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Risk of contralateral breast cancer associated with common variants in *BRCA1* and *BRCA2*: potential modifying effect of *BRCA1/BRCA2* mutation carrier status

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Abstract Rare deleterious mutations in *BRCA1* and *BRCA2* are associated with an elevated risk of breast and ovarian cancer. Whether or not common variants in these genes are independently associated with risk of breast cancer remains unclear. In this study, we included 632 Caucasian women with asynchronous contralateral breast cancer (CBC, cases) and 1,221 women with unilateral breast cancer (UBC, controls) from the WECARE (Women's Environment, Cancer and Radiation Epidemiology) Study. *BRCA1* and *BRCA2* deleterious mutation status was measured using denaturing high-performance liquid chromatography followed by direct sequencing, yielding including 88 *BRCA1* and 60 *BRCA2* deleterious mutation carriers. We also genotyped samples on the Illumina Omni1-Quad platform. We assessed the association between CBC risk and common (minor allele frequency (MAF) > 0.05) single-nucleotide polymorphisms (SNPs) in *BRCA1* (n SNPs $= 22$) and *BRCA2* (n SNPs $= 30$) and haplotypes using conditional logistic regression accounting for *BRCA1/BRCA2* mutation status. We found no significant associations between any single-SNPs or haplotypes of *BRCA1* or *BRCA2* and risk of CBC among all women. When we stratified by *BRCA1* and *BRCA2* mutation carrier status, we found suggestive evidence that risk estimates for selected SNPs in *BRCA1* (rs8176318, rs1060915, and rs16940) and *BRCA2* (rs11571686, rs206115, and rs206117) may differ in non-carriers and carriers of deleterious mutations in *BRCA1* and *BRCA2*. One common haplotype on *BRCA1* was inversely significantly associated with risk only among non-*BRCA1* and *BRCA2* carriers. The association between common

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variants in *BRCA1* and *BRCA2* and risk of CBC may differ depending on *BRCA1* and *BRCA2* mutation carrier status.

Keywords *BRCA1* · *BRCA2* · Haplotype · Polymorphism · Breast cancer · Contralateral

Abbreviations

BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
CBC	Contralateral breast cancer
CI	Confidence interval
OR	Odds ratio
SNP	Single-nucleotide polymorphism
UBC	Unilateral breast cancer

Introduction

Rare germline mutations in two breast cancer susceptibility genes, *BRCA1* [1] and *BRCA2* [2] account for 3–8% of all cases of breast cancer and 15–20% of familial cases. The penetrance of these mutations is highly variable between and within carrier families [3–5], suggesting that other environmental and genetic variants may act as modifying factors [6]. What is less clear is whether more common (presumably low penetrance) variants in *BRCA1* or *BRCA2* modify the risk of breast cancer in carriers of clearly deleterious mutations in *BRCA1* or *BRCA2* or are associated with risk of breast cancer in non-*BRCA1* or *BRCA2* carriers.

Results from studies of common genetic variants in *BRCA1* and *BRCA2* as potential risk factors for primary breast cancer have been largely inconsistent. Cox et al. used four haplotype tagging (ht)-single-nucleotide polymorphisms (SNPs) in *BRCA1* and identified one haplotype associated with a significant increased risk in the Nurses' Health Study [7], while Freedman et al. examined 9 tag-SNPs in *BRCA1* among women in the Multi-ethnic Cohort Study and found no significant effects [8]. For *BRCA2*, Freedman et al. also used 21 tagSNPs in *BRCA2* and found one (rs206340) to be associated with an increase in risk for the homozygous genotype compared to the wildtype [9]. The British East Anglian SEARCH Study, which used controls from the European Prospective Investigation in Cancer and Nutrition (EPIC)-Norfolk Study evaluated five SNPs in *BRCA1* and 16 SNPs in *BRCA2* individually and in combination, finding no associations with breast cancer risk [10]. In addition, several studies have examined single missense polymorphisms in *BRCA1* and *BRCA2* in relation to breast cancer risk with conflicting evidence including *BRCA2*-N372H [11–15] and *BRCA1*-Q356R [7, 16, 17]. None of these studies accounted for *BRCA1* or *BRCA2* mutation status. Some evidence suggests that mutations in *BRCA1* occur more often on specific haplotypes of *BRCA1* [18], but the potential risk of common variants in these genes in carriers is not known.

In this study, we investigate the association between common SNPs in *BRCA1* and *BRCA2* and risk of developing asynchronous contralateral breast cancer (CBC) among women with a prior unilateral breast cancer (UBC) whose carrier status for deleterious mutations in *BRCA1* and *BRCA2* is known.

Materials and methods

Study population

The WECARE (Women's Environmental Cancer and Radiation Epidemiology) Study has been previously described [19]. In brief, the WECARE Study is a multi-center, population-based case–control study of women with CBC (cases) and women with UBC only (controls). All participants were identified by five population-based cancer registries in the United States (Seattle, Iowa, Orange County/San Diego, and Los Angeles County) and Denmark (Danish Cancer Registry). CBC cases met the following eligibility requirements: (1) were diagnosed between 01/01/1985 and 12/31/2000 with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis and a second primary in situ or invasive breast cancer diagnosed in the contralateral breast at least 1 year after the first breast cancer diagnosis (reference date); (2) resided in the same study reporting area for both diagnoses; (3) had no previous or intervening cancer diagnosis except squamous cell or basal cell skin cancer; (4) were able to provide informed consent to complete the interview; (5) provided a blood sample; and (6) were under age 55 years at the time of diagnosis of the first breast cancer. The "at-risk" time period was defined as the number of days between the case's first and second breast cancer diagnoses.

Two control subjects were individually matched to each case on year of birth, year of diagnosis, registry region, and race, and were 1:2 counter-matched on registry-reported radiation exposure (for treatment of first primary breast cancer) so that each triplet consisted of one radiation-untreated and two radiation-treated subjects. Eligible UBC controls were (1) diagnosed between 01/01/1985 and 12/31/1999 with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis; (2) resided in the same study reporting area as the case to which they were matched at diagnosis and at a reference date equal to the date of diagnosis plus the at-risk period; (3) had no diagnosis of any other cancer (other than

squamous cell or basal cell skin carcinoma or cervical carcinoma in situ) prior to their breast cancer diagnosis or during the at-risk period; (4) were alive and able to provide informed consent to complete the interview; (5) provided a blood sample; and (6) had not had a prophylactic mastectomy of the contralateral breast prior to or within the at-risk period.

A total of 708 CBC cases participated in the study (of 998 eligible cases) and 1,399 women with UBC participated as controls (of 2,112 eligible women with UBC). Reasons for non-participation included: physician refusal, subject interview refusal, and subject blood draw refusal. For the current study, we restricted eligible women to Caucasians (649 eligible CBC cases and 1,288 UBC controls).

All participants were interviewed by telephone using a structured questionnaire that collected information on personal demographics, medical history, family history, reproductive history, body size, smoking, alcohol intake, oral contraceptive use, and post-menopausal hormone use. For all participants, medical records, pathology reports, and hospital charts, in addition to self-reported data, were used to collect detailed treatment information. Information on tumor characteristics of the first primary breast cancer was collected from medical records and cancer registry records.

The study protocol was approved by the Institutional Review Boards at each study site and by the ethical committee system in Denmark.

BRCA1 and *BRCA2* mutation screening

Screening for mutations in *BRCA1* and *BRCA2* [20] was performed in all cases and controls, as previously described [21]. In brief, coding and flanking intronic regions were screened for mutations or polymorphic variants by denaturing high-performance liquid chromatography (DHPLC). All PCR-amplified fragments with variant heteroduplex output traces were sequenced to confirm the nucleotide variants. Three laboratories performed the screening using fixed sets of primers and DHPLC protocols. Consistency in screening between and within laboratories was assured via a rigorous laboratory quality control plan previously described [22]. We classified mutations as deleterious according to the guidelines provided by the Breast Cancer Information Core (http://research.nhgri.nih.gov/projects/bic/). Sequence variants classified as having a clearly deleterious effect included changes known or predicted to truncate protein production, splice site mutations located within 2 bp of an intron/exon boundary or shown to cause aberrant splicing, and missense changes with known deleterious functional effects. Of the eligible Caucasian women, four (three CBC cases and one UBC control) did not consent to screening for deleterious mutations in *BRCA1* and *BRCA2*. Excluding these three cases and their respective matched controls (total $n = 9$) and the one non-consenting UCB control, 646 bilateral cases and 1,281 unilateral controls remained eligible.

Genotyping polymorphisms in *BRCA1* and *BRCA2*

DNA samples were genotyped with Illumina's Human-Omni1-Quad BeadChip. Samples with GenCall scores <0.15 at any locus were considered "no calls." Each 96-well plate included one inter-plate positive quality control samples (NA06990, Coriell Cell Repositories). In addition, 38 blinded and 46 un-blinded quality control replicates from the study sample were genotyped. SNP data obtained from both the Coriell and study sample replicates showed a high concordance rate of called genotypes: >99.99% (for un-blinded and blinded study replicates that had call rates >90% for both replicates; inter-plate positive control—not determined). Default Omni1-Quad cluster definitions supplied by Illumina were used to call genotypes. The genotype clusters were visually inspected for all SNPs with significant associations.

Of the 1,927 eligible Caucasian women, four individuals were excluded because they did not consent to genome-wide association study (GWAS) genotyping beyond the initial *BRCA1* and *BRCA2* mutation screening. A series of quality control steps were applied leading to further subject exclusions: (1) women with SNP call rates <95% were excluded ($n = 22$); (2) population stratification was investigated using EIGENSTRAT [23]; using the first two principal components, 22 outliers (eight of which were CBC cases) were identified for exclusion; and (3) identity by descent was examined using PLINK [24] identifying three pairs of sisters, including one pair of identical twins. Following these exclusions, 26 additional participants were excluded due to incomplete matched sets. Analyses are based on the remaining 1,853 participants (632 CBC cases and 1,221 UBC controls).

In this report, we focus on common variants in *BRCA1* and *BRCA2*. We defined the region for *BRCA1* as base pairs 38444655–38545479 and for *BRCA2* as base pairs 31782845–31871439 (Genome Build 36.2).

We performed additional quality control steps by comparing genotypes of common variants in *BRCA1* and *BRCA2* assayed on the Illumina Omni1-Quad platform with those we identified during DHPLC screening for deleterious mutations. Nine common (MAF > 0.05) SNPs in *BRCA1* and six common SNPs in *BRCA2* were identified. As homozygotes were not reliably determined in some instances from DHPLC screening, these common SNPS were also genotyped on a custom oligonucleotide probe panel using the Illumina GoldenGate™ assay on the

Sentrix Array Matrix (Illumina, Inc., San Diego). A high concordance rate between results on the Illumina GoldenGate and Omni1-Quad (>96%) was observed for all SNPs.

SNPs were excluded from analysis if they had a MAF < 0.05 (*n* SNPs = 73). The call rate for all SNPs was >96% on the Omni1-Quad. In total, we included 1,853 samples and 52 SNPs (22 in *BRCA1* and 30 in *BRCA2*) in the final analysis. The 22 SNPs in *BRCA1* and 30 in *BRCA2* captured 97 and 95% of all common variants in these genes, respectively, at $r^2 > 0.80$ using HapMap Phase II release 24.

Statistical analysis

We conducted single SNP and haplotype-based analyses. To investigate the association between each SNP or haplotype and the risk of CBC, we used conditional logistic regression analysis, including a log weight "covariate" in the model where the coefficient of this log weight was fixed at one (i.e., an "offset" in the model). The weights were created using the numbers of registry-reported radiation-treated and radiation-untreated women in the risk set to account for the counter-matched sampling design [19, 25]. All models were also adjusted for exact age at first breast cancer diagnosis (continuous). For individual SNP analysis, we considered both a log-additive and co-dominant model.

To investigate potential heterogeneity by *BRCA1* and *BRCA2* deleterious mutation carrier status, we included interaction terms between each SNP and mutation status indicator variables. To investigate heterogeneity in risk estimates across mutation carriers and non-carriers, we used a likelihood ratio test comparing the carrier status specific model to a model including only the main effect for the SNP.

For the haplotype-based analyses, we estimated the haplotype effects among all individuals irrespective of *BRCA1* and *BRCA2* mutation carrier status and among known non-*BRCA1* and *BRCA2* carriers. We were unable to estimate haplotype effects in *BRCA1* and *BRCA2* carriers due to small cell counts. Haplotype frequencies were estimated with the EM algorithm, as implemented in R version 2.10.1 (http://mayoresearch.mayo.edu/mayo/research/schaid_lab/software.cfm). The most common haplotype was used as the reference and rare haplotypes (combined frequency <0.5%) were combined into a single group.

When necessary, to account for missing information within a counter-matched set, a missing indicator variable was included in the conditional logistic regression models [26]. All statistical tests are two-sided. SAS release 9.2 (SAS Institute, Cary, NC) was used for the analyses.

Results

Among the WECARE Study Caucasian women, a total of 148 women carried a deleterious mutation in *BRCA1* ($n = 88$) or *BRCA2* ($n = 60$) (Table 1). *BRCA1* and *BRCA2* mutation carriers were more likely to be younger at first breast cancer diagnosis than non-carriers, but did not differ by time at risk. Women with CBC were more likely to have a family history of breast cancer and this proportion was higher among *BRCA1* and *BRCA2* carriers compared to non-carriers. *BRCA1* carriers were younger at diagnosis of their first breast cancer and were more likely to be estrogen receptor-negative and progesterone receptor-negative compared to *BRCA2* carriers and non-carriers.

Among all women, there were no significant associations with CBC risk for any single-SNP in *BRCA1* using either the log-additive or co-dominant model (Table 2). In the log-additive model, rs1060915 was associated with a non-significant increased risk of CBC in *BRCA1* carriers (per G allele, OR 1.96; 95% CI 0.91–4.26), no association in *BRCA2* carriers and an inverse association in non-*BRCA1* and *BRCA2* carriers (OR 0.84; 95% CI 0.70–1.00). Similar results were observed for two additional SNPs, rs8176318 and rs16940, both in complete linkage disequilibrium (LD) with rs1060915 ($r^2 = 1.0$, $r^2 = 1.0$, respectively). No association with CBC was observed for any synonymous or non-synonymous amino acid coding SNPs including *BRCA1*-Q356R (rs1799950).

For *BRCA2*-rs11571686, we found that the variant homozygous genotype (C/C) was significantly associated with an increased risk of CBC when compared to the wildtype homozygous genotype (OR 2.75; 95% CI 1.17–6.48, Table 3). When stratified by deleterious mutation status, we observed that the increased risk associated with this SNP was restricted to non-carriers (OR 1.32, 95% CI 1.04–1.68); there was no evidence of an association in *BRCA1* carriers (OR 0.60; 95% CI 0.18–2.18) or *BRCA2* carriers (OR 0.27; 95% CI 0.04–1.87).

Among *BRCA1* mutation carriers, we found evidence that two SNPs in *BRCA2* were significantly associated with the risk of CBC (Table 3). *BRCA2*-rs206115 was inversely associated with risk (OR 0.41; 95% CI 0.19–0.87) and *BRCA2*-rs206117 was associated with an increased risk (OR 2.46; 95% CI 1.10–5.48). These two SNPs are in modest LD ($r^2 = 0.61$). We found no evidence of an association between *BRCA2*-N372H (rs144848), V1269V (rs543304) or S2414S (rs17999555) and risk of CBC.

Combining CBC and UBC women, we estimated six common haplotypes with frequency ≥0.05 in *BRCA1* and six in *BRCA2* (Table 4). We found no association between these *BRCA1* or *BRCA2* haplotypes and risk of CBC among all women (Table 5). When we excluded carriers of deleterious *BRCA1* or *BRCA2* mutations, results suggested

Table 1 Selected characteristics of the *BRCA1* and *BRCA2* carriers and non-carriers in the WECARE Study

	Non carriers		*BRCA1* mutation carrier		*BRCA2* mutation carrier	
	CBC *n* (%)	UBC *n* (%)	CBC *n* (%)	UBC *n* (%)	CBC *n* (%)	UBC *n* (%)
Total	544	1161	53	35	35	25
Age at first breast cancer (years)						
20–34	18 (3.3)	58 (5.0)	13 (24.5)	8 (22.9)	3 (8.6)	2 (8.0)
35–44	172 (31.6)	394 (33.9)	32 (60.4)	17 (48.6)	19 (54.3)	10 (40.0)
45–55	354 (65.1)	709 (61.1)	8 (15.1)	10 (28.6)	13 (37.1)	13 (52.0)
Mean age (SD)	46.5 (5.9)	45.8 (6.0)	38.6 (5.9)	40.1 (7.2)	42.8 (6.6)	43.8 (7.4)
Age at reference date (years)[a]						
22–34	7 (1.3)	17 (1.5)	4 (7.6)	7 (20.0)	1 (2.9)	1 (4.0)
35–44	62 (11.4)	171 (14.7)	26 (49.1)	12 (34.3)	11 (31.4)	6 (24.0)
≥45	475 (87.3)	973 (83.8)	23 (43.4)	16 (45.7)	23 (65.7)	18 (72.0)
Mean age (SD)	51.6 (6.8)	51.0 (6.8)	43.5 (7.0)	44.1 (8.1)	48.0 (7.4)	48.4 (8.3)
At risk period (years)[b]						
Mean time interval (SD)	5.1 (3.2)	5.2 (3.2)	5.0 (2.8)	4.0 (2.6)	5.1 (3.0)	4.7 (2.6)
Geographic location						
Denmark	151 (27.8)	323 (27.8)	12 (22.6)	7 (20.0)	12 (34.3)	9 (36.0)
USA	393 (72.2)	838 (72.2)	41 (77.4)	28 (80.0)	23 (65.7)	16 (64.0)
Family history[c]						
None	369 (67.8)	911 (78.5)	28 (52.8)	22 (62.9)	19 (54.3)	16 (64.0)
1+	167 (30.7)	226 (19.5)	22 (41.5)	12 (34.3)	16 (45.7)	8 (32.0)
Adopted	8 (1.5)	24 (2.0)	3 (5.7)	1 (2.9)	0 (0.0)	1 (4.0)
Estrogen receptor status[d]						
Positive	277 (53.7)	632 (56.2)	4 (8.2)	11 (31.4)	20 (58.8)	13 (54.2)
Negative	121 (23.5)	261 (23.2)	36 (73.5)	20 (57.1)	8 (23.5)	6 (25.0)
Other	118 (22.9)	231 (20.6)	9 (18.4)	4 (11.4)	6 (17.7)	5 (20.8)
Progesterone receptor status[d]						
Positive	231 (45.7)	521 (47.2)	6 (12.8)	7 (20.0)	16 (50.0)	8 (33.3)
Negative	106 (21.0)	242 (21.9)	31 (66.0)	20 (57.1)	7 (21.9)	8 (33.3)
Other	169 (33.4)	341 (30.9)	10 (21.3)	8 (22.9)	9 (28.1)	8 (33.3)

CBC contralateral breast cancer, *UBC* unilateral breast cancer

Frequency counts do not necessarily sum to the total number of individuals due to missing data

[a] Reference date = date at second breast cancer for cases (bilateral breast cancer) and equivalent date for controls (unilateral breast cancer)

[b] Time interval between first and second diagnoses for cases and first diagnosis and equivalent date for controls

[c] Family history of breast cancer in a first-degree relative (number of relatives)

[d] Hormone receptor status of the first breast cancer

a lower risk of CBC among women who carried haplotype_3.

Discussion

In this large case–control study designed to determine genetic factors that increase risk of CBC, we observed that the association of common variants in *BRCA1* and *BRCA2* with CBC risk may be modified by *BRCA1* and *BRCA2* deleterious mutation carrier status. Selected SNPs in *BRCA1*, rs8176318, rs1060915 and rs16940, appeared to confer an increased risk of CBC among women who carried known deleterious mutations in *BRCA1*, but were associated with a lower risk in non-*BRCA1* and *BRCA2* carriers. *BRCA2*-rs11571686 conferred an increase risk among non-*BRCA1* and *BRCA2* carriers, and two other SNPs in *BRCA2*, rs206115 and rs206117, were associated with risk only in *BRCA1*-mutation carriers. We found no evidence that common haplotypes of *BRCA2* were significantly associated with risk of CBC among all women or among non-carriers. However, we identified one common

Table 2 Association between SNPs in *BRCA1* and contralateral breast cancer risk by *BRCA1* and *BRCA2* mutation status

SNP[a]	Major/minor allele	MAF	All			Non-carriers	*BRCA1* mutation carriers	*BRCA2* mutation carriers
			Per allele OR (95% CI)[b]	Heterozygous vs. wild-type homozygous OR (95% CI)[b]	Rare homozygous vs. wild-type homozygous OR (95% CI)[b]	Per allele OR (95% CI)[b]	Per allele OR (95% CI)[b]	Per allele OR (95% CI)[b]
rs11657053	C/A	0.33	0.88 (0.75–1.04)	0.89 (0.71–1.12)	0.77 (0.54–1.12)	0.84 (0.71–1.00)	1.72 (0.82–3.63)	1.13 (0.51–2.49)
rs7223952	A/G	0.34	0.87 (0.74–1.02)	0.86 (0.69–1.08)	0.77 (0.53–1.10)	0.83 (0.70–0.99)	1.55 (0.77–3.14)	1.05 (0.46–2.40)
rs11659028	T/A	0.33	0.88 (0.74–1.03)	0.88 (0.70–1.11)	0.76 (0.53–1.10)	0.84 (0.70–1.00)	1.72 (0.82–3.62)	1.04 (0.46–2.37)
rs12516	G/A	0.33	0.88 (0.74–1.03)	1.16 (0.80–1.67)	1.31 (0.91–1.90)	0.84 (0.70–1.00)	1.72 (0.82–3.62)	1.04 (0.46–2.37)
rs8176318	C/A	0.33	0.88 (0.75–1.04)	0.89 (0.71–1.11)	0.77 (0.53–1.11)	0.84 (0.71–1.00)	1.96 (0.91–4.26)	1.05 (0.46–2.39)
rs8176305	A/G	0.08	1.22 (0.92–1.61)	1.22 (0.91–1.63)	1.52 (0.33–7.08)	1.21 (0.90–1.64)	0.83 (0.22–3.17)	1.72 (0.38–7.81)
rs1799966	A/G	0.33	0.89 (0.75–1.05)	0.87 (0.70–1.10)	0.80 (0.55–1.16)	0.85 (0.71–1.02)	1.72 (0.82–3.62)	1.04 (0.46–2.37)
rs8176218	del/ins	0.33	0.88 (0.75–1.04)	0.91 (0.72–1.14)	0.76 (0.53–1.10)	0.85 (0.71–1.01)	1.73 (0.82–3.64)	1.02 (0.45–2.32)
rs3737559	G/A	0.09	0.81 (0.61–1.07)	1.76 (0.39–7.82)	2.11 (0.49–9.14)	0.76 (0.56–1.04)	2.40 (0.62–9.31)	1.84 (0.55–6.17)
rs1060915	A/G	0.33	0.88 (0.75–1.04)	0.89 (0.71–1.12)	0.77 (0.53–1.11)	0.84 (0.71–1.01)	1.96 (0.91–4.26)	1.05 (0.46–2.39)
rs8176156	ins/del	0.33	0.87 (0.74–1.03)	1.18 (0.82–1.70)	1.34 (0.93–1.93)	0.83 (0.70–0.99)	1.72 (0.82–3.62)	1.04 (0.46–2.37)
rs16942	A/G	0.33	0.87 (0.74–1.02)	0.88 (0.70–1.11)	0.75 (0.52–1.08)	0.83 (0.70–0.99)	1.72 (0.82–3.62)	1.04 (0.46–2.37)
rs16941	A/G	0.33	0.88 (0.75–1.04)	0.91 (0.72–1.14)	0.76 (0.53–1.10)	0.85 (0.71–1.01)	1.75 (0.84–3.66)	1.04 (0.46–2.37)
rs799917	G/A	0.34	0.87 (0.74–1.03)	1.11 (0.78–1.60)	1.30 (0.90–1.86)	0.84 (0.70–1.00)	1.55 (0.77–3.14)	1.05 (0.46–2.40)
rs16940	A/G	0.33	0.88 (0.74–1.03)	0.89 (0.71–1.11)	0.76 (0.53–1.10)	0.84 (0.70–1.00)	1.96 (0.90–4.26)	1.05 (0.46–2.39)
rs1799949	A/G	0.33	1.12 (0.95–1.32)	1.05 (0.72–1.52)	1.21 (0.84–1.76)	1.17 (0.98–1.40)	0.58 (0.28–1.23)	0.96 (0.42–2.20)
rs4986850	G/A	0.08	1.20 (0.91–1.59)	0.79 (0.17–3.73)	0.66 (0.14–3.06)	1.20 (0.89–1.61)	0.83 (0.22–3.17)	1.73 (0.38–7.82)
rs1799950	A/G	0.06	1.01 (0.74–1.38)	0.98 (0.70–1.36)	1.96 (0.27–14.22)	0.94 (0.67–1.32)	4.05 (0.98–16.67)	–
rs8176150	del/ins	0.33	0.87 (0.74–1.02)	0.87 (0.70–1.10)	0.74 (0.51–1.07)	0.83 (0.70–0.99)	1.71 (0.82–3.60)	1.02 (0.45–2.32)
rs799923	G/A	0.23	1.03 (0.86–1.24)	0.73 (0.43–1.23)	0.76 (0.46–1.27)	1.10 (0.90–1.33)	0.58 (0.25–1.34)	0.48 (0.13–1.70)
rs799912	A/G	0.34	0.88 (0.75–1.04)	0.88 (0.70–1.11)	0.78 (0.54–1.12)	0.85 (0.71–1.01)	1.56 (0.77–3.14)	1.05 (0.46–2.40)
rs8176092	A/C	0.33	0.88 (0.75–1.03)	0.89 (0.71–1.12)	0.76 (0.52–1.09)	0.85 (0.71–1.01)	1.62 (0.77–3.41)	1.03 (0.45–2.34)

SNP single nucleotide polymorphism, *MAF* minor allele frequency, *OR* odds ratio, *CI* confidence interval

–, Not estimated due to small cell counts

[a] Amino acid change: rs1060915 (S1436S), rs16942 (K1183R), rs16941 (E1038G), rs799917 (P871L), rs16940 (L771L), rs1799949 (S694S), rs4986850 (D693N), and rs1799950 (Q356R)

[b] Adjusted for age and counter-matching design

Table 3 Association between SNPs in *BRCA2* and contralateral breast cancer risk by *BRCA1* and *BRCA2* mutation status

SNP[a]	Major/minor allele	MAF	All			Non-carriers	*BRCA1* mutation carriers	*BRCA2* mutation carriers
			Per allele OR (95% CI)[b]	Heterozygous vs. wild-type homozygous OR (95% CI)[b]	Rare homozygous vs. wild-type homozygous OR (95% CI)[b]	Per allele OR (95% CI)[b]	Per allele OR (95% CI)[b]	Per allele OR (95% CI)[b]
rs206115	A/G	0.42	1.04 (0.89–1.21)	1.04 (0.82–1.33)	1.08 (0.79–1.48)	1.07 (0.91–1.26)	0.41 (0.19–0.87)	1.23 (0.53–2.81)
rs206117	G/A	0.39	0.94 (0.81–1.10)	1.09 (0.86–1.38)	0.82 (0.58–1.14)	0.92 (0.78–1.09)	2.46 (1.10–5.48)	1.12 (0.43–2.92)
rs206118	A/G	0.18	0.86 (0.70–1.05)	0.89 (0.70–1.13)	0.65 (0.34–1.25)	0.82 (0.66–1.02)	2.41 (0.89–6.55)	1.05 (0.32–3.38)
rs206119	A/G	0.24	0.94 (0.78–1.12)	0.92 (0.74–1.16)	0.90 (0.56–1.46)	0.92 (0.76–1.12)	1.28 (0.57–2.89)	0.60 (0.22–1.67)
rs9562605	G/A	0.23	1.07 (0.89–1.28)	1.03 (0.82–1.29)	1.26 (0.77–2.08)	1.08 (0.89–1.30)	1.31 (0.61–2.79)	1.31 (0.48–3.55)
rs9567552	C/A	0.23	1.05 (0.88–1.25)	0.99 (0.79–1.24)	1.25 (0.78–2.00)	1.06 (0.88–1.28)	0.97 (0.47–1.97)	1.21 (0.47–3.10)
rs1799943	G/A	0.25	1.02 (0.86–1.21)	0.96 (0.77–1.20)	1.19 (0.76–1.88)	1.04 (0.87–1.25)	1.01 (0.48–2.13)	0.92 (0.35–2.38)
rs11571579	A/G	0.29	1.06 (0.90–1.26)	0.96 (0.77–1.20)	1.33 (0.89–1.97)	1.10 (0.93–1.31)	0.87 (0.42–1.80)	0.92 (0.36–2.40)
rs206070	G/A	0.18	0.89 (0.73–1.09)	0.89 (0.70–1.13)	0.81 (0.43–1.52)	0.86 (0.69–1.06)	1.68 (0.64–4.41)	1.33 (0.47–3.77)
rs2126042	G/A	0.20	1.01 (0.83–1.22)	1.02 (0.81–1.29)	0.97 (0.55–1.71)	1.00 (0.82–1.22)	1.58 (0.64–3.90)	0.68 (0.22–2.09)
rs144848	A/C	0.28	0.98 (90.83–1.16)	1.02 (0.82–1.28)	0.90 (0.59–1.37)	0.97 (0.81–1.17)	0.81 (0.39–1.68)	0.85 (0.36–2.03)
rs2320236	A/G	0.20	1.01 (0.83–1.22)	1.02 (0.81–1.29)	0.97 (0.55–1.71)	1.00 (0.82–1.22)	1.56 (0.63–3.84)	0.73 (0.24–2.20)
rs543304	A/G	0.19	0.89 (0.73–1.09)	0.87 (0.69–1.10)	0.87 (0.47–1.63)	0.86 (0.70–1.07)	1.63 (0.62–4.28)	1.33 (0.47–3.78)
rs206079	G/A	0.47	0.92 (0.79–1.08)	0.85 (0.66–1.10)	0.87 (0.64–1.18)	0.90 (0.76–1.06)	1.06 (0.57–1.98)	1.05 (0.45–2.44)
rs206081	G/A	0.19	0.88 (0.73–1.08)	0.88 (0.70–1.11)	0.79 (0.42–1.49)	0.85 (0.69–1.05)	1.68 (0.64–4.41)	1.33 (0.47–3.77)
rs11571686	A/C	0.11	1.18 (0.93–1.48)	1.04 (0.80–1.36)	2.75 (1.17–6.48)	1.32 (1.04–1.68)	0.60 (0.18–2.08)	0.27 (0.04–1.87)
rs9943876	G/A	0.32	1.03 (0.88–1.22)	1.09 (0.87–1.36)	1.00 (0.68–1.46)	1.02 (0.86–1.21)	1.16 (0.48–2.80)	1.14 (0.41–3.13)
rs9943888	A/G	0.28	1.03 (0.87–1.22)	1.14 (0.92–1.42)	0.86 (0.56–1.33)	1.01 (0.84–1.20)	1.54 (0.63–3.78)	0.89 (0.33–2.41)
rs1799955	A/G	0.22	1.06 (0.89–1.28)	0.98 (0.78–1.23)	1.40 (0.85–2.31)	1.13 (0.93–1.37)	0.97 (0.41–2.29)	0.77 (0.28–2.15)
rs9534262	G/A	0.47	0.93 (0.80–1.09)	0.95 (0.74–1.23)	0.86 (0.63–1.19)	0.91 (0.77–1.07)	0.91 (0.41–2.02)	1.08 (0.49–2.38)
rs9634672	C/A	0.21	1.07 (0.89–1.28)	0.96 (0.76–1.21)	1.49 (0.90–2.47)	1.13 (0.93–1.37)	0.97 (0.41–2.29)	0.77 (0.28–2.15)
rs4942486	G/A	0.47	0.92 (0.78–1.07)	0.93 (0.72–1.20)	0.84 (0.61–1.15)	0.89 (0.76–1.05)	0.91 (0.41–2.02)	1.09 (0.50–2.38)
rs11571789	C/A	0.10	1.05 (0.80–1.37)	1.03 (0.78–1.35)	–	1.20 (0.90–1.59)	0.48 (0.13–1.72)	0.28 (0.04–1.93)
rs4942505	A/G	0.46	0.90 (0.77–1.06)	0.92 (0.71–1.19)	0.81 (0.58–1.12)	0.87 (0.73–1.03)	0.91 (0.41–2.02)	1.24 (0.54–2.83)
rs206340	G/A	0.22	0.91 (0.76–1.09)	0.94 (0.74–1.18)	0.76 (0.44–1.29)	0.88 (0.73–1.08)	1.72 (0.71–4.17)	1.09 (0.39–3.07)
rs1012130	A/G	0.28	1.04 (0.88–1.24)	1.14 (0.91–1.42)	0.93 (0.60–1.43)	1.02 (0.85–1.22)	1.54 (0.63–3.77)	0.89 (0.33–2.41)
rs517118	A/G	0.26	0.97 (0.81–1.16)	0.95 (0.75–1.19)	0.98 (0.62–1.57)	0.95 (0.79–1.16)	0.59 (0.27–1.31)	1.03 (0.45–2.36)
rs15869	A/C	0.21	0.91 (0.75–1.09)	0.93 (0.74–1.17)	0.76 (0.45–1.31)	0.88 (0.72–1.07)	1.72 (0.71–4.18)	1.02 (0.36–2.91)
rs11571836	A/G	0.21	1.08 (0.90–1.29)	0.99 (0.78–1.24)	1.46 (0.88–2.41)	1.14 (0.94–1.38)	1.08 (0.43–2.70)	0.77 (0.28–2.15)
rs1801406	A/G	0.30	1.10 (0.94–1.29)	1.00 (0.80–1.26)	1.36 (0.93–1.98)	1.14 (0.96–1.36)	0.81 (0.40–1.65)	0.98 (0.40–2.40)

SNP single nucleotide polymorphism, *MAF* minor allele frequency, *OR* odds ratio, *CI* confidence interval

–, Not estimated due to small cell counts

[a] Amino acid change: rs144848 (N372H), rs543304 (V1269V), rs1799955 (S2414S)

[b] Adjusted for age and counter-matching design

Table 4 Common haplotypes among all women in the WECARE Study

Haplotype	Frequency	rs11657053	rs7223952	rs11659028	rs12516	rs8176318	rs8176305	rs8176218	rs3737559	rs1060915	rs8176156	rs16942
(a) BRAC1												
Hap_ref	0.42	C	A	T	G	C	A	del	G	A	ins	A
Hap_1	0.17	C	A	T	G	C	A	del	G	A	ins	A
Hap_2	0.16	A	G	A	A	A	A	ins	G	G	del	G
Hap_3	0.08	A	G	A	A	A	A	ins	A	G	del	G
Hap_4	0.08	A	G	A	A	A	G	ins	G	G	del	G
Hap_5	0.06	C	A	T	G	C	A	del	G	A	ins	A

Haplotype	Frequency	rs16941	rs799917	rs16940	rs1799949	rs4986850	rs1799950	rs8176150	rs799923	rs799912	rs8176092	rs1799966
(a) BRAC1												
Hap_ref	0.42	A	G	A	G	G	A	del	G	A	A	A
Hap_1	0.17	A	G	A	G	G	A	del	A	A	A	A
Hap_2	0.16	G	A	G	A	G	A	ins	G	G	C	G
Hap_3	0.08	G	A	G	A	G	A	ins	G	G	C	G
Hap_4	0.08	G	A	G	A	A	A	ins	G	G	C	G
Hap_5	0.06	A	G	A	G	G	G	del	A	A	A	A

Haplotype	Frequency	rs206115	rs206117	rs206118	rs206119	rs9562605	rs1799943	rs2126042	rs144848
(b) BRCA2									
Hap_ref	0.14	A	A	G	A	G	G	G	A
Hap_1	0.14	A	G	A	G	G	G	A	A
Hap_2	0.13	G	G	A	A	G	G	G	C
Hap_3	0.07	G	G	A	A	G	G	G	C
Hap_4	0.05	A	A	A	A	A	A	G	A
Hap_5	0.05	A	A	A	A	A	A	G	A

Haplotype	Frequency	rs543304	rs206079	rs11571686	rs9943888	rs1799955	rs9534262	rs517118	rs1801406
(b) BRCA2									
Hap_ref	0.14	G	A	A	A	A	A	A	A
Hap_1	0.14	A	G	A	G	A	G	A	A
Hap_2	0.13	A	A	A	A	A	A	G	A
Hap_3	0.07	A	A	A	G	A	G	A	A
Hap_4	0.05	A	G	C	A	G	G	A	G
Hap_5	0.05	A	G	A	A	G	G	A	G

BRCA1 haplotype that was inversely associated with risk, but only among non-*BRCA1* and *BRCA2* carriers.

BRCA1 and *BRCA2* are involved in the detection and repair of DNA double-strand breaks in response to DNA damage [27]. Selected mutations in these genes have been classified as deleterious, but the role of common variants is less clear and to date has only been examined in relation to the risk of first primary breast cancer. Our findings suggest that selected common variants in *BRCA1* may contribute to the risk of CBC among *BRCA1* carriers, although our results did not reach statistical significance. The risk estimates for CBC associated with being a deleterious *BRCA1* mutation carrier are significantly higher than those among non-carriers [28] and the penetrance of selected *BRCA1* deleterious mutations may in part be modified by common allelic variants.

A few studies have used LD patterns to define haplotype blocks that describe the majority of common variation in *BRCA1* in Caucasian women. Cox et al. genotyped four haplotype (ht)-SNPs in *BRCA1* and identified one haplotype associated with an increased risk of breast cancer among Caucasians in the Nurses' Health Study (OR 1.18; 95% CI 1.02–1.37) [7]. Freedman et al. examined 9 tag-SNPs in both coding and non-coding regions of *BRCA1* across different ethnic/racial groups in the Multiethnic Cohort Study and found no evidence of association with the risk of a first primary invasive breast cancer [8]. Furthermore, results from the British East Anglian SEARCH Study of Caucasian women found no association between any individual or combination of the 5 tagSNPs in *BRCA1* and breast cancer risk [10]. Unlike these previous studies, we focused on CBC in the WECARE Study and accounted

Table 5 Association between haplotypes in *BRCA1* and *BRCA2* and contralateral breast cancer risk

Haplotype	All			Non-*BRCA1/BRCA2* mutation carriers		
	Frequency		OR (95% CI)[a]	Frequency		OR (95% CI)[a]
	Bilateral	Unilateral		Bilateral	Unilateral	
BRCA1						
Hap_ref	0.43	0.42	1.00	0.43	0.42	1.00
Hap_1	0.17	0.17	0.99 (0.79–1.24)	0.18	0.16	1.08 (0.85–1.37)
Hap_2	0.16	0.16	0.80 (0.63–1.00)	0.16	0.17	0.78 (0.61–1.00)
Hap_3	0.07	0.09	0.79 (0.59–1.07)	0.07	0.09	0.70 (0.50–0.97)
Hap_4	0.08	0.08	1.13 (0.85–1.52)	0.08	0.08	1.12 (0.81–1.55)
Hap_5	0.06	0.06	0.94 (0.68–1.31)	0.06	0.06	0.88 (0.61–1.27)
Hap_others	0.02	0.03	0.85 (0.49–1.49)	0.02	0.02	0.79 (0.43–1.45)
BRCA2						
Hap_ref	0.13	0.15	1.00	0.13	0.15	1.00
Hap_1	0.14	0.14	1.17 (0.88–1.55)	0.14	0.14	1.19 (0.87–1.63)
Hap_2	0.13	0.13	1.03 (0.77–1.40)	0.14	0.13	1.09 (0.78–1.52)
Hap_3	0.07	0.06	1.29 (0.90–1.85)	0.08	0.06	1.34 (0.91–1.99)
Hap_4	0.06	0.05	1.43 (0.96–2.11)	0.06	0.05	1.45 (0.95–2.22)
Hap_5	0.05	0.05	1.17 (0.77–1.76)	0.05	0.05	1.21 (0.77–1.90)
Hap_others	0.41	0.42	1.12 (0.88–1.43)	0.41	0.42	1.23 (0.95–1.59)

OR odds ratio, *CI* confidence interval

[a] Adjusted for age and counter-matching design

for *BRCA1* and *BRCA2* mutation carrier status. We identified one common haplotype that was associated with a lower risk of CBC in non-*BRCA1/BRCA2* deleterious mutation carriers that requires further confirmation in other studies.

Several studies have examined the role of *BRCA1*-Q356R in the risk of developing breast cancer. Johnson [17] found that this SNP was associated with an increased risk of first primary (OR 1.31; 95% CI 1.14–1.51) and second primary breast cancer (OR 1.72, $P = 0.0002$). In a review by Dunning et al., this SNP had previously been described as being inversely associated with breast cancer risk [16], but this was not replicated in the Nurses' Health Study [7] or in the current analysis of CBC in the WECARE Study.

For *BRCA2*, Freedman et al. examined 21 tagSNPs in *BRCA2* in a breast cancer case–control study nested within the Multiethnic Cohort Study and found one (rs206340) to be associated with an increase in risk for the homozygous genotype compared to the wildtype (OR 1.59; 95% CI 1.18–2.16) [9]. In our study, *BRCA2*-rs543304 was not associated with CBC. In addition, a few studies have suggested that *BRCA2*-1342A>C/N372H (rs144848) is associated with an increased risk of breast cancer [12, 13], but not other cancers [11, 14, 15]. Our results also do not support an association between *BRCA2*-N372H and risk of CBC. We did not find that any of the common haplotypes of BRCA2 were associated with risk, in agreement with the British East Anglian SEARCH Study of Caucasian women [10]. However, when we stratified by *BRCA1* and *BRCA2* carrier status, we observed that *BRCA2*-rs11571686 conferred an increase risk among non-*BRCA1* and *BRCA2* carriers, and two other SNPs in *BRCA2*, rs206115 and rs206117, were significant risk alleles in *BRCA1*-mutation carriers.

Recent results from genome-wide association studies suggest that identified susceptibility loci may have different effects in *BRCA1* and *BRCA2* carriers compared to non-carriers [29]. These results may partially explain the variability in risk among carriers [6]; however, published studies examining haplotypes in *BRCA1* and *BRCA2* did not examine potential heterogeneity by carrier status.

In spite of the strengths of this study, there were some limitations. We considered only common variants occurring at a frequency of at least 5% in the population and we may have missed low-frequency haplotypes that are subtypes of the major haplotypes. The relevance of rare alleles may be critical and merits further investigation. Further, we are limited by the small number of *BRCA1* and *BRCA2* deleterious mutation carriers, which precluded more detailed analyses with carrier status. Our statistical power to detect modest SNP effects among *BRCA1* and *BRCA2* carriers is limited.

This is the first study to investigate the role of common variants in *BRCA1* and *BRCA2* in the development of CBC

by *BRCA1* and *BRCA2* mutation carrier status. We have used both a comprehensive tagging and haplotype-tagging approach to account for the majority of common variants in *BRCA1* and *BRCA2*. We have also implemented strong quality control procedures to ensure accurate genotyping of *BRCA1* and *BRCA2*. We have limited the potential for population stratification by restricting our analysis to Caucasians and matching by center/country of origin. Further, by ascertaining cases and controls through population-based cancer registries, our study avoided biases associated with use of high-risk or selected populations thereby increasing the generalizability of the findings.

In conclusion, we provide evidence that selected common alleles of *BRCA1* and *BRCA2* may modify risk of CBC conditional on *BRCA1* and *BRCA2* mutation carrier status. These results add to a growing literature suggesting that risk may be influenced by multiple loci with modest effects and may help explain the variability in penetrance estimates for *BRCA1* and *BRCA2* mutations in carrier families [3–5].

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Conflict of interest The authors declare that they have no conflict of interest.

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