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ORIGINAL REPORT

Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in *BRCA1/2* Mutation Carriers

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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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ABSTRACT

Purpose
To determine prospectively overall and age-specific estimates of contralateral breast cancer (CBC) risk for young patients with breast cancer with or without *BRCA1/2* mutations.

Patients and Methods
A cohort of 6,294 patients with invasive breast cancer diagnosed under 50 years of age and treated between 1970 and 2003 in 10 Dutch centers was tested for the most prevalent *BRCA1/2* mutations. We report absolute risks and hazard ratios within the cohort from competing risk analyses.

Results
After a median follow-up of 12.5 years, 578 CBCs were observed in our study population. CBC risk for *BRCA1* and *BRCA2* mutation carriers was two to three times higher than for noncarriers (hazard ratios, 3.31 [95% CI, 2.41 to 4.55; $P < .001$] and 2.17 [95% CI,1.22 to 3.85; $P = .01$], respectively). Ten-year cumulative CBC risks were 21.1% (95% CI, 15.4 to 27.4) for *BRCA1*, 10.8% (95% CI, 4.7 to 19.6) for *BRCA2* mutation carriers and 5.1% (95% CI, 4.5 to 5.7) for noncarriers. Age at diagnosis of the first breast cancer was a significant predictor of CBC risk in *BRCA1*/2 mutation carriers only; those diagnosed before age 41 years had a 10-year cumulative CBC risk of 23.9% (*BRCA1*: 25.5%; *BRCA2*: 17.2%) compared with 12.6% (*BRCA1*: 15.6%; *BRCA2*: 7.2%) for those 41 to 49 years of age ($P = .02$); our review of published studies showed ranges of 24% to 31% before age 40 years (*BRCA1*: 24% to 32%; *BRCA2*:17% to 29%) and 8% to 21% after 40 years (*BRCA1*: 11% to 52%; *BRCA2*: 7% to 18%), respectively.

Conclusion
Age at first breast cancer is a strong risk factor for cumulative CBC risk in *BRCA1/2* mutation carriers. Considering the available evidence, age-specific risk estimates should be included in counseling.

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INTRODUCTION

Women affected with a first breast cancer have a higher risk of developing a second new primary tumor in the contralateral breast than the risk of a first breast cancer in the general female population.[1,2] Women carrying a germline mutation in either the *BRCA1* or *BRCA2* gene especially face an increased lifetime risk of developing a contralateral breast cancer (CBC). Published 10-year absolute risk estimates vary widely, ranging from 16% to 40%, and are three to six times higher than the risk for noncarriers.[3-37] Most previously published studies included *BRCA1/2* mutation carriers ascertained through clinical genetic centers (CGCs),[5,6,8-10,12,13,15-18,20-22,24-27,30,32-38] comparing these with noncarriers also selected from CGCs[8,16,17,27] or with hospital- or population-based sporadic breast cancer cases.[5,6,8,10,12,15-18,24,26,32,35,37] Only a few studies[4,7,11,14,23,28,29,31] tested a consecutive series of patients with breast cancer for *BRCA1/2* mutations; these studies were small (number of included carriers, 20 to 57) and included young patients (maximal age, 46 years)[4,14,23,28] and/or Ashkenazi Jewish patients.[7,11,28,29,31]

A more precise estimate of CBC risk for a patient with *BRCA1/2*-associated breast cancer is greatly warranted; it would enable more individualized counseling regarding surveillance versus prophylactic mastectomy, as well as selection of an optimal surveillance regimen for different mutation

carrier groups. Age at diagnosis of the first breast cancer may be a potential risk stratifier.[13,19,21,22,25,27,30,36]

In this study, we aim to give unbiased risk estimates of CBC risk by age at diagnosis of the first breast cancer for *BRCA1* or *BRCA2* mutation carriers compared with noncarriers diagnosed before age 50 years in an unselected cohort, and to explore the impact of other risk predicting factors. Additionally, we compare our results with previously published CBC risk estimates.

PATENTS AND METHODS

Patients

This retrospectively ascertained cohort study is composed of a consecutive series of 7,403 female patients with invasive breast cancer diagnosed at an age younger than 50 years without a previous cancer diagnosis (except for nonmelanoma skin tumors). Patients included in the study were treated for a first primary breast cancer between 1970 and 2003 in hospitals/centers throughout the Netherlands (Data Supplement). Complete identification and updates of follow-up of all patients with breast cancer were performed through the medical registries of the hospital and through patient records (second cancers, recurrences, and survival data) or through the Netherlands Cancer Registry (second cancers and survival data since 1989).[39] Data on oophorectomies and (contralateral) mastectomies during follow-up were obtained through linkage with the nationwide network and registry of histo- and cytopathology (PALGA).[40] Data regarding the family history of cancer (mostly information on first- and second-degree relatives) were obtained from five hospitals (ie, Antoni van Leeuwenhoek, Leiden University Medical Center,[41] Erasmus University Medical Center Cancer Institute,[41] Albert Schweitzer Hospital, and Medisch Spectrum Twente), using the medical registries and/or patient records. Patients were considered family history negative when there was no family history of breast cancer reported at the time of the first breast cancer diagnosis.

For 6,484 patients with breast cancer (88% of total cohort), we were able to collect germline DNA of sufficient quality. Patients without germline DNA were from earlier years of breast cancer diagnosis, but had an age distribution similar to patients with germline DNA of sufficient quality. For 88% of these patients, paraffin-embedded tissue blocks containing normal tissue were used for DNA isolation; for 12%, DNA was obtained from blood. The methods for DNA isolation and mutation analyses have been described elsewhere (M.K. Schmidt, personal communication, March 2015). In short: *BRCA1/2* mutation analysis included testing for 92 variants representing approximately 64% of the *BRCA1/2* mutations prevalent in families in the Netherlands, using Allelic discrimination or Fragment length analyses; Sanger sequencing was used for confirmation of mutations (M.K. Schmidt, personal communication, March 2015). One patient identified as having both a *BRCA1* and *BRCA2* mutation was classified as a *BRCA1* mutation carrier.

Using a coding procedure, the clinical data and *BRCA1/2* mutation study results were anonymized before linkage.[42] The secondary use of long-term stored tissue samples and clinical data in this study was in accordance with the Dutch codes of conduct[42a,43] and was approved by the review boards of the participating institutions.

For the analyses of CBC risks, 190 patients were excluded: 52 patients with a synchronous bilateral breast cancer and 138 patients who were diagnosed with metastases, died, or were lost to follow-up, within 3 months after the first breast cancer diagnosis; thus, there remained 6,294 patients with unilateral breast cancer in the analysis.

Statistical Analysis

The main outcome of interest in our study was the risk of CBC, defined as a second primary invasive breast cancer in the contralateral breast in the original pathology and clinical records, and diagnosed at least 3 months after the diagnosis of the first breast cancer. Time at risk started 3 months after the diagnosis of the first breast cancer and ended at the date of diagnosis of CBC, contralateral mastectomy, first distant metastases, death, or date of most recent follow-up information, whichever came first. An oophorectomy, a new primary ipsilateral breast cancer or ovarian cancer, local recurrences, and regional recurrences were taken into account as time-varying covariates in the multivariate analyses. We report standardized incidence ratios (SIRs) comparing the CBC incidence in our study population with the incidence of breast cancer in the Dutch female population (reference rates from the Netherlands Cancer Registry[39]) for *BRCA1, BRCA2* mutation carriers and noncarriers separately, and stratified by follow-up period and age at diagnosis of the first breast cancer; see Data Supplement.

Absolute overall and subgroup risk estimates for *BRCA1/2* mutation carriers and noncarriers were derived using cumulative incidence curves accounting for competing risks. First distant metastasis and death were taken into account as competing events. The Fine and Gray method[44] was used for univariate and multivariate competing risk regression analyses to determine the subdistribution hazard ratios (HRs; Data Supplement). Our main study aim was to estimate CBC risks for patients with breast cancer who had not yet chosen risk-reducing surgery while taking into account possible comorbidities and death; to substantiate why we used the methods as described under Statistical Analysis, three alternative methods are shown in the Data Supplement. All statistical tests were two sided; $P < .05$ was considered significant. Analyses were performed using STATA11.0 (STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

Systematic Review

A systematic review was performed including 21 studies which reported 10-year CBC risk estimates for *BRCA1/2* mutation carriers; details of the methods and results are shown in the Data Supplement and are summarized in forest plots.

RESULTS

Clinicopathologic characteristics of the 6,294 included patients with breast cancer are shown in the Data Supplement. Of all patients, 4.3% were identified as carrying a *BRCA1* (n = 200) and/or a *BRCA2* (n = 71) mutation. Associations between the *BRCA1* and *BRCA2* mutation status and different clinicopathologic characteristics are listed in Table 1.

CBC Risk in Comparison With the Breast Cancer Incidence of the Dutch Female Population Younger Than Age 50 Years

After a median follow-up of 12.5 years, 578 CBCs were observed in our study population, resulting in a significantly increased SIR of 3.01 (95% CI, 2.77 to 3.27) compared with breast cancer rates in the general Dutch female population. Results for different subgroups of the cohort compared with breast cancer rates in the general population are listed in the Data Supplement. Both for *BRCA1/2* mutation carriers and noncarriers, SIRs were highest for younger patients and in the first 5 years of follow-up.

CBC Risk in Subgroups of the Cohort

The 10-year cumulative CBC risk was 5.1% (95% CI, 4.5 to 5.7) for noncarriers, 21.1% (95% CI, 15.4 to 27.4) for *BRCA1* mutation carriers, and 10.8% (95% CI, 4.7 to 19.6) for *BRCA2* mutation carriers (Fig 1A; Data Supplement). Carriers of a *BRCA1* or a *BRCA2* mutation were at a significantly increased CBC risk

Table 1. Correlations of the *BRCA1/2* Gene Mutation Status With Clinicopathologic Characteristics, Follow-Up, and Treatment Data

	Noncarriers		*BRCA1*			*BRCA2*		
BRCA1/2 Mutation Status	No.	%	No.	%	*P*	No.	%	*P*
Total (N = 6,294)	6,023	95.7	200	3.2		71	1.1	
Median follow-up, SD	14.8	8.4	12.2	8.2	.02*	12.5	8.0	.10*
Median follow-up to first event†, SD	12.7	8.8	4.1	7.9	< .001*	7.5	8.7	.01*
Event of interest: CBC	521	8.7	45	22.5	< .001	12	16.9	.01
Events during follow-up, excluding CBC								
Distant metastasis	1,521	25.3	49	24.5	.81	22	31.0	.27
Deaths	893	14.8	32	16.0	.65	9	12.7	.61
Mastectomy of contralateral breast	233	3.9	34	17.0	< .001	7	9.9	.01
Mastectomy < 3 mo after diagnosis	29	12.4	10	29.4		0	0.0	
CBCs after mastectomy	4	1.7	0	0.0		0	0.0	
Oophorectomy	481	8.0	33	16.5	< .001	11	15.5	.02
Oophorectomy < 3 mo after diagnosis	107	22.2	4	12.1		1	9.1	
CBCs after oophorectomy	26	5.4	2	6.1		1	9.1	
Ipsilateral breast cancer/ovarian cancer	106	1.8	16	8.0	< .001	1	1.4	.82
Local recurrence	391	6.5	7	3.5	.09	8	11.3	.11
Regional recurrence	140	2.3	7	3.5	.28	1	1.4	.61
Alive at end follow-up	2,855	47.4	40	20.0	< .001	21	29.6	.003
Family history (type of cancer in affected relatives)								
No affected relatives	1,033	42.7	19	16.5	< .001	9	25.0	.01
Yes, breast cancer	902	37.2	79	68.7		22	61.1	
Yes, only other cancers	487	20.1	17	14.8		5	13.9	
Information first breast tumor								
Median age at diagnosis, SD	44	5.4	39	6.3	< .001	42	5.9	.16
Age at diagnosis categories, years								
< 30	138	2.3	21	10.5	< .001	6	8.5	.005
30-34	444	7.4	32	16.0		6	8.5	
35-39	990	16.4	50	25.0		12	16.9	
40-44	1,811	30.1	57	28.5		25	35.2	
45-49	2,640	43.8	40	20.0		22	31.0	
Surgery								
No surgery	80	1.4	5	2.6	.10	0	0.0	.54
Breast-conserving treatment plus radiotherapy	2,547	43.2	91	46.7		33	47.1	
Mastectomy (without radiotherapy)	1,314	22.3	49	25.1		12	17.1	
Mastectomy plus radiotherapy	1,950	33.1	50	25.6		25	35.7	
Radiotherapy (breast/axillary with any surgery)	4,638	77.1	148	74.4	.37	59	83.1	.23
Systemic therapy								
No systemic therapy	2,516	50.2	75	43.4	< .001	25	42.4	.68
Only chemotherapy	1,729	34.5	87	50.3		23	39.0	
Only hormonal therapy	301	6.0	7	4.0		4	6.8	
Chemo- and hormonal therapy	467	9.3	4	2.3		7	11.9	

NOTE. Patients included were treated for a first primary breast cancer in hospitals/centers throughout the Netherlands: Antoni van Leeuwenhoek, Leiden University Medical Center, Erasmus University Medical Center Cancer Institute, Diaconessenhuis Leiden, Rijnland hospital, Elkerliek hospital, Viecuri Medical Center, Albert Schweitzer Hospital, Medisch Spectrum Twente, and hospitals using the pathology services of the PAMM Laboratories. *P* value of the Pearson χ^2 test, *BRCA1* or *BRCA2* carriers compared with noncarriers.

Abbreviations: CBC, contralateral breast cancer; SD, standard deviation.

*Nonparametric Pearson χ^2 test of the equality of the medians used.

†The event of interest, events that exclude a CBC occurrence or alive at end of follow-up, whichever came first.

compared with noncarriers, with age-adjusted HRs of 3.31 (95% CI, 2.41 to 4.55; $P < .001$) and 2.17 (95% CI, 1.22 to 3.85; $P = .01$), respectively (Data Supplement). Adjustment for time interactions with oophorectomy, other second primaries of breast (ipsilateral) or ovaries, local recurrence, regional recurrence, and adjustment for treatment given for the first breast cancer did not alter these results (Data Supplement).

CBC risks for subgroups according to age at breast cancer diagnosis and presence of a family history of (breast) cancer, stratified by the *BRCA* mutation status, are listed in Table 2 and the Data Supplement. The 10-year cumulative risk of CBC for *BRCA1/2* mutation carriers diagnosed with a first breast cancer before age 41 years was 23.9% (95% CI, 16.7 to 31.8) compared with 12.6% (95% CI, 7.4 to 19.3) for those 40 to 49 years old at diagnosis (Fig 1B; HR, 1.89; 95% CI,1.09 to 3.29; $P = .02$). This age effect was not seen in noncarriers (Fig 1A; HR, 1.06; 95% CI, 0.89 to 1.28; $P = .50$), and there was a statistically significant effect modification when comparing *BRCA1/2* carriers with noncarriers ($P_{interaction} = .05$; Table 2). Including age as a linear factor showed similar results (per year increase: HR, 1.00; 95% CI, 0.98 to 1.01; $P = .54$ and HR, 0.97; 95% CI, 0.93 to 1.01; $P = .10$ for noncarriers and *BRCA1/2*, respectively; $P_{interaction} = .20$). Including time-dependent interactions with oophorectomy, other second primaries of breast (ipsilateral) or ovaries, local recurrence, regional recurrence, and adjustment for treatment given for the first breast cancer did not substantially alter the results (Data Supplement). In addition, adjustment for the estrogen receptor status of the first breast cancer did not alter the results (data not shown). Analyses in *BRCA1*

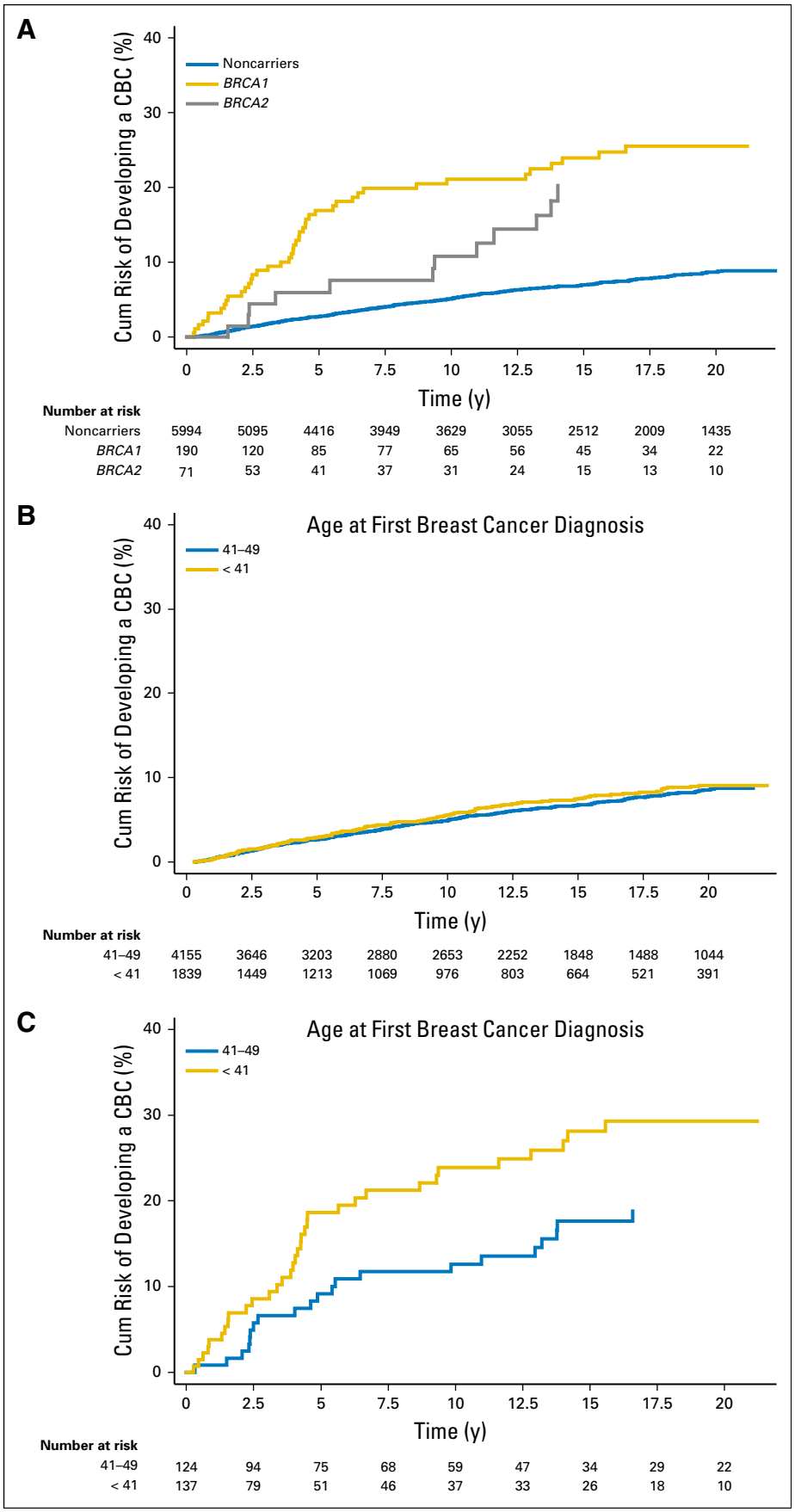

Fig 1. (A) Cumulative incidence curves showing the risk of CBC for *BRCA1* mutation carriers and *BRCA2* mutation carriers compared with noncarriers. (B) Cumulative incidence curves showing the risk of CBC for noncarriers stratified according to the age at diagnosis of the first breast cancer, ie, patients diagnosed at ages 41 to 49 years and younger than 41 years. (C) Cumulative incidence curves showing the risk of CBC for *BRCA1/2* mutation carriers stratified according to the age at diagnosis of the first breast cancer, ie, patients diagnosed at ages 41 to 49 years and younger than 41 years. In all panels, 39 patients (29 noncarriers; 10 *BRCA1* mutation carriers) were left censored because they had a contralateral mastectomy before or within 3 months after the first breast cancer diagnosis. CBC, contralateral breast cancer; Cum, cumulative.

Table 2. Risk of Contralateral Breast Cancer Related to Different Factors, Stratified by *BRCA1/2* Mutation Status

	Noncarriers								*BRCA1* + *BRCA2* Mutation Carriers								
Factor	No.*	No. CBCs†	Risk Period (years)	Cum CBC Risk	95% CI	HR	95% CI	*P*	No.*	No. CBCs†	Risk Period (years)	Cum CBC Risk	95% CI	HR	95% CI	*P*	*P* interaction
Age at diagnosis BC, years‡																	
41-49	4,168	357	5	2.7	2.2 to 3.2	Ref			126	21	5	9.2	4.9 to 15.2	Ref			.05
			10	4.9	4.2 to 5.6						10	12.6	7.4 to 19.3				
< 41	1,855	164	5	2.9	2.2 to 3.8	1.06	0.89 to 1.28	.50	145	36	5	18.7	12.3 to 26.0	1.89	1.09 to 3.29	.02	
			10	5.6	4.6 to 6.7						10	23.9	16.7 to 31.8				
Any systemic therapy given for the first BC§																	
No systemic therapy	2,516	225	5	2.5	2.0 to 3.2	Ref			100	25	5	17.0	10.0 to 25.5	Ref			.69‖
			10	5.1	4.2 to 6.0						10	21.9	13.9 to 31.1				
Any systemic therapy	2,497	158	5	2.4	1.9 to 3.1	0.74‖	0.61 to 0.91	< .01	132	23	5	11.2	6.3 to 17.7	0.65‖	0.37 to 1.17	.15	
			10	4.3	3.6 to 5.2						10	14.8	9.0 to 21.9				
Chemotherapy given for the first BC§																	
No chemotherapy	2,817	238	5	2.4	1.9 to 3.1	Ref			111	26	5	16.6	10.0 to 24.7	Ref			.68‖
			10	4.9	4.1 to 5.7						10	21.2	13.6 to 29.9				
Chemotherapy	2,196	145	5	2.5	1.9 to 3.2	0.80‖	0.65 to 0.98	.03	121	22	5	11.1	6.1 to 17.8	0.70‖	0.39 to 1.26	.23	
			10	4.5	3.6 to 5.4						10	14.9	9.0 to 22.3				
Family history of breast cancer at first BC diagnosis¶																	
No BC	1,520	103	5	1.8	1.2 to 2.6	Ref			50	9	5	10.3	3.8 to 20.7	Ref			.56‖
			10	4.1	3.2 to 5.2						10	14.9	6.5 to 26.4				
BC	902	97	5	3.6	2.5 to 5.0	1.65‖	1.25 to 2.18	< .01	101	28	5	19.2	11.5 to 28.3	2.11‖	0.98 to 4.55	.06	
			10	7.0	5.4 to 8.8						10	25.8	16.8 to 35.6				
Family history of BC at first BC diagnosis + age at first BC diagnosis¶																	
No BC	1,520	103	5	1.8	1.2 to 2.6	Ref			50	9	5	10.3	3.8 to 20.7	Ref			
			10	4.1	3.2 to 5.2						10	14.9	6.5 to 26.4				
BC and 41-49	613	70	5	3.3	2.1 to 5.0	1.75‖	1.29 to 2.39	< .01	42	9	5	10.2	3.3 to 22.0	1.31‖	0.51 to 3.37	.57	.56‖
			10	7.1	5.2 to 9.3						10	12.9	4.7 to 25.4				
BC and < 41	289	27	5	4.28	2.3 to 7.3	1.31‖	0.51 to 3.37	.57	59	19	5	27.2	15.1 to 40.9	2.97‖	1.28 to 6.86	.01	.13‖
			10	6.70	4.1 to 10.2						10	38.1	23.5 to 52.6				

NOTE. *P* value from Wald test statistic. Additional models are shown in the Data Supplement.
Abbreviations: BC, breast cancer; CBC, contralateral breast cancer; Cum, cumulative; HR, unadjusted hazard ratio; Ref, reference; 5, 5-year cumulative CBC risk; 10, 10-year cumulative CBC risk.
*At start of follow-up.
†During follow-up.
‡Thirty-nine patients (29 noncarriers and 10 *BRCA1* mutation carriers) were left censored because they had a contralateral mastectomy before, or within 3 mo after, the first breast cancer diagnosis.
§One thousand forty-nine patients were excluded because of missing systemic therapy data; 39 patients (29 noncarriers and 10 *BRCA1* mutation carriers) were left censored because they had a contralateral mastectomy before, or within 3 mo after, the first breast cancer diagnosis.
‖Hazard ratio adjusted for age at diagnosis of the first breast cancer.
¶Three thousand seven hundred and nine patients were excluded because of missing family history data; 27 patients (20 noncarriers and 7 *BRCA1* mutation carriers) were left censored because they had a contralateral mastectomy before, or within 3 mo after, the first breast cancer diagnosis.

mutation carriers alone also showed the effect of age, but it was not statistically significant ($P_{interaction}$ = .14; age at diagnosis < 41 years *v* age at diagnosis 41 to 49 years; HR_{BRCA1}, 1.77; 95% CI, 0.93 to 3.38; *P* = .08; Data Supplement). For *BRCA1* and *BRCA2* mutation carriers separately, the 10-year cumulative CBC risks for those diagnosed before age 41 years were 25.5% (95% CI, 17.4 to 34.4) and 17.2% (95% CI, 5.4 to 34.7), respectively, and for those 41 to 49 years old, 15.6% (95% CI, 8.5 to 24.5) and 7.2% (95% CI, 1.9 to 17.5), respectively.

Adjuvant systemic therapy (any type) given for the first breast cancer decreased the risk of CBC in noncarriers. In *BRCA1/2* mutation carriers, there was also a suggestion of a decreased risk, but the effect was not statistically significant (systemic therapy *v* no systemic therapy: $HR_{noncarriers}$, 0.74; 95% CI, 0.61 to 0.91; *P* < .001; $HR_{BRCA1/2}$, 0.65; 95% CI, 0.37 to 1.17; *P* = .15; Table 2).

A positive family history of breast cancer was associated with an increased CBC risk in noncarriers (HR, 1.65; 95% CI, 1.25 to 2.18; *P* = .001) and with a marginally significant risk increase in *BRCA1/2* mutation carriers (HR, 2.11; 95% CI, 0.98 to 4.55; *P* = .06; Table 2). The highest risk of CBC was found in *BRCA1/2* mutation carriers who were diagnosed with a first breast cancer before age 41 years and who had a positive family history of breast cancer at that time, with a 10-year cumulative CBC risk of 38.1% (95% CI, 23.5 to 52.6; Data Supplement; Table 2).

Review of Previously Published CBC Risk Estimates for BRCA1/2 Mutation Carriers and Comparison With These Study Results

A description of methodologic issues of the studies and interpretation of the results can be found in the Data Supplement. In short: 21 published studies reported 10-year cumulative CBC risk estimates for *BRCA1* and/or *BRCA2* mutation carriers.[6,8-10,12-16,18-21,24,26,27,30,31,33-36] In Figure 2A, the results of these studies are summarized in three forest plots; the range of reported 10-year CBC risks was 16.6% to 40% for *BRCA1/2*, 20.4% to 42% for *BRCA1*, and 10.1% to 30% for *BRCA2* mutation carriers, with our results at the lower end of the ranges. Five previous studies[13,19,21,27,36] reported 10-year CBC risks for subgroups based on age at first breast cancer diagnosis (Fig 2B). For *BRCA1/2* mutation carriers combined, the range of 10-year cumulative CBC risks reported was 23.7% to 30.7% (*BRCA1*: 24% to 32%; *BRCA2*: 17% to 29%) for mutation carriers diagnosed with a first breast cancer before age 40 years, and 8.4% to 21% (*BRCA1*: 11% to 52%; *BRCA2*: 7% to 18%) for those older than age 40 years. Again, our risk estimates are at the lower end of the range of previously published risk estimates.

DISCUSSION

In our unselected cohort of patients with breast cancer , we found 10-year cumulative CBC risks of 21.1% for *BRCA1* mutation carriers and 10.8% for *BRCA2* mutation carriers, which were two to three times higher than for noncarriers (HR, 3.31 for *BRCA1*; and HR, 2.17 for B*RCA2* mutation carriers).

With an aim toward optimized and individualized counseling of patients with *BRCA1/2*-associated breast cancer, it is important to identify factors that better predict the risk of CBC in this group of high-risk women because this may influence the choice for either prophylactic mastectomy or intensive surveillance. Factors predicting the risk of CBC in *BRCA1* and/or *BRCA2* mutation carriers are largely unknown and therefore are not yet incorporated in online prediction models.[45-47] We were able to define subgroups with an increased versus a decreased 10-year cumulative CBC risk based on age at primary breast cancer, ie, 24% for *BRCA1/2* mutation carriers diagnosed with a first breast cancer before age 41 years (*BRCA1*: 26%; *BRCA2*: 17%) *v* 13% for *BRCA1/2* mutation carriers affected with a first breast cancer between 40 and 49 years of age (*BRCA1*: 16%; *BRCA2*: 7%). Age at first breast cancer diagnosis was also a predictor of CBC risk in the group of *BRCA1* mutation carriers alone (although it was not significant, probably because of the small numbers). Unfortunately, we could not draw firm conclusions about the effect of age in *BRCA2* mutation carriers because the number of *BRCA2* mutation carriers in our cohort was too small. However, the data of our study suggest that *BRCA1* and *BRCA2* are also different entities regarding the CBC risk (different SIRs for the time periods and higher cumulative CBC risk for *BRCA1* over *BRCA2*).

Adjustment for treatment given for the first breast cancer and other events during follow-up (eg, locoregional recurrences) did not alter these results, indicating that these effects cannot be explained by a differential treatment effect in younger and older patients. As has been shown before,[22,24,52] adjuvant systemic therapy decreased CBC risk in noncarriers in our study. A decreased risk was also seen in mutation carriers, although the effect was not statistically significant possibly because of the small numbers. However, only a few patients received hormonal treatment: in the time period of this study, only postmenopausal women with estrogen receptor–positive disease were considered for adjuvant hormonal therapy in the Netherlands.[53] Therefore, we were unable to study the effect of hormonal therapy separately.

We observed that family history is a predictor of CBC risk in both noncarriers and mutation carriers, which is in line with previous literature.[19,21] Because of missing data regarding systemic therapy and family history in a large proportion of women (Data Supplement), the numbers in these subanalyses are small. Furthermore, the family history data we used were gathered from the clinical charts, and may therefore be of lower quality, even though previously we showed sufficient correlation with data from the Clinical Genetic Center.[48] Therefore, results of the family history subanalyses should be interpreted with caution.

To our knowledge, this cohort study is the first large study unselected for family history that reports unbiased CBC risk estimates for *BRCA1* and *BRCA2* mutation carriers separately in comparison with noncarriers. Although the cohort in this study is large, a relatively small number of *BRCA1/2* mutation carriers were included, especially accounting for *BRCA2* mutation carriers. Because we were unable to test for all known *BRCA1/2* mutations, some *BRCA1/2* mutation carriers may have been misclassified as noncarriers. Assuming these rare mutations are of equal penetrance, this may have led to a slight underestimation of the CBC risks (M.K. Schmidt, personal communication, March 2015). In the analyses we corrected for prophylactic measures, although the effect on CBC prevention[49,50] was not an end point in this article. Importantly, because a large proportion of patients were diagnosed before 1995, many *BRCA1/2* mutation carriers were unaware of their mutation status at diagnosis.[42,48]

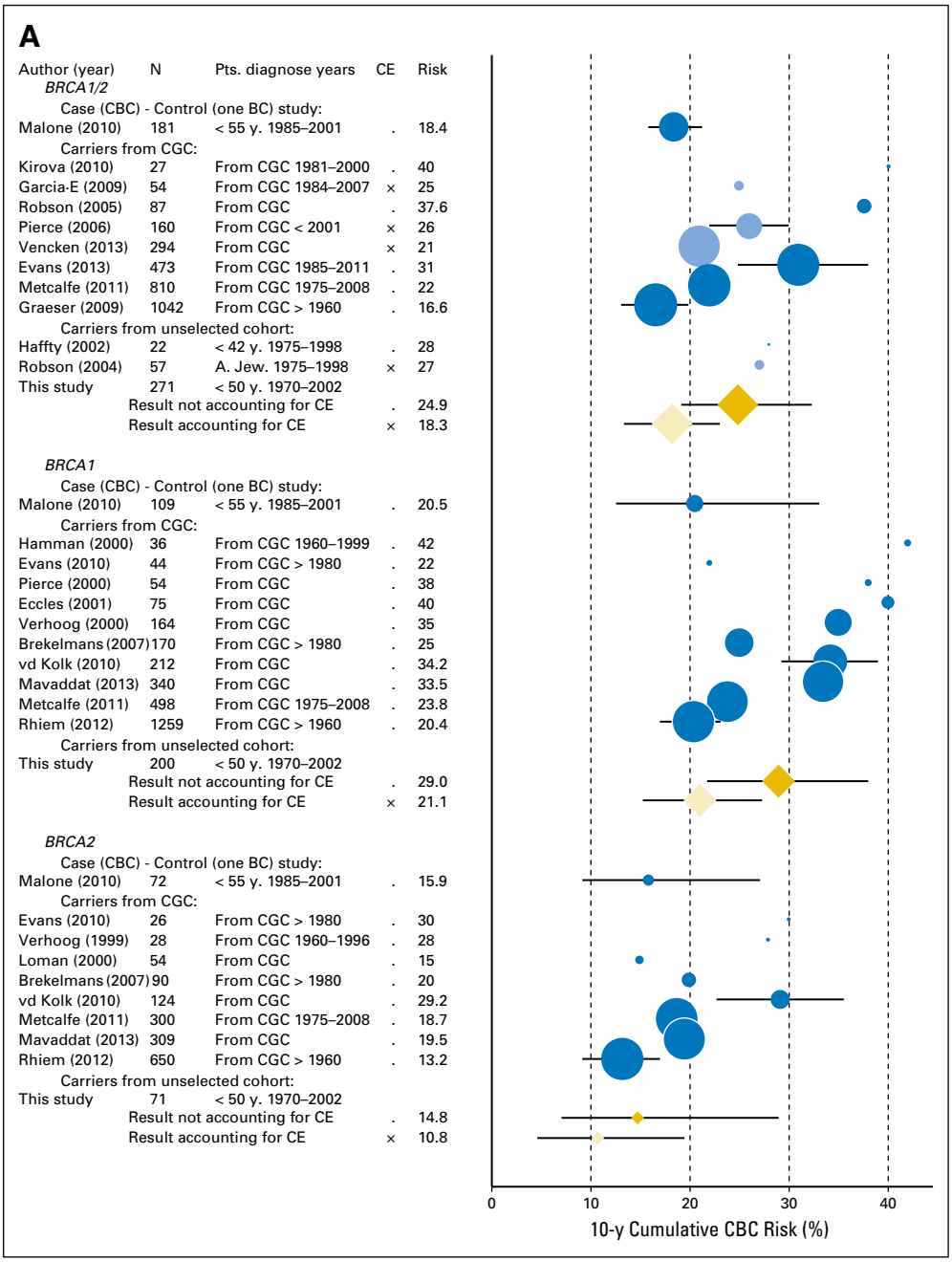

Fig 2. Forest plots of the results of studies reporting 10-year cumulative CBC risks for *BRCA1/2* mutation carriers, *BRCA1* mutation carriers, or *BRCA2* mutation carriers. (A) Without stratification. (B) Stratified by subgroups according to the age at diagnosis of the first breast cancer. Studies are ordered by the method of inclusion of the carriers and the number of included carriers. The size of the bullet represents the number of included carriers. Round bullet: estimates reported by previously published studies; diamond-shaped bullet: estimates from this study; In A, darkest shade bullet: estimates from analyses not taking into account competing events; lightest shade bullet: estimates from analyses taking into account competing events; In B, darkest shade bullet: estimates for patients diagnosed with the first breast cancer before age 41 years; medium shade bullet: estimates for patients diagnosed with the first breast cancer between 40 and 50 years; lightest shade bullet: estimates for patients diagnosed with the first breast cancer after age 50 years. BC, breast cancer; CBC, contralateral breast cancer; CE, competing events taken into account in the analyses; CGC, Clinical Genetic Center; Pts, type of patients included in the study; Result(s) accounting for CE, estimates from this study taking into account competing events (Data Supplement; Table 2); Result(s) not accounting for CE, estimates from this study without taking into account competing events (Data Supplement); Risk, 10-year cumulative CBC risk (%).

The 10-year CBC risk estimates for *BRCA1/2* mutation carriers found in this study are of the same magnitude as those published previously, ie,13% to 42%, with *BRCA2* mutation carriers tending to be in the lower part of this range.[6,8-10,12-16,18-21,24,26,27,30,31,33-36] The variation in all reported risk estimates is large, which reflects the heterogeneity of breast cancer in the different groups (and thus the differential effect of various factors, such as treatment), and, conversely, the methodologic aspects. There is no consensus about a precise CBC risk estimate that can be communicated to physicians and their patients. Almost all published studies suffered from potential selection and testing bias, including "selected" high-risk *BRCA1/2* mutation carriers, eg, from CGCs, and may therefore have overestimated the risk of CBC. Furthermore, only three studies accounted for competing risks in their analyses, which is important to prevent risk overestimation.[51] In our own study with unselected mutation carriers and accounting for competing risks, we found a 10-year CBC risk for *BRCA1/2* mutation carriers of 18%. Four studies including "selected" patients and accounting for competing risks reported higher risk estimates, ranging from 21% to 27%,[12,24,31,34] which was similar to the 10-year CBC risk observed in our study for mutation carriers with a family history of breast cancer (25%; Table 2).

In conclusion, the overall 10-year CBC risk for unselected *BRCA1/2* mutation carriers will be around 18%, whereas for

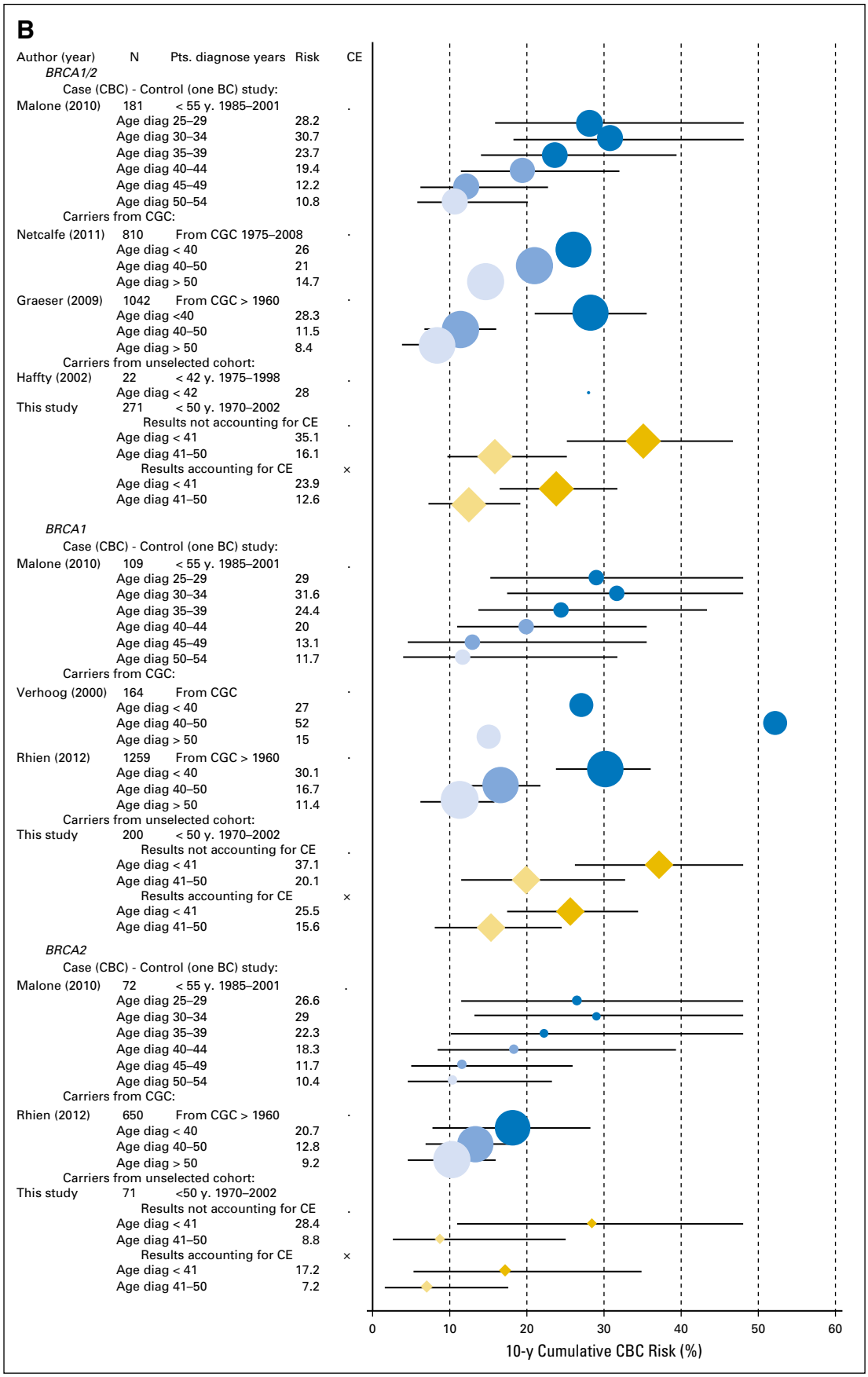

Fig 2. (Continued).

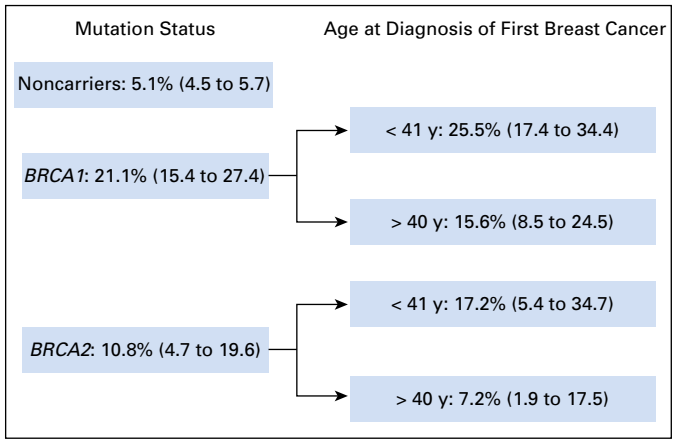

Fig 3. Summary of the 10-year cumulative contralateral breast cancer risks for noncarriers and *BRCA1/2* mutation carriers, stratified on the risk predictor (age) of this study in patients younger than 50 years of age. Numbers in brackets are 95% confidence intervals.

"selected" mutation carriers, the risk will be somewhat higher, around 21% to 27%, with *BRCA2* mutation carriers being at the lower and *BRCA1* mutation carriers at the higher end of this range (Fig 3). Furthermore, based on our study and those published previously, age at primary breast cancer diagnosis is an important predictor of the CBC risk in *BRCA1/2* mutation carriers, with a range of 10-year cumulative CBC risks of 23.7% to 30.7% for mutation carriers diagnosed with the first breast cancer before age 40 years (*BRCA1*: 24% to 32%; *BRCA2*: 17% to 29%), and 8.4% to 21% for those diagnosed after age 40 years (*BRCA1*: 11% to 52%; *BRCA2*: 7% to 18%; Fig 3). In our study, we found the highest CBC risk in *BRCA1/2* mutation carriers diagnosed at young ages who also had a family history of breast cancer (10-year cumulative CBC risk of 38.1% [95% CI, 23.5 to 52.6]). This is in concordance with previously published risk estimates, which were based mainly on *BRCA1/2* carriers recruited through CGCs, ie, those with a substantial family history.

Because genetic testing is performed increasingly, it is important to be able to provide precise and unbiased risk estimates of CBC for a patient with *BRCA1/2*-associated breast cancer. The data of this study contribute to further knowledge regarding CBC risks for this group of high-risk women, enabling an improvement in counseling regarding the optimal strategy concerning prophylactic mastectomy versus surveillance, as well as to optimal screening regimens in the follow-up after breast cancer. Our reported age-specific risks, as shown in Figure 3, can be taken into account when counseling *BRCA1/2* mutation carriers about prophylactic mastectomy versus optimal screening.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

***BRCA1*:** a tumor suppressor gene 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*:** 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. Also known as the breast cancer 2 early onset gene.

competing risk regression: a statistical method that accounts for competing risks. Cumulative incidence functions are compared instead of survival functions (Fine J, et al: J Am Stat Assoc 94:496-509, 1999).

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

germline mutation: an inherited variation in the lineage of germ cells. Germline mutations can be passed on to offspring.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in *BRCA1/2* Mutation Carriers

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