Risk Factors, Pathological and Phenotypic Features of Male Breast Cancer in Greece

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Abstract. *Background: Breast cancer (BC) in males is a rare disease and comprises 0.5-1% of all BC cases. Due to its rarity, there are limited data regarding risk factors, biology and relevant treatment. Aim: A prospective observational study of demographic, clinical and histological characteristics of serially-admitted men with breast cancer was carried out from 1999 to 2009. Patients and Methods: Data were recorded and analyzed from a database including 1,315 cases of BC. Registered data concerned age, initial presentation, family and lifestyle history (risk factors), histological features, phenotypic subtypes and TNM staging. Results: Twenty two men with BC were identified, with a median age of 63 years. The most common initial presentation was a palpable lump in 12 patients, nipple contraction in three and ulceration in three. According to their medical history, nine men were overweight, 10 suffered from hypertension and 12 were smokers. The most prevalent phenotype was luminal-A followed by triple-negative type. BC in none of the cases was HER 2-amplified. The majority of cases were grade II or III and stage II or III. Conclusion: In the present small study, we confirm that BC in males is rare. It is a disease of middle-age and presents at advanced stages. Most of patients had 1-3 risk factors for BC. Expression of hormonal receptors occurs in the majority of BC tumors in males and with rarity in HER 2 amplification.*

This work was presented at the 2009 ESMO (European Society of Medical Oncology) meeting. The study was supported with Research Funds from the Ministry of Health (study MOK-1) and The Hellenic Society for the Study of Breast Cancer.

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Key Words: Male breast cancer, risk factors, clinical features, histological features, familial predisposition.

Breast cancer (BC) in males is a rare malignant disease, accounting for 0.5-1% of all BC and 1.0% of all cancer in males. Approximately 2,000 men are diagnosed with BC annually in the USA, with a rising incidence, accounting for one case for every 100,000 males (1-3). Its incidence rises steadily in urban areas in USA and Canada with advancing age until a plateau is reached around the age of 80 years. Over the past 25 years, the incidence has risen by 26%.

The highest incidence of BC in males is 1.24 per 100,000 man-years and was noticed in Israel while the lowest incidence is 0.16 per 100,000 man-years and was noticed in Thailand (4). The number of men diagnosed with BC corresponds to approximately 1% of the number of women diagnosed with BC (5). Despite the lower incidence, its case-fatality rate is quite similar to that for female breast cancer (6).

The mean age at-diagnosis is 67 years, approximately 5-10 years older than that for women, with the peak incidence occurring between 68 and 71 years (5, 7, 8). Because of the rarity of the disease, there is limited clinical research in the field and the treatment standards for men are generally based on our clinical experience from women, despite the distinct features of the two diseases attributable to differences such as hormonal background.

There is a paucity of data regarding the features of male BC in Greece. In the present study, we attempt to present data on men with BC collected prospectively over a period of 10 years, monitored during 1999-2009 under the main referral BC program in Greece, to add and correlate our experience and findings to those of current international literature.

Patients and Methods

After obtaining relevant approval from our Hospital's Scientific Committee, we carried out a prospective observational study of all male patients with BC who were treated and evaluated under the Breast Program of Agios Savvas Anticancer Hospital of Athens, during a period ranging from September 1999 to September 2009. All data were recorded electronically and extracted from the digital data bank. Data were collected by personal interview between a trained Oncologist and the patient upon their first Clinic visit. A total of 1,315 male and female patients with BC are registered. A total of 22 male patients with BC (22/1315) (1.67%) were eligible for our study in this period of time.

Recorded data concerned age, initial presentation, medical and family history, histological and phenotypic features of the neoplasm and TNM staging. Medical history included obesity, hypertension, diabetes, hyperlipidemia, smoking and alcohol consumption, all of which could be considered as possible risk factors for BC in both males and females.

Family history was checked to relate the disease with sporadic or familial phenomena, as well as age of disease onset. Disease features included clinical presentation, pathology, grade, metastasis at diagnosis, pTNM staging. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor (HER2) status were immunohistochemically defined, while HER2++ cases were further clarified by Fluorescence In Situ Hybridization (FISH) and HER2- or HER2+ indicates no amplification. Postoperative and pathological TNM staging system for breast cancer and regional lymph nodes was based on the Cancer Staging Manual, 7th edition (9).

Results

A total of 22 male patients with BC were recorded. Their median age at-diagnosis was 63 (range=48-79) years. Initial presentation included palpable lump in 12 (54.55%) patients, nipple contraction in three (13.7%), ulceration in three (13.7%), nipple discharge and palpable lump in two (9%) and one (4.5%) patient BC was diagnosed by mammogram. One (4.5%) patient with metastatic disease presented with a palpable lump and back pain (Table I).

According to their history and physical examination, nine (41%) patients were overweight, 10 (45%) suffered from hypertension, six (27%) from diabetes, four (18%) from hyperlipidemia and five (23%) were diagnosed with metabolic syndrome. Moreover, 12 (54.55%) patients were smokers and five (23%) were alcohol abusers (>3 glasses/day). Eleven out of 22 patients (50%) had positive medical history of familial or documented hereditary breast cancer, while the remaining 50% were sporadic cases. *BRCA1* was mutated in three cases (13.67%).

Nearly all tumors (21/22; 95.45%) were ductal invasive carcinomas and only one (4.55%) patient was diagnosed with lobular carcinoma. Twelve (54.55%) tumors were grade II and the other 10 (45.45%) were grade III. Examination of hormone receptor status revealed 15 (68.18%) ER+ cases and 14 (63.64%) PR+; six cases were characterized as triple-negative (27.25%), 13 (59.1%) were ER+PR+HER2–, two (9.1%) were ER+PR-HER2– and one (4.55%) was ER-PR+HER2–. All 22 patients were thus negative for *HER2* amplification (Table II).

Initial tumor size was T <2 cm in 10 (45.45%) patients. Four out of 22 patients (18.18%), had bone metastases without visceral metastases, while disease in 18 (81.81%) was non-metastatic with TNM stages of I-IIIC. In particular, disease in two (9.1%) patients was stage I, in 10 (45.45%) stage IIA or IIB, and in six (27.25%) was stage IIIA, IIIB or IIIC. Finally, 13 out of the 18 patients with non-metastatic disease (72.22%) had lymph node-positive disease.

All patients received multimodality treatment consisting of lumpectomy or mastectomy for the majority of non-metastatic cases, adjuvant radiotherapy, adjuvant or first line chemotherapy (anthracyclines-and taxane-based regimens) and hormonal therapy (tamoxifen-aromatase inhibitors) according to our Institution Treatment Protocols.

Discussion

In published literature, we can find data regarding epidemiology and risk factors for BC in males, pathological and biological characteristics, clinical features and presentation of the disease. Most data originate from relatively small series of patients compared to those of BC in women. However, recently the interest in BC in males is rising, and there is an attempt to collect retrospective data from hospital records in order to clarify many grey areas, as we see contradictive findings between reports of small studies.

There are no well-established risk factors for BC, in men with the exception of familial predisposition and inherited *BRCA2* mutations (7). For example, lifestyle risk factors such as alcohol intake and smoking have not consistently been associated with higher risk for BC in males, although one small study reported that excessive alcohol consumption was indeed linked to the disease (10). Other studies failed to demonstrate such a link between alcohol, smoking and BC in males (8). In our study, most patients had one to three predisposing factors (obesity, alcohol or smoking) but most importantly half of them indicated a strong family history of BC, and three patients had a documented *BRCA2* deleterious mutation.

The most interesting finding in our study was the absence of *HER2* amplification in all patients. *HER2* amplification is indeed a rare phenomenon in male BC (11). Most of our cases (72.73%) expressed ER or PR. Almost all tumors were ductal invasive carcinomas (95.45%) but there was one rare lobular invasive carcinoma (4.55%).

These findings are in accordance with the data published so far and are explained by the nature of male breast tissue as it is predominantly made up of ductal elements, but not lobular structures, which in women are responsible for lactation (12). As a result, 85-90% of BC in males are ductal

Table I. *Initial presentation of male breast cancer in Greece.*

Initial presentation	Number of patients (n=22)	Percentage
Palpable lump	12/22	54.55%
Nipple contraction	3/22	13.67%
Ulceration	3/22	13.67%
Nipple discharge and palpable lump	2/22	9%
Mammogram	1/22	4.55%
Back pain and palpable lump	1/22	4.55%

Table II. *Histopathology features of male breast cancer in Greece.*

Histopathology features	Number of patients (n=22)	Percentage
Ductal invasive carcinoma	21	95.45%
Lobular invasive carcinoma	1	4.55%
Grade I	0	0%
Grade II	12	54.55%
Grade III	10	45.45%
Luminal A (ER+ PR+ HER2–)	13	59.1%
Luminal A (ER+ PR– HER2–)	2	9.1%
Luminal B (ER– PR+ HER2–)	1	4.55%
Triple negative (ER– PR- HER2-)	6	27.25%
HER 2 negative (HER2–)	22	100%

invasive carcinomas. Data from more than 2,000 male patients in the Surveillance, Epidemiology and End Results cancer registry show that 93.7% of male BC are ductal or unclassified carcinomas and only 1.5% lobular (5, 8, 13). Approximately 90% of male BC express ER and 81% PR whereas HER2 is less likely to be overexpressed, with overexpression rates ranging from 2%-42% in different studies (5, 13, 14, 15). Additionally, 65-90% of tumors are both ER- and PR- positive (8), while this percentage in our study was 59.1%.

Published data imply that males present with BC mainly as a painless palpable lump (5, 7, 16). Our findings are in line with this, and more than 68% of the patients presented with a palpable lump, while the rest presented with nipple retraction or discharge from the nipple.

We recorded advanced-stage tumors (90.9% stage IIA-IV in our study) at-diagnosis. It is believed that BC in males presents at more advanced stages than in female patients, perhaps due to poor awareness of the disease, a fact that may be responsible for diagnostic delays. However, recent data seriously question this belief (11) and indicate the real necessity for conducting an international collaborative study in order to better understand the biology of this rare disease and improve treatment and preventative approaches.

Summary and research recommendations from a multi-disciplinary meeting on male breast cancer was published in the Journal of Clinical Oncology three years ago (11) indicating this necessity; however, to our knowledge, this need remains unfulfilled. The scientific society should collaborate in such an effort. This need is indicated by the internationally rising incidence of male breast cancer and lack of knowledge of BC in males, due to the rarity of this disease.

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Received December 16, 2013
Revised January 27, 2014
Accepted January 29, 2014