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Second Primary Cancers in Spanish Male Breast Cancer Patients

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Abstract

Introduction: Male breast cancer (BC) comprises less than 1% of all BCs. The development of second primary cancers in men with BC is an under-studied topic, with inconsistent data in the literature. The objective of this study is to analyze the cases of male BC in our series and to investigate its relationship with other primary cancers.

Material and Methods: Case series of male BC patients from our health area of Vigo diagnosed between October 1997 and March 2019.

Results: 71 men with primary BC were included, three of them presented bilateral BC. The mean age was 69.0 years (SD 9.6), with ages between 41 and 90 years. One third (33.8%) of men (24 of 71) had two or more primary cancers. Likewise, 14% of men (10 of 71) had at least three primary cancers. Of the 24 men with multiple primary cancers, we knew the familial cancer aggregation in 15 of them. More than 90% of them (14 of 15) had at least one first-degree relative with cancer and 20% (3 of 15) had a mutation in the BRCA2 gene.

Conclusion: Men with BC have a higher risk of developing a second primary cancer. This may be partly explained by the advanced age of men at the time of BC diagnosis and by the genetic predisposition associated with hereditary syndromes. These results encourage intensive and long-term follow-up and also the possibility of offering preventive measures, both for patients and their families.

Keywords: Male breast cancer; Second primary cancer; Multiple primary cancers.

Introduction

Male breast cancer (BC) is a rare clinical entity. It is estimated that it represents less than 1% of all cases of BCs (1). In women with BC, the risk of developing a primary non-breast cancer has been reported to range between 18-30%, with higher incidences associated with diagnosis at an early age (2, 3). Little is known in the literature on this topic in men with BC.

Multiple primary cancers are generally defined according to the criteria of Warren and Gates (4): (a) each tumor should present a definite picture of malignancy (b) each tumor should be histologically distinct (c) the possibility that one is metastasis of the other must be excluded.

Studying the development of second primary cancers has important preventive implications. They could be caused by common patient risk factors; such as genetic alterations, intrinsic or extrinsic hormonal

imbalances, shared environmental exposures/ lifestyles, or therapeutic factors (side effects of first cancer treatment).

In the present study, we present our series of male BC cases and discuss their relationship with multiple primary cancers.

Material and Methods

In this case series study (5, 6), we included men diagnosed with BC from various hospitals in our health area of Vigo (Xeral-Cíes University Hospital, Meixoeiro University Hospital, Álvaro Cunqueiro University Hospital and Povisa Hospital) in the period between October 1977 and March 2019.

The study variables were collected retrospectively and prospectively during all those years, including: personal and family history as well as genetic studies. The individualized follow-up of each patient allowed us to collect information on the existence or appearance of second primary cancers.

The data collected in this study was introduced in a database built in Microsoft Excel and statistically analyzed with SPSS-PC software.

Results

The study population included 71 men with primary BC, three of them presented bilateral BC (Total = 74 BCs). The mean age at diagnosis was 69.0 years (SD 9.6), with ages ranging from 41 to 90 years.

Regarding the presence of primary cancers in our series (Table 1), we observed that a third (33.8%) of men with BC (24 of 71) had two or more primary cancers. Likewise, 14% (10 of 71) had at least three primary cancers. The most frequent locations of primary cancers associated with male BC in our series were: prostate (n = 8), colon and rectum (n = 4), bladder (n = 4) and cutaneous basal cell carcinoma (n = 4).

The mean age of the men with multiple malignancies was 68.3 years (SD 7.7). Age slightly lower than that of the men diagnosed with single primary BC in our series, which was 69.5 years (SD 10.6); although this difference was not statistically significant (p> 0.05).

Table1. *Case series of male BC patients with multiple primary cancers.*

MULTIPLE PRIMARY CANCERS 24 of the 71 men with BC in our series (33.8%)				
BREAST CANCER AND AGE AT DIAGNOSIS			OTHER ASSOCIATED MALIGNANT TUMORS	FAMILIAL CANCER AGGREGATION
1	*Bilateral Breast Cancer*	*66 & 69*		***BRCA2 mutation***
2		*66 & 74*	*Prostate adenocarcinoma and CCR*	***BRCA2 mutation***
3		*58 & 66*		***Hereditary phenotype*** *Variants of unknown significance in MSH6 and TP53*
4	*Unilateral Breast Cancer*	*66*	*Glioma*	***BRCA2 mutation***
5		*70*	*CCR and Pancreatic-biliary duct adenocarcinoma*	***Hereditary phenotype*** *BRCA1/2 negative*
6		*54*	*CCR and Transitional cell carcinoma of the bladder*	***Hereditary phenotype*** *No genetic study*
7		*67*	*Transitional cell carcinoma of the bladder*	***Hereditary phenotype*** *No genetic study*
8		*83*	*Prostate adenocarcinoma and Cutaneous squamous cell carcinoma*	***Hereditary phenotype*** *No genetic study*
9		*68*	*Prostate adenocarcinoma*	***Mother: CCR*** *No genetic study*
10		*65*	*Prostate adenocarcinoma and Cutaneous basal cell carcinoma*	***Mother: Melanoma*** *No genetic study*
11		*79*	*Prostate adenocarcinoma and Post-radiotherapy cutaneous angiosarcoma*	***Mother: Breast Cancer*** *No genetic study*
12		*70*	*Clear cell carcinoma of the kidney*	***Mother: CCR; Maternal aunt: Leukemia*** *No genetic study*
13		*65*	*Transitional cell carcinoma of the bladder*	***Father: Bladder*** *No genetic study*
14		*63*	*Squamous cell carcinoma of the lung*	***Family history (1st degree): Lung cancer*** *No genetic study*

15		***68***	*Squamous cell carcinoma of the lung*	***Maternal aunt: Gastric cancer*** *No genetic study*
16		***78***	*Prostate adenocarcinoma, Clear cell carcinoma of the kidney, Cutaneous basal cell carcinoma and Neuroendocrine tumor of the pancreas*	***Familial aggregation of cancer unknown***
17		***83***	*Prostate, CRC and Cutaneous basal cell carcinoma*	
18		***56***	*Prostate adenocarcinoma and Cutaneous squamous cell carcinoma*	
19		***78***	*Transitional cell carcinoma of the bladder and Chronic lymphatic leukaemia*	
20		***63***	*Cutaneous basal cell carcinoma*	
21		***74***	*Cutaneous squamous cell carcinoma*	
22		***56***	*Melanoma of the skin*	
23		***67***	*Squamous cell carcinoma of the larynx*	
24		***72***	*Stomach adenocarcinoma*	

CCR: Carcinoma colorrectal.

We knew the familial cancer aggregation in 57 men (Table 1 and 2). Two out of three (66.6%) of the families of these 57 men had at least one first-degree relative with cancer, and almost one in ten (8.8%) had a mutation in the BRCA1/2 genes.

From the series of 24 men with multiple primary cancers, we knew the familial cancer aggregation in 15 of them. More than 90% (14 of 15) had at least one first-degree relative with cancer and 20% (3 of 15) had a mutation in the BRCA2 gene.

Tabla2. *Familial cancer aggregation: in the whole series and in the series of men with multiple primary cancers.*

Familial cancer aggregation	Male BC	Multiple Primary Cancers
Hereditary syndromes (BRCA1 / 2 positive)	5 (7.0 %)	3 (12.5 %)
*Clinical phenotype suspected of being hereditary cancer **	18 (25.3 %)	5 (20.8 %)
At least one first-degree relative with cancer	15 (21.1 %)	6 (25.0 %)
No first-degree relative with cancer	19 (26.7 %)	1 (4.2 %)
No cancer familial aggregation data	14 (19.7 %)	9 (37.5 %)
Total Series	**71 (100 %)**	**24 (100 %)**

* Clinical phenotype: it was suspected when in addition to male BC there was an intense familial cancer aggregation, although it did not necessarily affect three generations.

We investigated comorbidity in our series trying to relate it to other risk factors for male MC. We did not observe testicular or pituitary diseases. We also did not find any men with Klinefelter syndrome. The results highlighted the association with prostate adenocarcinoma (8 of 71), which represented 11.3% of the whole series of male BC. We also highlighted the presence of liver diseases: 11.3% (8 of 71) had chronic liver disease (in seven cases due to chronic enolism and in the other due to the hepatitis C virus). The mean age at diagnosis of BC in the 8 men with chronic liver disease was 64.88 years (SD 9.03) versus 69.55 years (DS 9.61) in the rest of the men without chronic liver disease (p> 0.05).

Discussion

To date, few studies have evaluated the risk of developing a second malignancy in men with BC (3, 7-13). People with a personal history of BC have a higher risk of having a second contralateral BC. Men have a 30 to 93 times significantly higher risk (Table 3), compared to women where the risk is 1.5 to 3.2 times (3). However, the absolute risk of contralateral BC in men is lower (0.1% per year) than in women (0.6% per year) (14). Men under the age of 50 at the time of the diagnosis of the first BC are those with the highest risk (3).

In the literature, data on second primary non-breast cancers in men with a personal history of BC are inconsistent (Table 3). Heimminki et al. (7) elucidate an excess risk of a second primary cancer of the small intestine, rectum, pancreas and prostate, as well as non-melanoma skin cancer and myeloid leukaemia. Auvinen et al. (8) found a 2-fold increased risk for cutaneous melanoma. Hung et al. (10) observed a

2-fold increased risk for colorectal carcinoma and a 4-fold increased risk for skin cancer in general. Some authors did not find an increase in the overall risk of subsequent cancer in men diagnosed with BC (8, 9).

Table3. *Literaturereview: standardized incidence rates of second primary cancer in men with BC.*

	Hemminki et al. [7]	Auvinen et al. [8]	Satram-Hoang et al.[9]	Hung et al. [10]
Contralateral breast	*93,1**	*29,64*	52,12	-
Other cancers (less BC)	*1,34*	0,99	1,05	*2,07*
Small intestine	*4,95*	-	-	-
Colorectal	*1,35*	-	1,15	*2,18*
Colon	1,05	0,84	-	-
Rectum	*1,78*	0,80	-	-
Stomach	1,09	0,99	*2,11*	2,02
Pancreas	*1,93*	-	-	1,77
Liver and bile duct	1,85	1,51	-	1,34
Lung	1,26	0,73	0,7	2,05
Prostate	*1,61*	1,09	0,95	1,94
Bladder	0,86	1,31	1,49	1,41
Kidney	0,85	0,76	-	0,00
Skin (general)	-	-	-	*4,88*
Melanoma	1,29	*2,41*	*2,98*	-
Skin (non-melanoma)	*1,65*	-	-	-
Hematologic tumors	*1,63*	-	-	2,39
Lymphomas	1,33	0,73	-	-
Non-Hodgkin lymphoma	1,44	-	-	-
Multiple mieloma	1,18	-	-	-
Leukaemia	*2,21*	-	-	-
Lymphoid leukaemia	1,86	-	-	-
Myeloid leukaemia	*3,42*	-	-	-

Numbers in italics represent statistically significant values (95% CI, not including 1.00). * Standardized incidence rate published by Dong and Hemminki [11].

Cutuli et al. (12) described a series of 404 men with BC, 68 of these (17%) developed another primary cancer: 11 were contralateral BC; and the rest were mainly prostate, lung, colon and esophagus carcinomas. Anderson and Badzioch (13) observed that 22% of men with BC had other primary malignancies: skin cancers (squamous and basal cell carcinomas), melanomas, lymphomas, oropharyngeal, thyroid, prostate, colon and bladder carcinomas.

In our series of men with BC, we observed that a third (33.8%) had multiple primary cancers. Likewise, 14% presented at least three primary cancers. The most frequently associated non-breast cancer was prostate cancer (11.3%); followed by colorectal, bladder and basalioma (each representing 5.6%). In our series: 3 patients (4%) had a contralateral BC.

There are several possible causes of the development of another primary tumor among male BC survivors. Some second primary tumors are sporadic (they would have also occurred in the absence of BC). Most are the consequence of advanced age (sharing a late-onset age with male BC) or genetic factors (which predispose the development of other cancers). Other causes may be exposure to environmental or hormonal factors that also predispose to BC, or they may also be the consequence of BC treatment.BC treatment (radiotherapy or chemotherapy) can facilitate the development of other tumors.

Thanks to the study of survivors of atomic bomb explosions in Japan we know the effects of radiation and its ability to induce cancer. We have also learned this by studying populations exposed to radiation in their work and patients treated with radiotherapy (15).

Radiotherapy is an important factor in the generation of second primary cancers, after a long latency period and with increasing risk over time (16). It has been shown that it can cause a second BC, as well as induce carcinogenesis in organs located near the radiation field (lung, esophagus, thyroid and soft tissues) (16). This association has been demonstrated in female BC; although it is doubtful in the male, probably because in these the age at diagnosis is more advanced, making them less sensitive to radiation (1).

Different treatment strategies with chemotherapy and hormone therapy have significantly improved the survival of BC. However, they are also implicated in the development of some second primary cancers. Chemotherapy in BC patients was associated with increased incidences of second cancer for several sites (eg. acute myeloid leukaemia), and its risk varies with age and latency (17, 18).

Regarding prostate cancer, the most frequently associated cancer in our series, we know that its incidence increases with: age, family history and hyperestrogenism (risk factors shared by breast and prostate cancer) (19).Furthermore, a 4-fold increased risk of BC has been reported after hormonal treatment for prostate cancer (20). Breast and prostate cancer, as synchronous or metachronous primary cancers, are very rare and may be sporadic or as a result of genetic mutations in the BRCA1/2 genes.Therefore, despite this rarity, it should be recommended that when diagnosing breast or prostate cancer in a male patient, we should be on the lookout for other cancer(12, 21, 22).

Male BCs are sensitive to hormonal changes (hyperestrogenism) (23, 24). This imbalance can occur endogenously due to testicular abnormalities or liver disease. In our series, when studying comorbidity, we observed that 11.3% had chronic liver disease. The 47XXY genotype (Klinefelter syndrome) characterized by testicular dysgenesis, gynecomastia, and hyperestrogenism is associated with a high risk of BC (25). This chromosomal alteration was not found in our series. Excess estrogen may also be due to the treatment of prostate cancer (with the use of antiandrogenic therapies) or in transsexuals (with exogenous estrogens). Other risk factors are associated with testicular diseases associated with environmental/occupational factors.

Likewise, the genetic component is a relevant factor in the predisposition to BC. Approximately 15-20% of male BCs are hereditary (26). In our series of the 24 men with multiple primary cancers, we knew the familial cancer aggregation in 15 of them. More than 90% (14 of 15) had at least one first-degree relative with cancer. As in women, BRCA1/2 genes are responsible for most cases of hereditary male BC; although the BRCA2 gene is the most frequent and the one that provides the greatest risk in men (27, 28). In our series of the 24 men with multiple primary cancers: 20% (3 of 15) present a mutation in the BRCA2 gene.

Other genes have been implicated: PALB2, CHEK2, PTEN (Cowden syndrome), ATM, TP53 (Li-Fraumeni syndrome) and mismatch repair genes (Lynch syndrome) (29-33). The CYP17 gene (which encodes an enzyme that produces sex steroids) and the MUTYH gene (gene found in our series, whose germ biallelic mutations cause MUTYH-associated polyposis syndrome) have also been proposed (34).

Despite the fact that most of our patients did not carry out any genetic study, all men diagnosed with BC should receive genetic counseling since they are currently candidates for a genetic study (NCCN Clinical Practice Guidelines in Oncology) (35). It is essential to study the presence of these mutations in order to be able to offer personalized advice, assess the risk of future cancers and determine preventive strategies, as well as study other family members.

The association of certain genetic mutations with other cancers has been demonstrated. Thus, BRCA2 mutations confer an increased risk of prostate cancer (RR = 4.65), gallbladder (RR = 4.97), pancreas (RR = 3.51) and malignant melanoma (RR = 2, 58) (36). Furthermore, BRCA1 mutations have also been reported to be associated with an increased risk of colorectal (double), pancreatic (triple), and gastric (quadruple) cancers, compared to the general population (37).

Conclusion

The development of second malignancies in men with BC is an under-studied topic with inconsistent data in the literature. In our series, one third of the men with BC had two or more primary cancers. The causes of this association are multiple and still need to be investigated.Most cancers are sporadic and

are explained by the increased risk associated with advanced age.Men with BC have been shown to had increased risk of developing a second primary cancer compared to the general population.There are genetic factors that predispose to BC and other primary cancers from other locations.Two out of three families with male BC had at least one first-degree relative with cancer, and about one in ten had a mutation in the BRCA1/2 genes.From our series of the 24 men with multiple primary cancers, we knew the familial cancer aggregation in 15 of them. More than 90% (14 of 15) had at least one first-degree relative with cancer and 20% (3 of 15) had a mutation in the BRCA2 gene.These results encourage intensive and long-term follow-up and also the possibility of offering preventive measures, both for patients and their families.

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