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Genetic Risk of Second Primary Cancer in Breast Cancer Survivors: The Multiethnic Cohort Study

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Abstract

Women who have had breast cancer in the past are at increased risk of developing a second primary cancer (SPC), including second primary breast cancer (SPBC) or a second primary non-breast cancer (SPNBC). In the Multiethnic Cohort (MEC) Study, we conducted a prospective cohort analysis in 3,223 female breast cancer survivors from five racial/ethnic populations (White, African American, Japanese American, Latino, and Native Hawaiian) to assess the association of rare pathogenic variants (PVs) in 37 known cancer predisposition genes with risk of SPC. A total of 719 (22.3%) women developed SPC, of which 323 (10.0%) were SPBC. Germline PVs in *BRCA1* (HR=2.28, 95% CI=1.11-4.65) and *ERCC2* (HR=3.51, 95% CI=1.29-9.54) were significantly enriched in women with SPC. In the subtype analysis for SPBC, a significant association of *ERCC2* PVs (HR=5.09, 95% CI=1.58-16.4) and a suggestive association of *BRCA2* PVs (HR=2.24, 95% CI= 0.91-5.55) were observed. There was also a higher risk of SPNBC in carriers of *BRCA1* PVs (HR=2.98, 95% CI=1.21-7.36). These results provide evidence that germline PVs in *BRCA1*, *BRCA2*, and *ERCC2* contribute to the development of SPC in breast cancer survivors. These findings also suggest that compromised DNA repair mechanisms could be a predisposition factor for SPC in breast cancer patients, supporting the need for closer monitoring of SPC in women carrying PVs in these genes.

Keywords

second primary cancer; breast cancer; multiethnic cohort; germline pathogenic variants

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Conflict of Interest Statement

The authors declare no competing interests.

INTRODUCTION

Women who have had breast cancer in the past are at increased risk of developing a second primary cancer (SPC), with contralateral breast cancer (CBC) being the most common secondary malignancy. Identifying risk factors for SPC is essential for cancer prevention efforts, especially with an increasing population of breast cancer survivors(1). Past epidemiological studies have identified several factors associated with the development of CBC or second primary breast cancer (SPBC) in breast cancer survivors. The risk of developing SPBC is significantly higher among women with younger age at initial diagnosis (<40 years)(2–6), a positive family history of breast cancer in first-degree relatives(6,7), and women with hormone receptor (HR) negative tumors(2,5,8–10). Women treated with radiotherapy have a 16-26% higher risk of developing a subsequent breast tumor than non-irradiated women(2,5,11). In contrast, hormonal therapy and chemotherapy were associated with a modest protective effect(2,7,12). SPBC is also found to be more common in African American breast cancer survivors compared to European Americans(2,4–6,8).

Genetic predisposition, notably pathogenic variants (PVs) in *BRCA1* or *BRCA2* susceptibility genes, contributes to the risk of SPBC. A meta-analysis of 20 cohort studies reported that the 5-year cumulative risk of SPBC in women carrying *BRCA1* and *BRCA2* PVs was approximately 5-fold and 3-fold, respectively, as in non-BRCA carriers(13). Furthermore, the increased risk of SPBC was much greater in *BRCA1/2* carriers with an initial breast cancer diagnosis before age 40(14). In addition to *BRCA1* and *BRCA2*, a recent targeted sequencing study including 75,550 women with unilateral breast cancer and 7,728 women with SPBC also reported significant associations with PVs in *CHEK2*, *PALB2*, and *TP53* in European American and African American women. These associations were non-significant or not tested in Latino or Asian Americans, due to the low prevalence of the PVs in these two ethnic groups(15).

In addition to SPBC, breast cancer survivors have been reported to have a significantly elevated risk for subsequent cancers of the thyroid(16–19), uterine corpus(16,19–21), ovary(16,19,20), esophagus, stomach, colon, lung, melanoma of the skin, sarcoma, and acute myeloid leukemia (AML)(16). Second primary non-breast cancers (SPNBC) have been associated with older age at initial breast cancer diagnosis (17,19,20,22–24) as well as radiotherapy treatment (24–27). There is also a small increased risk of developing AML, melanoma, and uterine cancer after receiving chemotherapy. Hormonal treatment with tamoxifen is known to increase the risk for uterine cancer(24).

Little is known regarding the genetic risk of developing a non-breast SPC among breast cancer survivors. The familial clustering of multiple primary cancers involving breast, ovary, and uterine corpus, the increased risk of thyroid cancer and melanoma after breast cancer, as well as the reciprocally elevated risk of breast cancer after these tumors, all suggest shared genetic etiology. In 3,223 female breast cancer survivors from the Multiethnic Cohort (MEC) Study, we conducted a prospective analysis to test the hypothesis that known cancer predisposition genes may play a role in the development of SPC in breast cancer survivors.

MATERIALS AND METHODS

Study Population

The MEC is an ongoing prospective cohort study designed to examine the association of lifestyle and genetic factors with the incidence of cancer. The design and establishment of the MEC in 1993-1996 has been described elsewhere(28). Incident cases of breast cancer were identified through a linkage of MEC participants to the SEER tumor registries in Hawaii and California. The linkage also provided clinical information on tumor stage, grade, hormone receptor status, and first course of treatment. The University of Hawaii and the University of Southern California institutional review boards approved the study protocol, and all participants provided written informed consent in accordance with the principles outlined in the Declaration of Helsinki.

Previously, a nested case-control study of 3,641 female breast cancer patients and 3,689 unaffected women from the MEC was included in the CAnceR RIsk Estimates Related to Susceptibility (CARRIERS) Consortium for targeted sequencing(29–31). The CARRIERS study was approved by the institutional review board at the Mayo Clinic. From this targeted sequencing study population, the current analysis included 3,223 women with invasive breast cancer during follow-up (December 31, 2017), excluding women with any in-situ cancer (N = 297) or women who had any cancer diagnosed before cohort entry (N = 372). According to the SEER Breast Multiple Primary and Histology Coding Rules(32), 719 (22.3%) women had later developed SPC. Based on the first cancer diagnosis following breast cancer, 323 cases (10.0%) were SPBC and 396 (12.3%) were SPNBC.

Targeted Sequencing and Pathogenic Variants

Germline DNA from these 3,223 breast cancer patients was isolated from peripheral blood (89.4%), mouthwash (4.7%), or saliva (5.9%) samples using QIAGEN DNA extraction kits. Along with the remaining CARRIERS study samples, the MEC DNA samples were analyzed using a custom amplicon-based QIAseq panel (Qiagen, Hilden, Germany) covering all coding regions and consensus splice sites from 37 cancer predisposition genes, as described previously(29,31). High-quality sequence data (read depth of > 20 times) were obtained for 99.3% of the targeted regions. From the variants with a minor allele frequency less than 0.01 in breast cancer patients, all loss-of-function variants (nonsense, frameshift, consensus splice sites) or intronic and missense variants identified as “pathogenic” or “likely pathogenic” in the ClinVar database were classified as pathogenic variants (PVs)(29). We restricted germline PVs to those with an alternate allele fraction (AAF) between 0.30 and 0.70 to exclude suspected mosaic somatic variants derived from the expansion of clonal populations of blood cells. Based on the existing evidence on breast cancer susceptibility, the genes included in the custom panel were categorized as established breast cancer predisposition genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, and *TP53*), candidate breast cancer predisposition genes (*BLM*, *BRIP1*, *CDKN2A*, *ERCC3*, *FANCC*, *FANCM*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *NCN*, *RAD50*, *RECQL*, *RINT1*, *SLX4*, and *XRCC2*) and other cancer predisposition genes (*APC*, *EPCAM*, *ERCC2*, *KRAS*, *MEN1*, *MUTYH*, *PMS2*, *PPM1D*, and *PRSS1*).

Statistical Analysis.

In this prospective cohort analysis, we assessed the association of known cancer predisposition genes with the incidence of SPC (N = 719), and subsequently with SPBC (N = 323) or SPNBC (N = 396). The subtype analysis in SPNBC excluded women with SPBC and vice versa. In addition, 33 women who had undergone a bilateral mastectomy were further excluded from the analysis of SPBC. Women who harbored any PV in each of the sequenced genes were considered carriers. The single gene association test was performed comparing carriers to non-carriers. Our ability to estimate the relative risks for individual genes was limited to 11 genes with at least five carriers observed in all women and at least one carrier in women with and without SPC (*ATM, BRCA1, BRCA2, CHEK2, PALB2, BLM, BRIP1, ERCC3, FANCC, ERCC2,* and *MUTYH*). In all analyses, women contributed person-time at risk from the diagnosis date of the initial breast tumor until the diagnosis date of the second primary cancer of interest, death, or end of follow-up (December 31, 2017). The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models with age as the time metric. The proportionality assumption was tested by Schoenfeld residuals and found to be met. To control for potential confounders, all regression models were adjusted for age at 1st breast tumor diagnosis, race/ethnicity (White, African American, Japanese American, Latino, and Native Hawaiian), family history of breast cancer in first-degree relatives (positive vs. negative), SEER summary stage of the 1st breast tumor (localized, regional, and distant), estrogen receptor (ER) status (positive vs. negative) and progesterone receptor (PR) status (positive vs. negative) of the 1st breast tumor. First-course of radiotherapy (administered vs. not administered) was also included in the final model on SPBC. These variables were included because they were potential confounders ($P < 0.05$ in univariate analysis) or because they are established or suspected risk factors for the specific SPC phenotype. Missing values were included as an “unknown” category so that all observations could be included in the analyses. We also performed sensitivity analyses that (1) estimated the p values from the Cox proportional hazard models using a saddlepoint approximation to account for the small number of carriers(33), (2) imputed the missing values of covariates with the ethnic-specific expected values (imputation method), and (3) used multi-state models to model a third primary cancer (N = 96) as a subsequent event following the diagnosis of a SPC while accounting for competing risk of death. All statistical analyses were performed with R v.3.6(34). P values less than 0.05 were considered statistically significant. Tests of statistical significance were two-sided.

We performed gene set analysis to assess whether being a carrier of any gene in the gene set was associated with the risk of SPC. Gene sets were determined either by prior evidence of these genes with breast cancer (12 established breast cancer genes, 16 candidate breast cancer genes, and 9 other cancer predisposition genes) or by DNA repair pathways. We tested six DNA repair pathways including 25 DNA repair genes (DRGs) involved in base excision repair (BER; *MUTYH*), nucleotide excision repair (NER; *ERCC3, ERCC2*), double-strand break repair via homologous recombination (HR; *ATM*, *BLM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *MRE11A*, *PALB2*, *RAD50*, *RAD51C*, *RAD51D*, *RECQL*, *SLX4, XRCC2*), mismatch repair (MMR; *MLH1*, *MSH2*, *MSH6*, *PMS2*), Fanconi Anemia (FA; *BRCA1*, *BRCA2*, *BRIP1*, *FANCC*, *FANCM*, *PALB2*, *RAD51C*, *SLX4*), and other related genes (*CHEK2, TP53*)(35,36). We performed additional analysis on DNA repair pathways,

excluding genes that were associated with SPC in our single-gene association analysis (P < 0.10). All variables adjusted in the single gene regression models were also included in the gene set tests.

Data Availability

The data analyzed in this study are publicly available in Database of Genotypes and Phenotypes (dbGaP) at phs002820.v1.

RESULTS

Patient demographics and clinical characteristics

The overall study cohort included 3,223 females with incident breast cancer, of which 719 SPC cases were identified during an average follow-up time of 11.2 years (up to 24.7 years), including 323 SPBC cases and 396 SPNBC cases (Table 1, Supplementary Figure 1). On average, women with SPC, SPBC, or SPNBC were first diagnosed with breast cancer at age of 66.5, 65.5, and 67.3, respectively, in comparison to 68.1 for women with primary breast cancer (PBC) only, but these differences were not statistically significant. Among the 323 women with SPBC, 253 (78.3%) had two breast cancer diagnoses more than 6 months apart, 60 (18.6%) had synchronous bilateral breast cancer, and the remaining 10 SPBC cases had two breast tumors of different histological subtypes diagnosed within 6 months. With the adjustment for the other covariates, women with a positive family history of breast cancer in first-degree relatives were more likely to be diagnosed with SPC (HR = 1.30, 95% CI = 1.07-1.56, P = 0.007; Supplementary Table 1) with the association being slightly stronger for SPBC (HR = 1.42, 95%CI = 1.08-1.88, P = 0.01) than for SPNBC (HR = 1.28, 95% CI = 0.99-1.64, P = 0.06). Compared to White women, Latinas had a substantially lower risk of SPC, SPBC, or SPNBC (HR of 0.59-0.75, P of 0.002-0.06), and Japanese American women were less likely to be diagnosed with SPC and SPNBC (HR of 0.65-0.76, P of 0.002-0.006). The risks of SPC, SPBC, or SPNBC were not statistically different between African American women and White women. Although we observed no significant relationship between hormone receptor status and SPC, positive PR status of the 1st breast cancer was marginally associated with a lower risk of SPNBC (HR = 0.74, 95% CI = 0.55-1.00, P = 0.05; Supplementary Table 1). We also found a significant inverse association of first-course radiotherapy with SPBC (HR = 0.78, 95% CI = 0.62-0.99, P = 0.04).

Association of PVs in cancer predisposition genes with SPC

We were able to test for association with 11 genes that had at least five carriers in all women and at least one carrier in women with and without SPC (Table 2). *BRCA2* was the most frequently affected gene, with 20 of 3,233 (0.62%) breast cancer patients harboring a germline PV, followed by *PALB2* (16 carriers, 0.50%), *BRCA1* (14 carriers, 0.43%), and *ATM* (14 carriers, 0.43%, Supplementary Figure 2, Supplementary Table 2). Two genes were significantly associated with SPC: *BRCA1* (HR = 2.28, 95% CI = 1.11-4.65, P = 0.024) and *ERCC2* (HR = 3.51, 95% CI = 1.29-9.54, P = 0.014), after controlling for potential confounders. We observed a significant association of *ERCC2* (HR = 5.09, 95% CI = 1.58-16.4, P = 0.007) and a suggestive association of *BRCA2* (HR = 2.24, 95% CI

= 0.91-5.55, P = 0.08) with SPBC. The association of *BRCA1* remained significant in the analysis of SPNBC (HR = 2.98, 95% CI = 1.21-7.36, P = 0.02), and a similar suggestive association was also found for SPBC (HR = 2.64, 95% CI = 0.82-8.43, P = 0.10). There were no appreciable differences in the results from the sensitivity analyses (Supplementary Table 3).

Associations of PVs in gene sets with SPC

In the gene set analysis, we observed a higher risk of SPC among women carrying a PV in any of the 37 genes (HR = 1.44, 95% CI = 1.07-1.94, P = 0.02) as well as in carriers of the nine other cancer predisposition genes (HR = 2.08, 95% CI = 1.14-3.79, P = 0.02; Table 3). Women carrying a PV in any DRG had a significantly higher risk of SPC (HR = 1.40, 95% CI = 1.02-1.92, P = 0.04), especially among carriers of genes of the MMR pathway (HR = 4.03, 95% CI = 1.23-13.20, P = 0.02) and NER pathway (HR = 2.57, 95% CI = 1.06-6.27, P = 0.04). Carriers of other DNA repair related genes (i.e. *CHEK2* and *TP53*) were suggested to have a 2.73-fold risk of SPC (95% CI = 0.99-7.50, P = 0.05).

Carrying a PV in any of the 37 cancer predisposition genes was significantly associated with a higher risk of SPBC (HR = 1.56, 95% CI = 1.01-2.40, P = 0.045). The risk of SPBC was not statistically different between carriers and non-carriers of PVs in established or candidate breast cancer genes, or PVs in other cancer predisposition genes (Table 3). Women carrying a PV in any DRG had a 1.60-fold risk of SPBC (95% CI = 1.02-2.51, P = 0.04). A positive association with SPBC was also suggested for carriers of genes in the FA pathway (HR = 1.76, 95% CI = 1.00-3.12, P = 0.05) and NER pathway (HR = 3.04, 95% CI = 0.96-9.69, P = 0.06). These associations appeared to be largely driven by *BRCA1, BRCA2,* or *ERCC2* gene (Supplementary Table 4).

Among the 396 women with SPNBC, the top commonly diagnosed cancer sites included uterine corpus (16.4%), lung (14.9%), colon/rectum (14.8%), leukemia (8.1%), pancreas (6.8%), and melanoma (6.8%). There was a suggestive association with SPNBC for carrying a PV in any of the 37 genes (HR = 1.44, 95% CI = 0.96-2.15, P = 0.08). The risk of SPNBC was similar between non-carriers and carriers of the established or candidate breast cancer genes (Table 3). Carriers of PVs in other cancer predisposition genes had a significantly elevated risk of SPNBC (HR = 2.43, 95% CI = 1.14-5.17, P = 0.02) than non-carriers. Although the association of PVs in all DRGs was not statistically significant, carrying a PV in genes involved in the MMR pathway (HR = 4.99, 95% CI = 1.17-21.38, P = 0.03) and in other related genes (HR = 3.55, 95% CI = 1.10-11.46, P = 0.03) was associated with a higher risk of SPNBC.

DISCUSSION

In this multiethnic cohort of breast cancer patients, we identified three genes, *BRCA1*, *BRCA2*, and *ERCC2,* in which germline PVs were associated with an increased risk of SPC in breast cancer survivors. In the analysis by SPC subtypes, *BRCA2* and *ERCC2* were the most associated genes with risk of SPBC while for SPNBC, the strongest association was observed with *BRCA1*. Our gene set analyses also found that the MMR genes and other DNA repair related genes were strongly associated with risk of SPNBC. In general, women

carrying a PV in any of these 37 cancer predisposition genes were 44% to 56% more likely to be diagnosed with SPC.

Both *BRCA1* and *BRCA2* are known to contribute to the risk of subsequent breast malignancies among breast cancer survivors. In a nested case-control study of 705 patients with contralateral breast cancer and 1,398 patients with unilateral breast cancer, all of whom had their 1st breast cancer diagnosed before age 55, the risk of contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers was 4.5-fold and 3.4-fold, respectively, in comparison to non-BRCA carriers(37). In a large multiethnic targeted sequencing study comprised of 75,550 women with PBC and 7,728 with SPBC, PVs in *BRCA1* and *BRCA2* were found to be significantly associated with SPBC in White, African American and Hispanic women with the odds ratios (ORs) estimated to range from 1.3 to 2.2(15). Although in our study the association of *BRCA1* and *BRCA2* with SPBC was suggestive due to the small number of SPBC patients, they were similar in magnitude to these published studies.

We found strong and statistically significant associations of germline PVs in the *ERCC2* gene with SPC and SPBC. Like *BRCA1* and *BRCA2* genes, *ERCC2* is also involved in DNA damage repair, though via nucleotide excision repair processes rather than homologous recombination. Deleterious autosomal recessive variants in the *ERCC2* gene cause a cancer-prone syndrome, xeroderma pigmentosum (XP) complementation group D (XPD). Most individuals with XP develop multiple skin cancers during their lifetime(38). Although the association between heterozygous germline PVs in XP-related genes and cancer risk is less clear, genetic studies suggest that the two common *ERCC2* polymorphisms (Asp312Asn and Lys751Gln) might contribute to the susceptibility of bladder cancer(39), lung cancer(40,41), and gastric cancer(41,42), and studies on the association with breast cancer risk have reported conflicting findings(41,43). These *ERCC2* polymorphisms have been previously implicated in the development of SPC. The *ERCC2* Asp312Asn variant was found to be associated with the risk of developing second primary esophageal carcinoma in long-term cancer survivors who received radio-chemotherapy for a prior lymphoma or breast cancer(44). In a cohort study of 481 patients with non-melanoma skin cancer, carriers of the *ERCC2* Lys751Gln variant were at an increased risk of SPC, with breast cancer being the 3rd most common SPC observed(45). Because the *ERCC2* gene was generally not considered a breast cancer predisposition gene, rare germline PVs in *ERCC2* had not been previously examined for association with SPC in breast cancer survivors. Consistent with results from the overall CARRIERS study, in an analysis of breast cancer cases and cancer-free controls from the MEC, germline *ERCC2* PVs were not associated with primary breast cancer risk (Supplementary Table 5). Results from this cohort analysis on SPC phenotypes provide initial evidence that women carrying heterozygous germline PVs in *ERCC2* genes have a higher risk of developing a second malignancy, especially an SPBC, after their initial breast cancer diagnosis.

Inherited alterations in genes involved in DNA damage recognition and repair have been linked to a variety of cancer predisposition syndromes, where affected individuals are at risk of developing multiple primary tumors over time(46). Previously, PVs in DRGs were found to be associated with subsequent neoplasms in 4,402 survivors of childhood cancer (35).

Specifically, PVs in HR or FA genes were significantly associated with an increased risk of subsequent female breast cancer and sarcoma, while PVs in NER genes were positively associated with subsequent thyroid cancer. These observed associations appeared to be stronger among patients who received a higher cumulative dosage of chemotherapy or body region-specific radiotherapy. Consistent with these findings, our results further support the contribution of DRGs in the development of multiple primary cancers.

Our study has several strengths and limitations. The MEC is a population-based cohort. The breast cancer cases included in this study represent approximately 70% of all incident invasive breast cancer cases in the MEC identified through 31 December 2017, with similar demographic and clinical characteristics, suggesting that our findings may be broadly generalizable(47). Our study is one of the first multiethnic studies of SPC phenotypes in breast cancer survivors. However, the relatively small numbers in each race/ethnicity group limited our statistical power to perform ethnic-specific analysis. Due to the high number of missing values of hormone receptor status, we were unable to adjust for specific tumor subtypes such as triple-negative or HER2-positive tumors. Finally, although we included first-course chemo/radiation/hormonal treatment from the SEER registry in our analysis, the lack of detailed information on subsequent breast cancer treatments prevented us from fully assessing treatment effects and their potential interactions with PVs on SPC phenotypes.

Results from our analysis provide further evidence that germline PVs in *BRCA1* and *BRCA2* genes contribute to the development of SPC in breast cancer survivors, and add *ERCC2* to the list of non-*BRCA1/2* genes associated with SPC. These results also suggest that compromised DNA repair mechanisms could be a predisposition factor for the risk of second malignancies in breast cancer survivors, or more broadly in populations of any cancer survivors. Our findings provide further support for closer monitoring of SPC for women carrying PVs in these genes. The suggestive associations that we observed with SPC phenotypes for other genes (e.g. *CHEK2*, *BLM*, *PRSS1*) and DNA repair pathways (e.g. MMR pathway) require investigation in larger studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance

This multiethnic study links germline pathogenic variants in *BRCA1*, *BRCA2*, and *ERCC2* to the development of second primary cancer in breast cancer survivors, providing biological insights and biomarkers to guide patient monitoring.

Table 1

Demographic and clinical characteristics of study population (N = 3,223)

Characteristics	Overall[1] N = 3,223	PBC N = 2,504	SPC[1] N = 719	SPBC N = 323	SPNBC N = 396
Race/Ethnicity					
White	755 (23.4)	563 (22.5)	192 (26.7)	79 (24.5)	113 (28.5)
African American	600 (18.6)	466 (18.6)	134 (18.6)	60 (18.6)	74 (18.7)
Native Hawaiian	268 (8.3)	197 (7.9)	71 (9.9)	38 (11.8)	33 (8.3)
Japanese American	992 (30.8)	786 (31.4)	206 (28.7)	102 (31.6)	104 (26.3)
Latino	608 (18.9)	492 (19.6)	116 (16.1)	44 (13.6)	72 (18.2)
Age at cohort entry, mean (sd)	59.4 (8.2)	59.3 (8.3)	59.8 (8.0)	58.8 (8.0)	60.7 (7.8)
Age at 1st BC diagnosis					
Mean (sd)	67.7 (9.0)	68.1 (9.1)	66.5 (8.7)	65.5 (9.1)	67.3 (8.2)
45-60	690 (21.4)	513 (20.5)	177 (24.6)	100 (31.0)	77 (19.4)
60-70	1184 (36.7)	910 (36.3)	274 (38.1)	110 (34.1)	164 (41.4)
70-80	1077 (33.4)	842 (33.6)	235 (32.7)	100 (31.0)	135 (34.1)
80+	272 (8.4)	239 (9.5)	33 (4.6)	13 (4.0)	20 (5.1)
First-degree family history of BC					
Negative	2571 (79.8)	2023 (80.8)	548 (76.2)	240 (74.3)	308 (77.8)
Positive	505 (15.7)	366 (14.6)	139 (19.3)	63 (19.5)	76 (19.2)
Missing	147 (4.6)	115 (4.6)	32 (4.5)	20 (6.2)	12 (3.0)
Tumor stage of 1st BC					
Localized	2318 (71.9)	1784 (71.2)	534 (74.3)	242 (74.9)	292 (73.7)
Regional	786 (24.4)	615 (24.6)	171 (23.8)	74 (22.9)	97 (24.5)
Distant	55 (1.7)	47 (1.9)	8 (1.1)	5 (1.5)	3 (0.8)
Missing	64 (2.0)	58 (2.3)	6 (0.8)	2 (0.6)	4 (1.0)
Estrogen receptor (ER) status of 1st BC					
Negative	538 (16.7)	420 (16.8)	118 (16.4)	55 (17.0)	63 (15.9)
Positive	2333 (72.4)	1831 (73.1)	502 (69.8)	222 (68.7)	280 (70.7)
Missing	352 (10.9)	253 (10.1)	99 (13.8)	46 (14.3)	53 (13.4)
Progesterone receptor (PR) status of 1st BC					
Negative	801 (24.9)	621 (24.8)	180 (25.0)	77 (23.8)	103 (26.0)
Positive	1935 (60.0)	1526 (60.9)	409 (56.9)	186 (57.6)	223 (56.3)
Missing	487 (15.1)	357 (14.3)	130 (18.1)	60 (18.6)	70 (17.7)
Radiation Treatment of 1st BC[2]					
Not administered	1523 (47.3)	1185 (47.3)	338 (47.0)	163 (50.5)	175 (44.2)
Administered	1655 (51.3)	1281 (51.2)	374 (52.0)	156 (48.3)	218 (55.1)
Missing	45 (1.4)	38 (1.5)	7 (1.0)	4 (1.2)	3 (0.8)
Chemotherapy of 1st BC[2]					
Not administered	2249 (69.8)	1751 (69.9)	498 (69.3)	218 (67.5)	280 (70.7)
Administered	899 (27.9)	692 (27.6)	207 (28.8)	100 (31.0)	107 (27.0)

Characteristics	Overall[1] N = 3,223	PBC N = 2,504	SPC[1] N = 719	SPBC N = 323	SPNBC N = 396
Missing	75 (2.3)	61 (2.4)	14 (1.9)	5 (1.5)	9 (2.3)
Hormonal Therapy of 1st BC[2]					
Not administered	1675 (52.0)	1291 (51.6)	384 (53.4)	181 (56.0)	203 (51.3)
Administered	1452 (45.1)	1138 (45.4)	314 (43.7)	133 (41.2)	181 (45.7)
Missing	96 (3.0)	75 (3.0)	21 (2.9)	9 (2.8)	12 (3.0)

Abbreviation: BC, breast cancer; PBC, primary breast cancer; SPC, second primary cancer; SPBC, second primary breast cancer; SPNBC, second primary non-breast cancer.

[1]The first primary breast cancer was diagnosed between 1993 and 2016 and the second primary cancer was diagnosed between 1994-2017.

[2]First-course treatment from SEER cancer registry.

Table 2

Association of germline PVs in cancer predisposition genes with SPC, SPBC or SPNBC

	PBC	SPC			SPBC[2]			SPNBC		
Gene[1]	Carriers (%)	Carriers (%)	HR (95% CI)[3]	P	Carriers (%)	HR (95% CI)[3]	P	Carriers (%)	HR (95% CI)[3]	P
Established Breast Cancer Predisposition Gene										
ATM	10 (0.40)	4 (0.56)	1.48 (0.55 - 3.98)	0.44	1 (0.31)	0.85 (0.12 - 6.29)	0.88	3 (0.76)	1.91 (0.61 - 6.00)	0.27
BARD1	2 (0.08)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
BRCA1	6 (0.24)	8 (1.11)	2.28 (1.11 - 4.65)	0.024	3 (0.93)	2.64 (0.82 - 8.43)	0.10	5 (1.26)	2.98 (1.21 - 7.36)	0.018
BRCA2	15 (0.60)	5 (0.70)	1.18 (0.49 - 2.88)	0.71	5 (1.55)	2.24 (0.91 - 5.55)	0.08	0 (0.00)	-	-
CDH1	0 (0.00)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
CHEK2	3 (0.12)	3 (0.42)	2.03 (0.64 - 6.46)	0.23	1 (0.31)	1.81 (0.24 - 13.55)	0.56	2 (0.51)	2.32 (0.56 - 9.60)	0.25
NF1	2 (0.08)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
PALB2	12 (0.48)	4 (0.56)	0.89 (0.33 - 2.40)	0.82	2 (0.62)	0.96 (0.24 - 3.94)	0.96	2 (0.51)	0.95 (0.23 - 3.87)	0.95
PTEN	0 (0.00)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
RAD51C	5 (0.20)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
RAD51D	2 (0.08)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
TP53	0 (0.00)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
Candidate Breast Cancer Predisposition Gene										
BLM	4 (0.16)	2 (0.28)	2.50 (0.61 - 10.18)	0.20	1 (0.31)	4.12 (0.55 - 30.92)	0.17	1 (0.25)	2.74 (0.38 - 19.79)	0.32
BRIP1	4 (0.16)	1 (0.14)	1.02 (0.14 - 7.34)	0.98	1 (0.31)	1.99 (0.27 - 14.40)	0.50	0 (0.00)	-	-
CDKN2A	1 (0.04)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
ERCC3	4 (0.16)	1 (0.14)	1.24 (0.17 - 8.90)	0.83	0 (0.00)	-	-	1 (0.25)	2.21 (0.31 - 16.07)	0.43
FANCC	5 (0.20)	2 (0.28)	1.28 (0.32 - 5.16)	0.73	1 (0.31)	1.32 (0.18 - 9.52)	0.78	1 (0.25)	1.07 (0.15 - 7.66)	0.95
FANCM	2 (0.08)	1 (0.14)	-	-	1 (0.31)	-	-	0 (0.00)	-	-
MLH1	0 (0.00)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
MRE11A	1 (0.04)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
MSH2	0 (0.00)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
MSH6	0 (0.00)	1 (0.14)	-	-	1 (0.31)	-	-	0 (0.00)	-	-
NBN	3 (0.12)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-

	PBC	SPC			SPBC[2]			SPNBC		
Gene[1]	**Carriers (%)**	**Carriers (%)**	**HR (95% CI)[3]**	**P**	**Carriers (%)**	**HR (95% CI)[3]**	**P**	**Carriers (%)**	**HR (95% CI)[3]**	**P**
RAD50	3 (0.12)	1 (0.14)	-	-	1 (0.31)	-	-	0 (0.00)	-	-
RECQL	3 (0.12)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
RINT1	3 (0.12)	1 (0.14)	-	-	1 (0.31)	-	-	0 (0.00)	-	-
SLX4	2 (0.08)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
XRCC2	5 (0.20)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
Other Cancer Predisposition Gene										
APC	0 (0.00)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
EPCAM	0 (0.00)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
ERCC2	2 (0.08)	4 (0.56)	3.51 (1.29 - 9.54)	0.014	3 (0.93)	5.09 (1.58 - 16.41)	0.007	1 (0.25)	2.00 (0.27 - 14.59)	0.49
KRAS	0 (0.00)	0 (0.00)	-	-	0 (0.00)	-	-	0 (0.00)	-	-
MEN1	0 (0.00)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
MUTYH	5 (0.20)	1 (0.14)	0.51 (0.07 - 3.65)	0.50	0 (0.00)	-	-	1 (0.25)	0.88 (0.12 - 6.30)	0.90
PMS2	3 (0.12)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-
PPM1D	1 (0.04)	2 (0.28)	-	-	1 (0.31)	-	-	1 (0.25)	-	-
PRSS1	2 (0.08)	1 (0.14)	-	-	0 (0.00)	-	-	1 (0.25)	-	-

[1]The association analysis was limited to 11 genes with at least five carriers in all women and at least one carrier in women with and without the event of interest.

[2]A total of 33 women with bilateral mastectomy were further excluded in the analysis of SPBC.

[3]Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from Cox proportional hazard models adjusting for age at initial breast cancer diagnosis, race/ethnicity, first-degree family history of breast cancer, SEER summary stage, ER status and PR stats of 1st breast tumor. Further adjustment on radiotherapy was included in the analysis of SPBC.

Table 3

Gene set associations with SPC, SPBC or SPNBC

Gene Set (no. genes)	PBC No. Carriers (%)	SPC No. Carriers (%)	HR (95% CI)	P
		SPC		
All cancer genes (37)	110 (4.39)	49 (6.82)	1.44 (1.07 - 1.94)	0.01
BC susceptibility genes (28)[1]	97 (3.87)	38 (5.29)	1.31 (0.94 - 1.82)	0.11
Established BC genes (12)	57 (2.28)	26 (3.62)	1.40 (0.93 - 2.09)	0.10
Candidate BC genes (16)	40 (1.60)	12 (1.67)	1.14 (0.64 - 2.02)	0.66
Other cancer genes (9)[1]	13 (0.52)	11 (1.53)	2.08 (1.14 - 3.79)	0.02
DNA repair genes (25)[2]	98 (3.91)	42 (5.84)	1.40 (1.02 - 1.92)	0.04
HR pathway (14)	74 (2.96)	26 (3.62)	1.18 (0.79 - 1.76)	0.42
FA pathway (8)	51 (2.04)	21 (2.92)	1.26 (0.81 - 1.97)	0.30
MMR pathway (4)	3 (0.12)	3 (0.42)	4.03 (1.23 - 13.20)	0.02
NER pathway (2)	6 (0.24)	5 (0.70)	2.57 (1.06 - 6.27)	0.04
BER pathway (1)	5 (0.20)	1 (0.14)	0.51 (0.07 - 3.65)	0.50
Other related genes (2)	3 (0.12)	4 (0.56)	2.73 (0.99 - 7.50)	0.05
		SPBC[3]		
All Cancer Genes (37)	108 (4.37)	23 (7.12)	1.56 (1.01-2.40)	0.045
BC susceptibility genes (28)[1]	95 (3.84)	19 (5.88)	1.47 (0.92 - 2.37)	0.11
Established BC genes (12)	56 (2.27)	12 (3.72)	1.46 (0.81 - 2.65)	0.21
Candidate BC genes (16)	39 (1.58)	7 (2.17)	1.46 (0.69 - 3.11)	0.33
Other cancer genes (9)[1]	13 (0.53)	4 (1.24)	1.95 (0.72 - 5.28)	0.19
DNA repair genes (25)[2]	96 (3.89)	21 (6.50)	1.60 (1.02 - 2.51)	0.04
HR pathway (14)	72 (2.91)	14 (4.33)	1.45 (0.84 - 2.50)	0.19
FA pathway (8)	50 (2.02)	13 (4.02)	1.76 (1.00 - 3.12)	0.05
MMR pathway (4)	3 (0.12)	1 (0.31)	3.43 (0.43 - 27.20)	0.24
NER pathway (2)	6 (0.24)	3 (0.93)	3.04 (0.96 - 9.69)	0.06
BER pathway (1)	5 (0.20)	0 (0.00)	--	--
Other related genes (2)	3 (0.12)	1 (0.31)	1.81 (0.24 - 13.55)	0.56
		SPNBC		
All cancer genes (37)	110 (4.39)	26 (6.57)	1.44 (0.96 - 2.15)	0.08
BC susceptibility genes (28)[1]	97 (3.87)	19 (4.80)	1.23 (0.77 - 1.97)	0.38
Established BC genes (12)	57 (2.28)	14 (3.54)	1.44 (0.84 - 2.49)	0.19
Candidate BC genes (16)	40 (1.60)	5 (1.26)	0.88 (0.36 - 2.13)	0.77
Other cancer genes (9)[1]	13 (0.52)	7 (1.77)	2.43 (1.14 - 5.17)	0.02
DNA repair genes (25)[2]	98 (3.91)	21 (5.30)	1.32 (0.85 - 2.07)	0.22
HR pathway (14)	74 (2.96)	12 (3.03)	1.06 (0.59 - 1.91)	0.83

Gene Set (no. genes)	PBC No. Carriers (%)	SPC No. Carriers (%)	HR (95% CI)	P
FA pathway (8)	51 (2.04)	8 (2.02)	0.93 (0.46 - 1.89)	0.84
MMR pathway (4)	3 (0.12)	2 (0.51)	4.99 (1.17 - 21.38)	0.03
NER pathway (2)	6 (0.24)	2 (0.51)	2.11 (0.52 - 8.58)	0.30
BER pathway (1)	5 (0.20)	1 (0.25)	0.88 (0.12 - 6.30)	0.90
Other related genes (2)	3 (0.12)	3 (0.76)	3.55 (1.10 - 11.46)	0.03

[1]Gene were grouped by their prior evidence on breast cancer susceptibility. Established breast cancer (BC) genes included *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D,* and *TP51*. Candidate BC genes included *BLM, BRIP1, CDKN2A, ERCC3, FANCC, FANCM, MLH1, MRE11A, MSH2, MSH6, NCN, RAD50, RECQL, RINT1, SLX4,* and *XRCC2*. Other cancer predisposition genes included *APC, EPCAM, ERCC2, KRAS, MEN1, MUTYH, RMS2, PPM1D*, and *PRSS1*.

[2]DNA repair genes (DRGs) were grouped by DNA repair pathways. Homologous recombination (HR) pathway included *ATM, BLM, BARD1, BRCA1, BRCA2, BRIP1, MRE11A, PALB2, RAD50, RAD51C, RAD51D, RECQL, SLX4,* and *XRCC2*. Fanconi Anemia (FA) pathway included *BRCA1, BRCA2, BRIP1, FANCC, FANCM, PALB2, RAD51C,* and *SLX4*. Mismatch repair (MMR) pathway included *MLH1, MSH2, MSH6,* and *PMS2*. Nucleotide excision repair (NER) pathway included *ERCC3* and *ERCC2*. Base excision repair (BER) pathway included *MUTYH*. Other related genes included *CHEK2* and *TP53*. Note that some genes were included in more than one pathway.

[3]A total of 33 women with bilateral mastectomy were further excluded in the analysis of SPBC.