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Heredity and Male Breast Cancer: A Series of 72 Men with Breast Cancer

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Abstract

Male breast cancer (BC) comprises less than 1% of all BCs. Family history of BC and the presence of genetic mutation are the main risk factors. Our objective is to estimate the prevalence of familial cancer aggregation and genetic mutations in a series of cases of male BCs. We studied a series of male BC patients from the health area of Vigo diagnosed between October 1997 and December 2020. 72 men with primary BC were included. The mean age of all male BCs was 69.0 years, similar to those of hereditary BCs (66.2). We observed a high frequency of bilaterality (4%). We highlight the underuse of genetic testing: only in 14 men (19.4%). The most frequently detected pathogenic mutation (n = 5: 7%) was in the BRCA2 gene, and 3 of them presented the same type of mutation (c.9382C> T (p.Arg3128Ter) in exon 25). We also detected a pathogenic mutation in the BRCA1 gene and the MUTYH gene. 34.6% of male BCs that were not genetically studied had an intense familial aggregation of cancer that was compatible with a hereditary cancer syndrome. 33.3% men had at least one other malignant neoplasm in addition to their BC, with prostate adenocarcinoma being the most frequent associated neoplasia (n = 8). Up to 15.3% were diagnosed with 3 or more malignant neoplasms. It is necessary to increase the genetic testing in male BC in order to o identify hereditary BC and offer the pertinent preventive measures to them and their families.

Keywords: BRCA2 gene; Germline testing; Hereditary breast cancer; Male breast cancer.

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Acronyms

Breast cancer	BC

Introducción

Breast cancer (BC) in men is a rare clinical entity. It is estimated to represent less than 1% of all BCs [1]. Risk factors include conditions associated with primary and secondary hyperestrogenism, radiation exposure and, in particular, a family history of BC, which points to a relevant genetic component in predisposition to this disease. As in women, BRCA1 and BRCA2 (BRCA1/2) genes give rise to the majority of known cases of hereditary BC in men. The frequency of deleterious BRCA1/2 mutations has been shown to be considerably higher in male than female BCs. BRCA2 is the most commonly mutated gene and the one with the highest risk, unlike in women [2].

The objective of this article was to estimate the proportion of male BCs with familial aggregation of cancer, the prevalence of genetic mutations related to an increased risk for BC in men, and the number of men who received genetic counseling in a series of male BC cases in our health area.

Material and Methods

In this case series study [3, 4], we included men diagnosed with BC from various hospitals in our health area. A protocol was designed to record retrospective and prospective data from male patients diagnosed with BC from October 1977 to December 2020 at four different hospitals in the area of Vigo (Hospital Xeral Universitario de Vigo, Hospital Meixoeiro, Hospital Universitario Álvaro Cunqueiro and Hospital Povisa).

The variables analyzed were studied retrospectively and prospectively during all these years, including: personal data, family history of cancer and genetic studies performed. The data collected in this study was introduced in a database built in Microsoft Excel and statistically analyzed with SPSS-PC software.

Results

In our series of 5000 BCs, the male BC represented 0.9% of all BCs. We studied a total of 72 men with BC, three (4%) of them had bilateral BC. The mean age of the total series of male BCs (n = 75) was 69.0 years (standard deviation -SD- 9.6), with the youngest patient presenting 41 years and 90 years being the oldest.

Of the total of 72 men with BCs, only 14 (19.4%) had performed a germline testing: five men had a BRCA2 gene mutation and only one man had a BRCA1 gene mutation. In addition, one male BC was associated with a mutation in the MUTYH gene and another male presented a Variant of Uncertain Significance in MSH6 and TP53 genes (Table 1 and 2).

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Table 1. Germline testing in our series of male BCs

Germ line testing	no. of cases
No genetic study was done	58
Complete genetic panel with negative results *	3
BRCA1/2 negatives	3
MSH6 and TP53 -Variant of Uncertain Significance	1
MUTYH positive	1
BRCA1 positive	1
BRCA2 positive	5
Serie Total	**72 CM (100 %)**

Note: In three cases (*) a first negative study for BRCA1 / 2 was expanded with a genetic panel (PTEN, TP53, CDH1, RAD51C, RAD51D, MLH1, MSH2, MSH6, PALB2, CHEK2, BRIP1, STK11 and ATM) that it was also negative

Table 2. Type of genetic mutations (Hereditary BC) in our series of male BCs

Age of male BC	Gen	Mutation	Familial aggregation of cancer
67 years	***BRCA 1***	*BRCA1 c.5530T>A, p.Val1804Asp exon 23; pathogenic variant*	Maternal aunt: BC 40 years, Son: Hodgkin lymphoma 41 years; Grandson: Osteosarcoma 13 years.
66 years &Brain tumor	***BRCA2***	*BRCA2 c.4088delA, (c.3860delA according HGVS) p.Asn1287IlefsX6 of exon 11*	Mother: Ovarian Cancer 68 years. Brother: Osteosarcoma 28 years. Son: Pancreatic Cancer 42 years.
66 y 74 years	***BRCA2***	*BRCA2 c.5374_5375del; p.Tyr1716LysfX8 exon 11*	Sister: Bilateral BC 55 and 58 years. Brother: Tongue Cancer 70 years. Brother: Liver metastasis with unknown primary 71 years
54 years	***BRCA2***	*BRCA2 c.9382C>T (p.Arg3128Ter) exon 25*	Mother: Ovarian Cancer 70 years. Maternal aunt: Ovarian Cancer. Maternal aunt: Ovarian cancer. Maternal aunt: Colorectal cancer and BC. Granddaughter: Colorectal cancer
66 y 69 years	***BRCA2***		Paternal Grandfather: Probable male BC Sister: BC 34 years. Brother: Cancer ENT.
71years	***BRCA2***		Mother: Gynecological Cancer. Daughter: BC 47 years.
71 years	***MUTYH***	*MUTYH c536A>G, pTyr179Cys; pathogenic variant*	It is unknown
58 y 66 years	***MSH6***	***Variant of Uncertain Significance*** *MSH6 and TP53*	Father: Prostate Cancer. Maternal Aunt: Gynecologic Cancer

By excluding from the series of 72 male BCs the 6 cases associated with known genetic mutations and the 14 patients for whom we did not have clinical data on familial aggregation of cancer, we were able to classify the remaining 52 male BCs as follows:

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- In about one out of every three male BCs not genetically studied (19 of 52 BCs, 36.5%) there was no familial aggregation of cancer among first-degree relatives.
- In about one out of every three male BCs not genetically studied (18 of 52 BCs, 34.6%) presented an intense familial aggregation of cancer that made us suspect that we were facing a Hereditary Cancer Syndrome.
- Finally, among one out of every three or four male BCs not genetically studied (15 of 52 BCs, 28.8%) had at least one first-degree relative with cancer.

In our series, one in three (24 of 72 BCs, 33.3%) had at least one other malignant neoplasm in addition to their BC, with prostate adenocarcinoma being the most frequent associated neoplasm (n = 8). Both types have in common that they are hormone dependent cancers. The other most frequent associated cancers were colorectal carcinomas (n = 4), transitional bladder carcinomas (n = 4), and cutaneous basal cell carcinomas (n = 4). Up to 15.3% of all male BCs (11 of 72) were diagnosed with 3 or more malignant neoplasms (Table 3) [5].

Table 3. Men with three or more cancers (including at least one BC

Patient	*Breast*	*Prostate*	*Skin*	*Colorectal*	*Bladder*	*Other malignant tumors*
nº 1	*Bilateral*	*Prostate*				
nº 2	*Unilateral*	*Prostate*				
nº 3	*Unilateral*	*Prostate*	*Basal Cell Carcinoma*			
nº 4	*Unilateral*	*Prostate*	*Basal Cell Carcinoma*			*Kidney*
nº 5	*Unilateral*	*Prostate*	*Basal Cell Carcinoma*	*Colorectal Carcinoma*		
nº 6	*Unilateral*	*Prostate*		*Colorectal Carcinoma*		
nº 7	*Unilateral*	*Prostate*	*Basal Cell Carcinoma*			
nº 8	*Unilateral*	*Prostate*	*Basal Cell Carcinoma*			*Angiosarcoma*
nº 9	*Unilateral*			*Colorectal Carcinoma*		*Adenocarcinoma of the Pancreatic Billary Duct*
nº 10	*Unilateral*			*Colorectal Carcinoma*	*Bladder*	
nº 11	*Unilateral*				*Bladder*	*Chronic Lynphocytic Leukemia*

Discussion

As is the case in most large published series [6, 7], male BC accounts for less than 1% of all BCs (0,9% in our series).

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Although some authors report that bilaterality in male BC is exceptional, it is striking that in our series 4% of the 72 male BCs (3 of 72) had a bilateral disease. In the series published by Auvinen et al. [8] only 12 (0.6%) of the 1,788 men developed BC in the contra lateral breast.

Although BC occurs sporadically in most cases, a percentage of male or female BCs have an inherited genetic predisposition. BRCA1/2 mutations are the most frequently found. In the case of male BCs, germ line BRCA2 mutations are the most frequently associated with hereditary BC. In our series of 72 male BCs, only 14 (19.4%) had performed a genetic testing. BRCA2 mutations were most frequently associated with male hereditary BC: five men had a mutation in the BRCA2 gene and only one man had a mutation in the BRCA1 gene. In addition, one male BC was associated with a mutation in the MUTYH gene and another male presented a Variant of Uncertain Significance in MSH6 and TP53 genes. In the remaining 6 cases, the genetic studies were negative (Table 1).

The presence of BC in men within a family with BC has been reported to indicate a high probability of a BRCA2 mutation, with a 60–76% probability of carrying this mutation [9]. Csokay et al. [10] found 6 BCs with BRCA2 mutations (33%) in their total series of 18 male BCs.

Men who inherit a germline BRCA2 mutation have an estimated absolute risk of BC of 7-8%; risk almost 100 times higher than in the general male population, whose lifetime risk is estimated to be 0.1% [11-13]. The risk is lower for BRCA1 carriers, with an estimated absolute risk of 1% [11]. Men with mutations in the BRCA2 gene have a 7 in 100 chance of developing BC, while men with BRCA1 gene mutations have a 1 in 100 chance of developing BC.

The incidence of BRCA mutations varies based on ethnicity and the strength of family history. Of the men with BC, regardless of family history, Couchet al. [11] found that 14% had a deleterious mutation in BRCA2. The incidence of BRCA2 mutations varies in the literature (Table 4).

Table4. Review of the literature. Mutaciones BRCA2 en el CM masculino.

Author / year	Men with BRCA2 mutations (no. of cases and percentage)	% of men with a family history
Couch FJ/ 1996[14]	7 of50 (14 %)	80
Friedman LS/ 1997 [15]	2 of54 (4 %)	17
Haraldsson K/ 1998 [16]	7 of34 (21 %)	13
Díez O/ 2000 [17]	3 of 17 (18 %)	53
Kwiatkowska E/ 2001[18]	4 of37 (11 %)	13
Basham VM/ 2002 [19]	3 of 94(8 %)	20
Ottini L/ 2003 [20]	4 of25 (16%)	28
Ding YC/ 2011 [21]	18 of 115 (16 %)	22
André S/ 2019 [22]	13 of 44 (29 %)	15
Vietri MT/ 2020 [23]	8 of 28 (29 %)	82

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BRCA1 mutations occur very rarely (0–4%) [24, 25], except in individuals of Ashkenazi Jewish ethnicity. One study found that 4.5% of Ashkenazi Jewish men with BC carried a BRCA1 mutation [26]. In this ethnic group, two founder mutations in BRCA1 and one in BRCA2 have been described.

As with female BC, family history is associated with an increased risk of BC in men. About 1 out of 5 men who develop BC has a family history of the disease. Approximately 15-20% of male BCs have a family history of BC and/or ovarian cancer, compared to 7% of the general male population; although only 10% of male BCs can be attributed to a known genetic origin [27]. Zheng et al showed in their study that 16.2% of men with BC had a first-degree family history of female BC [28].

We highlight the fact that the male BCs in our series associated with germline mutations had an intense familial aggregation of cancer and three of them presented bilateral BCs (Table 2). Likewise, we highlight that 3 of the 5 men (not related to each other) with BRCA2-positive BC presented the same type of mutation: c.9382C> T (p.Arg3128Ter) (Table 2).

In our series, more than half (53.4%) had at least one first-degree relative with cancer. One in three male BCs that were not genetically studied (18 of 52 BCs, 34.6%) presented an intense familial aggregation of cancer that made us suspect that we were facing a hereditary cancer syndrome phenotype. Men with first-degree relatives of BC have a 2-3 times higher risk of BC [5], this risk increases if the history was early onset (<35 years) and as the number of affected first-degree relatives increases [29].

Genes other than BRCA are less common, but may also be associated with a greater predisposition to male BC: PALB2 [30, 31], CHEK2 [32], PTEN (Cowden syndrome) [33], TP53 (Li-Fraumeni syndrome) [34] and repair genes or mismatch repair (Lynch syndrome) [35]. The CYP17 gene, which encodes an enzyme that produces sex steroids, has also been proposed [36]. In our study, we found a pathogenic variant mutation (MUTYH c536A> G, pTyr179Cys) in the MUTYH gene (DNA repair gene whose biallelic germ line variants cause the MUTYH-associated polyposis syndrome), several studies suggest that pathogenic variants of this gene may have a role in male BC [37, 38]. Other genes are more disputed. However, while these genes may increase relative risk, the absolute risk for male BC is quite low (Table 5) [13]. Only the BRCA2 gene is considered a high-risk gene.

Table 5. Review of the literature: Genes for predisposition to male BC and their relative risk.

Gene	**Relative risk (RR) of BC in men**
BRCA2	70-80
BRCA1	15-18
PALB2	4-13
CHEK2	4-10

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In our series, the mean age of onset of all male BCs was 68 years, according to other studies [39, 40], very similar to the mean age of men with BC carrying mutations (66.2 years). It is important to insist that the age at diagnosis of male BC cannot be used as an indicator of genetic mutation since, unlike what happens with female BC, the age of presentation of sporadic and hereditary male BC is late and does not show significant differences between the two [41, 42].

All men diagnosed with BC should receive genetic counseling, as they are candidates for genetic testing (National Comprehensive Cancer Network -NCCN- Clinical Practice Guidelines in Oncology) [43]. We must bear in mind that male BC may be the first manifestation of a BRCA mutation in a family, which reinforces the indication to perform a genetic study in all men with MC. In our series, it is striking that more than 80% of the men did not undergo any genetic testing, despite the fact that more than 50% had familial aggregation of cancer.

Men are not usually the first members in the family to get genetic testing. A family member who did get tested usually refers them. One possible reason is medical bias: the information given during genetic counseling for men with BRCA is considered to be, in many cases, insufficient. Other reasons include: a lack of social awareness that BC can affect men or that genes with a higher predisposition to BC can be transmitted by men, and also a less willingness of men to perform genetic studies. Their main motivation for conducting the genetic study is usually concern for his daughters [24].

Globally, male BC is similar to postmenopausal female (hormone dependent). The ultrastructural features of BC in men are very similar to BC in women [44]. However, men tend to have a lower histological grade and a higher proportion of hormone receptors (in our series, 92.4% of BC were estrogen receptor positive). Current knowledge of the histological and molecular characteristics in male BRCA1/2 mutation carriers is limited. Studies show that male BCs in BRCA2 mutation carriers have a higher stage and histological grade, greater lymphatic involvement, and greater positivity for hormone receptors and HER2, compared to BRCA2-positive female BCs [42, 45]. Most of these are non-special invasive breast carcinomas, but there is also an overrepresentation of invasive micro papillary carcinomas [41]. Immunophenotypically, there is an association with a higher frequency of the intrinsic luminal B phenotype [46].

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) [47]. Additionally, 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 [48].

We must be aware to the possibility of synchronous/metachronous development of new cancers in male BC patients, especially those with mutations in the BRCA2 gene. In our series, one in three (24 of 72 BCs, 33.3%) had at least one other malignant neoplasm in addition to their BC, with prostate adenocarcinoma being the most frequent associated neoplasm.

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Conclusion

The male BC represents 0.9% of our series of BCs. The mean age of male BCs was 68 years, similar to that of men with hereditary BCs (66.2 years). We observed a high frequency of bilaterality (4%). We highlight the underuse of genetic testing: only 14 of 72 male BCs (19.4%). The most frequently detected pathogenic mutation (n = 5, 7%) was in the BRCA2 gene, and 3 of them (unrelated) presented the same type of mutation (c.9382C> T (p.Arg3128Ter) in exon 25). We also detected a pathogenic mutation in the BRCA1 and the MUTYH gene. One in three male BCs that were not genetically studied (18 of 52 BCs, 34.6%) had an intense familial aggregation of cancer that was compatible with a hereditary cancer syndrome. In our series, one in three (24 of 72 BCs) had at least one other malignant neoplasm in addition to their BC, with prostate adenocarcinoma being the most frequent associated neoplasm, (n = 8). Up to 15.3% (11 of 72 BCs) were diagnosed with 3 or more malignant neoplasms.

It is necessary to increase the genetic testing of men with BC (to do it to all male BCs) to be able to identify hereditary BCs and thus be able to offer the pertinent preventive measures to them and their families.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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