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ORIGINAL ARTICLE

Male breast cancer: A survey at the Helsinki University Central Hospital during 1981–2006

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Abstract

Background. The purpose was to analyze the behavior of male breast cancer. *Methods*. Fifty-eight male breast cancer patients were treated at the HUCH during 1981–2006. Data on risk factors, tumor characteristics, clinical presentation, treatment and survival were obtained by chart review. *Results.* Presentation occurred at a median age of 63 years, most often due to a self-detected lump. The median size of the primary tumor was 1.8 cm and 14% were T4 tumors. Forty-seven percent had lymph node metastases and 4% distant metastases at diagnosis. Ductal carcinoma was the most common tumor type. All tumors with known receptor status were positive for estrogen receptor (ER) and 79% for progesterone receptor (PgR). Her-2 overexpression was found in 2/19 patients (11%). A family history of breast cancer, obesity, high alcohol intake and liver cirrhosis were the most often seen risk factors. Nineteen percent had one or two other malignancies, the most common second malignancy being prostate cancer in 7%. Ninety-seven percent were operated by mastectomy and 90% by axillary evacuation while sentinel node biopsy alone was done only in 7%. Sixty percent of the patients received radiotherapy, 64% adjuvant hormonal treatment, 20% adjuvant chemotherapy, and 2% adjuvant trastuzumab. Fourteen patients (25%) experienced a relapse of which 60% were distant, bone being the most common site. During follow-up 21 patients (37%) died, of whom nine of breast cancer and 12 due to other causes. The 5-year overall survival (OS) was 75%. *Conclusions*. Male breast cancer behaves and is today treated in many respects like postmenopausal breast cancer. However, due to rudimentary breast tissue the symptoms, diagnosis and especially a higher amount of T4 tumors differ from that of females. Also the risk factor profile and histologic subgroups seem different. The 5-year OS of 75% is clearly higher than 44% reported at our institution in 1982.

Male breast carcinoma is rare, accounting for less than 1% of all breast cancers diagnosed worldwide. The incidence of male and female breast cancer in Finland in 2007 was 0.4/100 000 (16 cases diagnosed) and 87.7/100 000 (4 154 cases diagnosed), respectively. As with most other cancers, the incidence of male breast cancer is increasing.

Risk factors for male breast cancer seem to relate to increased estrogen load as obesity (double the risk) [1], estrogen treatment for prostate cancer [2] and a high ratio of estrogen to androgen associated with Klinefelter's syndrome [3]. Alcohol intake [4] and liver cirrhosis [3] have also been suggested. Family history of breast cancer [1] and rare mutations in BRCA1, BRCA2 or CHEK2 may also be risk factors.

Due to the rarity of male breast cancer, there is a lack of prospective clinical trials to define optimum treatment. To our knowledge only one small study has been reported (n=31) [5]. Current data consists mostly of small retrospective studies. Therefore, treatment has generally followed the principles established for the treatment of female breast cancer.

Our aim was to analyze the behavior of male breast carcinoma in patients treated at the Department of Oncology at the Helsinki University Central Hospital (HUCH) during the last 25 years, reporting the risk factors, characteristics, treatment and survival of the male breast cancer patients.

Materials and methods

The study was approved by the local ethical committee. Male patients diagnosed with breast cancer during 1981–2006 at the Department of Oncology

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at HUCH were ascertained from the patient database. All 58 patients were included in the study. Data regarding risk factors, presenting signs and symptoms, patient and primary tumor characteristics, treatment, details of recurrence and survival were obtained by chart review. Obesity was estimated by calculating body mass index (BMI, > 30 obese) from height and weight recorded in patient charts or estimated and recorded by attending physician. As high alcohol intake was regarded the statement of that by physician in the patient record. Her-2 positivity was assessed both with immunohistochemistry and gene amplification tests. All causes of death and death dates were confirmed by the Cause of death registry. Overall survival (OS), disease free interval (DFI) and cause specific survival were estimated by using the Kaplan-Meier method. In the DFI analysis only the patients (n=56) without distant metastases at diagnosis were included. The 5-year OS was calculated by using life-tables.

Results

The median age (range) at diagnosis was 63 (35–91) years. Most reported risk factors as alcohol use, smoking status and obesity were underreported, remaining unknown in over half of the cases (Table I). Among the patients with reported risk factors 9/22 (41%) were obese, 8/30 (27%) smokers and 8/19 (43%) had high alcohol intake. Seven percent of the patients had liver cirrhosis. Family history of cancer was also underreported and known in only half of the cases, where 11/35 (32%) had breast and 3/31 (10%) had prostate cancer in their families, but none ovarian cancer. One patient of the four tested for a BRCA 1/2 mutation had a BRCA2 mutation, with a family history of breast, renal and stomach cancer, and two patients (4%) had Klinefelter´s syndrome. No BRCA1 mutations were found.

Eleven patients (19%) had one or two other malignancies, as prostate cancer (n=4, 7%). In one patient, diagnosed with Klinefelter's syndrome, prostate cancer was the first primary. Two patients were diagnosed with two other malignancies: oral cavity cancer and prostate cancer (n=1) and melanoma and colon cancer (n=1).

Most patients detected themselves a lump, and only few patients experienced local pain, nipple retraction, nipple discharge or inflammatory skin changes (Table II). The median time (range) from the onset of symptoms to diagnosis was 6 (0–108) months. Mammography, ultrasonography or both were done for half of the patients as the first diagnostic procedure while the rest were diagnosed with fine needle or core biopsy or excision of the tumor (Table II). Most patients were sent for secondary health care for diagnosis.

The median size of the primary tumor was 1.8 cm and half of the tumors with known size were T1 tumors and 14% T4 tumors (Table III). Half of the patients had lymph node metastases at diagnosis and the mean number of positive lymph nodes was 1.7. Histopathology showed ductal carcinoma (n=55), and lobular carcinoma (n=2), with one patient having Klinefelter's syndrome, the other liver cirrhosis. Distant metastases at diagnosis were bone, pulmonary and mediastinal lymph node metastases (n=1),

Table I. The occurrence of risk factors.

Parameter	Number of patients (%)
Obesity (n=22)	
Obese	9 (41)
Normal weight	13 (60)
Smoking (n=30)	
Smoker	8 (27)
Non-smoker	22 (74)
Alcohol intake (n=19)	
None	5 (27)
Occasional	6 (32)
High	8 (43)
Liver cirrhosis (n=58)	4 (7)
Previous radiotherapy to chest (n=58)	1 (2)
Family history of breast carcinoma (n=35)	
Negative	24 (69)
Positive	11 (32)
Family history of ovarian cancer (n=30)	
Negative	30 (100)
Positive	0
Family history of prostate carcinoma (n=31)	
Negative	28 (91)
Positive	3 (10)
BRCA (n=4)	
BRCA1	0
BRCA2	1 (25)
Klinefelter's syndrome (n=58)	2 (4)
Other malignancy (prior or subsequent) (n=58)	11 (19)

Table II. Diagnostics (n=58).

	Number of patients (%)
Initial symptoms	
Breast mass	41 (71)
Breast mass and inflammatory skin	1 (2)
Breast mass and nipple retraction	1 (2)
Inflammatory skin	3 (6)
Local pain	5 (9)
Local pain and nipple retraction	2 (4)
Nipple retraction	4 (7)
Nipple discharge	1 (2)
Diagnostic methods	
Mammography alone	8 (14)
Ultrasonography alone	10 (18)
Mammography and ultrasonography	9 (16)
Biopsy	13 (23)
Excision	18 (32)

Table III. Tumour characteristics (n=58).

Characteristic		No. (%)
Tumour size (cm)	Median (range)	1.8 (0.5–6.4)
	T1	27 (47)
	T2	16 (28)
	T3	1 (2)
	T4	8 (14)
	Bifocal	1 (2)
	Unknown	5 (9)
Lymph node status	Positive	27 (47)
	Negative	29 (50)
	Unknown	2 (3)
Lymph nodes removed	Median (range)	10 (0–29)
Distant metastases at diagnosis		2 (4)
Histologic tumour type	Ductal	55 (95)
	Lobular	2 (4)
	Unknown	1 (2)
DCIS component included		8 (14)
ER status	Positive	47 (82)
	Negative	0
	Unknown	11 (19)
PR status	Positive	37 (64)
	Negative	10 (18)
	Unknown	11 (19)
Grade	1	7 (13)
	2	24 (42)
	3	13 (23)
	Unknown	14 (25)
Ki-67/mib-1 (n=32)	Median (range)	20 (2–60)
Her2	Positive	2 (4)
	Negative	17 (30)
	Unknown	39 (68)

and pulmonary, pleural and mediastinal lymph node metastases (n=1). Hormone receptor status and grade were underreported, but among patients with known receptor status, all were ER positive and 79% were PgR positive. Half of the patients with known histological grade had grade 2 tumors and the median value of mib-1/Ki-67 was 20%. Her-2 overexpression was assessed in 19 (33%) cases, of which two (11%) were positive (Table III).

Surgery was done as mastectomy (97%) or lumpectomy (3%), and as axillary evacuation (90%) or sentinel node biopsy without evacuation (7%). The axillary lymph nodes were not dissected in only one patient and evacuation was incomplete in one. Sixty percent of the patients received postoperative local radiotherapy, 18% to the breast, 37% to the breast and the axilla and 4% to the breast and other local lymph node regions. Sixty four percent of the 56 patients without distant metastases at diagnosis were treated with adjuvant hormonal therapy. One patient received letrozole and goserelin while the rest (n=35) were treated with tamoxifen. One patient with HER-2 positive tumor was given adjuvant trastuzumab.

Adjuvant chemotherapy (n=11) was given as CEF (cyclophosphamide, epirubicin, fluorouracil, n=5), docetaxel and CEF (n=5) or CMF (cyclophosphamide, methotrexate, fluorouracil, n=1). Of the 27 patients with lymph node metastases at diagnosis, 18 did not receive any chemotherapy. These patients were more than 65 years old (n=9), diagnosed before the year of 2000 (n=5) or with schizophrenia (n=1) or had strongly receptor positive grade 1 (n=2) or 2 tumors (n=1) and treated with only tamoxifen.

The median follow-up time was five years, ranging from one month to 24 years. Fourteen patients experienced a relapse, six as local (axilla or scar and axilla) and eight as distant. Axillary recurrences were operated (n=2) or treated with radiotherapy (n=4). Scar was operated (n=2) or given radiotherapy (n=1). Systemic treatment for local recurrence was tamoxifen (n=3), docetaxel (n=1) or none (n=2). Distant metastases were only bone (n=4), only visceral (n=2) or metastases at several sites (n=2). Bone metastases were treated with radiotherapy and tamoxifen or medroxyprogesteroneacetate as the first line systemic therapy (n=7), and visceral metastases with tamoxifen (n=1) or docetaxel (n=1).

DFI of the patients (n=56) without distant metastases at diagnosis (Figure 1), and the OS together with breast cancer specific survival (Figures 2 and 3) are shown using the Kaplan-Meier method. During follow-up, 21 patients died (37%), due to breast cancer (n=9) or other causes (n=12). The estimated 5-year OS was 75%.

Discussion

The median age at diagnosis of 63 years is within the range reported in the literature [6,7], compared to the 61 years in female patients in Finland [8]. However, the age distribution was wide (35–91 years). All the investigated tumors (n=47) were ER-positive, while PgR positivity was seen in 37 tumors. In previous reports some ER negativity has been

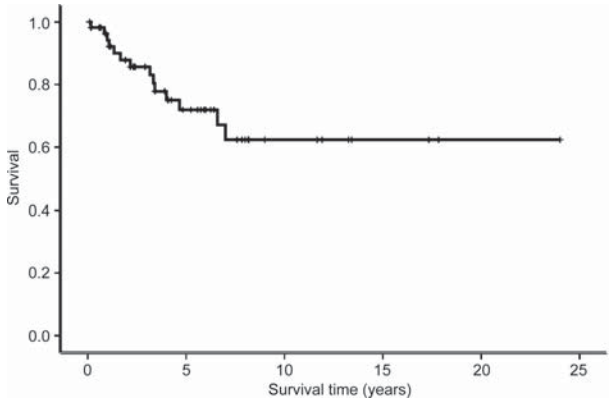

Figure 1. Disease-free interval (n=56).

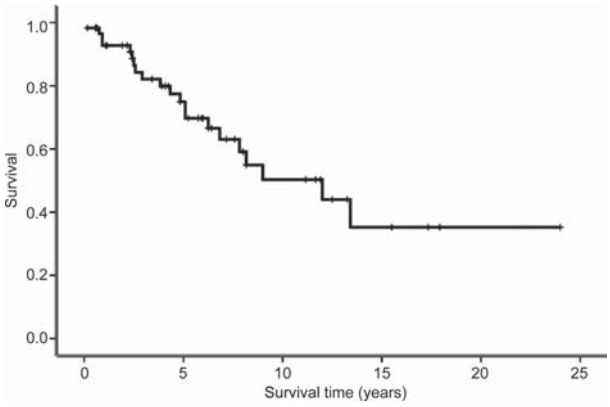

Figure 2. Overall survival (n=58).

reported [6,7]. HER-2 positivity was diagnosed in two tumors out of the 19 tested (11%), which is in line with previous reports [9], but a little less than seen in female breast cancer [10].

Most of the tumors were invasive ductal carcinoma (n=55), as seen in other materials [6,7]. Male breast tissue does not normally form lobules unless exposed to increased concentrations of endogenous or exogenous estrogen, and, lobular carcinoma has been reported in men with Klinefelter's syndrome (XXY) [11] but also in genotypically normal men [11,12]. The two tumors diagnosed as lobular carcinomas were from a patient with Klinefelter's syndrome (n=1) and a patient with liver cirrhosis (n=1), both conditions known to increase estrogen load.

Among the patients with reported risk factors, 41% were obese, compared to 20% on average among Finnish men and 43% were heavy alcohol drinkers which is clearly higher than 20% in normal population. Also the amount of liver cirrhosis in 7% of the patients can be considered high. However, these results should be taken with caution due to the high number of patients with unknown risk factors and a small patient population. Interestingly, in a recent prospective study a history of bone fracture was associated with increased risk of male breast cancer [13]. The authors suggest that this finding could be explained by a high ratio of bioavailable estrogen to androgen causing low bone density and osteoporosis as in Klinefelter's syndrome. They also found obesity as well as a history of a first degree relative with breast cancer to be related and physical activity to be inversely related to the risk. These identified risk factors indicate that hormonal mechanisms play a major role in male breast cancer.

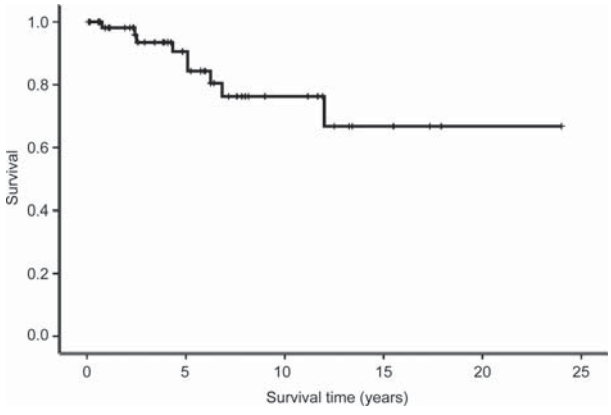

Figure 3. Breast cancer specific survival (n=58).

Seven percent of the patients in the present study were also diagnosed with prostate cancer. The incidence of breast cancer in prostate cancer patients has previously been reported to be increased [14] as well as the incidence of prostate cancer in patients with breast cancer as the first primary [15]. Prostate cancer was the first primary in one patient, and the second malignancy in three patients. None of the patients had second contralateral breast cancer although in the literature the risk in male breast cancer is clearly increased [16]. An excess of melanoma and stomach cancer have also been reported earlier [14,16] but in our group of patients we only detected one melanoma.

The median time from the onset of symptoms to diagnosis of six months in our study is longer than in women. This probably results from the rarity of the disease, and from non-indicated screening for male breast cancer. The significance of the delay is unclear: in earlier studies a longer delay correlated to a decreased survival, while in later reports no such correlation has been detected [6,17]. However, there is a need for updated information about this disease especially for general practitioners and physicians who treat prostate cancer patients. The relatively infrequent use of mammography in 30% of the patients in our series reflects both the large proportion of palpable tumors at presentation as well as the absence of mammography screening in this rare disease. The triple diagnosis consists nowadays most often of palpation, ultrasound and biopsy. We saw quite a few T4 tumors confirming that the disease is more often locally advanced in men. Due to this and the elevated risk for second breast cancer regular contralateral breast surveillance is recommended for male breast cancer patients.

Axillary evacuation was performed in 90% of the cases and sentinel node biopsy without evacuation in 7% reflecting the state of art in the earlier decades. Sentinel node technique has lately become practice also in male patients. Sixty percent of the patients received postoperative radiotherapy and the indications were similar to those of female patients. Sixty four percent of the patients were treated with

adjuvant hormonal therapy which is less than nowadays in postmenopausal women.

Only one patient received letrozole and goserelin while the rest (n=35) were treated with tamoxifen. The side effects of tamoxifen are known to be considerable in men [7]. So far, 26 cases of male breast cancer patients treated with aromatase inhibitors alone or in combination with leuprolideacetate or trastuzumab have been published [18–24]. Although monotherapy with aromatase inhibitors induce responses, total inhibition of estrogen production in men with aromatase inhibitors is problematic since in men 80% of circulating estrogens result from peripheral aromatization of androgens to estrogens but testicular aromatase independent production of estrogen accounts for the rest. Additionally, recently et al. proposed a feedback loop hypothesis according to which monotherapy with aromatase inhibitors cause a significant release of luteinizing hormone and follicle-stimulating hormone leading to an increase in estrogen levels [24]. Therefore, single use of aromatase inhibitors is not recommended and combinations of aromatase inhibitors with gonadotropin-releasing hormone analogs (GnRH) are under investigation [18].

Twenty percent of the patients were given adjuvant chemotherapy, which can be considered low in a patient population with lymph node metastases in half of the patients and is mainly due to the treatment modalities in the earlier decades as well as elderly patients with strongly hormone receptor positive disease. Adjuvant trastuzumab was given for only one patient of the two tested positive for Her-2 overexpression. Today trastuzumab is recommended for all HER-2 positive patients, both male and female, without a contraindication for the drug.

Every fourth patient experienced a relapse of which 40% were local. The first line therapy for distant metastases consisted of hormonal treatment and radiotherapy in most cases like in postmenopausal women. During follow-up 21 patients (37%) died of breast cancer (n=9) or other causes (n=12). This partly explains why the 5-year OS of 89% in Finnish female breast cancer patients resembles more the breast cancer-specific survival curve of males than the OS curve and is higher than the 5-year OS of 75% in the present study. Stage-adjusted prognosis has previously been considered similar in men and women [25]. In the previous clinical report on male breast cancer at our institution in 1982 the 5-year OS was 44% [17]. The longer OS in the present study is most likely the consequence of better treatment according to the principles of postmenopausal breast cancer today but also of earlier diagnosis and men dying later of other causes as well.

In conclusion, the 5-year OS of male breast cancer has improved in 25 years. Male breast cancer behaves and is nowadays treated in many respects like postmenopausal breast cancer. However, due to rudimentary breast tissue the symptoms, diagnosis and especially a higher amount of T4 tumors differ from that of females. Attention should be paid to earlier diagnosis by updating the information of this disease to general practitioners, and doctors who treat prostate cancer patients. Also the risk factor profile and histologic subgroups seem different from women. To better detect possible other differences between female and male breast cancer, more systematic characterization of tumors, identifying tumor subtypes and genetic mutations as well as gathering of clinical data prospectively are warranted.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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