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Frequency of breast cancer with hereditary risk features in Spain: Analysis from GEICAM "El Álamo III" retrospective study

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Abstract

Purpose

To determine the frequency of breast cancer (BC) patients with hereditary risk features in a wide retrospective cohort of patients in Spain.

Methods

a retrospective analysis was conducted from 10,638 BC patients diagnosed between 1998 and 2001 in the GEICAM registry "El Álamo III", dividing them into four groups according to modified ESMO and SEOM hereditary cancer risk criteria: *Sporadic breast cancer group (R0)*; *Individual risk group (IR)*; *Familial risk group (FR)*; *Individual and familial risk group (IFR)* with both individual and familial risk criteria.

Results

7,641 patients were evaluable. Of them, 2,252 patients (29.5%) had at least one hereditary risk criteria, being subclassified in: FR 1.105 (14.5%), IR 970 (12.7%), IFR 177 (2.3%).

There was a higher frequency of newly diagnosed metastatic patients in the IR group (5.1% vs 3.2%, p = 0.02). In contrast, in RO were lower proportion of big tumors (> T2) (43.8% vs 47.4%, p = 0.023), nodal involvement (43.4% vs 48.1%, p = 0.004) and lower histological grades (20.9% G3 for the R0 vs 29.8%) when compared to patients with any risk criteria.

Conclusions

Almost three out of ten BC patients have at least one hereditary risk cancer feature that would warrant further genetic counseling. Patients with hereditary cancer risk seems to be diagnosed with worse prognosis factors.

Introduction

Breast cancer is the most frequent malignancy in women [1]. In Spain, it is estimated an age-standardized (European standard population) incidence of 85 cases per 100,000 women [2], that would be translated in 25,200 new cases per year. Breast cancer deaths are estimated to be 18% of cancer mortality [3]. Known risk factors are age, late and non-parity, post-menopausal status, and familial background. Preventive and early diagnostic strategies are necessary to reduce the disease burden. However, these strategies vary among countries and even within regions of the same country [4], while there is an increasing interest in adapting screening strategies to the basal breast cancer risk [5]. In this sense, identifying high-risk groups in terms of frequency and prognosis is mandatory for a rationale preventive approach.

It is widely described in the literature that up to 25% of breast cancer patients have a familial/hereditary background, that can be explained through a genetic condition only in a small percentage [6]. Population studies that support this data are scarce, and whether these patients have different prognostic factors or not is a term of debate. Identification of patients at risk of hereditary breast cancer is especially important for those cases that harbor pathological genetic germline mutations in BRCA1 or 2.

Recently, the Spanish Medical Oncology Society (SEOM) have suggested clinical criteria for genetic test selection of hereditary breast cancer patients through a clinical guideline [7]. In the European context, the European Society for Medical Oncology (ESMO) has its own guidelines [6]. In the North American context, the criteria seem to be less restrictive [8].

The implications of genetic testing are nowadays going beyond the prevention and early detection area, influencing also therapeutic decisions with the use of specific treatments, such as oral PARP inhibitors or platinum-based regimens. Currently, several clinical trials are ongoing for different clinical scenarios with these treatments, from the metastatic disease to the adjuvant setting, being in the spotlight of the oncology breast cancer community [9].

In summary, a better understanding of the epidemiological landscape of breast cancer patients with hereditary risk features is of interest.

El Álamo Project is a retrospective observational study that includes 26,658 breast cancer patients diagnosed between 1990 and 2001 across 43 Spanish Hospitals and distributed in three cohorts: El Alamo I with 4,532 patients diagnosed between 1990 and 1993, El Alamo II with 10,849 patients diagnosed between 1994 and 1997 and El Alamo III with 11,277 patients diagnosed between 1998 and 2001. El Alamo project has the aim to describe patterns of presentation, management and outcomes of breast cancer in Spain [10, 11]. The latest version, *El Álamo III*, included for the first time the familial background of patients, in addition to clinical and personal features linked to hereditary risk (i.e age, bilaterality, triple negative histology).

With more than eleven thousand invasive breast cancer patients diagnosed in 11 of the 17 Spanish regions [12], this is an unique opportunity to explore the previously mentioned questions regarding hereditary breast cancer epidemiology in Spain, since no studies of this kind are currently available in the European context.

The objectives of this study are to analyze the frequency and clinical/pathological characteristics of Spanish invasive breast cancer patients with hereditary risk features.

Patients and methods

Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the participant institutions and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. "Comité Etico de Investigación Clínica del Area 1" IRB reviewed and approved the Alamo project.

Study design

This is a retrospective analysis from *El Álamo III* project that included 11,277 breast cancer patients. *El* Alamo focused on female breast cancer and only some centers recruited a small number of male patients (37 cases, 0.3% of the total sample), so they were excluded from this analysis. Non invasive carcinoma breast cancer cases (602 patients, 5.3%) were also excluded.

Questionnaires including data regarding individual tumor information and familial features were completed by the clinical investigators (it can be found in reference [12]. Based on these data, hereditary risk groups were defined, according to the following modified SEOM and ESMO criteria [6, 7].

Modified ESMO-SEOM Criteria for hereditary breast cancer risk

The individual criteria were: breast cancer diagnosis under 40 years or breast cancer diagnosis under 50 years if one of the following: triple negative breast cancer (TNBC) histology and/or bilateral (synchronous or metachronous) breast cancer or breast cancer at any age together with ovarian cancer. The familial criteria were: the presence of first or second degree relatives with the following features: 3 relatives (including the patient) with breast and /or ovarian cancer or 2 relatives (including the patient), if the relative fulfill any of the individual criteria above mentioned, regardless degree; or 2 relatives (including the patient) if is first degree and diagnosed with breast and/or ovarian cancer.

According to the individual and familial criteria, patients were divided into 4 different subgroups: *Sporadic breast cancer group (R0)* (Control group) without individual or familial risk criteria; *Individual risk group (IR)* with no familial or not determined (ND) familial risk, but with individual risk criteria; *Familial risk group (FR)* with no individual or ND individual risk, but with familial risk criteria; *Individual and familial risk group (IFR)* with both individual and familial risk criteria. Global hereditary risk group (GHR) comprises the three last categories, namely IR or FR or IFR.

Statistical methods

Chi-square and unpaired t student/Anova were used to compare categorical and continuous variables respectively. All statistical tests had a significance level of 0.05 unless stated otherwise. Data were analysed using SPSS® version 21 (IBM corporation).

Table 1. Individual and familial features distribution in the global sample.

Individual risk features: 1902 patients (17,9%) had not information		
	N	%
Age < 40 y[a]	973	11,1
> = 40 y & <50y & TNBC	122	1,4
> = 40 y & <50y & Bilateral	19	0,2
Ovarian cancer	33	0,4
Non personal risk features	7589	86,9
Total	8736	100,0
Familial background features: 1944 patients (18,3%) had not information		
	N	%
2 relatives (patient + relative with ovarian cancer)	111	1,3
3 or more relatives (patient + 2 relatives with BC and/or ovarian cancer, regardless degree)	434	5,0
2 relatives (patient + 1 BC of first degree)	737	8,5
No family features[b]	7412	85,2
Total	8694	100,0

[a] 67 patients were also TNBC; 6 were also bilateral BC; 4 had also ovarian cancer; 1 was TNBC and bilateral BC;

[b]528 of them had 1 relative but in second degree with BC, not considered in consequence at hereditary risk

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Results

Frequency and characteristics of hereditary risk breast cancer patients

From 1998 to 2001, 10,638 women with invasive breast cancer were included in the study. Patients who had enough information to be sub-classified as one of the four risk subgroups accounted for 7,641 (71.8%). The individual and familial risk criteria for hereditary breast cancer of the global sample are described in Table 1. Eleven out of the 17 different Spanish regions were represented (64.7%).

Of these evaluable patients, 2,252 patients (29.5%) had at least one hereditary risk criteria, constituting the global hereditary risk group (GHR). The 5,389 (70.5%) remaining patients, with no risk features, were considered the R0 group (Table 2). Table 3 describes the pathological characteristics of patients evaluable for hereditary risk (N = 7,641).

Analysis of prognostic factors in sporadic and hereditary breast cancer groups

In the univariate analysis we found that R0 group presented a lower proportion of big tumors ($\geq$ T2) than the GHR group (43.8% vs 47.4%, p = 0.023), a lower proportion of nodal

Table 2. Hereditary risk distribution.

2533 patients (23,8%) had some feature missing	Excluding those without information	
	N	%
R0 (Sporadic)	5389	70,5
IFR (both individual and familial)	177	2,3
IR (only individual risk)	970	12,7
FR (only familial risk)	1105	14,5
Total	7641	100,0

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Table 3. Description of the TNM, histological subtype and grade of the evaluable patients, including TN patients. Only pathological T and N were considered.

	R0	GHR (IFR+IR+FR)	p-value	IFR	IR	FR	p-value
	N (%)	N (%)		N (%)	N (%)	N (%)	
pT (N = 6746)	N = 4813	N = 1933	0.023 (T0+T1 vs T2+T3+T4)	N = 153	N = 804	N = 976	<0.001 (T0+T1 vs T2+T3+T4)
T0 (Tis)	10 (0.2)	9 (0.5)		0	2 (0.2)	7 (0.7)	
T1 (52 T1mic)	2703 (56.2)	1017 (52.6)		87 (56.8)	365 (45.5)	565 (57.9)	
T2	1738 (36.1)	752 (38.9)		57 (37.3)	361 (44.9)	334 (34.2)	
T3	164 (3.4)	74 (3.8)		6 (3.9)	46 (5.7)	22 (2.3)	
T4	180 (3.7)	65 (3.4)		2 (1.3)	21 (2.6)	42 (4.3)	
TX	18 (0.4)	16 (0.8)		1 (0.7)	9 (1.1)	6 (0.6)	
pN (N = 6746)	N = 4813	N = 1933	0.004 (NX not analysed)	N = 153	N = 804	N = 976	<0.001 (NX not analysed)
N0	2721 (56.6)	1003 (51.9)		84 (54.9)	385 (47.9)	534 (54.7)	
N1	1671 (34.7)	748 (38.7)		55 (35.9)	347 (43.2)	346 (35.5)	
N2	243 (5.0)	112 (5.8)		7 (4.6)	55 (6.8)	50 (5.1)	
N3	76 (1.6)	28 (1.4)		5 (3.3)	9 (1.1)	14 (1.4)	
NX	102 (2.1)	42 (2.2)		2 (1.3)	8 (1.0)	32 (3.3)	
M (N = 7641)	N = 5389	N = 2252	0.256 (M ND not analysed)	N = 177	N = 970	N = 1105	0.02 (M ND not analysed)
M0	5219 (96.8)	2165 (96.1)		172 (97.2)	920 (94.9)	1073 (97.1)	
M1	167 (3.1)	81 (3.6)		5 (2.8)	47 (4.8)	29 (2.6)	
M ND	3 (0.1)	6 (0.3)		0	3 (0.3)	3 (0.3)	
Grade H (N = 7641)	N = 5389	N = 2252	<0.001 (GX not analysed)	N = 177	N = 970	N = 1105	<0.001 (GX not analysed)
GX	947 (17.6)	429 (19.0)		30 (16.9)	188 (19.4)	211 (19.1)	
G1	1140 (21.2)	335 (14.9)		21 (11.9)	97 (10.0)	217 (19.6)	
G2	2177 (40.3)	817 (36.3)		54 (30.5)	349 (36.0)	414 (37.5)	
G3	1125 (20.9)	671 (29.8)		72 (40.7)	336 (34.6)	263 (23.8)	
Subtypes (N = 7641)	N = 5389	N = 2252	<0.001(unknown not analysed)	N = 177	N = 970	N = 1105	<0.001 (unknown not analysed)
TN	208 (3.9)	225 (10.0)		33 (18.6)	159 (16.4)	33 (3.0)	
Her2+	552 (10.2)	224 (9.9)		15 (8.5)	124 (12.8)	85 (7.7)	
RH+ Her2-	1452 (26.9)	499 (22.2)		36 (20.3)	200 (20.6)	263 (23.8)	
Unknown	3177 (59.0)	1304 (57.9)		93 (52.6)	487 (50.2)	724 (65.5)	

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involvement (43.4% vs 48.1%, p = 0.004) and lower histological grades (20.9% G3 for the R0 vs 29.8% for the GHR group, p<0.001). Metastases at diagnosis were present in similar proportion in both groups (3.2% vs 3.9%, p = 0.26). As expected, a higher proportion of TNBC was found in the GHR group, given that the TN phenotype is included in the criteria to define hereditary cancer (Table 3). In order to rule out an effect by TN phenotype itself in this observation, we conducted the same analysis excluding from all subgroups the TN patients (Table 4), and we found that RO maintained a statistically significant lower proportion of nodal involvement (43.6% vs 48.7%, p = 0.00173) and lower histological grades (19.4% G3 for the R0 vs 26.8% for the GHR group, p<0.001). However, tumor size was not statistically significant between the two subgroups (Table 4)

Analysis according to different hereditary risk subgroups

Comparing each specific GHR subtype with sporadic cases, we observed that the differences seen before are only observed for the IR group. In contrast, similar clinic-pathological features were seen between R0 and IFR and FR groups respectively (Table 3). Moreover, there was a higher frequency of newly diagnosed metastatic patients in the IR group (5.1% vs 3.2%, p = 0.02)

Table 4. Description of the TNM, histological subtype and grade of the evaluable patients, excluding those TN patients. Only pathological T and N were considered.

	R0	GHR (IFR+IR+FR)	p-value	IFR	IR	FR	p-value
	N (%)	N (%)	0.061 (T0+T1 vs T2+T3+T4)	N (%)	N (%)	N (%)	
pT (N = 6382)	**N = 4637**	**N = 1745**		**N = 125**	**N = 672**	**N = 948**	0.146 (T0+T1 vs T2+T3+T4)
T0 (Tis)	10 (0.2)	9 (0.5)		0	2 (0.3)	7 (0.7)	
T1 (49 T1mic)	2634 (56.8)	936 (53.6)		68 (54.4)	309 (46.0)	559 (59.0)	
T2	1640 (35.4)	658 (37.7)		48 (38.4)	292 (43.4)	318 (33.6)	
T3	158 (3.4)	66 (3.8)		6 (4.8)	40 (6.0)	20 (2.1)	
T4	177 (3.8)	61 (3.5)		2 (1.6)	20 (3.0)	39 (4.1)	
TX	18 (0.4)	15 (0.9)		1 (0.8)	9 (1.3)	5 (0.5)	
pN (N = 6382)	**N = 4637**	**N = 1745**	0.00173 (NX not anlysed)	**N = 125**	**N = 672**	**N = 948**	0.001 (NX not anlysed)
N0	2614 (56.4)	896 (51.3)		67 (53.6)	307 (45.7)	522 (55.0)	
N1	1617 (34.9)	678 (38.9)		46 (36.8)	299 (44.5)	333 (35.1)	
N2	229 (4.9)	106 (6.1)		6 (4.8)	51 (7.6)	49 (5.2)	
N3	76 (1.6)	24 (1.4)		4 (3.2)	7 (1.0)	13 (1.4)	
NX	101 (2.2)	41 (2.3)		2 (1.6)	8 (1.2)	31 (3.3)	
M (N = 7208)	**N = 5181**	**N = 2027**	0.1139 (M ND not analysed)	**N = 144**	**N = 811**	**N = 1072**	0.01383 (M ND not analysed)
M0	5020 (96.9)	1945 (96.0)		139 (96.5)	766 (94.5)	1040 (97.0)	
M1	159 (3.1)	77 (3.8)		5 (3.5)	43 (5.3)	29 (2.7)	
M ND	2 (0.0)	5 (0.2)		0	2 (0.2)	3 (0.3)	
Grade H (N = 7208)	**N = 5181**	**N = 2027**	<0.001 (GX not analysed)	**N = 144**	**N = 811**	**N = 1072**	<0.001 (GX not analysed)
GX	912 (17.6)	399 (19.7)		26 (18.1)	168 (20.7)	205 (19.1)	
G1	1128 (21.8)	324 (16.0)		19 (13.2)	88 (10.9)	217 (20.2)	
G2	2134 (41.2)	760 (37.5)		49 (34.0)	303 (37.3)	408 (38.1)	
G3	1007 (19.4)	544 (26.8)		50 (34.7)	252 (31.1)	242 (22.6)	
Subtypes (N = 7208)	**N = 5181**	**N = 2027**	0.079 (unknown not analysed)	**N = 144**	**N = 811**	**N = 1072**	<0.001 (unknown not analysed)
Her2+	552 (10.7)	224 (11.1)		15 (10.4)	124 (15.3)	85 (7.9)	
RH+ Her2-	1452 (28.0)	499 (24.6)		36 (25.0)	200 (24.7)	263 (24.5)	
Unknown	3177 (61.3)	1304 (64.3)		93 (64.6)	487 (60.0)	724 (67.6)	

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Discussion

According to this large and representative sample of the Spanish breast cancer landscape, we can say that three out of ten patients have, at least, one hereditary breast cancer risk feature, and, in consequence, could be candidate for genetic testing and counselling. Overall, patients with hereditary cancer risk features have larger tumors and more frequently nodal involvement in comparison to patients without hereditary cancer risk features, while both subgroups have a similar rate of distant metastases at initial diagnosis. However, these differences probably are related to the greater aggressiveness observed in patients fulfilling the individual criteria. Interestingly, when patients with TNBC were excluded for this analysis, presence of nodal involvement and higher grades, although not tumor size, remained higher in patients with hereditary risk features.

Strong points of this study are the large number of patients analyzed and the representativeness' of Spanish population, since two thirds of the regions are represented. Few studies exist in Spain analyzing the frequency of different familial cancer from a population point of view, with the exception of melanoma [13], pancreatic [14] and colorectal cancer [15]. However, several limitations must be also taken into account when interpreting our results. First, the retrospective nature of our work that could concur in some bias, since almost 30% of patients analyzed lack information to be included in a given risk group. Based on that, we decided to analyze only those that could be categorized in a risk group. This could be a selection bias,

over-estimating the risk percentage. However, due to the large number of patients analyzed, this possibility might be ameliorated.

Another weakness, in order to classify patients in a given risk group, is the fact that nearly 60% of patients had an unknown HER2 status, in consequence, a substantial number of patients, could not be evaluated regarding the TN phenotype, one of the major risk factors for hereditary breast cancer. Within the time-frame of data collection (patients diagnosed from 1998 to 2001), although the role of HER2 was well known as a prognostic factor, the determination of this biomarker was not widely used, given that appropriate targeted therapy was only available for metastatic patients.

Patients with hereditary cancer risk features have worse pathological risk factors, according to T and N status, and to histological grade, all well-known bad prognosis factors. Data of prognosis from patients with known BRCA 1 and 2 mutations are conflicting in literature. A recent meta-analysis did not detect differences in breast cancer specific survival rate in BRCA2 mutation carriers when compared to sporadic ones [16]. I contrast, another meta-analysis confers a poorer prognosis for patients with BRCA1 mutations [17]. Another recent meta-analysis confer worse overall survival to BRCA1 mutation carriers and worse breast cancer specific survival [18]. In our study, we did not analyze survival, and we did not have data regarding BRCA1 and 2 status, so in consequence we cannot put our data into the context of theses meta-analysis.

One could think that patients concerned with their familial background are more prone to intensive surveillance, both by themselves and by their health care givers, what should be translated into earlier diagnostic presentations, something that is not reflected by our data. This is true in other familial cancers, such as melanoma, where patients at familial risk in Spain present with better prognosis pathological factors [13]. However, since the subgroup responsible for these differences is the individual risk group, which is enriched with the triple negative phenotype, the known biological aggressiveness of this subtype may account for these differences in TNM presentation.

It is important to analyze if our data are comparable to other countries. Our results are according to what is described in general literature [6]. However, studies conducted in other countries searching for similar endpoints as our present work, revealed mixed results. In a British study with more than 5,000 BC patients, a positive family history of BC (with no more specific details) was found in 22.2%, in contrast to 16.8% (14.5% FR and 2.3% IFR groups) found in our work [19]. In this study, a younger age of presentation was found among patients with family history. In a pooled analysis with more than 47,000 BC patients, in which 92% were of European ancestry, revealed that 11% of patients were <40y, 20% had a positive first degree family history and that 14% were TNBC. 18% of patients with TNBC had also a positive family history of cancer [20]. In African-American women, a study found that 16% of BC patients had first degree family history, 3% ovarian cancer and 15% were TNBC [21]. Finally, in Chinese population, a lower proportion of BC with family history (5.1%) was described in a study focused in Han Chinese population, the majority of Chinese population ethnicity [22]. These results reveal that family history and other risk factors associated with increased hereditary risk could be dependent of geographical origin, although the limitations of the heterogeneity of the different studies should be taken into account.

Finally, the practical consequences of our findings should be taken into consideration. In general, it is estimated that, according to different institutional series in Spain and western countries, BRCA 1 or 2 mutations are present from 7% to 20% of selected and unselected patients in western countries [23–27]. With this in mind, and since genetic testing will be easier and cheaper in the near future, our findings suggests that it is urgently needed an increase

in efforts to facilitate the detection and proper management of patients and relatives harboring genetic mutations and/or high familial risk features.

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