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ORIGINAL ARTICLE

A prior diagnosis of breast cancer is a risk factor for breast cancer in *BRCA1* and *BRCA2* carriers

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ABSTRACT

Background

The risk of breast cancer in carriers of *BRCA1* and *BRCA2* mutations is influenced by factors other than the genetic mutation itself. Modifying factors include a woman's reproductive history and family history of cancer. Risk factors are more likely to be present in women with breast cancer than in women without breast cancer, and therefore the risk of cancer in the two breasts should not be independent. It is not clear to what extent modifying factors influence the risk of a first primary or a contralateral breast cancer in *BRCA* carriers.

Methods

We conducted a matched case–control study of breast cancer among 3920 *BRCA1* or *BRCA2* mutation carriers. We asked whether a past history of breast cancer in the contralateral breast was a risk factor for breast cancer.

Results

After adjustment for age, country of residence, and cancer treatment, a previous cancer of the right breast was found to be a significant risk factor for cancer of the left breast among *BRCA1* or *BRCA2* carriers (relative risk: 2.1; 95% confidence interval: 1.4 to 3.0; $p < 0.0001$).

Conclusions

In a woman with a *BRCA1* or *BRCA2* mutation who is diagnosed with breast cancer, the risk of cancer in the contralateral breast depends on the first diagnosis. That observation supports the hypothesis that there are important genetic or non-genetic modifiers of cancer risk in *BRCA* carriers. Discovering risk modifiers might lead to greater personalization of risk assessment and management recommendations for *BRCA*-positive patients.

KEY WORDS

BRCA1, BRCA2, contralateral breast cancer

1. INTRODUCTION

The risk of breast cancer among women who carry a *BRCA1* or *BRCA2* mutation is approximately 70% to age 80[1,2]. It is therefore of interest to establish, among women who carry a *BRCA1* or *BRCA2* mutation, the extent to which the risk of breast cancer is determined by the mutation itself and the extent to which the risk is attributable to other factors. Several factors modify the risk, including a family history of breast cancer. We showed that the risk of first primary breast cancer in a *BRCA1* mutation carrier increases with the number of first-degree relatives diagnosed with breast cancer before the age of 50[3]. Information on risk modifiers is relevant for the estimation of gene penetrance and for counselling of patients and their families. If additional factors (genetic or non-genetic) are important in determining risk, then carriers from families with multiple cancer cases, or women who themselves have cancer, might not adequately represent carriers in the general population for the purposes of estimating risk[4]. Identification of risk modifiers could potentially facilitate a reduction in the risk of (primary or) contralateral breast cancer. Among women with a *BRCA1* or *BRCA2* mutation, the extent to which the risk of cancer is influenced by factors other than the mutation is not known.

Several modifying risk factors have been identified, including parity, oophorectomy, age of menarche, and breast feeding[5–8]. However, the extent to which these reproductive risk factors cluster in families is not clear, and these factors are not expected to result in familial correlation of

risk. Epidemiologic observations that support the existence of non-genetic modifying factors include cohort effects (increasing penetrance observed with calendar time)[1,9,10]. Evidence in support of genetic modifiers include the impact of family history on cancer risk[3], concordance in the clinical presentation of bilateral cancers among *BRCA* carriers[11], and variation in penetrance between groups of women with similar mutations but from different ethnic groups[12]. The risks of breast cancer and of contralateral breast cancer among carriers can also be predicted to some extent by the number of variant alleles of genes at other loci[13]. However, variation in risk might result from non-genetic factors as well.

Among women with breast cancer and a *BRCA1* mutation, the risk of contralateral breast cancer is approximately 2.5% per year, and the cumulative incidence of contralateral cancer reaches 30% at 10 years[14]. That incidence is approximately 6 times greater than the risk of contralateral breast cancer in non-carriers[15]. If the presence of the mutation wholly determines breast cancer risk, and if bilateral breast cancers represent two independent primaries, then we can consider all breasts in a population of carriers to be independent, each with an equal inherent risk—that is, the risk of cancer in the left breast should be independent of the cancer risk in the right. However, if other genetic risk factors are operating, those risk factors would be expected to be overrepresented in mutation carriers with breast cancer compared with the general population of carriers. Breast cancer in the first breast would then appear to be a risk factor for breast cancer in the opposite breast.

2. METHODS

The strategy here was to test the hypothesis that cancer of one breast is a risk factor for cancer of the contralateral breast. If so, then the risk of cancer in a particular breast would be expected to be higher if the woman has had a previous cancer in the opposite breast. To test that hypothesis, we used a case–control study design, considering cancer of the left breast to be the index cancer and cancer of the right breast to be the exposure of interest. That is, we considered women with cancer of the left breast to be "cases" and women with no cancer of the left breast to be "controls." Note that if women with bilateral cancers were considered to be "cases" and those with unilateral cancers to be "controls," then 100% of cases and 0% of controls would have a past history of breast cancer and the analysis would be non-informative.

Data for 13,916 *BRCA* carriers were submitted to the data centre by collaborators in 11 countries. All subjects provided informed written consent for genetic testing. The study was approved by the ethics committees and human subjects review boards of all participating centres. In most cases, testing was initially offered to women who were affected either by breast cancer or by ovarian cancer. When a mutation in either *BRCA1* or *BRCA2* was found in a proband or a relative, testing was offered to other at-risk women in the family. Mutation detection was performed using a range of techniques, but all nucleotide alterations were confirmed by direct DNA sequencing. A woman was eligible for the study when the molecular analysis established that she was a mutation carrier.

The study excluded 1929 women who had a diagnosis of ovarian cancer and 1761 women who had received a preventive mastectomy. Another 338 subjects were excluded because they were treated for breast cancer with bilateral mastectomy and were at very low risk of a second primary; 148, because of missing information on year of diagnosis or laterality; 103, because of having both a *BRCA1* and a *BRCA2* mutation; and 130, because bilateral breast cancer was diagnosed in the same year (in this latter group, the time sequence for the left and right breast cancers was not clear). Another 92 women were excluded because of missing information. Of the 9415 remaining eligible subjects, 3454 women had breast cancer, and 5961 women had no breast cancer. Of the women with breast cancer, 2077 women had cancer of the left breast, and 2064 had cancer of the right breast (687 women had cancer in both breasts diagnosed in different years).

An attempt was made to match each of the 2077 women with left breast cancer with 1 woman who did not have left breast cancer. Women were matched on year of birth (within 1 year), country of origin, and gene mutation present (*BRCA1* or *BRCA2*). In every case, the control was at least as old at interview as the case was at diagnosis of the left breast cancer. The result was 1960 matched sets of women (Table I).

3. RESULTS

Of the case women with left breast cancer and the control women without left breast cancer, 14.8% and 11.6% respectively had a previous diagnosis of right breast cancer (that is, before the year of diagnosis of left breast cancer in the case). The unadjusted odds ratio (calculated using conditional logistic regression for matched sets) for prior breast cancer was 1.3 (95% confidence interval: 1.1 to 1.6; $p = 0.003$).

That finding suggests that right breast cancer is associated with a predisposition to left breast cancer; however, because several breast cancer treatments (tamoxifen, oophorectomy, and chemotherapy) have been associated with a diminished risk of contralateral breast cancer[7,8], the data were re-analyzed using multivariate conditional logistic regression after adjustment for those three cancer treatments plus radiotherapy. After adjustment for treatments, a past history of right breast cancer was found to be a highly significant and independent risk factor for left breast cancer among *BRCA1* and *BRCA2* carriers combined

TABLE I Characteristics of patients with left breast cancer (BC) and control subjects without left BC

Variable	*Cases*	*Controls*	p *Value*
Participants (*n*)	1960	1960	
Birth year	1953	1952	0.12
Mutation			
BRCA1	76.5	76.5	Matched
BRCA2	23.5	23.5	
Parity			
Nulliparous (%)	16.8	17.0	0.86
Mean parity (*n*)	2.0	2.0	0.51
Ever smoked (%)	43.5	43.8	0.38
Ethnicity (%)			
Jewish	16	18	
French Canadian	6	6	
Other white	73	74	
Other	4	2	0.001
Oral contraceptives (% ever used)	55	54	0.26
Previous right BC (*n*)	290	227	0.003

(odds ratio: 2.1; 95% confidence interval: 1.4 to 3.0; $p < 0.0001$). The result was similar for *BRCA1* carriers and for *BRCA2* carriers individually (Table II).

We then included other known and possible risk factors in the model (age of menarche, parity, ethnic group, smoking history, oral contraceptives), but those adjustments did not materially affect the relative risk estimate associated with right breast cancer for *BRCA1* and *BRCA2* carriers combined (adjusted odds ratio: 2.0; 95% confidence interval: 1.3 to 3.0; $p = 0.007$).

4. DISCUSSION

This study indicates that, among carriers of *BRCA1* or *BRCA2,* the risk of cancer in the two breasts is not independent. After adjusting for treatments received, a history of cancer in one breast was found to be associated with an approximately doubled increase in the risk of cancer in the contralateral breast. Data on contralateral breast cancer should therefore not be used to estimate the penetrance of *BRCA1* or *BRCA2* mutations, because that approach will lead to an overestimation of the lifetime risk. Notably, one of the first papers used to estimate the penetrance of *BRCA1* (which has been cited more than 1000 times) was based on the assumption that cancer risk in unaffected *BRCA* carriers was roughly double the risk of experiencing a contralateral breast cancer[16].

The factors that are responsible for the observed association are not yet known. They might possibly be genetic (that is, genetic modifiers of the *BRCA1* or *BRCA2* gene, or allelic heterogeneity) or non-genetic (for example, environmental). Interestingly, a history of early-onset breast cancer in a first-degree relative is a risk factor for breast cancer in *BRCA1* and *BRCA2* carriers[3], and that observation favours the presence of modifying genes. Currently, large-scale genome-wide association studies are underway using populations of *BRCA1* and *BRCA2* carriers with the hope of identifying one or more modifying genes.

It is unlikely that many of the left breast cancers studied here are metastases of the cancer of the right breast, but it is theoretically possible that the two breast cancers developed from a common pre-malignant precursor. We showed that, among women with bilateral breast cancer and a *BRCA1* mutation, the two cancers are concordant for expression of the estrogen receptor more often than would be expected by chance[11]. Further studies are necessary to establish the biologic bases for those observations. We previously showed that the risk of contralateral breast cancer in women with a *BRCA1* or *BRCA2* mutation is sufficiently high that preventive mastectomy should be offered[14], and recently we showed that contralateral mastectomy is associated with reduced mortality from breast cancer[17].

5. CONCLUSIONS

A diagnosis of breast cancer in a woman with a *BRCA1* or *BRCA2* mutation is an indicator of an inherently increased risk for breast cancer beyond that attributable to the mutation alone and which is manifest by a statistically-increased risk of cancer in the contralateral breast.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors of this paper declare that no financial conflict of interest exists.

TABLE II Risk factors for cancer of the left breast among *BRCA1* and *BRCA2* mutation carriers

Participant group	*Univariate analysis*			Multivariate analysis[a]		
	OR	*95% CI*	p *Value*	*OR*	*95% CI*	p *Value*
All participants						
Right breast cancer	1.34	1.10 to 1.62	0.003	2.09	1.44 to 3.04	<0.0001
Radiotherapy	1.21	0.94 to 1.57	0.14	0.93	0.63 to 1.35	0.96
Chemotherapy	1.08	0.86 to 1.36	0.52	0.63	0.42 to 0.93	0.02
Tamoxifen	0.86	0.59 to 1.26	0.44	0.65	0.44 to 1.01	0.05
Oophorectomy	0.56	0.43 to 0.74	<0.0001	0.56	0.42 to 0.74	<0.0001
BRCA1 carriers only						
Right breast cancer	1.33	1.07 to 1.66	0.009	2.01	1.44 to 3.09	0.002
Radiotherapy	1.22	0.92 to 1.62	0.17	0.93	0.63 to 1.42	0.74
Chemotherapy	1.07	0.83 to 1.38	0.60	0.62	0.39 to 0.97	0.04
Tamoxifen	1.06	0.66 to 1.69	0.81	0.86	0.50 to 1.47	0.58
Oophorectomy	0.52	0.38 to 0.71	<0.0001	0.51	0.37 to 0.71	<0.0001
BRCA2 carriers only						
Right breast cancer	1.34	0.90 to 2.01	0.15	2.54	1.16 to 5.59	0.02
Radiotherapy	1.18	0.67 to 2.08	0.57	0.89	0.36 to 2.23	0.81
Chemotherapy	1.12	0.66 to 1.89	0.69	0.75	0.30 to 1.90	0.55
Tamoxifen	0.57	0.29 to 1.12	0.10	0.27	0.11 to 0.67	0.005
Oophorectomy	0.73	0.42 to 1.27	0.27	0.79	0.44 to 1.43	0.44

[a] Adjusted for other variables in the table and for ethnic group.
OR = odds ratio; CI = confidence interval.

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