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The Clinical Characteristics of Breast Cancers with A Familial Risk in Which No *BRCA1/2* Mutations were found are Sometimes Suggestive for A Genetic Etiology

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Abstract

Aim: We investigated the patient and tumor characteristics of breast cancer patients with a high familial risk. The families in which the standard genetic testing revealed a *BRCA1* or *BRCA2* mutation were excluded to identify clinical characteristics that can be linked with an unknown genetic mutation. These characteristics were compared with those from patients in the same cohort in whom a mutation was found in *BRCA1* or *BRCA2* and to those from sporadic breast cancer cases (Belgian cancer registry).

Methods: The files of familial cancer cases that underwent *BRCA1/2* testing between 1994 and 2012 were retrospectively analyzed.

Results: The *BRCA1* related breast cancers occur at a median age of 42, *BRCA2* at a median age of 44, familial non-*BRCA1/2* at a median age of 47 and sporadic breast cancer at the age of 63. The lower median age of incidence in the non-*BRCA1/2* group compared to the sporadic breast cancer group makes use conclude that there are probably moderate risk genes involved. Generational anticipation was also observed in some of the *BRCA1/2* negative families. We did not find any significant differences in the pathological characteristics of breast cancers occurring in *BRCA1/2* negative patients with a high familial risk compared to sporadic cases.

Conclusion: A shift towards a younger age of disease incidence and "anticipation" in some families suggests the involvement of a genetic factor. The identification of other genetic causes in these familial cases is therefore warranted.

Keywords: Breast cancer; Genetic; Germline mutations; Pathology

Introduction

Breast cancer (BC) is the most common malignancy in women in Western countries. One in nine women is affected. Age is an important risk factor for BC in women [1]. Most BCs are detected in the age group 50-75 years old.

The by far strongest risk factor for breast cancer is a positive family history. At least one close relative with a breast and/or ovarian cancer can be found in 15%-25% of all breast cancer cases [2,3]. The breast cancer risk for asymptomatic members in such families increases with the number of affected family members. Twin studies suggest a genetic origin for the majority of the familial risk cases [4].

A Mendelian inheritance pattern is present in 5-10% of BC families and 30% of them are due to rare germline mutations in *BRCA1* or *BRCA2* [4]. Pathogenic germline mutations in *BRCA1* generate a 60-85% lifetime risk for BC and a 40-50% lifetime risk for ovarian cancer (OC) [5]. Similarly, *BRCA2* mutation carriers have a 40-85% lifetime risk for BC and up to a 20-30% lifetime risk for OC. Other genes with highly penetrant rare mutations with relative risk above tenfold are p53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), STK11 (Peutz-Jeghers syndrome) and E-Cadherin (CDH1). Clinical screening and risk reduction guidelines are available for mutations in these genes (www.NCCN.org) [6]. A combination of family and population-based approaches led to the discovery of additional moderate penetrant mutations in CHEK2, ATM (Ataxia-telangectasia), BARD1, NBS1, RAD50, RAP80 (possible), BRIP1 and PALB2 [7]. Mutations in BRCA1/2, CHEK2, PALB2 and p53 have a clinically validated defined risk for BC, but for the other genes evidence suggests an increased risk to BC without defined confidence intervals [8]. Therefore, in most clinics only BRCA1/2, CHEK2 and PALB2 are used in routine testing and counseling while in some centers the other genes are tested and used cautiously in counseling [9].

The association of low-penetrance mutations and/or single nucleotide polymorphisms (SNP's) can contribute to BC in high-risk families [10]. These mutations/SNPs could act alone to create a modest increased risk or as modifiers of the risk provided by high-risk germline mutations. The cancer risk associated with dominant genes is well determined due to family studies. In contrast, it is a difficult task to uncover single gene mutations with low penetrance, recessive genes and oncogenic mechanisms that involve multiple genes. Limited information is available on possible gene-environment interactions [11]. The genetic cause is currently only found in a minority of probands with a familial risk and many cases remain unresolved [12,13]. Continued research aimed at more accurately defining the magnitude of the risk conferred by the already identified genes or uncovering novel candidates is necessary. Familial BC risk in families in which no mutations are found in established or candidate genes

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is probably a mixture of environmental and genetic causes or an interaction between both.

In the current work we have compared some phenotypic characteristics of familial cases with known *BRCA1/2* cases and sporadic cases. For the *BRCA1/2* genes, correlations with clinical characteristics of affected mutation carriers and the pathological characteristics of their cancers have been made in comparison with sporadic breast cancer [12].

BRCA1 associated breast cancers have a higher occurrence of medullary carcinomas and are more frequently poorly differentiated with a high mitotic count, high frequency of necrotic areas, a higher degree of immune infiltration and a low incidence of pre-invasive lesions (LCIS and DCIS). They are most often triple negative cancers. *BRCA2* related breast cancers have a higher frequency of invasive lobular, tubular and cribriform carcinomas and are moderately or poorly differentiated. They are mostly estrogen receptor positive [12]. The average age of breast cancer diagnosis is much lower for *BRCA1* related cancer than *BRCA2* related cancer and sporadic breast cancer. The phenotype generated by rarer hereditary susceptibility genes (such as p53) and candidate genes is not well described.

In the current study we have retrospectively analyzed the tumor and patient characteristics in a cohort of probands and their families that have an increased familial risk and were selected for germline testing based on the national entry criteria. The hypothesis was that the presence of unique tumor or clinical and familial characteristics could be related to a specific gene mutation. This could help in focusing the further definition of the role of candidate genes in these families and to perhaps approach possible environmental etiology in other families. In literature there is not much information available about high-risk families. However, we identified two studies in which a number of the pathological and phenotypic characteristics of non-*BRCA1/2* familial cases are described [14,15].

Methods

Family selection

In the familial cancer clinic in general we use national consensus criteria (KCE-College of oncology criteria) to see if the criteria that allow genetic testing are met. The remaining families are high-risk families with at least two patients with breast or ovarian cancer. The routine genetic testing includes screening for the high-risk genes

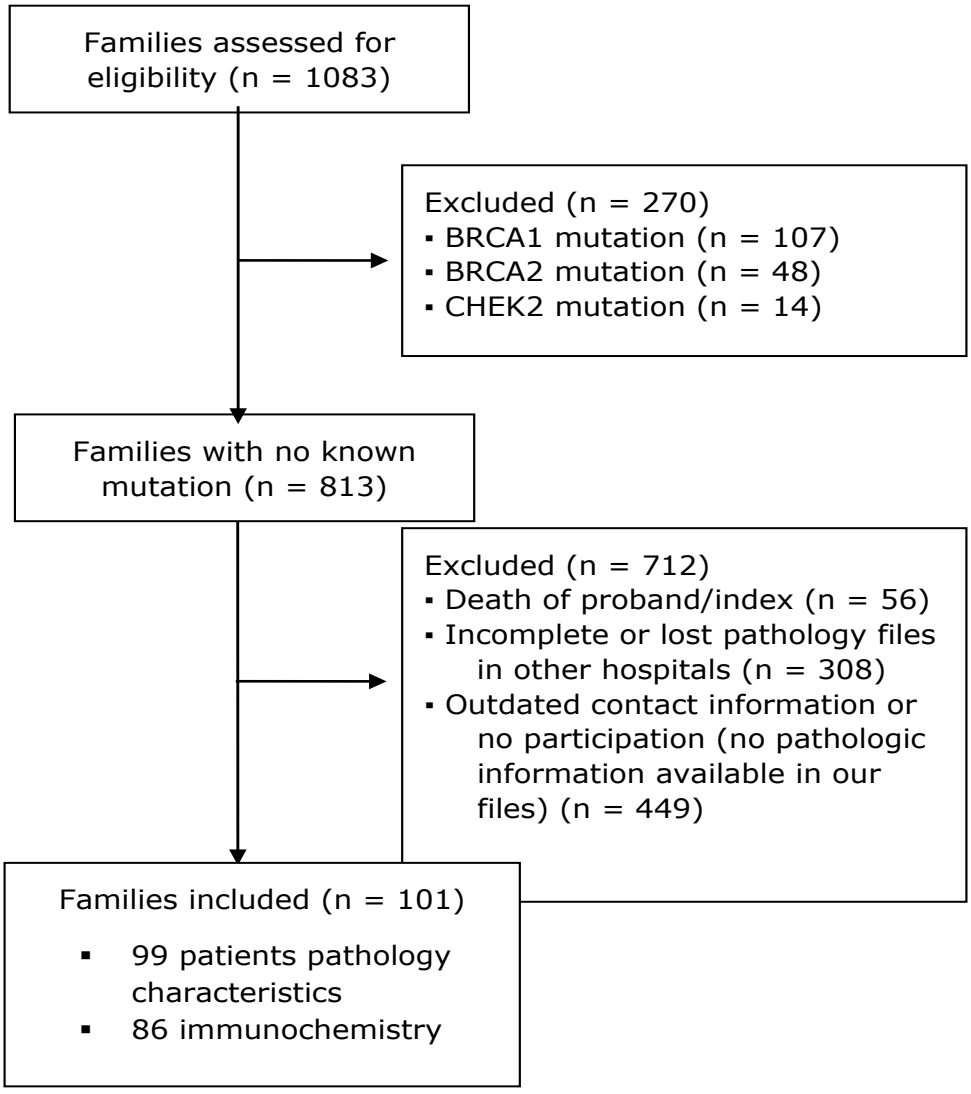

Figure 1: Consort flow diagram.

BRCA1 and *BRCA2* and the moderate risk gene CHEK2. In this study we were interested in the families in which the routine genetic testing came back negative. These families were selected from the files available at the familial cancer clinic that currently encompasses an archive of more than 2500 cancer families (any familial cancer syndrome) from the Oncology center UZ Brussel. Starting from a pool of 1083 families,

Variables	Lakhani et al. [14]				Brekelmans et al. [15]				Current study	
	BRCA1	BRCA2	Non-BRCA1/2 familial cases	Controls	BRCA1	BRCA2	Non-BRCA1/2 familial cases	Controls	Non-brca1/2 familial cases	95% CI
Number of cases	314	172	142	1463	170	90	238	759	99	
Cancer type										
Ductal	78	77	73	77	88	89	87	87	79	[71-87]
Lobular	**3**	9	15	10	**4**	9	11	10	13	[6-20]
Tubular	2	0	2	4	0	0	2	1	1	[0-3]
Mucoïd	1	2	0	0.2	0	0	0	0	0	
Medullary	**11**	2	1	1	**7**	2	1	2	1	[0-3]
Mixed	1	3	1	3	0	0	0	0	6	[1-11]
Other	4	6	8	6	1	0	0	0	0	
Grade										
1	**8**	14	27	20	**1**	3	8	8	16	[9-23]
2	**23**	49	50	41	**11**	32	31	29	43	[33-53]
3	**69**	38	23	38	**88**	**65**	61	63	41	[31-52]

Note: All data are displayed in percentages, with the exception of number of cases.
Mixed = Combination of lobular and ductal carcinoma

Table 1: Morphological characteristics of breast cancers in non-BRCA1/2 carriers, BRCA1 carriers, BRCA2 carriers and controls (General breast cancer population breast cancer cases).

Variables	Current Study	Brekelmans et al. [15]				Current study
	Non-BRCA1/2	Non-BRCA1/2	BRCA1	BRCA2	Controls	95% CI
Number of cases	86	238	170	90	759	
ER status						
Positive	78%	73%	**27%**	84%	67%	[69%-87%]
Negative	22%	27%	**73%**	16%	33%	[13%-31%]
PR status						
Positive	71%	74%	**33%**	64%	54%	[61%-81%]
Negative	29%	26%	**67%**	36%	46%	[19%-39%]
HER2-status						
Positive	20%	NA	NA	NA	NA	[12%-28%]
Negative	56%	NA	NA	NA	NA	[46%-67%]
Unknown	24%	NA	NA	NA	NA	[15-33%]

Note: ER: Estrogen Receptor, PR: Progesterone Receptor HER2: Human Epidermal Growth Factor receptor 2

Table 2: Pathological predictive biomarkers.

Variables	Current Study			Belgian Cancer Registry [19]	Hou N. et al. [18]	Van der Kolk et al. [20]		Brekelmans et al. [15]				95% CI
	Non-BRCA1/2	BRCA1	BRCA2	Women (2004-2012)	General population	BRCA1	BRCA2	Non-BRCA1/2 Familial cases	BRCA1	BRCA2	Controls	Current Study
Number of cases	166	134	72	88057	677774	145	83	238	170	90	759	
Age (in years)												
20-39	14%	**46%**	**24%**	4,8%	4,80%	**46,90%**	**32,50%**	**26,10%**	**48,20%**	**38,90%**	**42,30%**	[9%-19%]
40-49	34%	35%	40%	17,2%	18,30%	37,20%	37,40%	34%	31%	37%	33%	[27%-41%]
50-69	49%	**17%**	**29%**	47,3%	47,30%	**15,20%**	**30,10%**	NA	NA	NA	NA	[41%-57%]
70+	3%	2%	7%	30,7%	29,60%	0,70%	0%	NA	NA	NA	NA	[0%-6%]

Table 3: Distribution of incidence rates (%) for breast cancer over the age groups. Comparison with general BC data base in Belgium and published cohorts in studies similar to the current study.

Variables	Brekelmans et al. [15]				Current Study			
	BRCA1	BRCA2	Non-BRCA1/2	Controls	BRCA1	BRCA2	Non-BRCA1/2	General population
Number of cases	170	90	238	759	135	72	166	88057
Mean age	42	44	47	43	41	48	50	62

Table 4: Mean age at cancer diagnosis according to BRCA1/2 status.

Family number	Mean age of breast cancer onset of generation 1	Mean age of breast cancer onset of generation 2	Mean age of breast cancer onset of generation 3
46	/	53	44
91	39	60	42
102	52	/	34
174	68	51	/
175	70	66	46
199	41	62	44
298	63	61	43
415	40	39	63
435	58	52	/
531	70	55	40
551	48	35	/
571	47	48	/
596	35	45	/
622	62	47	/
718	52	49	/
734	53	50	/
746	44	50	/
786	73	40	/
805	56	48	/
824	59	46	/
853	53	43	/
855	50	62	/
920	48	49	/
925	59	45	/
928	50	48	/
1001	68	51	/
1014	/	58	33
1140	60	61	/
1141	51	46	/
1162	52	50	35
1172	65	39	36
1195	50	35	/
1210	62	65	/
1211	74	32	/
1221	36	36	/
1236	75	/	43
1291	52	43	/
1293	55	62	/
1301	50	52	/
1334	55	42	/
1339	67	50	/
1353	61	48	/
1363	89	46	44
1401	55	28	/
1426	30	38	/
1446	77	50	/
1466	45	63	/
1563	65	62	/
1569	79	52	/

Table 5: Mean age of cancer diagnosis for different generations in a family.

107 families tested positive for BRCA1, 48 families for *BRCA2* and 14 families for CHEK2 and were therefore excluded for this study. From the remaining 813 families, only 101 families were eventually selected for inclusion into the study. Where needed additional family members were contacted under a prior UZ Brussel ethical committee approval [16].

Please see the attached consort flow diagram for more details about the selection procedure. In literature there are two articles available that characterize non-*BRCA1/2* families, their inclusion criteria differ. In the study of Lakhani, families that were selected for the non-*BRCA1/2* group met the following criteria:

1. At least one breast cancer patient in the family underwent genetic testing for mutations in BRCA1/2
2. No male breast cancer or ovarian cancer cases occurred in the family (as these are likely to be attributable to a *BRCA1/2* mutation)
3. More than two cases of cancer occurred in the family, as the presence of only two cases could likely be a chance occurrence of two sporadic cancers.

The entry criterion for the non-*BRCA1/2* group in the study of Brekelmans is the following:

"Breast cancer cases within a family tested negative for a deleterious BRCA1-and BRCA-2 mutation."

Phenotypic characterization

Information about age of disease incidence and tumor histology was gathered from hospital records and pathological reports.

Statistical analysis

Descriptive statistics were used as the study cohort was relatively limited. For the comparison of our results and two similar published studies, 95% confidence intervals have been used. Values that fall outside the 95% confidence interval were considered different.

Results

Family selection

1083 families have been screened for enrollment (Figure 1). 270 families with known mutations in *BRCA1/2* or CHEK2 were excluded. Of the 813 remaining families that corresponded to our inclusion criteria, 712 families were dropped because of various reasons. This resulted in 101 families that were included in our analysis. In this retrospective study a number of difficulties were encountered related to the negative genetic testing results that did not provide an incentive for further contact. Several of the prospective families had lost contact with the familial cancer clinic for several years, resulting in outdated contact information which made it impossible to update the pedigree information. A lot of patients underwent their biopsy and/or mastectomy in other hospitals. When we contacted the patients to determine where the pathological analyses took place, multiple relatives refused to communicate us this information. Retrospective gathering of pathology information from external sites was often not possible.

Phenotypic characterization

Pathology: 101 families were included in the study. Information on pathological characteristics was available for 99 patients, while information with regard to immunohistochemistry was available for 86 patients. The results in our cohort were compared to two other cohorts, one of which more closely resembled our study [15]. In Tables 1 and 2, the pathology data from the two other published cohorts and the current study (conducted on 101 families and 166 breast cancer patients). For women with the diagnosis of bilateral breast cancer, only the histology of the first tumor is included in the statistics. Our results resemble those in the two earlier studies with the exception of tumor grade. In the study of Lakhani et al., there are more grade 1 and less grade 2 cancers while the study of Brekelmans et al. shows the opposite [14,15]. Only the *BRCA1* related cancers stand out by having less of the lobular histology and more medullary histology. Also, with regard to grading the *BRCA1* related cancers are much more aggressive. In the *BRCA1* group, tumors are more frequently poorly differentiated (grade 3) and medullary carcinomas are more common.

With regard to ER expression, only the *BRCA1* associated breast tumors differ in this area from the other cohorts (sporadic cases, *BRCA2* and non-*BRCA1/2* cases). *BRCA1* mutation related breast cancers more frequently have little to no expression of the estrogen receptor and progesterone receptor. The familial cancer cases have a pathological distribution comparable to the general breast cancer population and *BRCA2* related breast cancers

Age of incidence: The results in our cohort were compared to three other cohorts from other studies and to the data from the general breast cancer population which was obtained from the Belgian cancer registry. The first of these studies was by Brekelmans et al. and closely resembled our study because it also included non-*BRCA1/2* familial cases (high-risk families who tested negative for standard *BRCA1/2* testing) [15]. A second study performed by Van der Kolk et al. provides results of a *BRCA1* and *BRCA2* cohort of respectively 145 and 83 women.

Information about the general population was gathered from a third study by Hou N. et al. that includes results from 677774 women from 2000 to 2009 and the Belgian cancer registry from 2004 until 2012 (this registry does not take genetic testing into account) [17,18]. There are no data available for Belgium for the period before 2004 Age of onset results are shown in Tables 3 and 4. Due to the fact that the age of onset for every age group is not shown in the article of Lakhani, we only included the study of Brekelmans in our Table 4.

Our results on age of breast cancer incidence are similar to prior results. *BRCA1* carriers develop breast cancer at a younger age compared to the *BRCA2* mutation carriers or the familial non-*BRCA1/2* patients. If we compare the age of incidence of the non-*BRCA1/2* group to that of the *BRCA1/2* groups, we can conclude that it is generally higher. On the other hand, if we compare the results from that same group to those of the general population, we find that the age of incidence is generally lower. The *BRCA1* related breast cancers occur at a median age of 42, *BRCA2* at a median age of 44, familial non-*BRCA1/2* at a median age of 47 and sporadic breast cancer at the age of 63. This makes use conclude that there are probably moderate risk genes involved in our non-*BRCA1/2* group.

Anticipation: As anticipation is a general characteristic of dominantly inherited disease and also observed in *BRCA1/2* families, we examined whether we could detect this phenomenon in our families [17]. We calculated the average age of onset for every generation. If this reduced for every generation, then anticipation is present.

In 54 of the 101 families, the exact age of onset of breast cancer was not known in different family members and generations, so they were dropped for this analysis. There was no overall specific trend towards anticipation in the population studied. However, results compatible with anticipation were observed in 36 of the 47 families that could be

examined for this characteristic (Table 5). When we take a closer look at this group, it seems that their tumor characteristics do not differ from the other families (results not shown).

Genetic exploration: In a separate research effort, our group is performing Exome analysis in non-*BRCA1/2* families. At this time, results are available for 19 of the families included in the current study. Validated truncating germ-line mutations considered as experimental (and currently not proven to be pathogenic) were found in eight families. Seven of these families were characterized by the presence of anticipation. The only family without anticipation had a mean age of cancer onset of 30 years in the first generation.

In nine of the 11 families in which no germline mutations were found, the diagnosis of breast cancer took place above the age of 50 and the age of incidence of cancer between generations differed by less than five years. This leaves us with two families where there is a discrepancy between phenotype (anticipation and breast cancer diagnosis between 30 and 40 years) and genotype. Important to note is that missense mutations that are possibly/probably damaging have been found in almost every proband. Their role needs to be further elucidated.

Discussion

The phenotype of families without a *BRCA1/2* mutation has only been reported in two cohorts in the past [14,15]. A possible explanation is the discovery of the BRCA genes in 1994 and 1995. Before this discovery, a number of articles was published that set out to characterize families with multiple breast cancer patients. Afterwards, researchers focused on patients with a mutation in the BRCA genes, leaving the non-*BRCA1/2* families not characterized. In most articles, breast cancers in carriers of *BRCA1* or *BRCA2* mutations are compared with sporadic cases.

The current study intended to contribute information. The inclusion criteria in our own as well as the comparable studies were not identical but enriched for familial aggregation in all cohorts. Earlier age at diagnosis is a hallmark of genetic versus sporadic cancer [17]. If we compare the age of incidence of the non-*BRCA1/2* group to that of the *BRCA1/2* groups, we can conclude that it is generally higher. On the other hand, if we compare the results from that same group to those of the general population, we find that the age of incidence is generally lower. The *BRCA1* related breast cancers occur at a median age of 42, *BRCA2* at a median age of 44, familial non-*BRCA1/2* at a median age of 47 and sporadic breast cancer at the age of 63. This makes use conclude that there are probably moderate risk genes involved in our non-*BRCA1/2* group.

Pathological characteristics are similar in the two published studies and ours, except for tumor grade in which discordant results were obtained. Only *BRCA1* related cancers differ significantly in the prevalence of some more rare histology types (more medullar and less lobular), ER status and grading.

The receptor status of the tumor was also mapped. Literature shows us that 15-20% of the breast tumors exhibit amplification of the HER2-gene [19-21]. The results of the present study confirm these findings. These data were not available in the two other publications. It should be noted that almost all HER2 amplified breast cancers occurring in a familial context are *BRCA1/2* negative (our broader cohort, unpublished data). Anticipation, a general characteristic of dominantly inherited disease is present in several of our non-*BRCA1/2* families. In a separate research effort of our group, where exome sequencing is performed in non-*BRCA1/2* families, truncating mutations in possible cancer predisposing genes are more often found in families with anticipation [22].

There are several limitations to our study that are also relevant for the two published studies. First of all, this is a retrospective study in a cohort that was assembled over a relatively long-time interval. Some of the information was gathered through hetero-anamnesis, which could entail some inaccuracies. Pathology information was gathered from different hospitals without central review, with some being incomplete and assumable heterogeneity with quality of reading. Nevertheless, we believe that this study provides some valuable information on familial non-*BRCA1/2* breast cancer and suggests that at least some of these cases have a genetic etiology.

The preliminary results of exome sequencing in a fraction of these families suggests that the chances of detecting unknown truncating mutations is greater in families where anticipation and age of breast cancer diagnosis at a young age is present. This indicates that detection of new candidate cancer predisposition genes could be prioritized to familial cases with a young age of onset and showing a phenomenon of anticipation [23,24].

Conclusion

In conclusion, breast cancers with a familial history in which no *BRCA1/2* mutation was found have some characteristics that suggest a genetic etiology that does not reside in the currently known predisposition genes. We consider the current study as hypothesis generating. Larger cohorts are required to obtain more information related to the characteristics of breast cancer patients with a positive family history.

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