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Phenotypic analysis of familial breast cancer: Comparison of BRCAx tumors with BRCA1-, BRCA2-carriers and non-familial breast cancer

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Abstract

Aims: Women with inherited pathogenic mutations in the BRCA1 or BRCA2 genes have up to an 85% risk of developing breast cancer in their lifetime. However, only about 20% of familial breast cancer is attributed to mutations in BRCA1 and BRCA2, while a further 5–10% are attributed to mutations in other rare susceptibility genes such as TP53, STK11, PTEN, ATM and CHEK2. Despite extensive efforts to explain the missing heritability of this disease, the majority of familial clustering in breast cancer remains largely unexplained. We aim to analyze the pathology of familial cases of which no pathogenic mutation is yet identified.

Methods: We compared the pathological phenotype of BRCA1/BRCA2 negative familial breast cancer (BRCAx) to BRCA1-positive, BRCA2-positive and sporadic cases without a family history. Age-adjusted analysis is summarized in odd's ratios and confidence intervals for tumor type, grade, lymph node, ER and HER2 status.

Results: We found non-familial cases to be more likely to be ER positive ($P = 0.041$) as compared with BRCAx tumors. More cases of lobular carcinoma were found with BRCAx as compared to BRCA1 tumors ($P = 0.05$). After multivariate logistic regression analysis, BRCAx tumors are more likely ER positive ($P = 0.001$) and HER2 positive ($P = 0.047$) in comparison to BRCA1. Conversely, BRCAx cases are less likely to be ER positive ($P = 0.02$) but more likely to be HER2 positive ($P = 0.021$) as compared with BRCA2 tumors.

Conclusion: Our findings suggest that BRCA1, BRCA2 and BRCAx tumors differ in phenotype from non-familial and familial BRCA1-positive and BRCA2-positive tumors. Further studies will need to be performed in this important population in order to develop strategies for early detection and prevention.

Keywords: Breast cancer; BRCA1 gene; BRCA2 gene; Selective estrogen receptor modulators; Genetics; Chemoprevention

Introduction

It is well recognized that women who have a pathogenic mutation in either *BRCA1* or *BRCA2* genes have up to a 68–88% increased risk of developing breast cancer.[1] These patients are offered risk-reducing measures such as intensive radiological screening and prophylactic surgery.[2,3] However, the frequency of familial breast cancer cases attributed to mutations in *BRCA1* and *BRCA2* vary from only 12.5 to 31% in studies on a large series of

Abbreviations: BRCAx, non-BRCA1 or non-BRCA2 familial breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2 receptor; MLPA, multiplex ligation-dependent probe amplification; NCMG, Irish National Centre for Medical Genetics; CI, confidence interval; OR, Odds ratio; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

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patients of multiple ethnicities.[4,5] Therefore, the majority of familial cases have been defined as BRCAx (a term that has been used to describe familial breast cancer cases found to be negative for those two genes). Although other susceptibility genes such as *TP53*, *STK11*, *PTEN*, *ATM*, *PALB2* and *CHEK2* have since been identified, they still do not explain the majority of cases.[6–12]

While previously those at high-risk would be restricted to screening for *BRCA1* and *BRCA2* genes, developments in sequencing technologies have made it possible to test for multiple genes at lower cost, specifically using multigene panel testing with next-generation sequencing. Therefore, much like the efforts that have been made to describe *BRCA1* and *BRCA2* tumor phenotypes in order to estimating the chance to identifying new pathogenic mutations, characterizing the BRCAx phenotype may shed light on our understanding of the majority of the familial clustering that is yet to be explained.

Specific protein characteristics and tumor histology have been described in patients with pathogenic mutations in *BRCA1* and *BRCA2*. Studies have shown that mutation carriers do not necessarily all have the same phenotype.[13,14] Certain histological patterns have been demonstrated especially in *BRCA1* mutation carriers.[13,15–18] Triple negativity, i.e. lacking expression of estrogen, progesterone, and Her2 receptors, and high histological grade tend to be common amongst *BRCA1* mutation carriers.[13,15–18] On the other hand, *BRCA2* tumor histology seems to be more heterogeneous and similar to the common breast cancer pattern being intermediate grade, luminal B and estrogen/progesterone positive.[16–20]

Whilst the phenotypes of *BRCA1* and *BRCA2* have been reasonably well described, studies on BRCAx tumors, which make up the majority of familial cases are somewhat limited. Lakhani and colleagues compared *BRCA1*, *BRCA2*, BRCAx and sporadic breast cancer and noted that non-BRCA1/2 breast cancers were of significantly lower grade.[15] Palacious et al. observed similar features between these tumor types in Spanish samples.[20] These studies categorized BRCAx cases as having a more favorable long-term outcome than average.[21] In this current study, we present and analyze the associated phenotype of BRCAx tumors as compared to BRCA1, BRCA2 and non-familial tumors screen-detected through mammography.

Methods

Ethical approval

Permission for this study was obtained from the Research and Ethics Committee at Our Lady's Children's Hospital, Crumlin, Dublin, in the Republic of Ireland.

Samples

The familial groups, i.e. BRCAx (N = 209), BRCA1 (N = 63) and BRCA2 (N = 60) groups consisted of patients referred from 2007 to 2011 to the Irish National Centre for Medical Genetics (NCMG) for genetic counseling and testing. Cases were included on the basis of having a personal history of breast cancer, a Manchester score of >16, at least 2 other affected relatives or an affected relative and bilateral breast cancer, since both these features increase the likelihood of a familial predisposition (and the risk of developing breast cancer by 4-fold). All cases were screened for variants in the *BRCA1* or *BRCA2* genes by bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA). This analysis was performed externally at the West Midlands Regional Genetics Centre (Birmingham, United Kingdom). All patients were unrelated and asked to complete a detailed questionnaire, which required them to provide demographic details, cancer and family history of breast cancer for the previous three generations. A limited number of probands were subsequently contacted to clarify some of their clinical details.

Screen-detected breast cancer geographically-matched cases (N = 670) were obtained from the BreastCheck Merrion Unit, Dublin, Ireland database, which archives screen-detected patients with breast cancer from the years 2009–2011. BreastCheck invites females 50–64 for mammographic screening and thus these cases were discovered through mammography.

Histology review

Histological reports from the respective hospitals were collected for each familial case. Histological type, grade, stage, receptor status (ER, PR, Her2) was obtained for each case. In some instances, initial excision of the tumor was performed a significant time before referral to the NCMG and thus full histology reporting was incomplete; hence we had to exclude some index cases. However, 100% of the histology reports were successfully obtained from the screen-detected cohort.

Statistical methods

Statistical tests in this study were done with Stata version 12.0 (Stata Corporation, College Station, TX). We tested dichotomous variables with either Pearson's chi-2 statistic or Fisher's exact test. We tested continuous variables (tumor grade) with a t-test and Wilcoxon–Mann–Whitney test (a model which assumes they are from the same normal distribution). To assess multivariate analysis, we used a logistic regression analysis. We considered a p-value of 0.05 or less as significant. All p-values are two-sided.

Results

To examine the features of multiple-case BRCAx tumors, histological data from 332 familial (209 BRCAx, 63 *BRCA1*, 60 *BRCA2* tumors) and 670 non-familial breast

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Table 1
Demographics of BRCAx, BRCA1, BRCA2 and Non-familial cases included in the study. In age, asterisk* denotes that age is displayed in mean (min-max). DCIS = Ductal carcinoma in situ, IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma, ER = Estrogen receptor, HER2 = human epidermal growth factor receptor 2 receptor.

	BRCAx (N = 209)	BRCA1 (N = 63)	BRCA2 (N = 60)	Non-familial (N = 670)
Age of diagnosis*				
	42 (22–64)	40 (24–60)	44 (20–69)	57 (48–65)
Cancer type				
DCIS	19 (10.44%)	4 (6.90%)	4 (7.02%)	124 (18.51%)
IDC	137 (75.27%)	51 (87.93%)	46 (80.70%)	450 (67.16%)
ILC	21 (11.54%)	1 (1.72%)	4 (7.02%)	74 (11.04%)
Mixed	3 (1.65%)	2 (3.45%)	3 (5.26%)	15 (2.23%)
Grade				
1	16 (10.12%)	3 (5.66%)	3 (5.36%)	142 (21.23%)
2	70 (44.30%)	15 (28.30%)	23 (41.07%)	305 (45.60%)
3	72 (45.57%)	35 (66.04%)	30 (53.57%)	222 (33.18%)
Lymph node status				
	92 (51.69%)	68 (38.20%)	34 (62.96%)	149 (22.23%)
Receptor Status				
ER	130 (70.65%)	19 (36.54%)	45 (78.95%)	549 (87.7%)
Her2	40 (21.86%)	5 (9.43%)	6 (10.53%)	65 (12.31%)

tumors were collected for this study. Cohort features are listed in detail in Table 1. The phenotypic profiles of BRCAx tumors were established by analyzing tumor type, grade and receptor status and comparing them with *BRCA1*, *BRCA2* and screen-detected tumors. Statistical testing was adjusted for age (Table 2).

Non-Familial Breast Cancer Group

The non-familial breast cancer cohort included 670 breast cancer cases diagnosed by mammography through a national screening program in Ireland (BreastCheck). Not surprisingly, non-familial tumors were more likely to be DCIS with an Odds Ratio (OR) of 0.31, a 95% Confidence interval (CI) from 0.15 to 0.67 and an associated P value of P = 0.003. They were also less likely to have positive lymph nodes (OR 2.44, 95% CI 1.46 to 4.07, P = 0.001) and more likely ER receptor positive than the BRCAx tumors (OR 0.52, 95% CI 0.29 to 0.98, P = 0.041).

BRCA1-Positive Familial Breast Cancer Group

Interestingly, the likelihood of lobular carcinoma within the BRCAx cohort was higher than that of the BRCA1 cohort (OR 7.3, 95% CI 0.95–56.10, P = 0.050). BRCA1 tumors were also of higher grade than BRCAx. After controlling for other factors, the multivariate regression results showed that BRCAx tumors remained more likely receptor positive as compared with *BRCA1*: ER receptor showed an OR of 3.83 (CI 95% 1.76–8.34, P = 0.001) and HER2 receptor showed an OR of 2.99 (95% CI 1.01–8.87, P = 0.47).

Table 2
Uni-variate statistical analysis comparing BRCAx familial tumors to *BRCA1*, *BRCA2* and nonfamilial tumors. DCIS = Ductal carcinoma in situ, IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma, ER = Estrogen receptor, HER2 = human epidermal growth factor receptor 2 receptor, OR = Odds ratio, CI = confidence interval.

	BRCAx vs *BRCA1*			BRCAx vs *BRCA2*			BRCAx vs non-familial		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Type									
DCIS	1.68	0.54–5.23	0.365	1.39	0.45–4.32	0.567	0.31	0.15–0.67	0.003
IDC	0.42	0.18–0.99	0.048	0.76	0.36–1.59	0.465	1.43	0.84–2.44	0.185
ILC	7.3	0.95–56.10	0.050	1.84	0.60–5.70	0.289	1.68	0.83–3.42	0.148
Mixed	0.47	0.08–2.89	0.414	0.30	0.06–1.53	0.148	0.89	0.195–4.02	0.877
Grade									
1	0.38	0.21–0.70	0.002	0.59	0.35–1.00	0.050	1.09	0.71–1.68	0.679
2									
3									
Lymph node status									
	0.94	0.51–1.71	0.830	0.48	0.25–0.91	0.025	2.44	1.46–4.07	0.001
Receptor Status									
ER	4.21	2.17–8.14	<0.0001	0.55	0.26–1.17	0.119	0.52	0.29–0.98	0.041
HER2	2.70	1.01–7.27	0.049	2.24	0.89–5.64	0.085	1.37	0.70–2.68	0.362

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BRCA2-Positive Familial Breast Cancer Group

In comparison to BRCAx, BRCA2 tumors showed an aggressive phenotype of being of higher grade (OR 0.59, P = 0.05) and more likely to have positive lymph nodes (OR 0.48, 95% CI 0.25–0.91, P = 0.025). However, multivariate logistic regression results revealed that BRCAx tumors remained less likely to be ER positive (OR 0.35, 95% CI 0.14–0.85, P = 0.020) and more likely HER2 positive (OR 3.21, 95% CI 1.19–8.64, P = 0.21).

Discussion

By analyzing histological data from familial non-BRCA1/2 (BRCAx) with BRCA1-positive, BRCA2-positive and non-familial screen-detected breast cancer tumors, we report that BRCAx tumors are, in severity, between that of familial and non-familial cases. In particular, BRCAx receptor status is less likely ER positive than non-familial cases and after multivariate logistic regression analysis is more likely ER and HER2 positive as compared with BRCA1 tumors, and less likely ER positive and more likely HER2 negative as compared with BRCA2 tumors. We found that not only do BRCAx tumors have a trend towards a different histological profile than that of non-familial cases, but they generally also seem to have a more aggressive phenotype. This is in contrast to a the findings of a small number of previous studies that compared the BRCAx familial phenotype with sporadic breast cancer.[15]

In an attempt to characterize the phenotype of likely mutation carriers for clinical testing, several key studies aimed to examine *BRCA1*, *BRCA2* and sporadic breast cancer phenotypes.[13,22–24] While *BRCA1* tumors tend to be of high grade and triple negative, some have reported that BRCAx tumors are of lower grade, even compared to sporadic cases. However, their cohort selection was based on symptomatic sporadic cases.[15] They further commented that their results need to be interpreted with caution as biases may exist due to hereditary cancers being diagnosed early and may therefore appear to be of lower grade. Keeping that in mind, we decided to compare the phenotype of screen-detected breast tumors with familial cases to try and reduce that bias.

Similarly, the results of our study may be subject to other types of bias. Firstly, the BRCAx cohort was selected on the basis of having a personal history of breast cancer and presence of family history, while the screen-detected cohort was identified through a national screening program from the age of 50 through mammographic screening. The difference in the age of onset between the two groups may of course contribute to the differences we see in tumor stage. Nonetheless, we do not expect receptor status to be affected by this bias, since it is in essence representative of the tumor features regardless of disease progression. In addition, our observation that DCIS is more common in the non-familial than the familial cohort is inevitable since DCIS is more common in a screened rather than a non-screened cohort as DCIS rarely resents symptomatically. This bias can similarly be extended to lymph node status.

Preventative strategies for *BRCA1* and *BRCA2* carriers are relatively well-established and have been predominantly focused on surgical strategies, such as bilateral mastectomy and reducing estrogen exposure by bilateral salpingo-oophrectomy.[3,25,26] As breast cancer risk may be as high as 85% in *BRCA1* and *BRCA2* carriers, surgical intervention can be a good option to reduce risk.[1] The clinical management is not as clear cut for unaffected members of BRCAx families for whom breast cancer risk is relatively unknown.

Chemoprevention in BRCA1/2 carriers is controversial as tumors generally have differing hormonal phenotypes, especially in *BRCA1* mutation carriers for whom the tumor phenotype is typically basal-like and thus triple negative.[27] Selective estrogen response modifiers (or SERMs) such as Tamoxifen and Raloxifene are the gold-standard for treating both early and advanced hormone receptor-positive breast cancer.[28,29] Studies have shown their extended usefulness in breast cancer prevention in high-risk individuals.[30] The NSABP trial showed a 43% reduction in invasive breast cancer in high-risk women taking Tamoxifen, which was only seen in ER-positive cancers.[30] Data from the randomized primary prevention studies suggested that the benefit of Tamoxifen was confined to the prevention of ER-positive breast cancer.[31] Surprisingly however, there has been evidence that although BRCA1 tumors are less likely ER positive than BRCA2 tumors, the reduction in risk after Tamoxifen is relatively similar.[32,33] Although results from our study show that 70% of BRCAx cases had ER-positive tumors, ER receptor negativity in BRCAx cases was the only independent variable. The usefulness of chemoprevention is therefore questionable and should be carefully assessed in these cases. While Tamoxifen treatment is associated with a 37% reduction in breast cancer incidence, there are associated risks, such as potentially lethal venous thromboembolic events.[34] This risk is an important consideration in the case of at risk individuals who have not yet developed breast cancer and in whom ER receptor status is therefore unknown. An alternative would be the results from the MAP-3 trial, which showed a 65% reduction of invasive breast cancer in post-menopausal women with Aromatase inhibitor Exemestane with minimal side effects at 3 years.[35] Further studies will need to be performed to define the usefulness of chemoprevention for this important BRCAx familial population.

In conclusion, our study aimed to shed light on the familial BRCAx phenotype through a comparison with BRCA1, BRCA2 and non-familial breast cancer tumors. We have shown that BRCAx tumors are less likely ER-positive than non-familial cases, but more likely ER-positive than BRCA1 and BRCA2 tumors. Results from

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this study can be important when it comes to the management of unaffected members of families with breast cancer clustering found not to carry *BRCA1* or *BRCA2* mutations and further studies will need to be set our and sought for to assess the suitability of chemoprevention in these patients and their unaffected relatives. In addition, the ongoing dramatic improvements in the speed, scale and cost of DNA sequencing through developments in high-throughput methodologies have provided a realistic alternative to GWAS approaches to identify candidate genes, especially to high-risk rare disease variants.[36] Establishing phenotype–genotype databases can help us further find genetic causes of disease to aim for early diagnosis.[37]

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Conflict of interest statement

All authors have no conflicts of interest or financial ties to disclose.

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