Risk of Asynchronous Contralateral Breast Cancer in Noncarriers of *BRCA1* and *BRCA2* Mutations With a Family History of Breast Cancer: A Report From the Women's Environmental Cancer and Radiation Epidemiology Study

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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A B S T R A C T

Purpose

To fully characterize the risk of contralateral breast cancer (CBC) in patients with breast cancer with a family history who test negative for *BRCA1* and *BRCA2* mutations.

Patients and Methods

From our population-based case-control study comparing women with CBC to women with unilateral breast cancer (UBC), we selected women who tested negative for *BRCA1* and *BRCA2* mutations (594 patients with CBC/1,119 control patients with UBC). Rate ratios (RRs) and 95% CIs were estimated to examine the association between family history of breast cancer and risk of asynchronous CBC. Age- and family history-specific 10-year cumulative absolute risks of CBC were estimated.

Results

Family history of breast cancer was associated with increased CBC risk; risk was highest among young women (< 45 years) with first-degree relatives affected at young ages (< 45 years; RR, 2.5; 95% CI, 1.1 to 5.3) or women with first-degree relatives with bilateral disease (RR, 3.6; 95% CI, 2.0 to 6.4). Women diagnosed with UBC before age 55 years with a first-degree family history of CBC had a 10-year risk of CBC of 15.6%.

Conclusion

Young women with breast cancer who have a family history of breast cancer and who test negative for deleterious mutations in *BRCA1* and *BRCA2* are at significantly greater risk of CBC than other breast cancer survivors. This risk varies with diagnosis age, family history of CBC, and degree of relationship to an affected relative. Women with a first-degree family history of bilateral disease have risks of CBC similar to mutation carriers. This has important implications for the clinical management of patients with breast cancer with family history of the disease.

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INTRODUCTION

A family history of breast cancer is a well-established and significant risk factor for breast cancer.¹⁻³ Relative risks vary depending on the age at diagnosis of the affected relative(s) and the number of affected relatives, ranging from two-fold for one affected first-degree relative to three-fold for two affected first-degree relatives and four-fold for three affected first-degree relatives.¹⁻³ Young ages at diagnosis and bilaterality in first-degree relatives further increase risk.²

After diagnosis of a first primary breast cancer, women with an intact contralateral breast are at risk of developing contralateral breast cancer (CBC). The majority of studies,⁴⁻¹⁵ but not all,^{16,17} have identified family history as a risk factor for CBC. From the few studies presenting risk by detailed family history, there is evidence that a family history of bilateral breast cancer, multiple affected relatives, and early-onset disease significantly increase risk of CBC.^{5,13,18}

We¹⁹ and others²⁰⁻²² have shown that CBC risk is greatly increased in women carrying deleterious

mutations in *BRCA1* or *BRCA2* and that the magnitude of this association is modified by age at diagnosis of the first breast cancer. Graeser et al²⁰ found that women who were carrying a deleterious mutation in *BRCA1* or *BRCA2* and who were older than 50 years at first breast cancer diagnosis had a 10-year CBC risk of 8.4%, whereas carriers younger than 40 years had a 10-year CBC risk of 28.3%. In the Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study, we previously reported that the youngest women (25 to 29 years) who were carrying a deleterious *BRCA1* or *BRCA2* mutation had a 10-year CBC risk of 28.2% and those older than 50 years had an analogous risk of 10.8%.¹⁹ No studies to date have examined the predictive contribution of various components of family history in relation to the risk of CBC for women in whom no mutation in *BRCA1* or *BRCA2* has been identified. Our goal in this study is to more clearly define risk prediction for women with a first primary breast cancer who test negatively for deleterious *BRCA1* and *BRCA2* mutations.

The WECARE Study is a population-based case-control study comparing women with CBC (cases) to controls with unilateral breast cancer (UBC).²³ In the current analyses, we examined the relationship between family history of breast cancer and the risk of developing asynchronous CBC in women testing negatively for deleterious mutations in *BRCA1* and *BRCA2*. Age- and family history-specific 10-year cumulative absolute risks of CBC were also estimated.

PATIENTS AND METHODS

Study Population and Data Collection

The WECARE Study is a population-based case-control study that identified patients with CBC and UBC through four cancer registries in the United States (Los Angeles County Cancer Surveillance Program, the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center in Seattle, the State Health Registry of Iowa, and the Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control) and through the Danish Breast Cancer Cooperative Group Registry, supplemented by data from the Danish Cancer Registry. The study has been described in detail previously.²³ Women with CBC ($n = 708$ patient cases) and women with UBC ($n = 1,399$ controls) completed the study interview and provided a blood sample. Two controls were individually matched to each patient case on year of birth (5-year strata), year of diagnosis (4-year strata), cancer registry, and race. Additionally, to improve statistical efficiency for the original study aims, case-control triplets were counter-matched on cancer registry-reported radiation exposure such that two members of each triplet received radiation therapy and one member did not.²³ All participants were diagnosed with their first primary breast cancer between January 1985 and December 2000 at age 54 years or younger. Eligible CBC patient cases had at least 1 year between their two breast cancer diagnoses, resided in the same reporting area for both diagnoses, and had not been diagnosed with any prior or intervening cancers (except for nonmelanoma skin cancer or in situ cervical cancer). Eligible controls had no subsequent cancer diagnoses and had no prophylactic mastectomy of the contralateral breast. All eligible participants were alive at the time of contact and able to provide written informed consent, complete the interview, and provide a blood sample.

All WECARE Study participants were interviewed by telephone using a structured questionnaire on known or suspected breast cancer risk factors, including age at menarche, age at menopause, number of full-term pregnancies, treatment for breast cancer, and detailed family history of breast cancer in female first- and second-degree relatives. A first-degree family history of breast cancer was defined as a diagnosis of breast cancer in at least one first-degree relative (ie, mother, sister, or daughter). A second-degree family history involved a diagnosis of breast cancer in at least one grandmother, aunt, or

half-sister. In the event of multiple first-degree relatives affected with breast cancer, the age at diagnosis of the youngest relative was used in the analyses. Similarly, if there was at least one first-degree relative with bilateral breast cancer, then the woman was categorized as having a bilaterally affected first-degree relative.

As previously described,¹⁹ mutation screening of *BRCA1* and *BRCA2* coding exons and flanking introns in the WECARE Study population identified 113 unique deleterious mutations, including 73 frameshift deletions/insertions, 26 nonsense mutations, seven splice sites, and seven missense mutations. One hundred nine women were *BRCA1* mutation carriers, and 72 women were *BRCA2* mutation carriers. Women carrying these known deleterious mutations were excluded from the analyses, as were 14 adopted women without information on family history of breast cancer. In the analyses, if a patient case was excluded as a result of carrying a deleterious mutation, both of her matched controls were also excluded. In the two instances where both controls in a triplet were carriers, their matched patient case was also excluded. Women who were carriers of *BRCA1* and *BRCA2* variants of unknown significance were not excluded because most variants of unknown significance are likely to be neutral in effect. The final analyses were based on 594 patient cases and 1,119 matched controls.

Statistical Analysis

Multivariable-adjusted rate ratios (RRs) and corresponding 95% CIs were calculated using conditional logistic regression adjusting for variables known to affect breast cancer risk, including age at first primary breast cancer diagnosis, age at menarche, age at menopause, number of full-term pregnancies, histology, estrogen receptor (ER) and progesterone receptor status of the first primary cancer, and chemotherapy and hormonal treatments. Models included an offset term to take into account the counter-matched study design.²³ Cumulative risks of CBC by age at first breast cancer diagnosis and family history status were estimated using previously described methodology.¹⁹ Briefly, prevalences and relative risks were estimated directly from WECARE Study data and combined with population-based SEER*Stat software cancer incidence data for women age 18 to 54 years diagnosed between 1985 and 2000 for comparability to women in the WECARE Study.²⁴ Additionally, in a post hoc analysis, models from Table 2 were stratified by ER status. This was done where sample size allowed (any affected first- or second-degree relative, any affected first-degree relative, any affected second-degree relative, and affected second-degree relative only). Heterogeneity was tested using a likelihood ratio test of nested models.

RESULTS

Patient demographics and the distribution of risk factors and treatment by case-control status are listed in Table 1. By design, patient cases and controls were comparable with respect to matching factors but differed somewhat on chemotherapy and/or hormonal therapy treatment. Whereas 55% of controls and 51% of patient cases were ER positive, only 34% of controls and 30% of patient cases received hormonal therapy. Table 2 presents the relationship between family history and CBC risk for women in whom no mutation in *BRCA1* or *BRCA2* was identified. Compared with women who reported no affected relatives, those with a first-degree family history of breast cancer had a nearly two-fold greater risk of developing CBC (RR, 1.9; 95% CI, 1.4 to 2.6). Increases in CBC risks were similar (about two-fold), regardless of the relationship of the affected relative to the index patient (mother, sister, or grandmother; data not shown).

Early age at diagnosis (before age 45 years) in the proband and early age at diagnosis in the affected relative were both associated with increased CBC risk (RR, 2.2; 95% CI, 1.4 to 3.6; and RR, 2.2; 95% CI, 1.3 to 3.9, respectively). When the proband or relative was diagnosed at age 45 years or older, the RRs remained statistically significantly elevated but were lower (1.7 and 1.8, respectively). The highest risk was

Table 1. Population Characteristics and Demographics of Noncarriers of *BRCA1* and *BRCA2* Deleterious Mutations in the WECARE Study Population

Characteristic or Demographic	Patient Cases (CBC)		Controls (UBC)	
	No.	%	No.	%*
Cancer registry†				
Iowa	93	16	179	14
UC Irvine	97	16	180	17
Los Angeles	160	27	298	24
Seattle	90	15	169	18
Denmark	154	26	293	27
Race/ethnicity†				
Non-Hispanic white	550	93	1,041	95
Hispanic white	17	3	32	2
Black	17	3	29	2
Japanese, Chinese, or Filipino	8	1	16	1
Other Asian/other	2	0.3	1	0.1
Year of first breast cancer diagnosis†				
1985-1988	203	34	381	32
1989-1992	199	34	379	33
1993-1996	152	26	284	28
1997+	40	7	75	8
Age at first breast cancer diagnosis, years†				
< 45	227	38	415	39
45-54	367	62	704	61
Age at menarche, years				
< 13	290	49	500	42
≥ 13	304	51	619	58
Age at menopause at reference date, years				
Premenopausal	87	15	183	16
< 45	168	28	342	32
≥ 45	339	57	594	52
No. of full-term pregnancies at reference date				
None	112	19	171	15
1-3	433	73	812	73
≥ 4	49	8	136	12
Latency, years‡				
< 5	338	57	636	56
≥ 5	256	43	483	44
Histology of first breast cancer diagnosis				
Invasive lobular	85	14	107	9
Ductal	449	76	892	82
Other	60	10	120	9
Radiation§				
No	313	53	218	51
Yes	281	47	901	49
Chemotherapy				
No	342	58	538	46
Yes	252	42	581	54
Hormonal therapy¶				
No	418	70	719	66
Yes	176	30	398	34
Unknown	0	0	2	0.3
Chemotherapy and/or hormonal therapy¶				
No	257	43	362	32
Yes	337	57	757	68

(continued in next column)

Table 1. Population Characteristics and Demographics of Noncarriers of *BRCA1* and *BRCA2* Deleterious Mutations in the WECARE Study Population (continued)

Characteristic or Demographic	Patient Cases (CBC)		Controls (UBC)	
	No.	%	No.	%*
Estrogen receptor status of first breast cancer				
Positive	304	51	614	55
Negative	137	23	249	22
Other or unknown	153	26	256	23
Progesterone receptor status of first breast cancer				
Positive	257	43	504	44
Negative	120	20	230	22
Other or unknown	217	37	385	34

Abbreviation: CBC, contralateral breast cancer; UBC, unilateral breast cancer; UC, University of California; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

*Weighted proportions were used to reflect the counter-matched study design.

†WECARE matching variables.

‡Latency is defined as the time between the patient case's two primary breast cancer diagnoses or, in controls, as the time between first primary cancer and the matched patient case's second primary cancer.

§Radiation for the first diagnosis is based on cancer registry report. Radiation was counter-matched in the WECARE study.

||Chemotherapy for the first diagnosis is based on both self-reported and medical record data.

¶Hormonal therapy for the first diagnosis is based on both self-reported and medical record data.

seen when both the proband and the affected relative were diagnosed before age 45 years (RR, 2.5; 95% CI, 1.1 to 5.3). The RR for CBC was 3.6 (95% CI, 2.0 to 6.4) in women whose first-degree relative had experienced CBC. A history of bilateral breast cancer in an affected relative was observed to be a more important predictor of risk than the age at diagnosis of the first primary cancer in the relative (Table 2). Where sample size allowed, results from Table 2 were stratified by ER status (results not shown). There was no effect modification by ER status on the association between family history and CBC risk.

Table 3 lists the 10-year cumulative risks of CBC for women in whom no deleterious mutation in *BRCA1* or *BRCA2* was identified. Risks are shown as a function of age at diagnosis and the nature of the family history. For comparison, analogous previously published cumulative risks of CBC are also provided for *BRCA1* and *BRCA2* mutation carriers.¹⁹ Among women age 25 to 54 years, the 10-year cumulative risks of CBC for those with no family history, second-degree family history only, a first-degree family history, or a history of bilateral breast cancer in a first-degree relative were 4.6% (95% CI, 4.0% to 5.1%), 5.9% (95% CI, 4.6% to 8.6%), 8.6% (95% CI, 6.1% to 11.5%), and 15.6% (95% CI, 8.5% to 28.5%), respectively. For comparison, the previously published 10-year cumulative risk of CBC among women age 25 to 54 years carrying mutations in *BRCA1* or *BRCA2* was 18.4% (95% CI, 16.0% to 21.3%).¹⁹ Figure 1 provides the cumulative absolute risks by time since diagnosis for women diagnosed before age 55 years with varying degrees of family history and bilaterality; for comparison, previously published risks for *BRCA1* and *BRCA2* mutation carriers¹⁹ are also shown.

Table 2. Family History of Breast Cancer and Risk of Contralateral Breast Cancer Among Noncarriers* of *BRCA1* and *BRCA2* Deleterious Mutations in the WECARE Study Population

Variable†	No. of Patient Cases	No. of Controls	RR‡	95% CI
No affected first- or second-degree relative	272	651	1	
Any affected first- or second-degree relative	322	468	1.6	1.3 to 2.0
Any affected first-degree relative	180	220	1.9	1.4 to 2.6
Any affected second-degree relative	218	328	1.5	1.1 to 1.9
No first-degree affected relative, second-degree relative affected only	142	248	1.3	1.0 to 1.8
No. of affected first-degree relatives				
1	157	192	2.0	1.5 to 2.7
≥ 2	23	28	1.5	0.8 to 3.0
Age at diagnosis of the proband and affected first-degree relative, years§				
Proband age < 45	73	78	2.2	1.4 to 3.6
Proband age ≥ 45	107	142	1.7	1.2 to 2.5
Affected relative age < 45	35	39	2.2	1.3 to 3.9
Affected relative age ≥ 45	139	176	1.8	1.3 to 2.5
Proband age < 45, affected relative age < 45	19	21	2.5	1.1 to 5.3
Proband age < 45, affected relative age ≥ 45	52	55	2.1	1.2 to 3.4
Proband age ≥ 45, affected relative age < 45	16	18	2.0	0.9 to 4.6
Proband age ≥ 45, affected relative age ≥ 45	87	121	1.7	1.1 to 2.5
Bilaterality of the affected first-degree relative				
Unilateral only (first degree)	142	192	1.6	1.2 to 2.2
Bilateral (first degree)	35	27	3.6	2.0 to 6.4
Mother unilateral	97	131	1.7	1.2 to 2.4
Mother bilateral	22	12	4.1	1.8 to 9.3
Sister unilateral	61	75	1.7	1.1 to 2.6
Sister bilateral	15	15	3.4	1.5 to 7.7
Age (years) and laterality at diagnosis of the affected first-degree relative				
< 45, unilateral	23	30	1.8	0.9 to 3.5
< 45, bilateral	11	9	3.0	1.1 to 8.2
≥ 45, unilateral	114	157	1.6	1.2 to 2.2
≥ 45, bilateral	24	18	3.4	1.7 to 7.0

Abbreviation: RR, rate ratio; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

*One hundred nine *BRCA1* mutation carriers (67 patient cases and 42 controls) and 72 *BRCA2* mutation carriers (41 patient cases and 31 controls) were excluded.

†All results have reference group of no affected first- or second-degree relatives.

‡Adjusted for age at first diagnosis, age at menopause, age at menarche, number of pregnancies, histology, estrogen receptor status of the first primary breast cancer, progesterone receptor status of the first primary breast cancer, and chemotherapy and hormonal treatments.

§Six patient cases and five controls have missing information on first-degree relative's age at diagnosis.

||Three patient cases and one control have missing information on first-degree relative's bilaterality.

breast cancer have a high risk of CBC, even after testing negative for deleterious mutations in the known breast cancer susceptibility genes *BRCA1* and *BRCA2*.

The relative risks for the association of family history of CBC that we observed in non-*BRCA1* and *BRCA2* mutation carriers are comparable to those of prior studies that evaluated the relative risk of first primary incident breast cancer and used unaffected controls as the comparison group. A meta-analysis of case-control studies of first primary breast cancer reported a two-fold increased risk associated with having a first-degree family history of breast cancer (meta-analysis odds ratio, 2.1; 95% CI, 2.0 to 2.2; WECARE Study RR, 1.9; 95% CI, 1.4 to 2.6) and a three-fold increased risk when both the proband and relative were both diagnosed at younger ages (meta-analysis odds ratio, 3.3; 95% CI, 2.8 to 3.9; WECARE Study RR, 2.5; 95% CI, 1.1 to 5.3).³

Our results also confirm those from prior studies that reported associations of CBC risk with any family history of breast cancer, family history of bilateral breast cancer, and family history of early-onset breast cancer.^{4-15,18} In a study with 136 CBCs and 4,524 UBCs where *BRCA1* and *BRCA2* mutation status was unknown, Bernstein et al⁵ found that compared with women with no first-degree family history of breast cancer, women with a first-degree relative diagnosed at age 45 years or younger had 2.7-fold greater risk of CBC (RR, 2.7; 95% CI, 1.5 to 5.0)⁵ and also noted, as we did, a significantly increased risk of CBC for women whose first-degree relative was affected bilaterally.

In a recent study by Nichols et al,²⁵ temporal trends of CBC incidence in the United States were found to diverge starting in 1985, depending on ER status of the first primary breast cancer. A favorable decrease of 3% per year was found in women with ER-positive first primary breast cancer. No significant decrease was found in women diagnosed with ER-negative first primary breast cancer. In another study, Bedrosian et al²⁶ found that women with ER-positive tumors had a significantly lower risk of CBC when compared with women with ER-negative tumors. Because of these differential incidence patterns by hormone receptor status and because of the discrepancy in the current study between percentage of women who were ER positive and percentage of women who received hormonal therapy, we included both ER and progesterone receptor status of the first primary breast cancer as confounders in the current study. The addition of these variables did not substantively change estimates from models without these indicators. To further investigate the interplay between ER status, family history, and risk of CBC, where sample size allowed, we stratified family history of breast cancer models by ER status while adjusting for hormonal therapy. No significant heterogeneity was established, suggesting family history is an important risk factor of CBC regardless of a woman's ER status.

On the basis of data from the SEER cancer registry program, it is estimated that women with a first primary invasive breast cancer have an approximately 7% risk of developing CBC 25 years after the first diagnosis.²⁷ Ten-year cumulative incidence rates of CBC among *BRCA1* and *BRCA2* mutation carriers with breast cancer vary widely.^{20,22,28,29} In this WECARE Study population, we found that 10-year rates ranged from 10% to 32%, depending on age at first diagnosis,¹⁹ with women younger than 55 years having a 10-year cumulative CBC rate of 18%. In the present analysis, we estimated the age- and family history-specific absolute risks of CBC and found that

DISCUSSION

Family history of breast cancer is a well-established risk factor for CBC. In this study, we demonstrated that women with a family history of

Table 3. Cumulative 10-Year Risk of CBC According to Age at First Breast Cancer Diagnosis and Family History Status

Age of Proband (years) at First Diagnosis	Noncarriers With No Family History		Noncarriers With Affected Second-Degree Relative Only		Noncarriers With Any Affected First-Degree Relative		Noncarriers With Any Bilaterally Affected First-Degree Relative		<i>BRCA1</i> or <i>BRCA2</i> Mutation Carriers†	
	10-Year Cumulative Risk of CBC* (%)	95% CI (%)	10-Year Cumulative Risk of CBC* (%)	95% CI (%)	10-Year Cumulative Risk of CBC* (%)	95% CI (%)	10-Year Cumulative Risk of CBC* (%)	95% CI (%)	10-Year Cumulative Risk of CBC* (%)	95% CI (%)
25-29	6.3	4.4 to 8.7	8.1	4.5 to 14.2	13.4	7.7 to 24.5	21.7	11.1 to 42.3	28.2	16.0 to 50.0
30-34	7.0	5.4 to 8.7	9.0	5.2 to 14.9	14.7	8.9 to 25.5	23.7	12.8 to 44.2	30.7	18.4 to 51.5
35-39	5.2	4.1 to 6.3	6.7	3.9 to 11.0	11.1	6.8 to 19.1	18.1	9.8 to 33.4	23.7	14.3 to 39.3
40-44	4.2	3.3 to 5.1	5.4	3.2 to 8.9	9.0	5.5 to 15.4	14.8	8.0 to 27.2	19.4	11.8 to 32.1
45-49	4.5	4.1 to 5.6	6.2	4.4 to 9.9	7.5	5.3 to 11.9	15.1	8.2 to 27.7	12.2	6.5 to 22.9
50-54	4.0	3.6 to 4.9	5.5	3.9 to 8.8	6.7	4.7 to 10.6	13.4	7.3 to 24.7	10.8	5.8 to 20.3
All ages (25-54)	4.6	4.0 to 5.1	5.9	4.6 to 8.6	8.6	6.1 to 11.5	15.6	8.5 to 28.5	18.4	16.0 to 21.3

Abbreviation: CBC, contralateral breast cancer.

*Risk determined actuarially using previously described methodology¹⁹ combining annual SEER CBC rates and adjusted rate ratios from the Women's Environmental Cancer and Radiation Epidemiology Study.†Previously published data.¹⁹

noncarriers diagnosed with UBC before age 55 years with a first-degree family history of bilateral breast cancer had a cumulative risk of CBC of 15.6% 10 years after their first primary breast cancer diagnosis. Thus, noncarriers with a bilaterally affected first-degree relative have a 10-year cumulative risk of CBC that is nearly as high as that of women who are *BRCA1* or *BRCA2* mutation carriers (15.6% v 18.4%, respectively). It is important to note that other studies have found higher 10-year rates of CBC for *BRCA* carriers in the 30% to 40% range.^{22,29-32} However, these studies often differ from the current study by using even younger women or including just *BRCA1* carriers. We elected to compare results produced from the same population to take advantage of all similarities including study design and patient case ascertainment.

Previously, we reversed the time frame to estimate the cumulative risk to relatives of women with CBC or UBC. In that analysis,³³ we performed a kin-cohort analysis of WECARE data to estimate the breast cancer risks to relatives of patients with CBC and UBC by the proband's *BRCA1* and *BRCA2* carrier status and

ages of the relatives. We showed that relatives of patients with CBC were at a higher risk than relatives of patients with UBC, among both carriers and noncarriers. Although this provides evidence of the effect of family history of bilateral breast cancer, we did not specifically address the risk of CBC in the relatives either among carriers or noncarriers in the prior study.

The strengths of the present study include its population-based study design unselected for family history, the large number of CBCs, detailed family history data, and complete *BRCA1* and *BRCA2* mutation screening of all study participants. Additionally, all women were younger than age 55 years at the time of first breast cancer diagnosis, thereby focusing this study on an enriched population of young women at risk of CBC. Further, because controls were also affected with breast cancer, it is highly unlikely that differential recall of reported family history biased our results. Although our total sample size is large, a limitation of our study is the small number of women in several categories, which precludes further stratified assessments of the associations of CBC risk with family history.

We have demonstrated that after excluding carriers of pathogenic mutations in *BRCA1* and *BRCA2*, family history remains a substantial risk factor for CBC. In particular, young noncarriers who have a family history of breast cancer have a considerably greater risk of CBC than those without a family history. Further, women with a first-degree history of bilateral breast cancer have a 10-year cumulative risk of CBC that is comparable to risks previously reported for *BRCA1* and *BRCA2* mutation carriers. These results underscore the critical importance of obtaining detailed family histories from all women diagnosed with breast cancer, regardless of *BRCA1* and *BRCA2* mutation carrier status. Because women with a family history of bilateral breast cancer have risks of CBC similar to those of mutation carriers, these women should receive counseling for preventive measures.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

Fig 1. Cumulative absolute risk of contralateral breast cancer for women younger than age 55 years at first diagnosis.

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GLOSSARY TERMS

BRCA1: A tumor suppressor gene, the breast cancer 1 susceptibility gene is known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risks of developing breast or ovarian cancer.

BRCA2: Known as breast cancer 2 early onset gene, BRCA2 is a tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from BRCA1, BRCA2 has cellular functions similar to BRCA1. BRCA2 binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents.

Cumulative risk: A measure of risk of an event (usually disease occurrence) during a specified time period.

ER (estrogen receptor): Belonging to the class of nuclear receptors, estrogen receptors are ligand-activated nuclear proteins present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (α and β). ER α is one of the most important proteins controlling breast cancer function. ER β is present in much lower levels in breast cancer and its function is uncertain. Estrogen-receptor status guides therapeutic decisions in breast cancer.

Proband: The individual under investigation; the index case. In family studies, the individual who is the initial member of a family under investigation.