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EPIDEMIOLOGY

Clinical and pathologic characteristics of *BRCA*-positive and *BRCA*-negative male breast cancer patients: results from a collaborative multicenter study in Italy

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Abstract Recently, the number of studies on male breast cancer (MBC) has been increasing. However, as MBC is a rare disease there are difficulties to undertake studies to identify specific MBC subgroups. At present, it is still largely unknown whether *BRCA*-related breast cancer (BC) in men may display specific characteristics as it is for *BRCA*-related BC in women. To investigate the clinical–pathologic features of MBC in association with *BRCA* mutations we established a collaborative Italian Multicenter Study on MBC with the aim to recruit a large series of MBCs. A total of 382 MBCs, including 50 *BRCA* carriers, were collected from ten Italian Investigation Centres covering the whole country. In MBC patients, *BRCA2* mutations were associated with family history of breast/ovarian cancer ($p < 0.0001$), personal history of other cancers ($p = 0.044$) and contralateral BC ($p = 0.001$). *BRCA2*-associated MBCs presented with high tumor grade ($p = 0.001$), PR− ($p = 0.026$) and HER2+ ($p = 0.001$) status. In a multivariate logistic model *BRCA2* mutations showed positive

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association with personal history of other cancers (OR 11.42, 95 % CI 1.79–73.08) and high tumor grade (OR 4.93, 95 % CI 1.02–23.88) and inverse association with PR+ status (OR 0.19, 95 % CI 0.04–0.92). Based on immunohistochemical (IHC) profile, four molecular subtypes of MBC were identified. Luminal A was the most common subtype (67.7 %), luminal B was observed in 26.5 % of the cases and HER2 positive and triple negative were represented by 2.1 % and 3.7 % of tumors, respectively. Intriguingly, we found that both luminal B and HER2 positive subtypes were associated with high tumor grade ($p = 0.003$ and 0.006, respectively) and with *BRCA2* mutations ($p = 0.016$ and 0.001, respectively). In conclusion, our findings indicate that *BRCA2*-related MBCs represent a subgroup of tumors with a peculiar phenotype characterized by aggressive behavior. The identification of a *BRCA2*-associated phenotype might define a subset of MBC patients eligible for personalized clinical management.

Keywords Male breast cancer · *BRCA1* · *BRCA2* · Clinical–pathologic features · Molecular subtypes

Introduction

Breast cancer (BC) in men is a rare disease accounting for <1 % of all cancers in men and <1 % of all BCs. However, recent epidemiologic studies suggest that the incidence of male breast cancer (MBC) is increasing by 1.1 % yearly [1, 2].

Compared with female BC (FBC), MBC occurs later in life, with higher stage and lower grade and more often displays positive estrogen and progesterone receptors (ER and PR) status [3, 4].

MBC is likely to be caused by the concurrent effects of different risk factors, including hormonal, environmental and particularly genetic risk factors, such as mutations in *BRCA1* and, mainly, *BRCA2* genes [5, 6].

It is now well established that in women *BRCA*-associated BCs tend to manifest specific genotype–phenotype correlations [7]. In particular, *BRCA1*-related BCs have distinct morphology and show a triple negative (ER−, PR−, HER2−) phenotype [8]. By contrast, *BRCA2*-related BCs are a heterogeneous group not fully characterized [9–11]. The current knowledge on phenotypic characteristics of *BRCA*-associated MBCs is thus far quite limited [5].

Furthermore, while it is generally accepted that FBC is a heterogeneous disease, whether MBC can be classified into comprehensive molecular subtypes remains to be elucidated. Indeed, the classification into molecular subtypes based on immuno-phenotypic features, as proposed for FBC, is still controversial in MBC. It has been reported that the luminal A (ER+ and/or PR+, HER2−) and luminal B (ER+ and/or PR+, HER2+) are the most common subtypes in MBC, whereas triple negative (ER−, PR−, HER2−) and HER2 positive (HER2+/ER−, PR−) are very rare [12–14].

Overall, knowledge about specific biological and molecular characteristics of MBC is still largely unknown.

Given the paucity of data and the rarity of the disease, an effort in establishing collaborative studies is fundamental to obtain large series of MBCs with detailed epidemiological and molecular data. Therefore, we established the first Italian Multicenter Study on MBC to recruit a large series of cases from the whole Country, with the aim to better examine the clinical–pathologic features of MBC cases in association with *BRCA* mutational status and to identify molecular subtypes of MBC that could provide useful information for understanding the pathogenesis of this disease and, eventually, for clinical management of MBC patients.

Materials and methods

Study population

For this study, 382 MBC cases were enrolled in the framework of the collaborative Italian Multicenter Study on MBC. We recruited MBC cases from a total of ten Italian Investigation Centres in different areas of the Country including Northern (Istituto Nazionale dei Tumori, Milan; Istituto Europeo di Oncologia, Milan; Centro di Riferimento Oncologico, Aviano; Istituto Oncologico Veneto, Padua; University of Modena and Reggio Emilia, Modena; Istituto Nazionale per la Ricerca sul Cancro, Genoa), Central (Cancer Research and Prevention Institute, Florence; Sapienza University of Rome, Rome), and Southern (National Cancer Centre, Bari; University of Palermo, Palermo) Italy.

In this study, we have expanded our previous series of 108 MBC cases from Florence [5] up to 126 MBCs and enrolled 256 MBC cases from additional nine Italian Investigation Centres. For each case the following information was collected: (1) detailed information on personal history of other cancers at any site; (2) detailed information on family history (FH) for cancer at any sites; (3) clinical–pathologic and molecular data, including histology, grade, stage, node status, ER, PR, Ki-67, and HER2 status; and (4) *BRCA1* and *BRCA2* mutational status. All information was collected by a geneticist and validated by the relevant sources, mainly local Cancer and Mortality Registries.

Clinicopathological data were collected through several mechanisms, including medical records and pathology reports. For some centers, tumor pathology was independently reviewed by study pathologists. Four cases were excluded from the current analysis because of missing age

at diagnosis. Then, this study is focused on 378 subjects with 394 BCs (including 16 subjects with contralateral BC).

The study was approved by the local ethical committee. Written informed consent was obtained from all study subjects.

Molecular characterization

BRCA1 and *BRCA2* mutation analysis was performed in the frame of genetic counselling programs at the center of origin for all MBC cases. *BRCA1/2* mutations were classified according to their potential functional effect and only the pathogenic loss-of-function mutations were considered in the analysis.

ER, PR, Ki-67, and HER2 status of breast tumors were extracted from medical, pathology, or tumor registry records or obtained from IHC analysis of sections from formalin-fixed, paraffin-embedded primary mammary tumor blocks. HER2 status was assessed by FISH analysis in ambiguous cases (IHC score = 2+). Cut-off values were as previously reported [15, 16].

Based on IHC profiles, MBCs were classified according to the following molecular subtypes: luminal A (ER+ and/or PR+, HER2−), luminal B (ER+ and/or PR+, HER2+), HER2 positive (ER− and PR−, HER2+), and triple negative (ER−, PR−, HER2−).

Statistical analysis

The association between selected clinical–pathologic and molecular features and specific groups of MBCs was assessed by using Fisher's exact test or χ^2 for trend as appropriate (two sided). A multivariate logistic model including selected parameters (cancer personal history, 1st degree FH of breast/ovarian cancer, contralateral cancer, grading, stage, PR and HER2 status) was used to evaluate the association between the characteristics included in the model and *BRCA2* mutations. p values ≤ 0.05 were considered statistically significant.

Results

Clinical–pathologic characteristics of MBC cases

Clinical characteristics of 378 MBC patients and pathologic features of the 394 breast tumors from the 378 MBC patients included in this study are reported in Table 1.

Age at first MBC diagnosis ranged between 22 and 90 years, with a mean age of 60.9 years (SD: 11.9). Six out of 139 cases (4.3 %) with a positive FH of breast or ovarian cancer in first-degree relatives had a first-degree male

Table 1 Clinical–pathologic characteristics of 394 breast tumors from 378 MBC patients

Characteristics[a]	*N*	%
Age at diagnosis		
<30	3	0.8
31–40	22	5.8
41–50	47	12.4
51–60	98	25.9
61–70	129	34.2
71–80	69	18.3
>80	10	2.6
1st degree FH of breast/ovarian cancer		
Negative	239	63.2
Positive	139	36.8
Personal history of other cancers		
Negative	321	84.9
Positive	57	15.1
Contralateral BC		
No	362	95.9
Yes	16	4.1
BRCA1/2 Mutational status		
BRCA1 mutation positive	4	1.1
BRCA2 mutation positive	46	12.2
BRCA1/2 wild-type	328	86.7
Histology		
Invasive ductal carcinoma	261	87.0
In situ ductal carcinoma	22	7.3
Medullary carcinoma	1	0.3
Lobular carcinoma	4	1.4
Other	12	4.0
Grading		
1	33	12.5
2	153	57.7
3	79	29.8
Stage		
I	93	42.3
II	80	36.4
III	40	18.2
IV	7	3.1
ER		
Negative	23	8.6
Positive	245	91.4
PR		
Negative	43	16.1
Positive	224	83.9
HER2		
Negative	139	71.6
Positive	55	28.4
Node status		
Negative	145	58.0
Positive	105	42.0
Ki-67		
Low	119	58.0
High	86	42.0

[a] Some data for each parameter are non available

relative affected with MBC. 57 cases (15.1 %) had one or two other malignancies, prostate and bladder cancer being the most frequently reported (14 and 6 cases, respectively). Moreover, 16 patients (4.1 %) had a diagnosis of contralateral BC. Four MBC patients carried *BRCA1* (1.1 %) and 46 *BRCA2* (12.2 %) mutations. The majority of tumors were invasive ductal carcinoma (87 %), followed by ductal carcinoma in situ (7.3 %). About 58 % of MBCs were G2 and about 80 % of MBCs presented with stages I–II of the disease. The great majority of tumors were ER+ (91.4 %) and PR+ (83.9 %). About 28 % of tumors were HER2+ and 58 % showed negative node status and low proliferative activity (Ki-67 low).

The 4 *BRCA1* mutation positive MBC patients had a mean age at diagnosis of 62 years (SD: 7.7), and 3 out of 4 have a positive first-degree FH of breast and/or ovarian cancer. None of the 4 cases had a personal history of other cancers or a diagnosis of contralateral BC. All 4 *BRCA1*-related MBCs were invasive ductal carcinomas with HER2− status. The majority were G3 (2 out of 3), stage II (2 out of 3), PR+ (3 out of 4), lymph-node positive (2 out of 3), and Ki-67 high (2 out of 3) tumors. Two of the 4 *BRCA1*-related MBCs were ER+ and a statistically significant association ($p = 0.037$) emerged between *BRCA1* mutations and ER− status (data not shown).

The 46 *BRCA2* mutation positive MBC patients showed a mean age at diagnosis of 58.9 years (SD: 11.7), and 31 (67.4 %) had a positive first-degree FH of breast and/or ovarian cancer (Table 2). 12 cases (26.1 %) had a personal history of other cancers, mainly prostate cancer (58 %) and 7 patients (15.2 %) had a diagnosis of contralateral BC. *BRCA2*-related MBCs were mostly invasive ductal carcinomas (88.3 %), G3 (54.8 %), stages I–II (62.5 %), ER+ (89.7 %), PR+ (67.9 %), HER2+ (63.2 %), lymph-node positive (56.7 %), and Ki-67 high (56.2 %) tumors. As shown in Table 2, statistically significant associations emerged between *BRCA2* mutation and FH of breast and/or ovarian cancer ($p < 0.0001$), personal history of other cancers ($p = 0.044$), contralateral BC ($p = 0.001$), tumor grade 3 ($p = 0.001$), PR− ($p = 0.026$), and HER2+ status ($p = 0.001$). In a multivariate logistic analysis *BRCA2* mutations showed a positive association with cancer personal history (OR 11.42; 95 % CI 1.79–73.08; $p = 0.01$) and tumor grade 3 (OR 4.93; 95 % CI 1.02–23.88; $p = 0.048$) and, on the other hand, an inverse association with PR+ status (OR 0.19; 95 % CI 0.04–0.92; $p = 0.039$) (data not shown). In a separate age-adjusted logistic model the association with cancer personal history was confirmed ($p = 0.017$).

Molecular subtypes of MBC cases

The classification into molecular subtypes and their characterization was available for a subset of 189 tumors,

Table 2 Association between clinical–pathologic characteristics and *BRCA2* mutations in MBCs

Characteristics[a]	*BRCA1/2* wt *N* (%)	*BRCA2* mutation positive *N* (%)	p[b]
Age at diagnosis			
≤50	59 (18.0)	13 (28.3)	
>50	269 (82.0)	33 (71.7)	0.11
1st degree FH of breast/ovarian cancer			
Negative	223 (68.0)	15 (32.6)	
Positive	105 (32.0)	31 (67.4)	**<0.0001**
Personal history of other cancers			
No	284 (86.6)	34 (73.9)	
Yes	44 (13.4)	12 (26.1)	**0.044**
Contralateral BC			
No	319 (97.3)	39 (84.8)	
Yes	9 (2.7)	7 (15.2)	**0.001**
Histology			
Invasive ductal carcinoma	220 (86.6)	30 (88.3)	
In situ ductal carcinoma	20 (7.9)	2 (5.9)	
Medullary carcinoma	0 (0)	1 (2.9)	
Lobular carcinoma	4 (1.6)	0 (0)	0.08
Other	10 (3.9)	1 (2.9)	
Grading			
1–2	169 (74.4)	14 (45.2)	
3	58 (25.6)	17 (54.8)	**0.001**
Stage			
I–II	151 (80.7)	15 (62.5)	
III–IV	36 (19.3)	9 (37.5)	0.06
ER			
Negative	18 (7.8)	3 (10.3)	
Positive	213 (92.2)	26 (89.7)	0.71
PR			
Negative	33 (14.3)	9 (32.1)	
Positive	198 (85.7)	19 (67.9)	**0.026**
HER2			
Negative	126 (75.0)	7 (36.8)	
Positive	42 (25.0)	12 (63.2)	**0.001**
Node status			
Negative	129 (61.7)	13 (43.3)	
Positive	80 (38.3)	17 (56.7)	0.07
Ki-67			
Low	110 (60.1)	7 (43.8)	
High	73 (39.9)	9 (56.2)	0.29

BRCA1 mutated cases and secondary tumors were excluded from the analysis

Statistically significant values ($p \leq 0.05$) are indicated in bold

[a] Some data for each parameter are not available

[b] p value from Fisher exact test or χ^2 for trend, as appropriate

including 4 *BRCA1*− and 19 *BRCA2*− associated MBCs, with complete information on ER, PR, and HER2 status (Table 3). For 128 out of 189 tumors (67.7 %) a luminal A subtype (ER+ and/or PR+, HER2−) emerged, whereas 50 cases (26.5 %) showed a luminal B (ER+ and/or PR+, HER2+) subtype. HER2 positive (ER− and PR−, HER2+) and triple negative (ER−, PR−, HER2−) subtypes were much less common and represented by only 4 (2.1 %) and 7 (3.7 %) tumors, respectively. MBC cases with luminal B subtype tended to be younger (age ≤50 years) than those with luminal A subtype ($p = 0.049$).

Of the 4 *BRCA1*-related MBC cases, 3 showed a luminal A tumor and 1 a triple negative tumor. Of the 19 *BRCA2*-related MBCs, 7 were luminal A, 9 luminal B, and 3 HER2 positive. Notably, all 7 cases with triple negative tumors were *BRCA2* mutation negative MBCs. Indeed, *BRCA2* mutation positive status was significantly associated with both HER2 positive subtypes, luminal B and HER2 positive ($p = 0.016$ and 0.001, respectively).

The majority of the luminal A tumors (87/119, 73.1 %) and triple negative tumors (4/6, 66.7 %) had low and intermediate tumor grades (G1 and G2). In comparison, high grade (G3) tumors were more frequent in luminal B (24/45, 53.3 %) and in HER2 positive (4/4; 100 %) subtypes than in luminal A ($p = 0.003$ and 0.006, respectively).

Table 3 Molecular and clinical–pathological characteristics of MBC subtypes

	Luminal A[b] (total 128)	Luminal B[b] (total 50)		HER2 positive[b] (total 4)		Triple negative[b] (total 7)	
	N (%)	*N* (%)	*p**	*N* (%)	*p**	*N* (%)	*p**
Age at diagnosis							
≤50	18 (14.1)	14 (28.0)		1 (25.0)		0 (0)	
>50	110 (85.9)	36 (72.0)	**0.049**	3 (75.0)	0.47	7 (100)	0.59
1st degree FH of breast/ovarian cancer							
Negative	86 (67.2)	35 (70.0)		2 (50.0)		6 (85.7)	
Positive	42 (32.8)	15 (30.0)	0.86	2 (50.0)	0.60	1 (14.3)	0.43
Personal history of other cancers							
No	105 (82.0)	44 (88.0)		4 (100)		6 (85.7)	
Yes	23 (18.0)	6 (12.0)	0.38	0 (0)	1.0	1 (14.3)	1.0
BRCA1 mutations							
Negative	125 (97.7)	50 (100)		4 (100)		6 (85.7)	
Positive	3 (2.3)	0 (0)	0.56	0 (0)	1.0	1 (14.3)	0.19
BRCA2 mutations							
Negative	121(94.5)	41 (82.0)		1 (25.0)		7 (100)	
Positive	7 (5.5)	9 (18.0)	**0.016**	3 (75.0)	**0.001**	0 (0)	1.0
Grading[a]							
1 + 2	87 (73.1)	21 (46.7)		0 (0)		4 (66.7)	
3	32 (26.9)	24 (53.3)	**0.003**	4 (100)	**0.006**	2 (33.3)	0.66
Stage[a]							
I–II	76 (82.6)	31 (75.6)		2 (66.7)		6 (85.7)	
III–IV	16 (17.4)	10 (24.4)	0.35	1 (33.3)	0.45	1 (14.3)	1.0
Node status[a]							
Negative	54 (55.7)	20 (44.4)		0 (0)		4 (80.0)	
Positive	43 (44.3)	25 (55.6)	0.28	3 (100)	0.094	1 (20.0)	0.39
Ki-67[a]							
Low	70 (61.9)	20 (51.3)		1 (25.0)		4 (57.1)	
High	43 (38.1)	19 (48.7)	0.26	3 (75.0)	0.30	3 (42.9)	1.0

Combined hormonal status (ER, PR, HER2) was available for 189 cases

Statistically significant values ($p \leq 0.05$) are indicated in bold

[a] Some data are not available

[b] Luminal A: ER+ and/or PR+, HER2−; luminal B: ER+ and/or PR+, HER2+; HER2 positive: ER−, PR−, HER2+; triple negative: ER−, PR−, HER2−

* *p* value from Fisher exact test

Discussion

In this study, a large series of MBC cases, derived from the collaborative Italian Multicenter Study on MBC, was analyzed to investigate the clinical–pathologic features of MBC in association with *BRCA* mutations and to characterize immuno-phenotypic subtypes of MBC. A total of 382 MBC cases, including 50 *BRCA1/2* mutation carriers, and their clinical–pathologic characteristics, were collected from ten Italian Investigation Centres in different areas of the Country, from Northern to Southern Italy. Despite differences in study populations and method of collecting data, the distributions of clinical–pathologic variables considered in this study (i.e., ER, PR, and HER2) were generally consistent across different Investigation Centers. To the best of our knowledge this series represents the largest MBC series ever assembled in a single country for which *BRCA1* and *BRCA2* mutational status and extensive clinical–pathologic data are available.

As expected, *BRCA2* mutations were found to be more frequent than *BRCA1* mutations (12.2 vs 1.1 %). It is noteworthy that two of the four *BRCA1* mutation carriers found in our series harbor the same mutation that was previously identified as a founder mutation in Central Italy [17]. Compared with previous studies, in our series age at diagnosis was lower and the percentage of cases with a positive first-degree FH was higher [18–21]. This could reflect the presence of MBC patients enrolled in a context of genetic counselling programs, which are more frequently characterized by familial cancer and younger age at diagnosis. On the other hand, the pathologic characteristics of male breast tumors, including histology, stage, grade, and hormone receptor expression were consistent with former studies (Table 1 in Supplementary material). Thus, our series can be regarded as representative. Overall, MBCs present as invasive ductal carcinomas, G2 and stages I–II disease and express ER and PR.

Taken advantage of our large *BRCA1/2* characterized MBC series we investigated whether specific *BRCA*-associated phenotypes could be identified in MBC. We found that all four *BRCA1*-associated MBCs were HER2− with one case disclosing a triple negative phenotype. The majority of *BRCA1*-related MBCs were G3 tumors and show high proliferative activity. Although based on a few cases, our results may suggest that *BRCA1*-related BCs in men represent a rare event characterized by a phenotype similar to that observed in women. On the other hand, *BRCA2*-associated MBCs display a characteristic *BRCA2*-associated BC phenotype not identified in women [11]. In particular, *BRCA2*-associated MBCs present with high tumor grade, the absence of PR expression, and HER2 positive status. Indeed, we have previously reported statistically significant associations between *BRCA2* tumors and high tumor grade, PR− and HER2+ status in a series of 108 MBCs [5]. In this study, these associations also emerged either including or excluding (data not shown) the previous analyzed series thus confirming on a large and independent series our earlier results.

Here, we also observed that germ-line *BRCA2* mutations are associated with positive personal history of other cancers and contralateral BC in MBC patients. These findings are particularly relevant for a personalized clinical management of MBC patients. In fact, they confirm the needing of an intensive cancer surveillance, particularly prostate cancer surveillance [22], after first diagnosis of BC and might raise the question of performing a bilateral prophylactic mastectomy at the surgery time in *BRCA2*-associated MBC patients. Furthermore it is noteworthy that, in a multivariate logistic analysis, cancer personal history, high tumor grade, and PR− status emerged to be all statistically associated with *BRCA2* mutations independently. Taking into consideration that the majority of MBCs are PR+, the finding that PR− MBCs are associated with *BRCA2* mutations may have an important predictive value, thus improving the earlier detection of *BRCA2* mutation carriers.

Based on IHC profile, in this study we also characterized molecular subtypes of MBC. Luminal A resulted the most common subtype, followed by luminal B, triple negative, and HER2 positive subtypes. Overall, our results are consistent with a recent published article showing that luminal A and, to a lesser extent, luminal B types represent the vast majority of BC in men whereas triple negative and HER2 positive subtypes are rare [13]. Intriguingly, we found that both HER2 positive and luminal B subtypes were associated with *BRCA2* mutations. Notably, all previous studies were performed in MBCs not characterized for *BRCA2* mutations, and, based on *BRCA2* mutation frequency and on the number of cases analyzed, *BRCA2*-related MBCs were likely rare, if any, in the published series. This could probably explain why HER2 positive and luminal B subtypes have been, thus far, infrequently reported in MBC [12–14]. We also found a statistically significant association between both HER2 positive and luminal B subtypes with high tumor grade. Taken together, these data suggest that in men luminal B and HER2 positive BC subtypes are associated with characteristic unfavorable prognostic factors, such as high grade, and are *BRCA2*-related BCs.

Although we had a large sample size, missing data for molecular markers may have limited the power of our findings. Thus, a further effort in collecting more MBC cases together with their epidemiological and molecular features is currently in progress.

In conclusion, our findings indicate that *BRCA2*-related MBCs represent a subgroup of tumors with a peculiar phenotype characterized by aggressive behavior. The identification of a *BRCA2*-associated phenotype might

define a subset of MBC patients eligible for personalized clinical management and for targeted therapy. Overall, results from this study may be helpful in improving the understandings and the management of this rare disease and deserve to be confirmed in large international collaborative studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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