermal lymphatic involvement is more common in male patients than in female patients [131, 132]. In women, dermal lymphatic invasion is associated with a higher incidence of metastases at diagnosis [133], relatively rapid disease progression [134], and a poorer prognosis. Direct nipple involvement by the tumour is uncommon in women and even the incidence of Paget's disease is low (1.0–4.3%). It is seen frequently in male breast cancer and is associated with an ominous prognosis because the rich dermal and subareolar lymphatic network in the nipple facilitates invasion and spread to axillary nodes. Also, in women, the incidence of lymphovascular invasion is lower than in men; and this also correlates with lymph node metastases [135] and with recurrence and death [136].

Oestrogen receptor positivity can be seen in as many as 85% of male breast cancer patients, compared with approximately 60% in female breast cancer. In women, it can be used to predict a better survival. This has not been shown for male breast cancer, and in some studies oestrogen receptor positivity in male breast cancer is associated with a decreased survival [74]. This may be due to a paradoxical effect on tumour growth by hormonal manipulation.

CONCLUSION

Male breast cancer remains an uncommon disease. Most of our current knowledge regarding its biology, natural history and treatment strategies has been extrapolated from its female counterpart. Much research is needed to characterise further the molecular biological properties of male breast tumours and their prognostic significance, and to devise treatment strategies, including optimal chemotherapy regimens.

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