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Second primary breast cancer in *BRCA1* and *BRCA2* mutation carriers: 10-year cumulative incidence in the Breast Cancer Family Registry

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Abstract

Purpose—*BRCA1* and *BRCA2* (BReast CAncer genes 1 and 2) mutation carriers diagnosed with breast cancer are at increased risk of developing a second primary breast cancer. Data from high risk clinics may be subject to different biases which can cause both over and underestimation of

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this risk. Using data from a large multi-institutional family registry we estimated the 10 year cumulative risk of second primary breast cancer including more complete testing information on family members.

Patients and Methods—We prospectively followed 800 women diagnosed with breast cancer from the Breast Cancer Family Registry (BCFR) who were carriers of a *BRCA1* or *BRCA2* pathogenic mutation or a variant of unknown clinical significance. In order to limit survival and ascertainment bias, cases were limited to those diagnosed with a first primary breast cancer from 1994 to 2001 and enrolled in the BCFR within 3 years after their cancer diagnosis; We excluded women enrolled **after** being diagnosed with a second breast cancer. We calculated 10 year incidence of second primary breast cancers.

Results—The 10-year incidence of a second primary breast cancer was highest in *BRCA1* mutation carriers (17%; 95% CI 11-25%), with even higher estimates in those first diagnosed under the age of 40 (21%; 95% CI 13-34%). Lower rates were found in *BRCA2* mutation carriers (7%; 95% CI 3-15%) and women with a variant of unknown clinical significance (6%; 95% CI 4-9%).

Conclusions—Whereas the cumulative 10-year incidence of second primary breast cancer is high in *BRCA1* mutation carriers, the estimates in *BRCA2* mutation carriers and women with variants of unknown clinical significance are similar to those reported in women with sporadic breast cancer.

Introduction

Many patients with newly diagnosed breast cancer undergo genetic counseling and *BRCA1* and *BRCA2* (BRest Cancer genes 1 and 2) mutation testing prior to surgery. The information gained by *BRCA* testing may clarify the risk of a second primary cancer, but often adds more treatment options and may complicate the decision making process. A *BRCA* mutation carrier who is newly diagnosed with breast cancer and is a candidate for surgery is faced with complex decisions regarding surgery for the diagnosed cancer as well as risk-reducing surgery for the remaining breast or ovaries. Although recommendations exist regarding the different risk-reducing options available to *BRCA* mutation carriers (<http://www.guideline.gov/content.aspx?id=47749&search=brca>), a diagnosis of cancer complicates risk counseling as the patient is at risk of suffering a recurrence from her first cancer in addition to developing a second primary cancer [1]. Several studies have reported risk estimates for a second primary cancer in the contralateral breast [2-6]. Studies originating from high-risk clinics may overestimate this risk because of ascertainment and survival bias, meaning preferential *BRCA*-testing both in women diagnosed with bilateral breast cancer (as this is an indication for DNA testing), and in breast cancer survivors. On the other hand, studies including women from *BRCA* carrier families may underestimate this risk if untested women are included, as these women may not all carry a pathogenic mutation, despite the fact that they were diagnosed with cancer, and therefore have a lower risk for developing a second primary breast cancer. Despite the high risk of developing a subsequent breast cancer (as high as 3% yearly rate in some reports [2]), no survival benefit has been observed with risk-reducing contralateral mastectomy [7], highlighting the need to better select women for this treatment. Risk-reducing surgery, which usually includes

immediate breast reconstruction, may delay therapeutic surgery and subsequent adjuvant treatment [8], as complication rates are higher [9] and the recovery time is increased with bilateral surgery. Delay in treatment (both surgery and adjuvant treatment) may impede the chance of survival from the present cancer [10]. In order to make an informed decision, data on the cumulative incidence of second primary breast cancer (both ipsilateral and contralateral), the timing of these events as well as association with different clinical predictors are needed. The Breast Cancer Family Registry (BCFR; <http://www.bcfamilyregistry.org/>) was established in 1995, and has been collecting data since 1996 from families with and without breast cancer [11, 12]. The BCFR is unique in that it collects data from both population-based and clinic-based families. Data collected include lifestyle, medical and family history from more than 55,000 women and men from 14,000 families. We used data collected by the BCFR to estimate the cumulative 10-year risk of developing a second primary breast cancer in *BRCA1* or *BRCA2* mutation carriers (i.e., both ipsi and contralateral cancers), and to examine factors associated with this risk. The study was designed to limit ascertainment and survival bias. We included data from both population and clinic based registries and restricted the analyses to tested individuals diagnosed with breast cancer after the implementation of *BRCA* testing, and excluded women diagnosed with two breast cancers prior to their enrollment in the BCFR registry.

Methods

The BCFR includes six participating sites that recruited population-based (San Francisco Bay Area, California U.S.A, Ontario, Canada, and Australia) or clinic-based (New York City, New York U.S.A; Philadelphia, Pennsylvania U.S.A.; Utah, U.S.A.; Ontario, Canada; and Australia) families. A detailed description of the BCFR and protocol for recruitment of individuals is provided elsewhere [11, 12]. The BCFR database identified all women with a diagnosis of breast cancer who carried a mutation in *BRCA1* or *BRCA2* (either pathogenic mutation or a variant of unknown clinical significance). BCFR participants have undergone extensive *BRCA1* and *BRCA2* mutation testing using multiple techniques [13]. Definition of pathogenicity of *BRCA1* and *BRCA2* variants was based on classifications in the BIC (Breast Cancer Information Core) database, as supplemented by those recently classified by the ENIGMA consortium and as those listed in the website of classified misuses variants [14].

We excluded women with a previous history of another cancer. In order to limit survival and ascertainment bias, we included only women enrolled in the BCFR within 3 years of their first breast cancer diagnosis. We excluded women diagnosed with 2 breast cancers prior to their enrollment to the registry. All women therefore, were diagnosed with their first breast cancer after 1993, and to allow 10-year follow-up, cases were limited to those diagnosed before 2002. Data included demographic details (age, race/ethnicity, country of origin), menopausal status (at diagnosis), information on primary breast cancer (date of diagnosis, date and type of surgery, histology, grade, tumor size, nodal involvement, estrogen and progesterone receptor status), and self-reported use and type of adjuvant treatment (radiation, hormonal treatment and chemotherapy). Follow-up data included date of last follow-up and vital status at last follow-up, date and laterality of new breast cancer diagnoses, occurrence and timing of risk-reducing mastectomy.

Women were divided into three groups according to their *BRCA* mutation status: pathogenic mutation in *BRCA1*, pathogenic mutation in *BRCA2*, or a variant of unknown clinical significance in either gene. Women who had both a pathogenic mutation and a variant of unknown clinical significance were considered as having a pathogenic mutation. Women with a pathogenic mutation in both *BRCA1* and *BRCA2* were excluded.

For second primary breast cancer calculations, women with a first primary in-situ or invasive breast cancer undergoing breast-conserving treatment or unilateral mastectomy were included. Patients presenting with bilateral breast cancer at the time of diagnosis and those diagnosed with a contralateral cancer within one year were excluded. Patients with unilateral cancer who had a bilateral mastectomy were censored at the time of the second (risk-reducing) mastectomy. When another breast cancer was reported, determination of local recurrence vs. a second primary was based on the laterality of the new cancer in comparison to the first cancer, and the time that elapsed from first diagnosis: if ten years had passed from the first cancer it was considered a second primary regardless of laterality. All second breast cancer cases were reviewed by the BCFR sites to ensure that the second cancer was a second primary and diagnosed after enrollment to the BCFR.

We compared the characteristics of the women in the 3 groups, their tumors and treatments using t-tests for continuous data and the chi-square test for categorical data. We performed Survival analysis using Cox proportional hazard models, examining the association between second breast cancer events and treatment (hormonal, chemotherapy, radiation therapy and removal of ovaries within 2 years of first diagnosis). We estimated 10-year cumulative incidence rates of second primary breast cancer using Kaplan-Meier analysis for all cases combined and separately for each of the 3 case subgroups. Calculations were done using SAS 9.3. Institutional Review Board approval was obtained at all participating institutions.

Results

Table 1 includes all eligible women (n=800). The mean age at first diagnosis was 41 years (range 20-81). Two-thirds (n=525, 66%) were non-Ashkenazi white. The mean follow-up time was 107 months (range less than 1 month to 234). There were 159 (20%) women with a pathogenic mutation in *BRCA1*, 119 (15%) women with a pathogenic mutation in *BRCA2*, and 522 (65%) women with a variant of unknown clinical significance in *BRCA1* or *BRCA2* and no pathogenic mutation in either gene. As expected there were more Ashkenazi women in the groups with a pathogenic mutation in *BRCA1* or *BRCA2* (22% and 14%, respectively) compared to the group with a variant of unknown clinical significance (2%).

Most of the women for whom data on tumor characteristics are available had invasive carcinoma (n=237 of 246, 96%), and almost a third (n=94 of 297, 31%) had lymph node metastases (Table 1). *BRCA1* associated breast cancers tended to be of higher grade (67%) and were less often estrogen receptor positive (14%). Accordingly, use of tamoxifen or another hormonal treatment was significantly lower in *BRCA1* mutation carriers when compared to *BRCA2* mutation carriers and to women with a variant of unknown clinical significance (24% vs. 46% and 32%, respectively, p<0.0001). Adjuvant chemotherapy was

more frequently reported by *BRCA1* mutation carriers than the other groups, whereas use of radiation was similar in the 3 groups.

During the follow-up period there were 86 second breast cancers documented that were considered as second primaries. Overall, the probability of developing a second primary breast cancer within ten years from the first diagnosis was 11% (95% CI 9, 13). Mean age at diagnosis of a second primary breast cancer was 49 years (range 28-74). However, *BRCA1* mutation carriers were diagnosed earlier with a second primary breast cancer when compared to *BRCA2* mutation carriers and to women with a variant of unknown clinical significance (mean age 45 vs. 48 and 51, respectively). The cumulative incidence of a second primary breast cancer was higher in *BRCA1* mutation carriers, when compared to *BRCA2* mutation carriers and women with a variant of unknown clinical significance (overall 10-year probability of 17% vs. 7%, and 6%, respectively, $p<0.001$; Figure 1). The highest probability was observed in *BRCA1* mutation carriers that were diagnosed with breast cancer before age 40 years (10-year probability of 22%; Table 2). In the multivariate analysis, no association was seen between adjuvant treatment and oophorectomy within two years of the diagnosis and second breast cancer events (Table 4).

Discussion

In this study, using data from the BCFR, cumulative 10-year incidence of second primary breast cancer was associated with *BRCA* mutation status and age at diagnosis of the first breast cancer. Highest cumulative incidence (22%) was found in *BRCA1* mutation carriers younger than 40 years at first diagnosis. This rate is on the lower end of the range of reported 10-year cumulative incidence of contralateral breast cancer in *BRCA1* mutation carriers younger than 40 years (24- 31%, Table 4). The cumulative 10-year incidence of second primary breast cancer reported here for *BRCA2* mutation carriers is lower than the incidence reported by others (Table 4) and is similar to the incidence reported in women without mutations in *BRCA1* or *BRCA2* [16].

Predicting the risk of a second primary breast cancer using data collected by selective registries is prone to several types of bias. These were detailed by Klaren [17], and include mainly longevity or survival bias and ascertainment bias. Tilanus-Linthorst [18] showed the effect of survival and ascertainment bias in a study comparing survival and contralateral breast cancer in women with non-*BRCA* familial breast cancer; these findings are relevant to *BRCA* mutation carriers as well. In that study, women were divided into two groups according to the timing of *BRCA* mutation testing (less or more than 2 years from diagnosis) and compared to cases without mutations. Survival was improved in the late tested group (women tested over 2 years from diagnosis). In the late tested group the rates of contralateral breast cancer were higher when compared to both the unselected group (women tested earlier than 2 years from diagnosis) and the cases without mutations, pointing to a selection of women with contralateral cancer for genetic testing.

There are several ways to limit these biases. Van Sprundel [19] started follow-up at the date of *BRCA* testing result or at the time of contralateral mastectomy, in order to exclude women who were triggered to be tested by a second diagnosis of breast cancer. Others have

excluded index cases from their study group, after showing that they had higher incidence of contralateral cancer when compared to their relatives, pointing again to a selection bias [4, 6]. However, exclusion of index cases or those that were tested long after their diagnosis may introduce a bias towards unfavorable survival [6]. Others (e.g., the WECARE study) used a population-based case-control design to reduce the risk of ascertainment bias. However, in that study the rates of contralateral cancer were similar to those reported by other studies reporting data from high risk clinics [3]. We limited the study group to *BRCA*-tested women that were first diagnosed within 3 years of their enrollment or after their enrollment, and excluded cases that were enrolled after their second breast cancer diagnosis.

Apart from age at first diagnosis and *BRCA* mutation status, other predictors for developing a second primary breast cancer have been reported in the literature. Metcalfe [20], using data from a multicenter cohort of *BRCA* carrier families, reported an association with the number of first degree relatives affected with breast cancer. In women diagnosed before age 49 years, the 15-year risk of contralateral breast cancer increased from 33% to 50% when comparing women with no family history to women with 2 or more first degree relatives with breast cancer. Stage and grade of the cancer were not associated with the risk of a second primary breast cancer [21]. Use of adjuvant treatment was shown to reduce the risk of a contralateral cancer in several studies [15, 21-22]; Tamoxifen use was associated with a 50% reduction in contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers in a matched case-control study using data from the Hereditary Breast Cancer Clinical Study Group (a multicenter registry of *BRCA* associated breast cancer) [21]. However, the cases and the controls in that study were not matched for estrogen receptor status. The WECARE study is a population-based case-control study, which includes cases with contralateral breast cancer and matched controls diagnosed with unilateral breast cancer. All women were tested for *BRCA* mutations. In that study adjuvant chemotherapy was associated with reduced risk of a contralateral breast cancer in *BRCA* mutation carriers as well as non-carriers [15]. Adjuvant radiation was not associated with reduced risk of second primary breast cancer in our study or of contralateral breast cancer in other reports [5]. Oophorectomy was associated with decreased rates of a contralateral cancer [20].

Whereas the studies referenced here reported on cumulative incidence of contralateral cancer, we included both ipsilateral and contralateral breast cancers in order to assess the role of risk-reducing surgery in these women. We used time since diagnosis of first breast cancer greater than 10 years to limit the mislabeling of ipsilateral recurrence as a second breast primary.

In women with a variant of *BRCA1* or *BRCA2* of unknown clinical significance we found a much lower rate of second primary breast cancers (10-year risk of 6%), which is comparable to the risks reported for breast cancer cases without *BRCA* mutations [6]. Figueiredo [23], using data from the WECARE study, examined rates of contralateral breast cancer in women with common variants of *BRCA1* and *BRCA2*. No association was found between specific common polymorphisms and risk of contralateral cancer. Brekelmans [6] reported that in hereditary non-*BRCA* associated breast cancer, cumulative incidence of contralateral breast cancer was similar to that reported in sporadic cases, 6% over 10 years. Shahedi [24], on the other hand, reported in familial non-*BRCA* associated breast cancer, a 10-year

probability of 13% for contralateral cancer. As most mutations of uncertain significance in *BRCA1* and *BRCA2* are eventually determined to be benign polymorphisms, it is not surprising that they are not associated with increased risk of contralateral breast cancer. The modestly increased risk seen in some studies is likely related to a combination of some of the small percent of variants that are actually deleterious, and the family history that led to genetic testing in the first place.

As with other studies, the biases mentioned here can occur in this cohort as well. Data from large datasets are subject to information bias. Although the BCFR is a large registry, detailed pathology staging was not available for a large proportion of the cases. Data on adjuvant treatment, obtained by self-report, were not available for 20-30% of cases and may have limited the power of the study to show an association with risk of a second primary breast cancer. With constant improvement in outcome of breast cancer patients on the one hand and expansion of the indications for genetic testing, studies that include *BRCA* mutation carriers treated and tested close to 20 years ago may not reflect the outcome of patients diagnosed and treated today.

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Summary

The 10-year cumulative incidence of second primary breast cancer in *BRCA* mutation carriers is associated with age at diagnosis and type of *BRCA* mutation. Risks are high for *BRCA1* mutation carriers diagnosed before age 40 years. For *BRCA2* mutation carriers and women with mutations of unknown clinical significance, 10-year cumulative incidence is similar to that seen in women without mutations in *BRCA1* or *BRCA2*.

Figure 1.

Risk of second primary breast cancer over time, according to *BRCA1* and *BRCA2* mutation status in the BCFR. Blue-*BRCA1* mutation carriers, Green-*BRCA2* mutation carriers, yellow- carriers of *BRCA1* or *BRCA2* variant of unknown clinical significance.

Table 1

Characteristics of women and their first breast cancers in the BCFR, divided according to *BRCA* status.

	BRCA1 mutation carriers (N=159)	BRCA2 mutation carriers (N=119)	UV (N=522)	P-value
Age at diagnosis, years (range)	40 (23,81)	42 (25,69)	41(20,66)	NS
Race, number (%)				
Ashkenazi	35 (22%)	17(14%)	10(2%)	
White, non-Ashkenazi	110(69%)	82(69%)	333(64%)	
Black	6(4%)	6 (5%)	71(14%)	
Other/missing	8 (5%)	14(12%)	108(21%)	<.0001
Year of diagnosis, number (%)				
1993-1995	26 (16%)	23(19%)	153(29%)	
1996-1998	110(69%)	81(68%)	269(52%)	
1999-2001	23(14%)	15(13%)	100 (19%)	0.0001
Menopausal status at diagnosis				
Premenopausal	145(91%)	105(88%)	439(84%)	
Postmenopausal	14(9%)	14(12%)	83(16%)	NS
Bilateral oophorectomy within 2 years of diagnosis	15(9%)	10(8%)	8(2%)	<.0001
Age at bilateral oophorectomy, years (range)	45(24,70)	47(35,63)	45(29,66)	NS
Grade				
1	2 (1%)	7(6%)	45(9%)	
2	10 (6%)	21(18%)	88(17%)	
3	106(67%)	50(42%)	136(26%)	
Missing	41(26%)	41(34%)	253(48%)	<.0001
Estrogen receptor				
Negative	96 (60%)	19(16%)	121(23%)	
Positive	22(14%)	70(59%)	246(47%)	
Missing	41(26%)	30(25%)	155(30%)	<.0001
Progesterone receptor				
Negative	83(52%)	28(24%)	130(25%)	
Positive	35(22%)	61(51%)	237(45%)	
Missing	41(26%)	30(25%)	155(30%)	<.0001
Invasive tumor size, mm (range)	21 (2, 96)	22(1,96)	26(0.5,96)	0.02
Tumor stage				
In Situ	3(2%)	2(2%)	4(1%)	
1	39(25%)	30(25%)	55(11%)	
2	29(18%)	22(18%)	47(9%)	

	BRCA1 mutation carriers (N=159)	BRCA2 mutation carriers (N=119)	UV (N=522)	P-value
3+	2(1%)	5(4%)	8(2%)	<.0001
Missing	86(54%)	60(50%)	408(78%)	
Lymph node status				<.0001
Negative	56(35%)	40(34%)	107(20%)	
Positive	21(13%)	27(23%)	46(9%)	
Missing	82(52%)	52(44%)	369(71%)	
Surgery				NS
Breast conserving	77(48%)	50(42%)	233(45%)	
Mastectomy	71(45%)	59(50%)	225(43%)	
Missing	11(7%)	10(8%)	64(12%)	
Radiation				NS
Yes	82(52%)	56(47%)	233(45%)	
No	44(28%)	36(30%)	138(26%)	
Missing	33(21%)	27(23%)	151(29%)	
Chemotherapy				<.0001
Yes	108(68%)	66(55%)	241(46%)	
No	18(11%)	27(23%)	129(25%)	
Missing	33(21%)	26(22%)	152(29%)	
Hormone treatment				<.0001
Yes	38(24%)	55(46%)	166(32%)	
No	89(56%)	38(32%)	202(39%)	
Missing	32(20%)	26(22%)	154(30%)	

UV- variant in *BRCA1* or *BRCA2* of unknown clinical significance

Table 2

Second Breast cancers in women with a diagnosis of breast cancer from the BCFR, divided according to *BRCA* status.

	BRCA1 mutation carriers (N=159)	BRCA2 mutation carriers (N=119)	UV (N=522)	P Value
Mean follow-up, months (range)	95 (0,234)	102 (3,220)	111 (2,232)	0.02
Age at second breast cancer, mean years (range)	45 (31,69)	48 (33,62)	51 (28,74)	0.03
Second breast cancer, number (%)	30 (19%)	12 (10%)	44 (8%)	0.001
Cumulative rates of second breast cancer in 10 years (95% CIs)	17(11,25)	7(3,15)	6 (4,9)	<.0001
Cumulative rates of second breast cancer in 10 years (95% CIs) by age first cancer diagnosed:				
Under 40	21(13,34)	7(2,20)	7(4,12)	0.0004
Over 40	11(5,24) *	7(2,20)	5 (2,9)	0.046

UV- variant in *BRCA1* or *BRCA2* of unknown clinical significance

CI-confidence interval

* not statistically significant

Table 3

Cox Proportional Hazard Model - Association between Second Breast Cancer and use of Tamoxifen, Radiation, Chemo, Oophorectomy within 2 years of diagnosis

Parameter	Ratio (95% CI)	P-value
Hormone treatment	0.774 (0.47, 1.26)	0.31
Radiation	1.155 (0.70, 1.91)	0.57
Chemotherapy	1.361 (0.80, 2.32)	0.26
Oophorectomy within 2 years of diagnosis	0.635 (0.16, 2.59)	0.53

Table 4

Studies reporting cumulative 10-year contralateral breast cancer rates in BRCA mutation carriers.

Study	Study type	Number with known mutation	stage	Years of diagnosis	10-year contralateral breast cancer		No association	Association
					All	<40years		
Malone 2010 ³ Reding 2010 ¹⁵	WECARE- Population-based case-control, limited to survivors	181 1922-no mutation	I-III	1985-2000	BRCA1-21% BRCA2-16%	24-29% 22-27%		Age BRCA1 vs. 2 Chemotherapy Tamoxifen (NS).
Graeser 2009 ⁴	Multicenter cohort study, BRCA known families, index patients excluded	174 868-from BRCA families	All	>1960	BRCA1-19%	31%		Age BRCA 1vs. 2
					BRCA2-13%	21%		
Metcalf 2011 ²	Multicenter cohort study BRCA families, 88% BRCA status confirmed	711	I-II	1975-2008	BRCA1-24%	~25%	Grade Stage Adjuvant treatment	Age, Number of first degree relatives with breast cancer oophorectomy
					BRCA2-19%			
Brekelmans 2007 ⁶	Rotterdam Family Cancer Clinic-BRCA families, index cases excluded	260 from families that were known to carry BRCA1 or 2 mutation	I-IV	1980-2004	BRCA1-25%	NA		
					BRCA2-20%			
Pierce 2010 ⁵	Multicenter, high-risk clinic cohort	643	I-III	NA	24-32%		Radiation, type of surgery	BRCA1, age (not on multivariate)
Present study	Multicenter Population and high risk clinic based	278-BRCA1,2 522-UV	I-IV	1993-2001	BRCA1-17% BRCA2-7% UV-6%	BRCA1-22% BRCA2-8% UV-7%		Age BRCA1 vs. 2

NS-not significant