Population-Based Study of the Risk of Second Primary Contralateral Breast Cancer Associated With Carrying a Mutation in *BRCA1* or *BRCA2*

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Submitted May 28, 2009; accepted January 28, 2010; published online ahead of print at www.jco.org on April 5, 2010.

Written on behalf of the WE CARE Study Collaborative Group.

Supported by Grants No. R01CA097397 and NCI U01CA083178 from the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2814-2404/\$20.00

DOI: 10.1200/JCO.2009.24.2495

ABSTRACT

Purpose

Women with breast cancer diagnosed early in life comprise a substantial portion of those tested for *BRCA1/BRCA2* mutations; however, little information is available on the subsequent risks of contralateral breast cancer in mutation carriers. This study assessed the risk of subsequent contralateral breast cancer associated with carrying a *BRCA1* or *BRCA2* mutation.

Patients and Methods

In this nested case-control study, patients with contralateral breast cancer diagnosed 1 year or more after a first primary breast cancer ($n = 705$) and controls with unilateral breast cancer ($n = 1,398$) were ascertained from an underlying population-based cohort of 52,536 women diagnosed with a first invasive breast cancer before age 55 years. Interviews and medical record reviews were used to collect risk factor and treatment histories. All women were tested for *BRCA1/BRCA2* mutations. Relative (rate ratios) and absolute (5- and 10-year cumulative) risks of developing contralateral breast cancer following a first invasive breast cancer were computed.

Results

Compared with noncarriers, *BRCA1* and *BRCA2* mutation carriers had 4.5-fold (95% CI, 2.8- to 7.1-fold) and 3.4-fold (95% CI, 2.0- to 5.8-fold) increased risks of contralateral breast cancer, respectively. The relative risk of contralateral breast cancer for *BRCA1* mutation carriers increased as age of first diagnosis decreased. Age-specific cumulative risks are provided for clinical guidance.

Conclusion

The risks of subsequent contralateral breast cancer are substantial for women who carry a *BRCA1/BRCA2* mutation. These findings have important clinical relevance regarding the assessment of *BRCA1/BRCA2* status in patients with breast cancer and the counseling and clinical management of patients found to carry a mutation.

J Clin Oncol 28:2404-2410. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Germline mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* account for the majority of breast cancers in high-risk families and confer a 36% to 84% lifetime risk of first primary breast cancer.¹⁻⁵ This wide range of estimates reflects, in part, the varied populations assessed, with high-risk multicase family studies generally providing higher penetrance estimates than population-based studies.

The risk of subsequent contralateral breast cancer (CBC) among women with a first primary breast cancer is substantially greater than the risk of unilateral breast cancer (UBC) in the general

population.⁶⁻⁸ The rarity of CBC and *BRCA1/BRCA2* mutations in the general population has hindered population-based studies from assessing CBC risk in mutation carriers. Studies in high-risk families and hospital settings have generated results relevant to these populations but not necessarily to the full spectrum of breast cancer in the population.⁹⁻²⁴ The absence of data characterizing the risk of CBC associated with carrying a mutation among women in the general population is a significant knowledge gap. To address this, we estimated the relative and cumulative risk of CBC associated with carrying a *BRCA1* or *BRCA2* mutation among young women with invasive breast cancer in a large population-based case-control study of CBC.

PATIENTS AND METHODS

The WECARE Study²⁵ is a population-based, nested case-control study of CBC, which has been described previously. The study included 705 women with CBC (cases) and 1,398 women with UBC (controls), all of whom were ascertained through five population-based cancer registries covering the country of Denmark along with the State of Iowa, Los Angeles County and the Orange County-San Diego regions of California, and three western Washington counties in the United States (the US registries participate in the Surveillance, Epidemiology, and End Results [SEER] registry system).

All cases and controls were diagnosed before age 55 years from 1985 to 2000 with a first primary invasive breast cancer that had not spread beyond regional lymph nodes. Cases were diagnosed with a second primary invasive or in situ CBC at least 1 year after first primary diagnosis in 1986 to 2001. Two controls were matched individually to each case on birth year (5-year strata), year of first primary diagnosis (4-year strata), registry, and race/ethnicity and were required to have an intact contralateral breast. Cases and controls were counter-matched on registry-reported radiotherapy so that each triplet included one radiation-unexposed woman and two radiation-exposed women (for 12 cases with only one control, matched pairs included one exposed and one unexposed woman), as described previously.²⁵ Controls were assigned a reference date reflecting a cancer-free at-risk period following first breast cancer of equivalent length to the interval between first and second diagnoses of matched cases. Cases and controls were required to have had no other prior/intervening cancers, to have resided in a registry catchment area at both diagnoses/reference date, and to provide a blood sample. In total, 708 (71%) of 998 eligible CBC cases and 1,399 (66%) of 2,112 eligible controls completed telephone interviews regarding risk factors and treatment and donated blood (Appendix Table A1, online only). Three cases and one control declined genotyping. Medical record reviews collected detailed information on radiotherapy, chemotherapy, and hormonal therapy for the first breast primary cancer. The study protocol was approved by the U.S. site institutional review boards and by the ethical committee system in Denmark. Informed consent was obtained from participants.

Coding and flanking intronic regions of *BRCA1* and *BRCA2* were screened for variation by denaturing high-performance liquid chromatography followed by sequence confirmation, as previously described.² We focus on sequence variants known to have a clearly deleterious effect, including changes known or predicted to truncate protein production; splice site mutations located within two base pairs of an intron/exon boundary or shown to cause aberrant splicing; and missense changes with known deleterious functional effects. Our mutation classification strategy followed current clinical and Breast Cancer Information Core (<http://research.nhgri.nih.gov/projects/bic/>) classifications.

To evaluate the relative risks of developing CBC in mutation carriers, we estimated age-adjusted rate ratios and 95% CIs using conditional logistic regression. These models included exact age at diagnosis of first breast cancer to account for possible residual age confounding within strata. To account for counter-matching, models included a log weight covariate with a fixed coefficient of one.^{2,26} Heterogeneity tests were performed using the likelihood ratio test. Control proportions are estimates of the expected proportions had the controls been randomly sampled (ie, without counter-matching); proportions were computed as weighted averages of crude within-registry reported radiation exposed and unexposed control proportions. Adjusted proportions were similar to unadjusted proportions. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

We calculated 5- and 10-year cumulative risks of CBC in mutation noncarriers and carriers as follows. For any age group, let the CBC incidence rate be I_0 , I_1 , and I_2 for noncarriers, *BRCA1* carriers, and *BRCA2* carriers, respectively. Let corresponding prevalences among women with incident first primary breast cancer be p_0 , p_1 , and p_2 , respectively, and relative risks for *BRCA1* and *BRCA2* carriers relative to noncarriers be ϕ_1 and ϕ_2 , all of which are estimated directly from our study of CBC. The age-specific incidence rates in *BRCA1* and *BRCA2* carriers are estimated using $\hat{I}_1 = \hat{I}\phi_1/(p_0 + p_1\phi_1 + p_2\phi_2)$ and $\hat{I}_2 = \hat{I}\phi_2/(p_0 + p_1\phi_1 + p_2\phi_2)$, respectively, where $\hat{I}$ is the corresponding population incidence rate of CBC, ie, $\hat{I} = p_0\hat{I}_0 + p_1\hat{I}_1 + p_2\hat{I}_2$. We used

population-based SEER*Stat²⁷ cancer incidence data (from nine SEER areas that contributed from 1985 onward) to estimate population age-specific rates of CBC (ie, the term I for each age group) as follows. Person-years of follow-up were compiled in annual increments for breast cancer cases in SEER by age of first diagnosis (5-year intervals) until date of CBC, death, or last follow-up. The numbers of women subsequently diagnosed with CBC were counted in each category and divided by the accumulated follow-up person-years to obtain the rate. For each of the derived age-specific annual rates in each specific genetic category, these annual rates were then combined actuarially to obtain the cumulative rate, thereby representing the probability that a woman of a designated age who has just been diagnosed with breast cancer will experience a CBC within the specified time interval given that she survives the interval. CIs were derived using a first-order approximation, based on the variance of the estimate of I from SEER and of ϕ_1 and ϕ_2 from the logistic regression. Calculations were restricted to the calendar years 1985 to 2000 to parallel the diagnosis years of the WECARE Study.²⁸ Cases included in the SEER incidence rate estimates differed slightly from WECARE cases in that they included nonsynchronous CBC cases diagnosed within 1 year of initial diagnosis (whereas WECARE CBCs occurred at least 1 year after first diagnosis), and there was no restriction on migration from registry area.⁸ Relatively few women had a second breast cancer more than 10 years after diagnosis of first primary cancer (a design constraint), so our risk predictions are limited to 10 years after diagnosis.

RESULTS

Cases and controls were matched on age, race/ethnicity, and center (Table 1). A first-degree (mother, sister, or daughter) family history of breast cancer was reported more frequently by cases than by controls. Compared with controls, cases were older at menopause, more often had an estrogen receptor-negative first tumor, less often had an oophorectomy, and were less often treated with chemotherapy or hormone therapy.

Mutation screening of all coding exons and flanking intronic regions of *BRCA1/BRCA2* identified 113 unique deleterious mutations, including 73 frame-shift deletions/insertions, 26 nonsense, seven splice site, and seven missense mutations. One hundred eighty-one women carried a deleterious *BRCA1/BRCA2* mutation. No woman carried more than one deleterious mutation.

Carrying a mutation in either gene was associated with a four-fold increased risk of developing a subsequent CBC (95% CI, 2.8- to 5.7-fold). Compared with noncarriers, *BRCA1* mutation carriers had a 4.5-fold increased risk of developing CBC (95% CI, 2.8- to 7.1-fold), and *BRCA2* mutation carriers had a 3.4-fold increased risk (95% CI, 2.0- to 5.8-fold) of CBC (Table 2). Adjustment for adjuvant hormone therapy, chemotherapy, radiotherapy, and oophorectomy did not alter results, and the relative risks associated with each therapy did not vary by carrier status.

BRCA1 mutation prevalence varied by age at first breast cancer (Table 2). The relative risk of developing CBC for *BRCA1* mutation carriers (compared with *BRCA1/BRCA2* noncarriers) decreased with older age at first diagnosis, with an 11-fold increased CBC risk among women first diagnosed before age 35 years, a four-fold increased risk among women age 35 to 44 years at first diagnosis, and a 2.6-fold increased risk in women age 45 to 54 years at first diagnosis. Age-specific CBC relative risks for *BRCA2* mutation carriers showed no clear trend. Most participants were non-Hispanic white, limiting statistical power for assessing racial/ethnic differences. Relative risks were somewhat higher in women with no first-degree family history of breast cancer. However, since family history is a strong CBC risk

Table 1. Characteristics of 705 Cases (women with contralateral breast cancer) and 1,398 Controls (women with unilateral breast cancer only)

Characteristic	Cases (n = 705)		Controls (n = 1,398)	
	No.	%	No.	%
Age at diagnosis, years				
< 30	8	1.1	16	1.1
30-34	40	5.7	74	5.3
35-39	91	12.9	179	12.8
40-44	170	24.1	338	24.2
45-49	205	29.1	407	29.1
50-54	191	27.1	384	27.5
Median	46		46	
Range (interquartile)	41-51		42-50	
At-risk period, years*				
< 5	405	57.4	807	58.3
≥ 5	300	42.6	591	41.7
Race/ethnicity				
Non-Hispanic white	646	91.6	1,287	92.1
Hispanic white	24	3.4	48	3.4
Black	21	3.0	39	2.8
Japanese	2	0.3	4	0.3
Chinese	2	0.3	3	0.2
Filipino	7	1.0	14	1.0
Other Asian/other	3	0.4	3	0.2
Jewish ancestry				
No	637	90.4	1,272	92.7
Yes	54	7.7	108	6.1
Unknown	14	2.0	18	1.2
Family history of breast cancer				
No first-degree relative	475	67.4	1,098	78.8
Any first-degree relative	226	32.1	289	20.5
Adopted or unknown	4	0.6	11	0.7
Family history of ovarian cancer				
No first-degree relative	676	95.9	1,338	95.6
Any first-degree relative	25	3.5	49	3.6
Adopted or unknown	4	0.6	11	0.7
Center				
Iowa	113	16.0	222	15.9
University of California at Irvine	118	16.7	231	16.5
Los Angeles	199	28.2	390	27.9
Seattle	99	14.0	198	14.2
Denmark	176	25.0	357	25.5
Menopausal status				
Premenopausal	124	17.6	272	18.4
Postmenopausal, < 45 years	208	29.5	455	34.5
Postmenopausal, ≥ 45 years	372	52.8	665	46.5
Unknown	1	0.1	6	0.6
Estrogen receptor status of first primary breast cancer				
Positive	336	47.7	745	53.9
Negative	193	27.4	338	23.6
Other	69	9.8	155	11.9
Unknown	107	15.2	160	10.6
Chemotherapy for first primary breast cancer				
No	384	54.5	628	42.5
Yes	321	45.5	770	57.5
Adjuvant hormone therapy for first primary breast cancer				
No	530	75.2	969	70.2
Yes	163	23.1	399	27.5
Unknown	12	1.7	30	2.3

(continued in next column)

Table 1. Characteristics of 705 Cases (women with contralateral breast cancer) and 1,398 Controls (women with unilateral breast cancer only) (continued)

Characteristic	Cases (n = 705)		Controls (n = 1,398)	
	No.	%	No.	%
Radiation therapy				
No	361	51.2	266	50.1
Yes	344	48.8	1,132	49.9
Oophorectomy status				
Yes	47	6.7	123	8.4
No	657	93.2	1,273	91.6
Unknown	1	0.1	2	0.1

NOTE. Proportions are weighted for the counter-matching with the exception of factors contributing to the study matching schema (age, race/ethnicity, and center).

*Interval between first diagnosis and second diagnosis (cases) or reference date (controls).

factor, the baseline CBC risk is 1.8-fold higher in those with a family history of breast cancer.

Table 3 presents cumulative risks of CBC among mutation carriers and noncarriers. These data allow estimation of the 5- and 10-year risks of developing CBC for a given woman who has been diagnosed with UBC (and without a synchronous CBC) before age 55 who carries a mutation in either *BRCA1* or *BRCA2*. Thus, for example, a woman diagnosed with breast cancer in the 25- to 29-year-old age range who carries a *BRCA1* mutation would have a 16% cumulative probability of developing CBC within 5 years and a 29% cumulative probability within 10 years after diagnosis. As a benchmark, a woman of similar age without a mutation would have 3% and 6% probabilities, respectively, of developing CBC in the ensuing 5- and 10-year periods. We did not further stratify estimates by other factors because the paucity of data precluded reliable estimates. Note these calculations involved adjustment of the background incidence rate in 5-year intervals.

DISCUSSION

With more than 180,000 U.S. women diagnosed with breast cancer annually,²⁹ the magnitude of the burden related to the risk of second primary breast cancer is substantial. Increasingly, women with breast cancer, particularly younger cases including those without a positive family history, are likely to be referred for genetic testing and, thus, there is a growing need for information regarding CBC risk in mutation carriers. Here, we present population-based estimates of the risk of CBC in *BRCA1* and *BRCA2* mutation carriers derived from a large study of 2,103 women with UBC or CBC, all of whom were diagnosed with a first invasive breast cancer before age 55 years.

Overall, carrying a mutation in either gene was associated with a four-fold increased relative risk of CBC. A woman with breast cancer before age 55 who carried a *BRCA1* or *BRCA2* mutation was estimated to have a 20% or 15% probability, respectively, of developing CBC within 10 years. Risks were substantially greater for women

Table 2. Risk of Contralateral Breast Cancer in Relation to *BRCA1/BRCA2* Mutation Carrier Status Overall and According to Demographic, Familial, and Disease Characteristics

Characteristic	Cases						Controls						Cases and Controls			
	No <i>BRCA1/2</i> Mutation		<i>BRCA1</i> -Positive		<i>BRCA2</i> -Positive		No <i>BRCA1/2</i> Mutation		<i>BRCA1</i> -Positive		<i>BRCA2</i> -Positive		<i>BRCA1</i> -Positive		<i>BRCA2</i> -Positive	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	RR	95% CI	RR	95% CI
All women	597	84.7	67	9.5	41	5.8	1325	94.8	42	3.0	31	2.2	4.5	2.8 to 7.1	3.4	2.0 to 5.8
Age at first breast cancer, years																
21-34	22	45.8	22	45.8	4	8.3	76	84.4	9	10.0	5	5.6	10.9	3.4 to 34.6	2.4	0.5 to 10.9
35-44	204	78.2	35	13.4	22	8.4	484	93.6	23	4.4	10	1.9	4.0	2.1 to 7.5	6.3	2.6 to 15.4
45-54	371	93.7	10	2.5	15	3.8	765	96.7	10	1.3	16	2.0	2.6	1.0 to 7.2	2.3	1.0 to 5.1
<i>P</i> for heterogeneity													0.15		0.21	
Interval between first diagnosis and second diagnosis, years (cases)/reference date (controls)																
< 5	340	84.0	40	9.9	25	6.2	764	94.7	28	3.0	15	2.3	4.7	2.7 to 8.3	4.1	2.0 to 8.3
≥ 5	257	85.7	27	9.0	16	5.3	561	95.9	14	2.0	16	2.1	3.9	1.7 to 9.4	2.7	1.2 to 6.1
<i>P</i> for heterogeneity													0.73		0.43	
Jewish ancestry																
No	541	84.9	59	9.3	37	5.8	1,211	95.8	34	2.3	27	2.0	5.1	3.0 to 8.4	3.8	2.1 to 6.6
Yes	42	77.8	8	14.8	4	7.4	97	86.9	7	6.8	4	6.3	2.3	0.6 to 8.9	1.6	0.3 to 7.6
Unknown	14	100.0	0	0	0	0	17	95.7	1	4.3	0	0	—	—	—	—
<i>P</i> for heterogeneity													0.18		0.12	
First-degree family history*																
No	417	87.1	39	8.1	23	4.8	1,065	96.0	25	2.3	19	1.7	6.1	3.3 to 11.2	3.3	1.6 to 6.5
Yes	180	79.6	28	12.4	18	8.0	260	90.0	17	5.9	12	4.2	2.2	1.0 to 4.7	2.9	1.3 to 6.8
<i>P</i> for heterogeneity													0.11		0.89	
Race/ethnicity																
White	569	84.9	63	9.4	38	5.7	1,267	94.9	40	3.0	28	2.1	4.3	2.7 to 7.0	3.4	2.0 to 6.0
Non-Hispanic	552	85.4	59	9.1	35	5.4	1,223	95.0	38	3.0	26	2.0	4.1	2.5 to 6.8	3.2	1.8 to 5.8
Hispanic	17	70.8	4	16.7	3	12.5	44	91.7	2	4.2	2	4.2	10.4	1.1 to 95.3	9.3	0.7 to 122.7
Black	18	85.7	2	9.5	1	4.8	35	89.7	1	2.6	3	7.7	7.0	0.5 to 98.2	1.2	0.1 to 12.0
Asian or other	10	71.4	2	14.3	2	14.3	23	95.8	1	4.2	0	0	6.5	0.5 to 80.8	—	—
<i>P</i> for heterogeneity													0.82		0.26	

NOTE. Rate ratios (RRs) and CIs account for counter-matching, are adjusted for age at first diagnosis, and compare the risk of contralateral breast cancer in carriers versus noncarriers of mutations in either gene, overall and within each demographic, familial, or disease characteristic subgroup. Proportions are weighted for the counter-matching with the exception of factors contributing to the study matching schema (age, race/ethnicity, and center).

*First-degree family history includes mothers and sisters with breast cancer.

diagnosed with their first cancer at younger ages and, as in other studies,³⁰⁻³⁴ mutations were more common in patients with younger age at diagnosis.

A number of past studies,^{11-22,24} most including small numbers of CBCs and none of which was population-based, have assessed the risk of CBC in mutation carriers. Most of these studies involved retrospective case ascertainment from high-risk cancer genetics clinics,^{13-15,17,19,21,22,35} the three largest of which we review here. One study included 336 breast cancer cases from families with one or more confirmed mutation carriers, all ascertained through genetics clinics and 97 of whom had CBC.¹⁹ The 10-year cumulative CBC rate was 29.5% (*BRCA1*, 32%; *BRCA2*, 24.5%), 31% in women diagnosed before age 50 versus 23.5% in women diagnosed at age 50 to 64 years. Another study examined CBC risk in 160 mutation-positive breast cancer cases ascertained through high-risk clinics and a comparison group of 445 sporadic cases with minimal or no family history of breast cancer and no family history of ovarian cancer.²¹ The 12 and 36 CBCs among sporadic and mutation-carrying cases, respectively, translated into a 10-fold increased risk of CBC associated with carrying

a mutation in either gene and 10-year CBC rates of 26% and 3% in mutation-carrying and sporadic cases, respectively. A third study²² accrued 326 breast cancer cases through a high-risk genetics clinic from families with a known *BRCA1/BRCA2* mutation-carrying member, 311 cases from high-risk type families who tested negative for *BRCA1/BRCA2*, and a comparison series with minimal or no family history. Eighty-six CBC cases were observed, yielding 10-year cumulative CBC risk estimates of 25% and 20% in *BRCA1* and *BRCA2* mutation-associated cases, respectively, 6% in cases from *BRCA1/BRCA2*-negative families, and 5% in the comparison series. Compared with the comparison series, *BRCA1*- and *BRCA2*-associated cases had 5.8-fold and 6.1-fold increased risks of CBC, respectively.

Overall, these studies produced risk estimates approximately 10% to 15% higher than those in our study. Although these studies had a powerful design for accruing large proportions of mutation carriers and generating suitable estimates for high-risk families or patients in similar clinic settings, results from these studies may not extrapolate reliably to the broader spectrum of breast cancers in the general population. In addition, as noted by others,^{19,22,24} there is

Table 3. Cumulative 5- and 10-Year Risk of Developing CBC After a First Primary Invasive Breast Cancer According to Mutation Carrier Status and Age at Diagnosis of First Breast Cancer

Age at First Breast Cancer (years)	<i>BRCA1</i> Mutation Carrier		<i>BRCA2</i> Mutation Carrier		<i>BRCA1</i> or <i>BRCA2</i> Mutation Carrier		Noncarriers	
	Cumulative Risk (%)	95% CI	Cumulative Risk (%)	95% CI	Cumulative Risk (%)	95% CI	Cumulative Risk (%)	95% CI
5-Year risk for age group								
25-29	16.0	8.5 to 30.1	14.6	6.5 to 32.9	15.5	8.8 to 27.4	3.2	2.3 to 4.4
30-34	17.0	9.5 to 30.5	15.5	7.1 to 33.7	16.5	9.9 to 27.6	3.4	2.8 to 4.2
35-39	13.2	7.4 to 23.5	12.0	5.6 to 26.0	12.8	7.7 to 21.3	2.6	2.2 to 3.1
40-44	9.8	5.5 to 17.4	8.9	4.1 to 19.3	9.5	5.8 to 15.8	1.9	1.6 to 2.3
45-49	7.3	2.7 to 19.7	6.5	2.9 to 14.4	6.7	3.6 to 12.6	2.8	2.6 to 3.1
50-54	6.0	2.2 to 16.3	5.3	2.4 to 11.9	5.6	2.9 to 10.3	2.3	2.1 to 2.6
All ages combined (25-54)	10.9	6.7 to 17.5	8.3	4.8 to 14.2	9.7	8.4 to 11.2	2.5	2.3 to 2.7
10-Year risk for age group								
25-29	29.0	15.4 to 54.7	26.6	11.8 to 60.1	28.2	16.0 to 50.0	6.1	4.4 to 8.5
30-34	31.6	17.6 to 56.7	29.0	13.4 to 63.1	30.7	18.4 to 51.5	6.8	5.5 to 8.4
35-39	24.4	13.7 to 43.4	22.3	10.3 to 48.2	23.7	14.3 to 39.3	5.1	4.2 to 6.1
40-44	20.0	11.3 to 35.5	18.3	8.5 to 39.4	19.4	11.8 to 32.1	4.1	3.4 to 4.9
45-49	13.1	4.8 to 35.7	11.7	5.3 to 26.1	12.2	6.5 to 22.9	5.3	4.8 to 5.8
50-54	11.7	4.3 to 31.8	10.4	4.7 to 23.2	10.8	5.8 to 20.3	4.7	4.2 to 5.1
All ages combined (25-54)	20.5	12.7 to 33.0	15.9	9.2 to 27.2	18.4	16.0 to 21.3	4.9	4.5 to 5.4

NOTE. 5-Year and 10-year risks are calculated using the rate ratios for dichotomized age (< 45, ≥ 45).

potential for ascertainment bias within some high-risk clinic studies which could yield inflated CBC rate estimates. In general, high-risk clinic studies have reported the highest estimates of CBC risk in mutation carriers, with 10-year cumulative risks approaching 30% to 40%. To reduce ascertainment bias potential within the high-risk setting, a recent study assessed CBC risk in 1,042 women with breast cancer selected from families with a known mutation-carrying index case and reported some of the lowest CBC risk estimates to date.³⁶ The 10-year cumulative CBC risks for women from families with *BRCA1* and *BRCA2* mutations were 18.5% and 13.2%, respectively. As the authors noted, the absence of genotype information on 83% of the 1,042 women indicates that some noncarriers were included, which would reduce risk estimates since mutation noncarriers have a lower CBC risk than carriers.

Several investigators have sought to minimize selection bias potential through retrospective ascertainment of cases from hospitals, unselected on family history, age, or survival, and enrolled on the basis of Ashkenazi Jewish ethnicity and the availability of pathology tissue for testing the three Jewish founder mutations.^{10,12,23,24} The largest of these included 496 Ashkenazi cases who received breast-conserving surgery at either of two hospitals,^{12,37} observed a *BRCA1/BRCA2* mutation prevalence of 11.3%, and found mutation carriers were significantly more likely to develop CBC in 10 years (27%) than noncarriers (8%).²⁴ These studies, by not selecting cases on the basis of family history and instead by including all cases in an institution, accrued series with less extreme familial risk profiles than in high-risk clinic populations. It is notable that the mutation prevalence in cases appears somewhat high, reflecting the increased mutation prevalence in Ashkenazi Jewish populations.

Our study differed from previous studies by using a population-based design to investigate the relationship between *BRCA1/BRCA2* mutations and CBC risk. This design involves systematic case ascertainment, regardless of family history or treatment facility, in well-

defined geographic catchment areas and temporal periods and circumvents the ascertainment complexities of previous studies. Our nested case-control design within a population-based cohort of breast cancer cases allowed the accrual of a well-defined study population, the largest number of CBC cases to date, and substantial numbers of women without a first-degree family history. It is conceivable that differences in design contribute to the lower prevalence of mutations and somewhat lower risks of CBC observed in our study compared with most prior studies. For example, 5.2% of the UBC cases in our study carried a mutation in *BRCA1/BRCA2*, a much lower prevalence than observed in high-risk clinic and hospital-based studies of Ashkenazi Jews. Similarly, the 15% to 20% 10-year cumulative risks of CBC in mutation carriers in our study of a younger age group, in which genetic factors would be expected to have strong effects, are lower than those in previous studies. Nonetheless, the magnitude of these risks remains quite substantive, four-fold higher for carriers versus noncarriers of mutations, and warrants consideration by women with breast cancer and their clinicians.

Cumulative 5- and 10-year risks of CBC are provided as a general guideline for clinicians and patients regarding subsequent risk. These estimates were anchored on CBC rates in the national SEER cancer registry system, which includes a large number of cases and provides better precision for estimating the population risk of CBC than is possible in any individual study. However, this approach precluded us from examining whether cumulative risk profiles are modulated by other factors besides carrier status, such as treatment. The models underlying these results have not been validated for calibration in an independent data set, a step precluded by the unavailability of other population-based studies with sufficient numbers of CBC cases.

Strengths of our study include the comprehensive, centralized mutation detection approach used. Denaturing high-performance liquid chromatography followed by sequencing has been demonstrated to have high sensitivity and specificity and was the only method

to detect all *BRCA1* mutations in a validation study.³⁸ Despite stringent quality control, the presence of undetected mutations, including large deletions, cannot be ruled out. Another strength is the population-based design, which offers maximum efficiency for accruing large numbers of CBC patients without regard to family history and facilitates extrapolation to the general population. However, because our study excluded synchronous cancers and women with prophylactic contralateral mastectomy, results may underestimate mutation prevalence. Similarly, because our study was limited to women who survived breast cancer(s), we cannot exclude the possibility that findings might differ if otherwise eligible deceased women were included. Nevertheless, our design allowed us to address the single most relevant clinical question, since the estimation of future risk of CBC is of little relevance to patients with synchronous breast cancer or to those who have had a prophylactic contralateral mastectomy.

In summary, we provide population-based estimates of the risk of CBC following an invasive breast cancer diagnosis before age 55 years in women with mutations in the *BRCA1* or *BRCA2* genes. These findings have important clinical implications in terms of the potential value of *BRCA1/BRCA2* testing in patients with early-onset breast cancer as well as therapeutic, preventive, and surveillance considerations for patients found to carry a mutation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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