original reports

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*

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abstract

PURPOSE To estimate the risk of contralateral breast cancer (CBC) among women with germline pathogenic variants (PVs) in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*.

METHODS The study population included 15,104 prospectively followed women within the CARRIERS study treated with ipsilateral surgery for invasive breast cancer. The risk of CBC was estimated for PV carriers in each gene compared with women without PVs in a multivariate proportional hazard regression analysis accounting for the competing risk of death and adjusting for patient and tumor characteristics. The primary analyses focused on the overall cohort and on women from the general population. Secondary analyses examined associations by race/ethnicity, age at primary breast cancer diagnosis, menopausal status, and tumor estrogen receptor (ER) status.

RESULTS Germline *BRCA1*, *BRCA2*, and *CHEK2* PV carriers with breast cancer were at significantly elevated risk (hazard ratio > 1.9) of CBC, whereas only the *PALB2* PV carriers with ER-negative breast cancer had elevated risks (hazard ratio, 2.9). By contrast, *ATM* PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Among premenopausal women, the 10-year cumulative incidence of CBC was estimated to be 33% for *BRCA1*, 27% for *BRCA2*, and 13% for *CHEK2* PV carriers with breast cancer and 35% for *PALB2* PV carriers with ER-negative breast cancer. The 10-year cumulative incidence of CBC among postmenopausal PV carriers was 12% for *BRCA1*, 9% for *BRCA2*, and 4% for *CHEK2*.

CONCLUSION Women diagnosed with breast cancer and known to carry germline PVs in *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2* are at substantially increased risk of CBC and may benefit from enhanced surveillance and risk reduction strategies.

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BACKGROUND

Among breast cancer survivors, precise estimation of the risk of second breast and other cancers is essential to guide appropriate surveillance and risk-reducing strategies. The risk of contralateral breast cancer (CBC) among women with breast cancer in the general population is estimated to be 0.5% per year,[1,2] with germline mutation status, race/ethnicity, age at diagnosis, and menopausal status significantly influencing the risk.[3-6] Germline pathogenic variants (PVs) in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* are detected in 5%-7% of women with breast cancer in the general population and are associated with a significantly increased risk of breast cancer in unaffected women.[7-10] The CBC risk among carriers of germline PVs, especially for *ATM*, *CHEK2*, and *PALB2* PV carriers, is not well-defined. Even for *BRCA1* and *BRCA2* carriers, current CBC risk estimates are primarily derived from high-risk women with breast cancer qualifying for genetic testing because of young age at diagnosis or family history of breast or ovarian cancer and may not apply to women in the general population. Because of the lack of precise understanding of CBC risk, appropriate surgical management and surveillance strategies among breast cancer survivors with predisposition gene PVs have not been well-defined.

Recently, the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium reported on

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To estimate the risk of contralateral breast cancer (CBC) in carriers of germline pathogenic variants (PVs) in *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2* from prospective studies.

Knowledge Generated

Germline *BRCA1, BRCA2*, and *CHEK2* PV carriers with breast cancer were at a significantly elevated risk of CBC, whereas only the *PALB2* PV carriers with estrogen receptor–negative breast cancer had elevated risks. By contrast, *ATM* PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Age at diagnosis, menopausal status, and estrogen receptor status of the initial breast cancer significantly influenced the CBC risk in PV carriers.

Relevance *(K.D. Miller)*

Patients with genetic mutations who have had an index breast cancer often assume that they are at high risk of developing another cancer in the other breast. The ability to better predict risk can guide decisions about prophylactic surgery and enhanced screening strategies for those who opt against bilateral mastectomy.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

germline genetic testing of > 30,000 women with breast cancer and age-matched unaffected controls from US-based population-based studies.[8] Several contributing studies have prospective follow-up information on subsequent breast cancers, which presented a unique opportunity to study CBC risk among PV carriers in the general population. In addition, most women in these studies were unaware of their germline PV status at the time of breast cancer diagnosis, which permitted an unbiased assessment of the influence of germline PV status on CBC risk. In this article, we present CBC risk estimates among PV carriers from CARRIERS.

METHODS

Study Population

The CARRIERS consortium included 10 prospective studies with information on CBC after an initial breast cancer diagnosis (Data Supplement, online only). Women were enrolled at or before breast cancer diagnosis, except in the Two Sisters study, which enrolled up to four years after a breast cancer diagnosis. All studies prospectively followed women for CBC events from the time of enrollment. Baseline and follow-up questionnaires along with abstraction of medical records and linkage to state cancer registries were used for the assessment of CBC and covariates (Data Supplement). Women undergoing ipsilateral surgery for initial invasive breast cancer with at least one year of follow-up after initial breast cancer diagnosis were included (Data Supplement). Women diagnosed with bilateral breast cancer (CBC at initial diagnosis or within one year of initial diagnosis), undergoing bilateral mastectomy for initial breast cancer, or missing age at initial breast cancer or CBC diagnosis or with unknown CBC status at last follow-up were excluded. Both in situ and invasive breast cancers were considered CBC events. The patient selection schema is shown in the Data Supplement. The study was approved by the Mayo Clinic Institutional Review Board.

Germline Sequencing and Bioinformatics Analysis

Germline DNA samples were subjected to multiplex amplicon–based analysis covering all coding regions and consensus splice sites of established predisposition genes using a QIAseq custom panel (Data Supplement). Genetic variants were identified using the Genome Analysis Toolkit (GATK) Haplotype Caller and VarDict as described previously[8,11] (Data Supplement). Loss-of-function variants and pathogenic or likely pathogenic variants in the ClinVar database were classified as PVs. Since missense and low-penetrance variants in *CHEK2* have a lower risk of breast cancer than truncating variants,[12,13] these were excluded from the primary analysis. CBC risks associated with missense variants and the low penetrance *CHEK2* p.Ile157Thr (c.470T>C) variant were evaluated separately.[12]

Statistical Analysis

The rates of CBC for carriers of PVs in each of the five genes (Separately for *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were compared with the rates in women without germline PVs in the five genes in a time-to-event analysis beginning at the time of first breast cancer diagnosis and adjusting for competing risk of death using the Fine and Gray method.[14] Censoring occurred at the last follow-up or at contralateral prophylactic mastectomy (CPM, n = 57), whichever came first. The 5-, 10-, and 15-year risks of CBC for each gene were estimated from cumulative incidence curves. A multivariate proportional hazard regression analysis accounting for competing risk of death[15] was performed to compare the CBC risk between PV carriers in each of the five genes and non-PV carriers when adjusting for study, age of diagnosis,[16-18] race/

ethnicity,[19,20] menopausal status,[21] histology[22,23] and estrogen receptor (ER) status[24] of the first breast cancer, and use of endocrine therapy. Further analyses stratified by ER status, menopausal status, race/ethnicity, and age of diagnosis of first breast cancer were performed, adjusting for all relevant covariates in the original model. To account for the effect of ipsilateral breast cancer recurrence or second (nonbreast) cancers, sensitivity analysis censoring at ipsilateral recurrence, second (nonbreast) cancer, CPM, or last follow-up, whichever came first, was performed for studies with information on second cancers. All statistical analyses were performed in R, and the survival package cmprisk was used for analyses using competing risk of death.

RESULTS

Patient Characteristics

A total of 15,104 women were included in the final analysis. The median age at diagnosis of initial breast cancer was 62 years, and the median follow-up was 11 years. Approximately 66% were non-Hispanic White (NHW), whereas 15% were African American. Women with ER-negative primary breast cancer were more likely to be African American, younger, and premenopausal at initial diagnosis compared with women with ER-positive breast cancer (Table 1). The frequency of germline PVs in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2* was 4.4% for the overall study and 3.7% and 7.4% for the ER-positive and ER-negative subsets, respectively. The study population was similar to the overall CARRIERS study[8] in terms of the median age at diagnosis, proportion of ER-negative tumors, and frequency of germline PVs although the proportion of Black, Hispanic, and Asian women was higher in the current study.

CBC Risks for PV Carriers Overall and by ER Status

A total of 801 CBC events were observed during follow-up, with 90 events (11.2%) in carriers of *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* PVs (Table 2). In adjusted analysis, women with germline PVs in *BRCA1*, *BRCA2*, and *CHEK2* had a significantly increased risk ($P < .05$) of CBC compared with women without PVs (Table 2). In particular, *BRCA1* PV carriers had a 2.7-fold increased risk of CBC (hazard ratio [HR], 2.7; 95% CI, 2.0 to 3.8; $P < .001$) and *BRCA2* PV carriers had a 3.0-fold increased risk (HR, 3.0; 95% CI, 2.1 to 4.3; $P < .001$). Furthermore, *BRCA1* and *BRCA2* PV carriers with both ER-positive and ER-negative breast cancer had a significantly increased risk of CBC (Table 2). Germline *CHEK2* PV carriers had a 1.9-fold elevated risk of CBC overall (HR, 1.9; 95% CI, 1.1 to 3.3; $P = .03$) and a 2-fold increased risk of CBC among those with ER-positive breast cancer (HR, 2.0; 95% CI, 1.1 to 3.5; $P = .02$). Similar results were observed for carriers of the common c.1100delC *CHEK2* PV (Table 2). However, combined analysis of women with *CHEK2* truncating variants (n = 140), pathogenic or likely pathogenic missense variants, or missense variants predicted to be deleterious by functional assays[25,26] (n = 24) yielded a slightly lower risk of CBC (HR, 1.7; 95% CI, 0.9 to 2.9; $P = .08$). Furthermore, the *CHEK2* p.Ile157Thr (c.470T>C) variant was not significantly associated with CBC risk in the overall (HR, 1.3; 95% CI, 0.5 to 3.4; $P = .60$) or the ER-positive subset (HR, 1.1; 95% CI, 0.3 to 3.3; $P = .90$). Although *PALB2* PV carriers did not have a significantly increased risk of CBC overall, the risk was significantly increased among *PALB2* PV carriers with ER-negative primary breast cancer (HR, 2.9; 95% CI, 1.4 to 6.4; $P = .006$). By contrast, here was only one CBC event during follow-up of 54 *PALB2* PV carriers with ER-positive breast cancer (Table 2). Germline *ATM* PV carriers were not at significantly elevated risk of CBC overall (HR, 1.2; 95% CI, 0.6 to 2.6; $P = .56$) or among those with ER-positive disease.

CBC risks among 14,237 women with breast cancer from the general population were also evaluated (Data Supplement). These women were slightly older and more likely postmenopausal than those in the overall CARRIERS study population (Data Supplement). The estimated CBC risks for PV carriers in the general population were similar to results from the overall analysis (*BRCA1* HR, 2.1, 95% CI, 1.2 to 3.5, $P = .005$; *BRCA2* HR, 2.5, 95% CI, 1.5 to 4.0, $P < .001$; *CHEK2* ER-positive HR, 2.1, 95% CI, 1.1 to 4.1, $P = .03$; *PALB2* ER-negative HR, 3.1, 95% CI, 1.2 to 7.8, $P = .02$; Data Supplement). Sensitivity analysis for the general population, involving censoring at ipsilateral breast cancer recurrence and second (nonbreast) cancer, yielded results similar to those from the primary analysis (Data Supplement).

The Influence of Race, Menopausal Status, and Age at Diagnosis on CBC

The risks of CBC among NHW *BRCA1*, *BRCA2*, and *CHEK2* PV carriers were similar to the overall study results. *PALB2* was uninformative because only one of the 49 NHW *PALB2* PV carriers developed CBC (Data Supplement). Among 2,249 African Americans with a breast cancer diagnosis, the risk of subsequent CBC was increased > 2-fold for *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* PV carriers compared with noncarriers (*BRCA1* [HR, 2.5; 95% CI, 1.0 to 6.4; $P = .06$]; *BRCA2* [HR, 3.2; 95% CI, 1.5 to 6.9; $P = .003$]; *CHEK2* ER-positive [HR, 9.2; 95% CI, 2.9 to 28.9; $P < .001$]; *PALB2* ER-negative [HR, 4.8; 95% CI, 1.4 to 16.8; $P = .001$]; Data Supplement). *ATM* PV carriers did not exhibit significantly increased risk of CBC in either race.

Exploratory analyses by menopausal status and age at diagnosis were also performed to understand the CBC risk among PV carriers. The frequencies of germline PVs in the five genes among 4,054 premenopausal and 11,050 postmenopausal women were 6.9% and 3.7%, respectively. In premenopausal women, PVs in *BRCA1* and *BRCA2* were associated with an increased risk of CBC in women with either ER-positive or ER-negative breast cancer, whereas *CHEK2* PVs were associated

TABLE 1. Characteristics of the Study Population by ER Status at Initial Breast Cancer Diagnosis

Variable	All Cases (N = 15,104)	ER-Positive Breast Cancer (n = 11,406)	ER-Negative Breast Cancer (n = 2,582)
Age at diagnosis, years			
Median	62	63	59
Range	16-94	21-93	23-94
Race/ethnicity, No. (%)			
Non-Hispanic White	9,513 (63.0)	7,604 (66.7)	1,314 (50.9)
Black or African American	2,249 (14.9)	1,375 (12.1)	664 (25.7)
Hispanic	1,478 (9.8)	977 (8.6)	316 (12.2)
Asian	1,417 (9.4)	1,090 (9.6)	221 (8.6)
Others	367 (2.4)	294 (2.6)	57 (2.2)
Unknown	80 (0.5)	66 (0.6)	10 (0.4)
Menopausal status, No. (%)			
Premenopausal	4,054 (26.8)	2,954 (25.9)	860 (33.3)
Postmenopausal	11,050 (73.2)	8,452 (74.1)	1,722 (66.7)
Histology, No. (%)			
Ductal	11,882 (78.7)	8,988 (78.8)	2.41 (79.0)
Lobular	1,642 (10.9)	1,476 (12.9)	66 (2.6)
Others	461 (3.1)	238 (2.1)	139 (5.4)
Unknown	1,119 (7.4)	704 (6.2)	336 (13.0)
ER status, No. (%)			
Negative	2,582 (17.1)	NA	2,582 (100)
Positive	11,406 (75.5)	11,406 (100)	NA
Unknown	1,116 (7.4)	NA	NA
Surgery, No. (%)			
Ipsilateral lumpectomy	9,833 (65.1)	7,633 (66.9)	1,570 (60.8)
Ipsilateral mastectomy	5,237(34.7)	3,753 (32.9)	1,001 (38.8)
Ipsilateral surgery, unspecified type	34 (0.2)	20 (0.2)	11 (0.4)
Adjuvant endocrine therapy, No. (%)			
No	5,746 (38.0)	3,183 (27.9)	NA
Yes	7,004 (46.4)	6,332 (55.5)	NA
Unknown	2,354 (15.6)	1,891 (16.6)	NA

Abbreviations: ER, estrogen receptor; NA, not applicable.

with an increased risk in only ER-positive and *PALB2* PVs with only ER-negative breast cancer (Table 3). Despite the similar duration of follow-up and similar frequencies of *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* PV carriers among premenopausal and postmenopausal women (Data Supplement and Table 3), the number of CBC events was lower in postmenopausal women, and *BRCA2* was the only gene associated with increased risk of CBC (HR, 3.0; 95% CI, 1.7 to 5.2; $P < .001$; Table 3). The frequency of germline PVs in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* in 6,010 women diagnosed with initial breast cancer at ≥ 65 years was 2.6% (Data Supplement). Despite a median follow-up of 10 years in this group, only three CBC events were observed, one each in *ATM*, *BRCA1*, and *PALB2* PV carriers.

Cumulative Incidence of CBC in PV Carriers

The cumulative incidence of CBC in women without germline PVs in the five genes was 2.2% in 5 years, 4.3% in 10 years, and 6.2% in 15 years, with an annualized cumulative incidence rate of approximately 0.4% per year (Fig 1, Table 4, and Data Supplement). Among *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* germline PV carriers, the 10-year cumulative incidences of CBC were 4.0%, 23.1%, 16.9%, 7.9%, and 7.9%, respectively. *PALB2* PV carriers with ER-negative breast cancer had a 10-year CBC risk of 19.7% (Table 3). As expected, the 5-, 10-, and 15-year cumulative incidence of CBC among PV carriers was generally higher for premenopausal women although confidence intervals were wide. Importantly, the 15-year

TABLE 2. Contralateral Breast Cancer Risk Among Germline PV Carriers by ER Status

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No.	CBC	HR (95% CI)[b]	*P*	Total, No.	CBC	HR (95% CI)[b]	*P*	Total, No.	CBC	HR (95% CI)[b]	*P*
Noncarriers[c]	14,444	711	—	—	10,989	462	—	—	2,391	157	—	—
ATM	116	7	1.2 (0.6 to 2.6)	.56	92	5	1.4 (0.6 to 3.3)	.48	14	1	ND	ND
BRCA1	132	31	2.7 (2.0 to 3.8)	< .001	42	7	3.1 (1.7 to 5.6)	< .001	79	23	< .001	< .001
BRCA2	170	33	3.0 (2.1 to 4.3)	< .001	105	18	3.3 (2.0 to 5.5)	< .001	52	10	< .001	.002
CHEK2												
All PV[d]	140	12	1.9 (1.1 to 3.3)	.03	121	11	2.0 (1.1 to 3.5)	.02	12	1	ND	ND
c.1100delC	92	7	1.9 (0.9 to 3.8)	.07	79	7	2.2 (1.1 to 4.5)	.02	9	0	ND	ND
PALB2	97	7	1.3 (0.6 to 2.6)	.50	54	1	0.4 (0.1 to 2.8)	.37	33	6	2.9 (1.4 to 6.4)	.006

Abbreviations: CBC, contralateral breast cancer; ER, estrogen receptor; HR, hazard ratio; ND, not estimated because of the low number (≤ 2) of events except for *PALB2*; PV, pathogenic variant.

[a]ER status at initial breast cancer diagnosis.

[b]Cox proportional hazard regression model with death as competing risk adjusted for race/ethnicity, study, age, menopausal status, histology, ER status, and adjuvant endocrine therapy use at initial breast cancer diagnosis as applicable. Separate analysis was performed for each gene compared with noncarriers.

[c]Women in the comparison group (noncarriers) do not carry germline PVs in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2*.

[d]Excludes missense variants.

TABLE 3. CBC Risk Among PV Carriers by Menopausal Status at Initial Breast Cancer Diagnosis

Premenopausal

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*
Noncarriers[c]	3,775 (93.1)	251	—	—	2,775 (93.9)	147	—	—	781 (90.8)	74	—	—
ATM	38 (0.9)	3	1.1 (0.4 to 2.7)	.87	31 (1.0)	1	ND	ND	2 (0.2)	1	ND	ND
BRCA1	70 (1.7)	25	3.6 (2.5 to 5.2)	< .001	26 (0.9)	7	4.8 (2.6 to 8.7)	< .001	41 (4.8)	18	3.5 (2.1 to 5.8)	< .001
BRCA2	71 (1.8)	21	2.9 (1.8 to 4.8)	< .001	47 (1.6)	13	3.4 (1.8 to 6.6)	< .001	19 (2.2)	7	3.3 (1.6 to 6.6)	< .001
CHEK2												
All PVs[d]	62 (1.5)	7	2.0 (1.0 to 4.2)	.06	54 (1.8)	7	2.5 (1.2 to 5.4)	.01	4 (0.5)	0	ND	ND
c.1100delC	40 (1.0)	5	2.5 (1.1 to 5.5)	.02	35 (1.2)	5	3.2 (1.4 to 7.3)	.007	3 (0.3)	0	ND	ND
PALB2	36 (0.9)	4	1.6 (0.6 to 4.1)	.33	20 (0.7)	0	ND	ND	13 (1.5)	4	3.7 (1.5 to 9.0)	.003

Postmenopausal

Germline PV Carrier Status	Overall				ER-Positive[a]				ER-Negative[a]			
	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*	Total, No. (%)	CBC, No.	HR (95% CI)[b]	*P*
Noncarriers[c]	10,669 (96.6)	467	—	—	8,214 (97.2)	322	—	—	1,610 (93.5)	83		
ATM	78 (0.7)	4	1.3 (0.5 to 3.6)	.58	61 (0.7)	4	1.8 (0.7 to 4.8)	.25	12 (0.7)	0	ND	ND
BRCA1	62 (0.6)	6	1.6 (0.7 to 3.6)	.24	16 (0.2)	0	ND	ND	38 (2.2)	5	2.3 (0.9 to 5.6)	.07
BRCA2	99 (0.9)	11	3.0 (1.7 to 5.2)	< .001	58 (0.7)	5	2.7 (1.1 to 6.5)	.03	33 (1.9)	3	2.6 (0.9 to 7.7)	.09
CHEK2												
All PVs[d]	78 (0.7)	5	1.6 (0.7 to 3.9)	.24	67 (0.8)	4	1.5 (0.7 to 3.8)	.45	8 (0.5)	1	ND	ND
c.1100delC	52 (0.5)	2	ND	ND	44 (0.5)	2	ND	ND	6 (0.3)	0	ND	ND
PALB2	61 (0.6)	3	1.0 (0.3 to 3.3)	.95	34 (0.4)	1	ND	ND	20 (1.2)	2	2.2 (0.5 to 9.3)	.28

Abbreviations: CBC, contralateral breast cancer events; ER, estrogen receptor; HR, hazard ratio; ND, not estimated because of the low number (≤ 2) of events; PV, pathogenic variant.

[a]ER status at initial breast cancer diagnosis.

[b]Cox proportional hazard regression model with death as competing risk adjusted for race/ethnicity, study, age, histology, ER status, and adjuvant endocrine therapy use at initial breast cancer diagnosis as applicable. Separate analysis was performed for each gene compared with noncarriers.

[c]Women in the comparison group do not carry germline PVs in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2*.

[d]Excludes missense variants.

cumulative incidence of CBC among premenopausal women with PVs in *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* (ER-negative) was > 20% (Data Supplement).

DISCUSSION

In one of the largest prospective studies of CBC risk associated with germline PVs in predisposition genes, carriers of PVs in *BRCA1*, *BRCA2*, and *CHEK2* with breast cancer and carriers of *PALB2* PVs with ER-negative breast cancer were shown to be at increased risk of subsequent CBC, whereas carriers of *ATM* PVs did not have a statistically significantly elevated risk of CBC. The > 2-fold increased risk of CBC and the 15-year cumulative incidence of approximately 30% and 25% for CBC after an initial breast cancer diagnosis for *BRCA1* and *BRCA2* PV carriers, respectively, are consistent with previous studies.[6,27-31] Although previous studies focused predominantly on CBC risks in high-risk women qualifying for genetic testing on the basis of young age of breast cancer diagnosis or family history, the current study showed that CBC risk was significantly elevated even among *BRCA1* and *BRCA2* PV carriers with breast cancer in the general population. The median age at diagnosis of breast cancer and the annualized cumulative incidence of 0.4% per year for CBC among noncarriers in the study were consistent with other population-based studies from the United States,[1,2,32] suggesting that the present study closely mirrors women with breast cancer in the general population. The assessment of CBC using time-to-event analysis in prospective studies from the United States and the exclusion of women with synchronous bilateral breast cancer or those undergoing bilateral mastectomy at initial breast cancer diagnosis are significant strengths of this study that contribute to clinically relevant CBC risk estimation for each gene.

The association with increased risk of CBC in *CHEK2* PV carriers is consistent with previous studies[33-38] although the strength of association in previous studies was variable and several studies evaluated the c.1100delC variant only. In the current study, the c.1100delC variant was the most

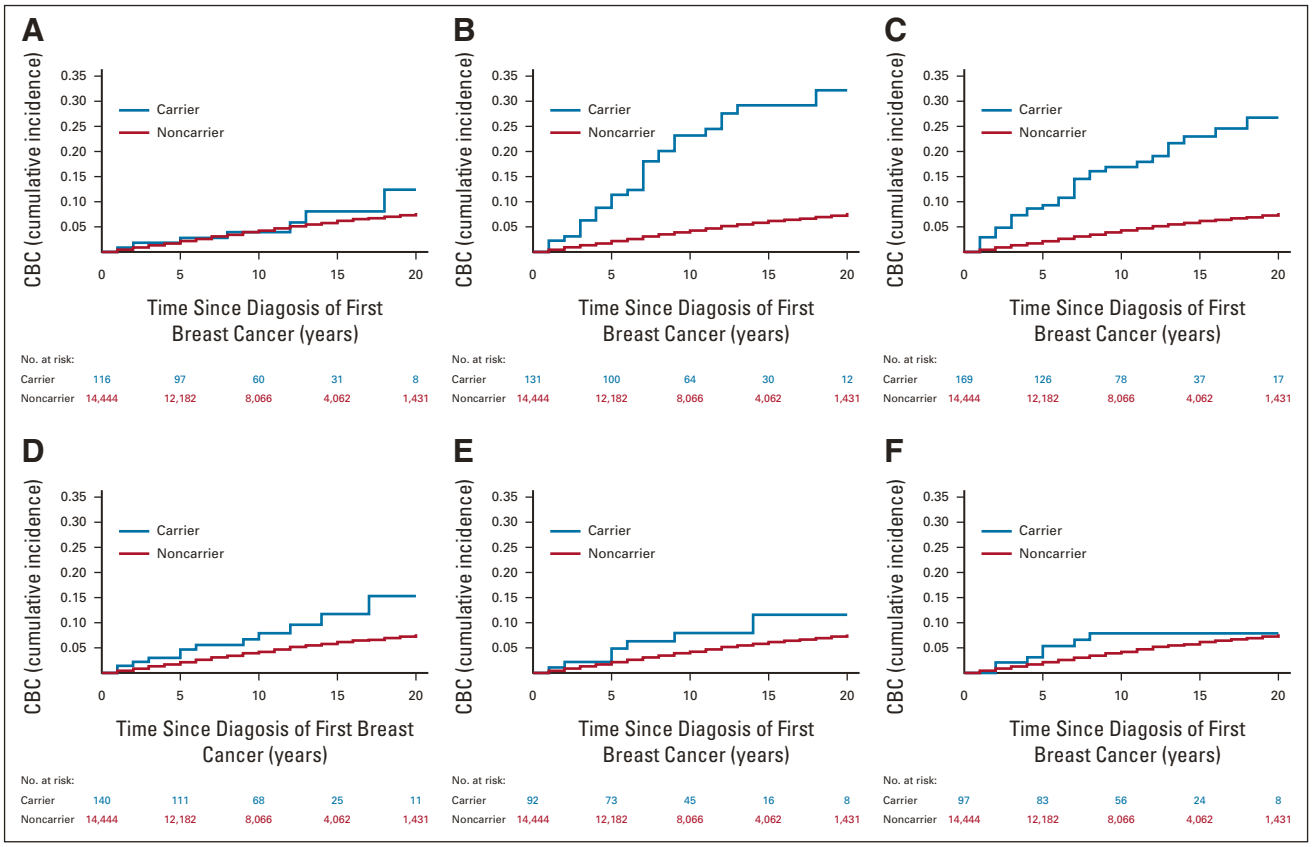

FIG 1. Cumulative incidence of CBC risk in PV carriers. Cumulative incidence plots for first contralateral breast cancers after primary breast cancer. Cumulative incidence is plotted against years since first breast cancer. Stepped plots for non-PV carriers (red), and carriers of variants are (A) *ATM*; (B) *BRCA1*; (C) *BRCA2*; (D) *CHEK2*, all pathogenic; (E) *CHEK2* c.1100delC; and (F) *PALB2*. Numbers of carriers and noncarriers at each time point are displayed below the individual graphs. CBC, contralateral breast cancer; PV, pathogenic variant.

commonly observed PV in *CHEK2* and was associated with an approximately two-fold increased risk of CBC, especially in women with ER-positive primary breast cancers. Inclusion of other truncating variants in *CHEK2* in the analysis resulted in a stronger association for CBC risk than with the c.1100delC variant alone, suggesting that all truncating variants in *CHEK2* likely contribute to CBC risk. However, addition of missense PVs to truncating variants led to attenuation of the CBC risk associated with *CHEK2*, which brings into question whether missense PVs in *CHEK2* contribute to CBC risk. Interestingly, the risk of CBC among African American *CHEK2* PV carriers appeared to be related primarily to truncating variants other than c.1100delC although the numbers of carriers and events were small in this subset. These findings are consistent with previous studies evaluating the risk of primary breast cancer among African American women with truncating variants in *CHEK2*.[10,20]

This study showed that ER status of the primary breast cancer provides important indications regarding the subsequent CBC risk for PV carriers, especially for women with *PALB2* PVs. Although *PALB2* PVs have been associated with increased risk of both primary ER-negative and ER-positive breast cancers,[7,8] the CBC events among *PALB2* PV carriers were almost exclusively among women with ER-negative disease. The etiology for these findings is unknown, but several possibilities including the effect of endocrine therapy on CBC risk and role of other genetic factors such as family history and polygenic risk scores need to be further evaluated in future studies to understand the differential effect of CBC risk by ER status in *PALB2* PV carriers.

Extrapolating from the current recommendations for women at high risk of primary breast cancer,[39,40] the > 20% 15-year cumulative incidence of CBC among premenopausal women with PVs in *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* offers support for clinical practice guidelines that advise aggressive surveillance for CBC with supplemental magnetic resonance imaging (MRI) in addition to mammograms. By contrast, the lack of association with significantly increased risk of CBC in postmenopausal PV carriers over age 65 years suggests that supplemental MRI for CBC may be of low yield and that CPM may not provide benefit in this subset. The current ASCO guideline on management of hereditary breast cancer already supports supplemental MRI screening for subsequent CBC risk among breast cancer survivors with PVs in high- or moderate-risk genes.[41] However, the findings of this study suggest that a more individualized

TABLE 4. Cumulative Incidence of Contralateral Breast Cancer by ER Status for PV Carriers

	5-Year Cumulative Incidence, % (95% CI)			10-Year Cumulative Incidence, % (95% CI)		
Germline PV Status	**Overall**	**ER+**	**ER–**	**Overall**	**ER+**	**ER–**
Overall						
Noncarriers	2.2 (2.0 to 2.4)	2.0 (1.7 to 2.3)	3.0 (2.3 to 3.8)	4.3 (3.9 to 4.6)	3.8 (3.5 to 4.2)	5.4 (4.5 to 6.5)
ATM	2.8 (0.9 to 8.5)	2.3 (0.6 to 9.3)	ND	4.0 (1.5 to 10.5)	3.9 (1.2 to 12.0)	ND
BRCA1	11.4 (6.9 to 18.7)	7.6 (2.5 to 23.0)	14.6 (8.4 to 25.3)	23.1 (16.4 to 32.6)	17.1 (8.1 to 36.2)	27.7 (18.7 to 41.0)
BRCA2	9.3 (5.7 to 15.1)	8.9 (4.8 to 16.7)	8.0 (3.1 to 20.7)	16.9 (11.8 to 24.3)	16.9 (10.5 to 27.1)	14.6 (7.3 to 29.3)
CHEK2	4.7 (2.1 to 10.3)	4.5 (1.9 to 10.7)	ND	7.9 (4.1 to 15.0)	8.2 (4.2 to 16.4)	ND
PALB2	5.4 (2.3 to 12.7)	1.9 (0.3 to 13.1)	12.3 (4.8 to 31.3)	7.9 (3.8 to 16.1)	1.9 (0.3 to 13.1)	19.7 (9.4 to 41.1)
Premenopausal						
Noncarriers	3.1 (2.6 to 3.8)	2.8 (2.2 to 3.5)	4.2 (3.0 to 5.9)	5.8 (5.0 to 6.6)	5.0 (4.2 to 6.0)	7.2 (5.5 to 9.4)
ATM	2.9 (0.4 to 20.3)	ND	ND	2.9 (0.4 to 20.3)	ND	ND
BRCA1	16.9 (9.8 to 29.2)	12.5 (4.2 to 36.9)	20.5 (10.9 to 38.4)	33.4 (23.1 to 48.2)	27.0 (13.3 to 54.8)	39.4 (25.8 to 60.3)
BRCA2	15.1 (8.5 to 26.9)	13.6 (6.4 to 28.9)	21.1 (8.6 to 51.6)	27.2 (18.0 to 41.1)	24.8 (14.3 to 43.2)	32.4 (16.3 to 64.1)
CHEK2	7.2 (2.8 to 18.8)	8.0 (3.1 to 20.8)	ND	13.2 (6.0 to 29.3)	14.9 (6.8 to 33.0)	ND
PALB2	5.8 (1.5 to 22.7)	ND	15.4 (4.1 to 58.1)	12.2 (4.8 to 31.1)	ND	35.5 (15.0 to 84.0)
Postmenopausal						
Noncarriers	1.8 (1.6 to 2.1)	1.7 (1.4 to 2.0)	2.4 (1.7 to 3.3)	3.7 (3.3 to 4.2)	3.5 (3.1 to 3.9)	4.4 (3.5 to 5.7)
ATM	2.7 (0.7 to 10.8)	3.5 (0.9 to 13.7)	ND	4.6 (1.5 to 14.1)	5.7 (1.9 to 17.6)	ND
BRCA1	5.2 (1.7 to 16.0)	ND	8.3 (2.8 to 24.9)	11.5 (5.3 to 24.7)	ND	15.1 (6.6 to 34.6)
BRCA2	5.3 (2.2 to 12.5)	5.3 (1.7 to 16.1)	ND	9.4 (4.8 to 18.4)	10.6 (4.5 to 25.1)	ND
CHEK2	2.8 (0.7 to 11.1)	1.8 (0.2 to 12.5)	ND	4.3 (1.4 to 13.3)	3.5 (0.9 to 14.0)	ND
PALB2	5.1 (1.7 to 15.6)	ND	ND	5.1 (1.7 to 15.6)	ND	ND

Abbreviations: ER, estrogen receptor; ND, not determined because of the low number (≤ 2) of events in the subset; PV, pathogenic variant.

approach to supplemental MRI screening in PV carriers on the basis of age and menopausal status at initial breast cancer diagnosis is warranted.

Since there are no well-established thresholds of CBC risk for recommending CPM, it is unclear whether premenopausal breast cancer survivors with PVs in *CHEK2* or *PALB2* can benefit from CPM despite the significantly elevated risk of CBC. Even for *BRCA1* or *BRCA2* PV carriers with breast cancer, the role of CPM in improving overall survival is controversial[42-46] although it is considered an acceptable option to reduce CBC risk.[41,47] Ultimately, the decision to undergo CPM for PV carriers should be individualized on the basis of estimation of the CBC risk considering several factors such as age at diagnosis, menopausal status, race/ethnicity, ER status of the initial breast cancer, cosmetic outcomes, and patient preference. The present study provides clinically valuable estimates of CBC risk in PV carriers on the basis of several of these factors, which will aid in decision making on CPM and surveillance strategies.

The lack of a statistically significant association with CBC risk for *ATM* PV carriers in the overall ER status and race analyses is consistent with recent studies.[48-50] However, these results should be interpreted with caution because the HRs for *ATM* PV carriers were > 1.5 in several subsets, including postmenopausal and NHW women with ER-positive breast cancer. By contrast, there were no CBC events among 16 African American *ATM* PV carriers. Overall, these findings argue against CPM for CBC risk reduction in *ATM* PV carriers and suggest that supplemental MRI for surveillance of CBC risk might play a limited role in specific subsets of *ATM* PV carriers.

To our knowledge, this is the largest study to prospectively evaluate the CBC risk in African American carriers of PVs in BC predisposition genes and establishes that African American women with PVs in *BRCA1*, *BRCA2*, *CHEK2*, or *PALB2* are at increased risk of CBC. However, the HRs for CBC associated with PVs in several genes appeared to be slightly higher among African American women compared with NHW, which may be due to younger age at breast cancer diagnosis and a higher proportion of premenopausal women among the African American cohort. On the basis of the results of this study, it appears that the surveillance and risk reduction strategies for CBC should be similar for NHW and African American PV carriers.

There are some limitations to this study. Despite being one of the largest studies of CBC in PV carriers, the numbers of PV carriers and events in some of the subset analyses were low, leading to wide confidence intervals for risk estimates.

Some of these exploratory subset analyses should be interpreted with caution because the small sample and larger well-powered studies are needed to confirm these findings. Similarly, although CBC risk in African American PV carriers was evaluated, it was not possible to estimate CBC risk among Hispanic and Asian women because of low numbers of PV carriers. Finally, the lack of comprehensive data on lifestyle factors, exposure to hormonal agents, and treatment-related variables, including chemotherapy, hormonal therapy, and radiation, is a limitation although it is unclear whether these would be significantly different in PV carriers compared with noncarriers.

In conclusion, germline *BRCA1*, *BRCA2*, and *CHEK2* PV carriers with breast cancer and *PALB2* PV carriers with ER-negative breast cancer are at significantly increased risk of CBC. Premenopausal PV carriers of these four genes are at a higher risk of CBC compared with postmenopausal carriers, whereas the CBC risk in PV carriers among women over age 65 years appears to be similar to noncarriers. Among African American women, the risk of CBC also appears to be elevated in *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* PV carriers. Germline PVs in *ATM* are not associated with a significantly increased risk of CBC in this study regardless of age at diagnosis, menopausal status, or race/ethnicity. This study provides clinically meaningful guidance for surveillance and risk reduction strategies for CBC risk among breast cancer survivors who are carriers of PVs in breast cancer predisposition genes.

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DISCLAIMER

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Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*

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