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Male breast cancer: a review

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Introduction

Breast cancer in males is an uncommon disease. In most countries it accounts for approximately 1 % of all breast cancers and in the United States about 600 cases per year (84, 86). It is frequently sensitive to steroid hormone manipulations with high response rates to endocrine ablation (42, 46, 63). Hormonal dependency, hormonal receptor status and clinical responses in female breast cancer have been correlated, but the mechanisms involved are poorly understood (52, 103). Male breast cancer potentially offers a unique opportunity to delineate hormonal interrelationships of importance in understanding and predicting responses to hormonal manipulations in breast cancer. For this reason a review of breast cancer in males with special attention to hormonal parameters has been undertaken.

Historical

The earliest allusions to male breast cancer occur in the writings of Francisus Arcaneus (1493-1573) (25) and Ambroise Paré (1510-1590) (68). The first documented case is credited to Fabricus Hildanus (1537-1619) (69). Porier (71) and Williams (102) first described the basic clinical features of this disease. The first systematic study of male breast cancer was reported in 1927 by Wainright who presented both the clinical features and the results of primary surgical treatment (98). Further reports confirming these clinical observations and the efficacy of surgical treatment of male breast cancer occurred during the 1930s and 1940s (58, 62, 76). The value of ablative endocrine therapy for advanced disease was documented over the next quarter century when orchiectomy (22),

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adrenalectomy (35), and hypophysectomy (49) were all shown to be effective modes of therapy. Several large series offer insight into the clinical features (47), epidemiology (84, 97), pathology (32, 33), surgical (13, 37, 95, 96) and hormonal (42, 46, 63) treatment, and prognostic factors influencing survival (60, 78). Reports from many countries attest to the universal presence and similarity of the disease (1, 41, 57, 66, 70, 82).

Etiology

Altered estrogen metabolism, gynecomastia and Klinefelter's syndrome appear to play a role in the development of breast cancer in males (Table 1). The role of exogenous estrogens, infectious orchitis, heredity and radiation is less clear.

**Table 1. Risk factors
(proposed) for
male breast
cancer**

Altered estrogen metabolism
Gynecomastia
Klinefelter's syndrome
Exogenous estrogens
Infectious orchitis
Heredity
Radiation

Altered hormonal metabolism

Disturbance of hormone metabolism has long been implicated in the development of breast carcinoma in males (45). The first suggestion of such a relationship was made by Stern in 1842 who found all four male deaths from breast cancer reported in Verona from 1760 to 1839 to have occurred in priests (90), and he suggested that frequent fasting might have contributed to the occurrence of breast cancer in monasteries. Clemmesen, reviewing Stern's paper, related this observation to the relationship between the suppression of "androgen substance" caused by deficient diet and gynecomastia seen among starving prisoners during World War II (6). Increased incidences of male breast cancer of 6.4% in Egypt (21, 61) and 15% in Zambia (3) have been reported although in two South African series there were no cases of male breast cancer (83, 99). Hyperestrogenism secondary to bilharziasis/liver fibrosis and malnutrition, respectively, has been suggested as a possible cause of the high incidences in Egypt and Zambia. Unfortunately, no hormone measurements are available in the patients in these studies.

Several studies in patients with male breast cancer have suggested altered hormone metabolism (18, 79, 104). In 1942 Farrow and Adair performed a bilateral orchiectomy on a patient with osseous metastases from an inoperable breast cancer and obtained definite regression of the tumor. The authors measured the urinary excretion of "estrogenic substance" before and after treatment and found a marked decrease in estrogen excretion (22). Dao *et al.* later demonstrated increased endogenous estrone (twice control), estradiol (1.5 times control), and estriol (2.5 times control) in males with breast cancer (18). The response of two of their patients to orchiectomy is of interest. One patient, whose disease regressed after orchiectomy, had a concomitant marked decrease in his estrone

levels while the second patient, whose disease failed to regress, had a rise in estrone levels. Zumoff *et al.* studied estradiol transformation in six patients with breast cancer and found that men with breast cancer exhibited a marked decrease in the formation of estrone (E_1) and 2-hydroxyestrone (2-OH E_1), accompanied by a pronounced increase in the production of estriol (E_3) (104). In two patients studied postorchietomy, no alteration of this abnormality was found; however, the clinical response of these two patients was not reported. In contradistinction to the above data, Scheike has noted no abnormalities in either estradiol transformation or urinary estrogen levels in 19 patients with male breast cancer (79). These conflicting results remain to be explained.

Gynecomastia

Antecedent or concurrent gynecomastia in males with breast cancer has been reported in from 0 to 20% of cases (33, 37, 47, 65, 80). The evidence suggesting that gynecomastia may be premalignant for male breast cancer is: (1) the finding of severe atypia of the epithelium in the ducts in concurrent gynecomastia and breast cancer; (2) the lower mean age of cases of breast cancer with concurrent gynecomastia; and (3) the higher ratio of male to female breast cancer and the low mean age of the male patients in an area with a high frequency of gynecomastia (65).

Klinefelter's syndrome

Patients with Klinefelter's syndrome have a 20 to 67-fold increased incidence of breast cancer (30, 39, 81). Patients with this syndrome are known to have altered hormonal metabolism with decreased testosterone levels and an increased incidence of gynecomastia. Hormonal studies have not been reported in patients with both Klinefelter's syndrome and breast cancer.

Exogenous estrogens

Exogenous estrogens may increase the risk of developing breast cancer in males. Animal experiments suggest that altered hormone metabolism plays an important role in the development of breast cancer in male rats (17). Inbred male rats treated with methylcholanthrene (MCA) do not usually develop mammary cancer. An occasional mammary tumor develops when ovaries are grafted into male rats prior to MCA exposure, but the tumor incidence rises markedly if ovaries are grafted into castrated male rats. The development of breast carcinoma in two orchietomized trans-sexuals treated with estrogens may represent the human correlate (92). Nevertheless, the failure to demonstrate the development of breast cancer in 3000 men treated with estrogen for prostatic cancer is an argument against either gynecomastia or exogenous estrogens being premalignant in males (47). However, the development of breast carcinoma might be missed in these patients due to their relatively shortened life expectancy.

Infectious orchitis

A history of histological testicular abnormalities in many cases of male breast cancer has been noted (64, 95). A case control study showing infectious orchitis in 4 of 53 patients with breast cancer but 0 of 53 controls has been reported (84). However, these results

were not statistically different. No studies of testosterone metabolism in patients with orchitis have been reported.

Radiation

Several cases of male breast cancer developing in previously irradiated breasts have been recorded (11, 84). In the female two reports implicate radiation as a cause of carcinoma of the breast (100, 103). Women treated for tuberculosis with multiple artificial pneumothoraces under fluoroscopic control experienced a 26-fold increase of breast carcinoma over a 10-year period compared to women who did not undergo pneumothoraces or fluoroscopies (50). A threefold increase in incidence of carcinoma of the breast in female survivors of Hiroshima and Nagasaki has been reported (100). An increased incidence of breast carcinoma in males who have undergone radiation therapy for benign gynecomastia has not yet been reported, but one case has been observed (48).

Heredity

The role of heredity in human male breast cancer remains to be defined. Although a family history of breast cancer in males has frequently been elicited (84), a recent series reports no difference in the transmission of human breast cancer through paternal and maternal lines of descent (2). However, a high incidence of breast cancer in mice has been demonstrated in the female offspring of female mice with a low mammary cancer incidence mated to males with a high incidence of mammary cancer (87). The contribution of heredity to the increased incidence of breast cancer in Klinefelter's syndrome remains undefined.

Clinical findings

The clinical findings in male breast cancer are well established (Table 2). The disease increases in incidence exponentially throughout life (60, 87), being described in males as young as 5 years of age (88) and as old as 93 (10). The median age at diagnosis in most series ranges from 58 to 64 years (60, 84) although a considerably younger median age of 48 years (at death) has been noted recently (67). The younger median age in this later study may reflect the younger population seen in Air Force hospitals. No mention of previous chest radiation or other possible etiologic associations was made.

The delay from onset of symptoms to diagnosis has decreased from 18 months in 1927 to 9 months in 1974 (67, 98). The pattern of disseminated disease in males does not ap-

Table 2. Clinical manifestations (references 11, 32, 33, 77, 98)

Sign	Per cent of cases
Central breast lump	80-85
Fixation or nipple abnormalities	60-80
Nipple discharge	15-25
Ulceration	15-25
Gynecomastia	0-20
Ipsilateral axillary node	50-60

pear to be different than in females and involvement of all major organ systems has been described (58, 62, 76, 77, 98).

Pathology and prognosis

Earlier reports of male breast cancer have suggested a very poor prognosis with a 5-year survival between 20 and 35% (58, 62, 76, 98, 102). Whether or not the survival rate has changed is not known. Overall 5-year survivals of 50 to 62% in localized disease compare favorably with the prognosis of female breast cancer (60, 78) although for all stages survival has been reported as 9% less for males (60).

All histologic types of breast cancer seen in women except lobular carcinoma have been described in men (13, 33, 37, 96, 97). Infiltrating ductal carcinoma comprises the predominant histologic type in all series, representing greater than 80% of all tumors. Medullary or papillary carcinomas are each seen in 2 to 7% of all cases (13, 33, 37, 96, 97). Males with papillary carcinoma have an excellent prognosis as compared to other histologic types; almost all patients with this cell type have survived 5 years (13, 33, 37, 96). Whether this is a function of the stage at the time of diagnosis or actually a difference in the natural history of the papillary variant is unknown. Paget's disease, which has a relatively good prognosis in females, has a poor prognosis in males; most patients with this variant die of metastases within 5 years and cures are extremely rare. Inflammatory carcinoma (94), cystosarcoma phylloides (73) and other rare histologic types seem to have no special features in males.

Several small series report on the relationship of histologic grading to prognosis (26, 47, 101). No series have correlated histologic grade, stage and prognosis; however, Visfeldt described a clear relationship between the World Health Organization's classification of histologic grade and survival in his series (97). Male patients with grade I histology had a 5- and 10-year survival of 55% and 39%, respectively. Patients with a grade II histology had a 5- and 10-year survival of 54% and 9%, and patients with a grade III histology had a 5-year survival of 5% and no survivors at 10 years. The comparable 5-year survival figures for females were generally better. Females had a 5-year survival of 75% with grade I histology, 47% with grade II histology and 31% with grade III histology.

Five- and 10-year survival of 80% and 62% in patients with histologically negative ipsilateral axillary nodes (N-) (12) is comparable to that reported in females (15, 23). The survival of patients with histologically involved ipsilateral axillary nodes (N+) is only 28% at 5 years and 4% at 10 years (12). These results are less favorable than in females with N+ nodes but are comparable with those females who have involvement of more than three axillary nodes (15, 23). The central location of 80% of breast cancer in males has also been noted to be an unfavourable prognostic feature in females. Central lesions in females have shown a 10-year survival of only 38% compared to a 52% survival of females with lateral lesions (23). Ulceration is recorded in up to 20% of males with breast cancer. The effect of ulceration in men with breast carcinoma upon survival is unknown, but the presence of ulceration in females has also been shown to be a bad prognostic feature decreasing survival from 45 to 36% at 5 years in one large series (27). The central location of most male breast cancers, the high incidence of ulceration and the apparent more malignant histology of this entity may help to explain the poor survival in patients with involvement of the axillary nodes. The comparable survival of males and females with uninvolved axillary nodes suggests that surgical extirpation of lesions confined to the breast may be curative in a large percentage of cases.

Treatment

Surgical

Radical mastectomy has long been advocated as the initial treatment of breast cancer in males (98). More recently comparable results have been obtained with simple mastectomy; however, the reported series are small and no controlled trial has been undertaken (33, 47). Careful correlation of clinical stage, histology, internal mammary node status, primary treatment and prognosis has not yet been reported.

Hormonal

The response data in the available reported cases receiving hormone therapy for advanced disease were evaluated. Those patients considered unevaluable were a result of insufficient clinical information and/or poorly defined response criteria. A response is defined as disappearance of all lesions recorded by the author lasting 3 months or longer.

Using these criteria we were able to identify 70 evaluable patients undergoing orchiectomy for advanced breast carcinoma (Table 3). These patients showed a 67% response rate with a median response duration of 22 months. Responders had a median survival of 56 months from primary diagnosis while non-responders survived only 38 months.

Table 3. Response to orchiectomy (references 8, 9, 16, 31, 34, 42, 46, 53, 63, 73, 89)

	Median response duration (months)	Median total survival (months)
Responders 47 (67%)	22	56
Non-responders 23 (33%)	—	38

Twenty-five patients undergoing adrenalectomy were considered evaluable. There were 19 responders. Of these 19 responders, 11 patients had had a prior orchiectomy with a median response duration of 32 months. Their subsequent median response duration to adrenalectomy was also 32 months and the survival was 42 months from adrenalectomy, giving a total median survival of 74 months from the time of their first treatment for metastatic tumor (Table 4). Eight of the patients undergoing adrenalectomy had not responded to previous orchiectomy. Four responded with an average response duration greater than or equal to 16 months (Table 4). Three patients underwent simultaneous bilateral orchiectomy and adrenalectomy; all responded with response durations of 15, 20 and 60 months. Three patients underwent primary adrenalectomy. There was one response of 11 months, a partial response of 4 months and one non-responder. Judging from these data orchiectomy followed by adrenalectomy appears to be a worthwhile intervention in advanced male breast cancer. Whether combined or sequential orchiectomy/adrenalectomy is warranted as the initial treatment of advanced disease has not yet been clarified.

Hypophysectomy also appears to be an effective palliative form of therapy for male breast cancer (Table 5). Of 17 evaluable cases, there were 10 responders with a median

Table 4. Responses to adrenalectomy (References 16, 20, 29, 34, 36, 38, 44, 46, 53, 72, 89, 93, 95)

	Adrenalectomy responders	Median response duration (months)	Median total survival (months)
Orchiectomy response (11 patients)	10	32	74
Orchiectomy non-response (8 patients)	4	16	N/E†

† N/E = not evaluable.

response duration of 20 months and a median survival from primary diagnosis of 90 months. Of these 10 responders, seven patients had undergone prior orchiectomy. Three of four patients who responded to orchiectomy responded to subsequent hypophysectomy, whereas the three orchiectomy non-responders did not respond to subsequent hypophysectomy. Three patients underwent primary hypophysectomy with two responding, both with response durations of 18 months. More complete survival data on these subcategories of patients and on the non-responders is not available. Insufficient data was available to assess whether or not endocrine ablative therapy has a differential effect on soft tissue, bone or visceral disease but there are several reports of long-term responses of pulmonary/pleural disease (32, 63, 95). The efficacy of endocrine ablative procedures for male breast cancer compares favorably with the results of comparable endocrine ablations for breast cancer in females. The response rate and duration of orchiectomy and adrenalectomy for breast cancer in males is twice that seen for oophorectomy and adrenalectomy in females with breast cancer (91). Hypophysectomy appears to be equally effective for both females and males with breast cancer (91). The reasons for these differences remain to be defined.

Table 5. Response to hypophysectomy (references 8, 33, 34, 40, 42, 49, 51, 85)

Patients	Responses	Median response duration (months)	Median total survival (months)
17	10	20	90

Estrogens and androgens clearly have a role in the treatment of female breast carcinoma (91); however, the role of additive hormones in male breast cancer is poorly defined (75). Several cases of tumor regressions lasting from 3 to 16 months (32, 37, 95) as well as exacerbations (32, 37, 46) have been reported with the use of estrogens in male breast carcinoma but no well-defined series has been reported. Except for a single case (19) androgens have been uniformly said to exacerbate the disease process; however, firm documentation is lacking (33, 75). Corticosteroids have been used with an occasionally reported short term remission, but the response criteria in these cases were not well defined (43, 95). One well documented objective remission of male breast carcinoma to

large doses of a progesterone derivative is reported (24). The availability of hormonal receptor analyses may more clearly define the role of hormone therapy in males as it has begun to do in females with breast carcinoma (52). In three of four patients with male breast cancer who have had the presence of an estrogen receptor in their tumor, there has been a favorable response to orchiectomy (4, 59).

Chemotherapy

Single agent and combination chemotherapy has been shown to be an effective form of palliative therapy in female patients with breast carcinoma (5). Only a few reports relate to the treatment of male breast carcinoma with chemotherapy.

An 18-month subjective response of severe osseous disease to 5-fluorouracil (500 mg I.V. qd $\times$ 5d q 1m) after no response to orchiectomy and a partial 6-month response to adrenalectomy was reported in one patient. With recurrence of osseous symptoms this same patient experienced a 5+ month subjective response to methotrexate (15 mg I.V. $\times$ 3d) followed by thiotepa (30 mg I.V. $\times$ 2d) with courses repeated every 6 to 8 weeks (46). Another patient with severe osseous disease failed to respond to the above methotrexate and thiotepa regimen after having failed to respond to previous sequential treatment by orchiectomy and adrenalectomy (46).

A third patient who had previously responded to sequential therapy with orchiectomy and hypophysectomy had a 14+ month response of pulmonary nodules, lymph node and skin disease to oral cyclophosphamide (dose, route and frequency not stated) (42). Finally, we have observed a 12+ month response of skin, node and bone disease to combination chemotherapy (cytoxan 100 mg/m² po qd 1-14, adriamycin 30 mg/m² iv d 1,8 and 5-fluorouracil 500 mg/m² iv d 1,8 repeated q 28d) following a 3-month partial response to orchiectomy (54).

The high response rate of advanced male breast carcinoma to endocrine ablative therapy suggests that at the present time chemotherapy should be reserved for patients who are not orchiectomy or adrenalectomy candidates or for patients with hormonally unresponsive disease.

Future considerations

The important questions regarding the type of surgical intervention for primary breast cancer, the efficacy of post-operative adjuvant therapy, and the type of chemotherapy to be used for advanced disease will be difficult to answer in male breast cancer due to the small number of patients available. The very high response rates and lengthy remission durations of advanced male breast cancer to endocrine ablations may indicate that important hormonal interrelationships exist in this disease which are presently not recognized. Recent biochemical studies of female mammary cancer report the conversion by the tumor of sex hormone precursors to both estrogens and androgens (43, 75). Hormonal dependence of the tumor and the response of the patient to endocrine manipulation appear not to be determined solely by the host hormonal milieu (52, 55, 56). The role of estrogen receptors in female breast cancer is currently being defined (52). The role of androgen, progesterone and corticosteroid receptors and their interrelationships to intratumor hormonal interconversions in predicting responses to hormonal manipulations is unknown. Male breast cancer, which has a higher hormonal responsiveness to endocrine manipulations compared to female breast cancer, would appear to offer a unique opportunity to

investigate the correlations between these various hormone receptors, intratumor hormonal interconversions and the host's hormonal milieu with hormonal responsiveness.

Conclusions

Breast cancer in males is an uncommon disease entity. The clinical features of a central lump frequently associated with fixation or a nipple abnormality in men in the seventh decade is the common presentation. Altered hormonal metabolism, gynecomastia and Klinefelter's syndrome appear to play a role in the development of the disease. The role of exogenous estrogens, infectious orchitis, radiation and heredity is less certain.

Radical mastectomy in early cases appears to offer an excellent chance of long-term survival. Orchiectomy, adrenalectomy and hypophysectomy are associated with high response rates with long remission durations in advanced male breast cancer. The role of additive hormones has not been defined, but favorable responses to estrogens have been noted in some patients. The overall survival of males with breast cancer appears to be slightly less than that of females with comparable stages of disease. Investigation of males with breast cancer may offer significant clues to further refine the hormonal treatment of the female disease.

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