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Common variants at the 19p13.1 and *ZNF365* loci are associated with ER subtypes of breast cancer and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers

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Disclosure of Potential Conflicts of Interest

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Abstract

Background—Genome-wide association studies (GWAS) identified variants at 19p13.1 and *ZNF365* (10q21.2) as risk factors for breast cancer among *BRCA1* and *BRCA2* mutation carriers, respectively. We explored associations with ovarian cancer and with breast cancer by tumor histopathology for these variants in mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).

Methods—Genotyping data for 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers from 40 studies were combined.

Results—We confirmed associations between rs8170 at 19p13.1 and breast cancer risk for *BRCA1* mutation carriers (hazard ratio (HR)=1.17; 95%CI 1.07–1.27; $p=7.42 \times 10^{-4}$) and between rs16917302 at *ZNF365* (HR=0.84; 95%CI 0.73–0.97; $p=0.017$) but not rs311499 at 20q13.3 (HR=1.11; 95%CI 0.94–1.31; $p=0.22$) and breast cancer risk for *BRCA2* mutation carriers. Analyses based on tumor histopathology showed that 19p13 variants were predominantly associated with estrogen receptor (ER)-negative breast cancer for both *BRCA1* and *BRCA2* mutation carriers, whereas rs16917302 at *ZNF365* was mainly associated with ER-positive breast cancer for both *BRCA1* and *BRCA2* mutation carriers. We also found for the first time that rs67397200 at 19p13.1 was associated with an increased risk of ovarian cancer for *BRCA1* (HR=1.16; 95%CI 1.05–1.29; $p=3.8 \times 10^{-4}$) and *BRCA2* mutation carriers (HR=1.30; 95%CI 1.10–1.52; $p=1.8 \times 10^{-3}$).

Conclusions—19p13.1 and *ZNF365* are susceptibility loci for ovarian cancer and ER subtypes of breast cancer among *BRCA1* and *BRCA2* mutation carriers.

Impact—These findings can lead to an improved understanding of tumor development and may prove useful for breast and ovarian cancer risk prediction for *BRCA1* and *BRCA2* mutation carriers.

Keywords

BRCA1; BRCA2; breast cancer risk; ovarian cancer risk; 19p13.1; ZNF365

Introduction

Genome-wide association studies (GWAS) have been used to identify several loci containing common variants that are associated ($p < 1.0 \times 10^{-7}$) with breast cancer risk in the general population. Variants from twelve of these loci have also been investigated as modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers (1–3). While only variants in *CASP8*, *TOX3*, 2q35, and 6q25.1 have been associated with breast cancer risk in *BRCA1* mutation carriers, variants in *FGFR2*, *TNRC9/TOX3*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7/NEK10*, 5p12 and 1p11.2 loci have been associated with breast cancer in *BRCA2* mutation carriers (1–3). This is consistent with the known associations between these SNPs and estrogen receptor (ER) status of breast cancers in the general population (4).

Most recently, a GWAS of *BRCA1* mutation carriers conducted through CIMBA identified five SNPs on 19p13 that were associated with breast cancer risk for *BRCA1* mutation carriers (5). Two of these showed independent associations (rs8170 hazard ratio (HR)=1.26; 95% CI 1.17–1.35; $P_{\text{trend}} = 2.3 \times 10^{-9}$ and rs2363956 HR=0.84; 95% CI 0.80–0.89; $P_{\text{trend}} = 5.5 \times 10^{-9}$). Imputation analysis of the 19p13 region, using 1000 Genomes Project data, identified several correlated SNPs with more significant associations than rs8170 and rs2363956. The 19p13.1 locus was also found to be associated with ER negative breast cancer (rs8170 OR=1.21, $p=0.003$) and triple negative breast cancer (tumors lacking expression of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)) (rs8170 OR=1.28, $p=1.2 \times 10^{-6}$) in the general population (5). In addition, the 19p13.1 locus has been associated with ovarian cancer in the general population (rs8170 OR=1.12; $p=3.6 \times 10^{-6}$) (6), but was not found to be associated with ovarian cancer in *BRCA1* mutation carriers (rs8170 HR=1.07; $p=0.33$) (5). A separate GWAS in *BRCA2* mutation carriers identified two breast cancer susceptibility alleles (rs16917302 at *ZNF365* (10q21.2), HR=0.75; 95% CI 0.66–0.86; $p=3.8 \times 10^{-5}$ and rs311499 at 20q13.33, HR=0.72; 95% CI 0.61–0.85; $p=6.6 \times 10^{-5}$) (7). A weakly correlated SNP at the *ZNF365* locus (rs10995190) has also been associated with breast cancer overall (OR=0.83; $p=5.1 \times 10^{-15}$) and ER positive ($p=4.1 \times 10^{-6}$) but not ER negative breast cancer in the general population (8).

Here, we genotyped more than 12,000 *BRCA1* and 7,000 *BRCA2* mutation carriers from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), for the previously genotyped variant at 19p13.1, rs8170, and one of the imputed SNPs that was found to have a stronger association with breast cancer risk for *BRCA1* mutation carriers (rs67397200). We also genotyped SNPs at *ZNF365* (rs16917302), and 20q13.3 (rs311499) in an effort to verify these loci as risk factors for ovarian cancer and to further validate these loci as risk factors for breast cancer in *BRCA1* and *BRCA2* mutation carriers.

Materials and Methods

Subjects

All mutation carriers participated in clinical or research studies at the host institutions under ethically approved protocols and provided written informed consent. Subjects were *BRCA1* and *BRCA2* mutation carriers recruited by 40 study centers in 22 countries and assembled through the CIMBA initiative (Supplementary Table 1). The majority were recruited through cancer genetics clinics and enrolled into national or regional studies. Others were

identified in research studies of high-risk families, by population-based sampling of cases and some by community recruitment. Eligibility to participate in CIMBA is restricted to female carriers of pathogenic *BRCA1* or *BRCA2* mutations, defined by generally recognized criteria (Breast Cancer Information Core), who were 18 years old or older at recruitment. Information collected included the year of birth; mutation description (including nucleotide position and base change); age at last follow-up; ages at breast and ovarian cancer diagnoses; and age or date at bilateral prophylactic mastectomy. Information was also available on the country of residence. Related individuals were identified through a unique family identifier. Women with pathogenic mutations in both *BRCA1* and *BRCA2* were excluded from the current analysis. The primary analysis was restricted to women self-reported as “white European”. Overlap of carriers between studies was evaluated by comparing the year of birth, exact mutation description, the reported ages, and previous SNP genotype data available within the CIMBA database. Duplicated mutation carriers were included only once in the analysis.

Genotyping

Rs311499 at 20q13.3, rs16917302 at *ZNF365* and both rs8170 and rs67397200 at 19p13.1 were genotyped using the iPLEX Mass Array platform at four genotyping centers as part of a larger study of 24 candidate SNPs. All centers included at least 2% duplicate samples and a random mixture of affected and unaffected carriers on each plate. Samples that failed for five or more of the SNPs genotyped were excluded from the analysis. Studies with a SNP call rate of <95% were excluded from the analysis of the SNP. The concordance between duplicates had to be at least 98%. To assess the accuracy of genotyping across genotyping centers, all centers genotyped 95 DNA samples from a standard test plate (Coriell Institute) for all SNPs. Genotyping centers with more than one concordance failure on the test plate for a SNP were excluded for analyses of that SNP. Deviation from Hardy-Weinberg equilibrium (HWE) was assessed for unrelated subjects separately for each SNP and study. The observed genotype frequencies were not significantly different from the expected under HWE for any of the SNPs and studies. After the above exclusions, a total of 19,731 unique mutation carriers (12,599 *BRCA1* and 7,132 *BRCA2*) from 40 studies had an observed genotype for at least one SNP (Supplementary Table 1).

Tumor pathology data collection

Tumor pathology data were collected from patient pathology reports, medical records, pathology review data, tumor registry records and results from tissue microarrays. ER status was identified as negative or positive, with immunohistochemistry scoring data and methodology provided when available. Most studies applied a cut-off of >10% tumor cells stained positive for ER positive status. For a small number of cases, where other scoring methods based on the proportion and intensity of staining were applied (Allred score, Remmele score and H-score), widely-accepted cut-offs were used. Consistency checks were performed to validate receptor data against supplementary scoring information if provided.

Statistical analysis

The aim of the primary analysis was to evaluate the association between each genotype and breast cancer risk. We conducted the analysis by modelling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described (9). The phenotype of each individual was defined by age at diagnosis of breast cancer or age at last follow-up. Individuals were censored at the earliest of age of first breast cancer diagnosis, ovarian cancer diagnosis, bilateral prophylactic mastectomy or age at last observation. Mutation carriers censored at ovarian cancer diagnosis were considered unaffected in the analysis of breast cancer. The effect of each SNP was modelled either as a per-allele HR (multiplicative model) or as separate HRs for heterozygotes and homozygotes.

We used a Cox proportional-hazards model and tested the assumption of proportional hazards by adding a “genotype×age” interaction term in order to fit models in which the HR changed with age. We examined heterogeneity across studies by comparing models that allowed for study-specific log-hazard ratios against models in which the same log-hazard ratio was assumed to apply to all studies. All analyses were stratified by country of residence and applied cohort specific breast cancer incidence rates for *BRCA1* and *BRCA2* (10). A robust variance-estimation approach was used to adjust for the non-independence among related carriers.

To evaluate the evidence of replication for each of the SNPs, analyses were restricted to mutation carriers who had not been used in any of the previous *BRCA1* and *BRCA2* studies. The number of new samples used in each of the SNP analyses are shown in Supplementary Table 2. In addition, analysis were performed using all available *BRCA1* and *BRCA2* carriers. The combined effects of the SNPs on breast cancer risk, were evaluated by fitting retrospective likelihood models while allowing for linkage disequilibrium between the loci. To test for potential effects of survival bias, prevalent cases, defined as mutation carriers diagnosed more than five years prior to the age at recruitment, were excluded. Associations with specific functional class of mutation were also assessed. Class 1 mutations are predicted to undergo nonsense mediated RNA decay resulting in reduced levels of mutant transcript while Class 2 mutations are predicted to generate stable mutant proteins (11). The associations with breast cancer subtypes defined by the estrogen receptor (ER) status of the tumors in *BRCA1* and *BRCA2* mutation carriers were assessed by an extension of the retrospective likelihood approach that models the simultaneous effect of each SNP on more than one tumor subtype (12). Associations with ovarian cancer risk were evaluated within a competing risk analysis framework (13) by estimating HRs simultaneously for breast and ovarian cancers. Since each mutation carrier was at risk of breast and ovarian cancer we assumed that the probabilities of developing each disease were independent conditional on the underlying genotype. In this analysis, individuals were followed to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. Individuals were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and were assumed to be unaffected for the corresponding disease. The remaining individuals were censored at the age at last observation and were assumed to be unaffected for both diseases.

Results

After quality control exclusions, genotype data from 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers including 5,408 *BRCA1* and 3,780 *BRCA2* mutation carriers not studied in the original GWAS were available for analysis. Of the *BRCA1* mutation carriers, 6,390 were affected with breast cancer and 6,209 were considered unaffected in the breast cancer analysis (censored at bilateral prophylactic mastectomy, ovarian cancer, or age at last follow up). Similarly, among the *BRCA2* mutation carriers, 3,810 were affected with breast cancer and 3,322 were unaffected. The characteristics of these mutation carriers are shown in Table 1 and the origins of the samples are summarized in Supplementary Table 1.

The associations between breast cancer risk in *BRCA1* and *BRCA2* mutation carriers and the minor alleles of rs8170 and rs67397200 (19p13.1), rs16917302 (*ZNF365*), and rs311499 (20q13.33) are summarized in Table 2. The minor allele of rs8170 at 19p13.1 was strongly associated with risk of breast cancer in *BRCA1* mutation carriers (HR=1.20; 95%CI 1.13–1.28; $p=8.7\times 10^{-9}$) but not *BRCA2* mutation carriers. This result for 12,599 *BRCA1* mutation carriers was consistent with the original finding in the *BRCA1* GWAS using 8,363 *BRCA1* mutation carriers (HR=1.26; 95%CI 1.17–1.35; $p=2.3\times 10^{-9}$). A separate analysis restricted to carriers not used in the *BRCA1* GWAS also confirmed the association

(HR=1.17; 95%CI 1.07–1.27; $p=7.42\times 10^{-4}$) (Supplementary Table 2). Similarly, rs67397200 at 19p13.1, which was imputed in the *BRCA1* GWAS, was strongly associated with breast cancer risk in *BRCA1* carriers (HR=1.17; 95%CI 1.11–1.23; $p=2.4\times 10^{-8}$) (Table 2). There was no evidence of heterogeneity in the HRs across studies for *BRCA1* mutation carriers (Figure 1). However, there was evidence that the per-allele HRs in *BRCA1* mutation carriers for rs8170 ($p=0.015$) and rs67397200 ($p=0.007$) at 19p13.1 decreased with increasing age of diagnosis of breast cancer. Since rs8170 and rs67397200 are located in the same region of 19p13.1 ($r^2=0.58$), we conducted an analysis for the joint effects of these SNPs on breast cancer risk in *BRCA1* mutation carriers ($n=10,173$). When accounting for haplotype structure, rs67397200 remained significant (P for inclusion= 2.75×10^{-3}) and was retained in the model, whereas rs8170 was excluded (P for inclusion=0.18). Rs8170 and rs67397200 were not associated with breast cancer risk for *BRCA2* mutation carriers (Table 2).

Among SNPs identified from the original *BRCA2* GWAS, an analysis of genotype data from 7,132 *BRCA2* mutation carriers confirmed that rs16917302 at the *ZNF365* locus was associated with a decreased risk of breast cancer (HR=0.83; 95%CI 0.75–0.93; $p=7.0\times 10^{-4}$). The association also replicated in the additional carriers, not previously included in the *BRCA2* GWAS (HR=0.84; 95%CI 0.73–0.97; $p=0.017$) (Supplementary Table 2). In contrast, rs311499 from 20q13.3, which was associated with breast cancer risk in the *BRCA2* GWAS (HR=0.72; 95%CI 0.61–0.85; $p=6.6\times 10^{-5}$) (7), was not associated with risk of breast cancer in *BRCA2* carriers in the overall analysis (HR=0.95; 95%CI 0.84–1.07; $p=0.36$) (Table 2) nor the replication study (HR=1.11; 95%CI 0.94–1.31; $p=0.22$) (Supplementary Table 2). There was no evidence for heterogeneity in the HRs across studies for *BRCA2* mutation carriers (Figure 1). HRs for rs16917302 and rs311499 did not vary by age at diagnosis.

To determine whether the inclusion of long-term survivors influenced the results, we repeated our analyses of the four SNPs, excluding *BRCA1* and *BRCA2* mutation carriers diagnosed with breast cancer more than five years before recruitment (prevalent cases). The strength of the associations for rs16917302 at *ZNF365* (per-allele HR=0.85) for *BRCA2* mutation carriers, and for rs8170 (per-allele HR=1.19) and rs67397200 at 19p13.1 (per-allele HR=1.16) for *BRCA1* mutation carriers were essentially unchanged (Supplementary Table 3). There was no influence of mutation type for *BRCA1* mutation carriers on breast cancer risk in the associations between mutations conferring susceptibility to nonsense mediated RNA decay (NMD) (Class 1) and missense or truncating mutations not triggering NMD (Class 2) for any of the SNPs (Supplementary Table 4).

Breast tumors in *BRCA1* mutation carriers are predominantly ER-negative (14) and rs8170 from 19p13.1 is strongly associated with ER-negative but not ER-positive breast cancer in the general population (5). Because of these previous findings, we evaluated whether rs8170 and rs67397200 at 19p13.1, as well as rs311499 at 20q13.3 and rs16917302 at *ZNF365*, were differentially associated with ER-positive and/or ER-negative tumor status in *BRCA1* and *BRCA2* mutation carriers. Although the stratified results suggested a slightly stronger association for the 19p13.1 rs67397200 SNP with ER-negative disease than with ER-positive disease in *BRCA1* mutation carriers (per allele ER-negative HR=1.22; 95%CI 1.14–1.30; $p=4.4\times 10^{-9}$; per allele ER-positive HR=1.14; 95%CI 1.01–1.30; $p=0.040$), the difference was not significant ($p=0.41$) (Table 3). Rs67397200, however, was associated with ER-negative disease (per allele HR=1.29; 95%CI 1.11–1.49; $p=8.7\times 10^{-4}$) but not ER-positive disease (per allele HR=0.92; 95%CI 0.85–1.01; $p=0.074$) in *BRCA2* mutation carriers (p -heterogeneity= 1.5×10^{-4}) (Table 3). The lack of association with rs311499 at 20q13.3 did not vary by ER-status in *BRCA1* or *BRCA2* mutation carriers. For *BRCA2* mutation carriers, the minor allele of rs16917302 at *ZNF365* was inversely associated with

both ER-positive (per allele HR=0.86; 95% CI 0.75–0.97; p=0.016) and ER-negative tumors (per allele HR=0.79; 95% CI 0.62–1.00; p=0.048) (p-heterogeneity=0.56) (Table 3). However, in *BRCA1* mutation carriers rs16917302 was associated with ER-positive (per allele ER-positive HR=0.77; 95% CI 0.62–0.95; p=0.016), but not ER-negative status (p-heterogeneity=0.028) (Table 3).

BRCA1 and *BRCA2* mutations are associated with elevated risk of ovarian cancer. In this CIMBA study 1,465 *BRCA1* mutation carriers and 453 *BRCA2* mutation carriers who developed ovarian cancer were also genotyped for the four SNPs under study. To assess the influence of these SNPs on ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers we used a competing risk analysis that evaluated the associations with breast and ovarian cancer risk simultaneously. While previous studies did not detect an association between rs8170 at 19p13.1 and ovarian cancer in *BRCA1* or *BRCA2* mutation carriers (5), in this competing risk analysis with larger numbers of *BRCA1* and *BRCA2* mutation carriers, rs8170 was significantly associated with ovarian cancer risk in both *BRCA1* (HR=1.15; 95% CI 1.03–1.29; p=0.015) and *BRCA2* (HR=1.34; 95% CI 1.12–1.62; p=1.9×10⁻³) mutation carriers (Table 4). Similarly rs67397200 at 19p13.1 was associated with ovarian cancer risk in both *BRCA1* (HR=1.16; 95% CI 1.05–1.29; p=3.8×10⁻⁴) and *BRCA2* (HR=1.30; 95% CI 1.10–1.52; p=1.8×10⁻³) mutation carriers (Table 4). Rs311499 at 20q13.3 and rs16917302 at *ZNF365* were not associated with ovarian cancer risk for either *BRCA1* or *BRCA2* mutation carriers (Table 4).

Discussion

GWAS of *BRCA1* and *BRCA2* mutation carriers previously identified variants at 19p13.1, *ZNF365* and 20q13.3 as candidate breast cancer risk modifiers (5, 7). In this study, we further evaluated associations between variants at these loci and both breast and ovarian cancer in *BRCA1* and *BRCA2* mutation carriers. For the first time, we found that both rs8170 and the previously imputed rs67397200 at 19p13.1 were strongly associated with ovarian cancer in both *BRCA1* and *BRCA2* mutation carriers. In addition, we found that rs8170 and rs67397200 at 19p13.1 were associated with breast cancer risk for *BRCA1* and rs16917302 at *ZNF365* was associated with breast cancer in *BRCA2* mutation carriers in this replication study using an independent set of mutation carriers and in the combined analyses of data from the original study and the replication study. In contrast, rs311499 at 20q13.3 showed no association with breast cancer in the replication study. We also report for the first time that the *BRCA1* GWAS SNP rs67397200 is associated with ER-negative breast cancer in *BRCA2* mutation carriers and that the *BRCA2* GWAS SNP rs16917302 is associated with ER-positive disease in *BRCA1* mutation carriers.

The GWAS for breast cancer in *BRCA1* mutation carriers originally identified significant associations between variants at the 19p13.1 locus and risk of breast cancer. Five SNPs including rs8170 from a 39 kb region were associated with risk of disease. In an analysis of joint effects of these SNPs on breast cancer risk, the best model included rs8170 or rs4808611 and rs8100241 or rs2363956 (P for inclusion=7.7×10⁻⁵ and P=6.7×10⁻⁵ for rs8170 and rs8100241, respectively) (5), suggesting that the associations were driven by a single causative variant partially correlated with all five SNPs. Imputation of additional SNPs in the region from the 1000 Genome Project identified eight perfectly correlated SNPs within a 13-kb region that were more significantly associated with breast cancer risk. Of these, we chose rs67397200, which has an $r^2=0.58$ with rs8170 and $r^2=0.37$ with rs8100241/rs2363956, for further genotyping in an effort to determine whether this SNP (or one of the seven other highly correlated SNPs) exhibited stronger associations with breast cancer. In an analysis of rs8170 in 11,669 and rs67397200 in 10,312 *BRCA1* mutation carriers, we observed similarly strong associations with breast cancer for *BRCA1* mutation carriers. In a

joint analysis of rs8170 and rs67397200, allowing for haplotype structure, only rs67397200 remained significant. We were unable to genotype some of the original GWAS SNPs (rs2363956/rs8100241) in the present study and, as a consequence, could not evaluate the joint associations with rs67397200. It is therefore still unclear whether rs67397200 accounts solely for the association signal. The 35kb region containing rs8170 and rs67397200 includes the *ABHD8* (abhydrolase domain containing 8), *ANKLE1* (ankyrin repeat and LEM domain containing 1) and *C19orf62* genes. *C19orf62*, encodes MERIT40 (Mediator of Rap80 Interactions and Targeting 40 kD), a BRCA1 interacting protein that forms a complex with BRCA1-BARD1, Abraxas1, RAP80, BRCC36 and BRCC45 and is required for recruitment and retention of the BRCA1-BARD1 ubiquitin ligase at sites of DNA damage (15). Because alterations in MERIT40 expression or function may modify *BRCA1* activity, variants in the *C19orf62* locus are attractive candidate breast cancer risk modifiers. However, since rs67397200 and the seven other imputed SNPs, that showed the most significant associations with breast cancer risk in *BRCA1* mutation carriers, are located at the 3' end of *ANKLE1* near *ABHD8* it is also possible that one of these genes rather than *C19orf62* is influenced by the underlying causative variants in this region. Further comprehensive genotyping of other common variants and/or rare SNPs from this locus and detailed functional studies will be required to resolve this issue.

Our GWAS for breast cancer in *BRCA2* mutation carriers previously identified strong associations between rs16917302 in the *ZNF365* (dbGENE id: 22891) locus and breast cancer (7). We have now replicated this association for *BRCA2* mutation carriers. Rs16917302 is located within intron 4 of *ZNF365* and is unique to isoform C, the longest of the four isoforms created by alternative splicing sites (16). In independent studies, rs10995195 in *ZNF365*, which is 27kb upstream from and only weakly correlated ($r^2=0.1$) with rs16917302, has been associated with breast cancer risk (8) and with mammographic density (17) in the general population. In addition, a cluster of SNPs located 154kb from rs16917302 in isoform D of *ZNF365* has been associated with Crohn's disease (18–20), and the region has also been implicated in family-based linkage analyses with uric acid nephrolithiasis (21) and hypotrichosis (22). It is unclear whether there is genetic or biologic linkage between these seemingly disparate phenotypes. Further fine-mapping of the *ZNF365* region and functional analyses will be needed to identify the causative variants for each phenotype and to understand the downstream biological effects.

Likewise, rs311499 at 20q13.3 was associated with breast cancer risk in *BRCA2* mutation carriers in the *BRCA2* GWAS (per allele HR=0.72; 95% CI 0.61–0.85; $p=6.6\times 10^{-5}$). However, this association was not confirmed in the replication study described above (HR=1.11; 95% CI 0.94–1.31; $p=0.22$) or in the combined analysis of the discovery and replication stages (HR=0.95; 95% CI 0.84–1.07; $p=0.36$). This result was not unexpected because the association between rs311499 and breast cancer did not reach significance ($p<0.05$) in Stage 2 of the *BRCA2* GWAS (HR=0.86; 95% CI 0.67–1.06; $p=0.13$) (7).

To further characterize the influence of the 19p13.1 and *ZNF365* loci on breast cancer risk, we assessed the strength of association with ER-negative and ER-positive breast cancer in *BRCA1* and *BRCA2* mutation carriers. As reported above, rs67397200 at 19p13.1 was associated with both ER-negative and ER-positive breast cancer in *BRCA1* mutation carriers, whereas rs8170 at 19p13.1 was only associated with ER-negative disease. Interestingly, rs67397200 and rs8170 were also associated with ER-negative breast cancer but not ER-positive breast cancer in *BRCA2* mutation carriers. This is consistent with our previous finding that rs8170 at 19p13.1 is more strongly associated with ER-negative than ER-positive breast cancer in the general population (5). Given that the majority of *BRCA1* breast tumors exhibit a basal breast cancer phenotype (14), it remains to be determined

whether ER-positive basal cases account for the mild association with ER-positive disease in *BRCA1* mutation carriers.

In contrast, we found that rs16917302 in the *ZNF365* locus was associated with both ER-positive and ER-negative disease in *BRCA2* mutation carriers. This was consistent with associations for both ER-positive and ER-negative breast cancer in a recent GWAS of breast cancer cases with a family history of the disease (8). In contrast, among *BRCA1* mutation carriers the association with breast cancer risk was restricted to ER-positive cases. This suggests that refinement of phenotype, perhaps in specific subpopulations, may result in detection of previously hidden associations.

Ovarian cancer is an important component of the cancer phenotype in both *BRCA1* and *BRCA2* mutation carriers. Because breast and ovarian cancer can occur in the same mutation carriers, it has been suggested that susceptibility SNPs common to breast and ovarian cancer may exist in these populations. However, to date none of the SNPs associated with breast cancer risk in *BRCA1* or *BRCA2* mutation carriers have been associated with ovarian cancer risk. Similarly, SNPs in the *BCN2* locus that are associated with ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers are not associated with breast cancer risk (13). Furthermore, in the general population, only SNPs in the 8q24 locus are known to influence both breast and ovarian cancer, and these appear to be independent disease-specific effects (23). Thus, the recent finding that SNPs at 19p13.1 were associated with breast cancer in *BRCA1* mutation carriers (5) and also with ovarian cancer in the general population (6) raised the possibility that a locus with common influences on breast and ovarian cancer does exist. However, the *BRCA1* GWAS failed to detect any association for 19p13.1 SNPs with ovarian cancer among *BRCA1* mutation carriers (843 ovarian cases) (HR=1.07; 95%CI 0.93–1.24; p=0.33) (5). Here we re-evaluated associations between 19p13.1 SNPs and ovarian cancer using larger numbers of *BRCA1* (n=1312) and *BRCA2* (n=429) carriers diagnosed with ovarian cancer. Rs67397200 at 19p13.1 was associated with ovarian cancer risk in both *BRCA1* (HR=1.16; 95%CI 1.05–1.29; p=3.8×10⁻⁴) and *BRCA2* (HR=1.30; 95%CI 1.10–1.52; p=1.8×10⁻³) mutation carriers. The magnitude of the effect on ovarian cancer risk in *BRCA1* carriers (HR=1.16) was similar to that observed for breast cancer. This is the first locus found to influence both breast and ovarian cancer risk in either *BRCA1* or *BRCA2* mutation carriers.

Including the SNPs from the present study, six loci are now known to modify the risk of breast cancer for *BRCA1* mutation carriers (*CASP8*, *TOX3*, 2q35, 6q25.1, 19p13, and *ZNF365* (ER-positive disease only)) (1–3, 5, 10, 24) and ten loci are known to modify the risk of breast cancer for *BRCA2* mutation carriers (*FGFR2*, *TOX3*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7*, 5p12, *ZNF365*, 1p11.2 and 19p13.1 (ER-negative only)) (5, 7, 10, 24). Taken together, these SNPs result in large variation in the absolute risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers and may further improve our ability to provide individualized risks of breast cancer for *BRCA1* and *BRCA2* mutation carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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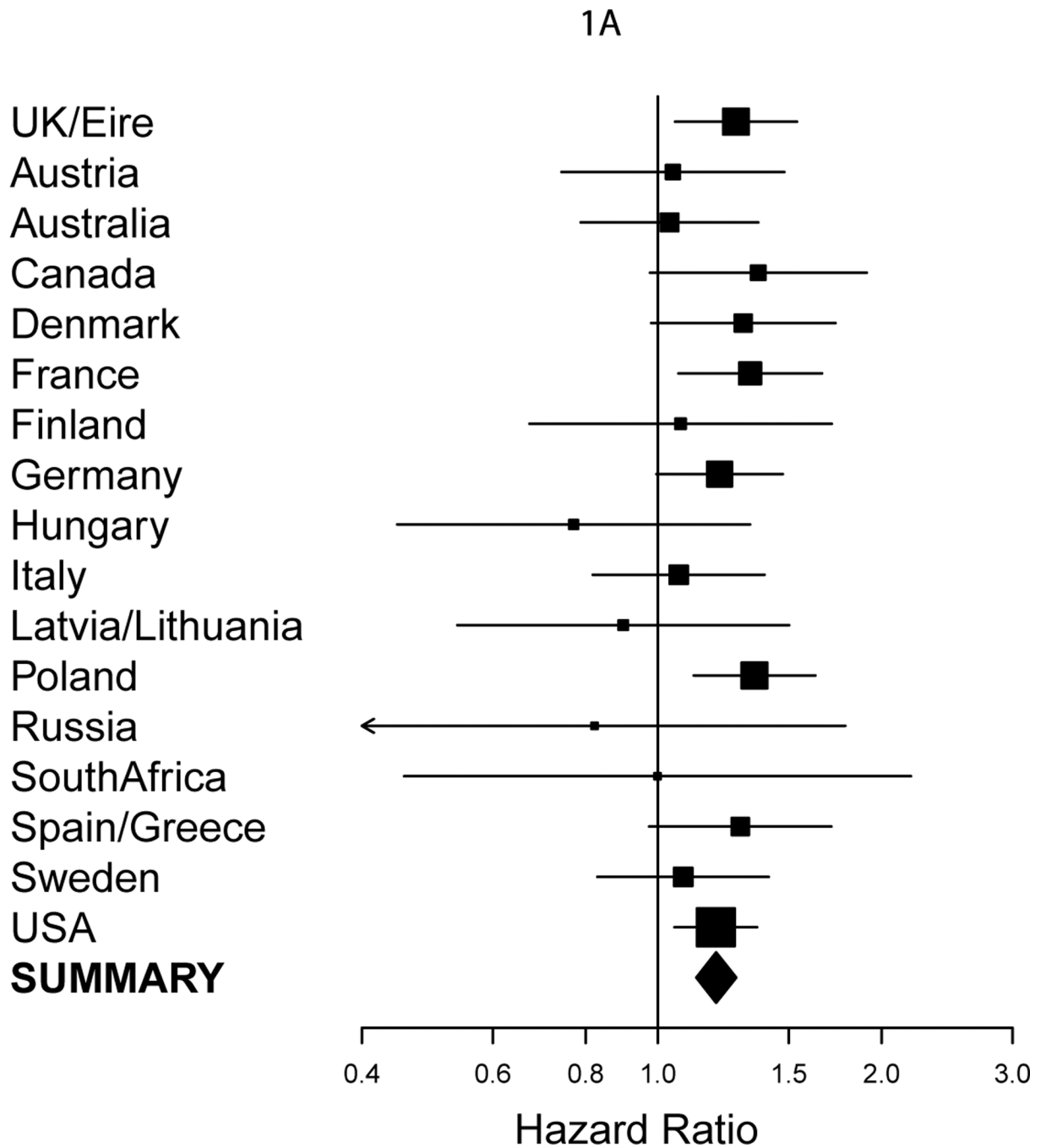
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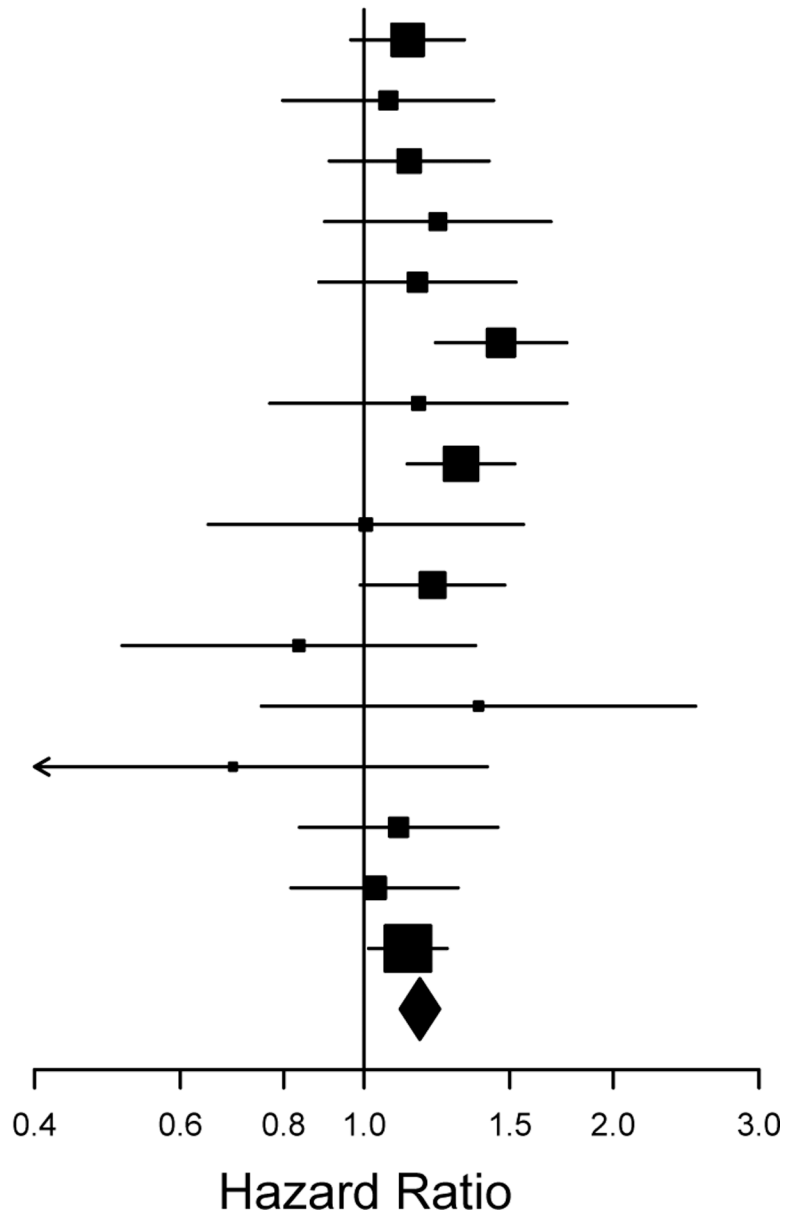
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1B

- UK/Eire
- Austria
- Australia
- Canada
- Denmark
- France
- Finland
- Germany
- Hungary
- Italy
- Latvia/Lithuania
- Russia
- SouthAfrica
- Spain/Greece
- Sweden
- USA
- SUMMARY**



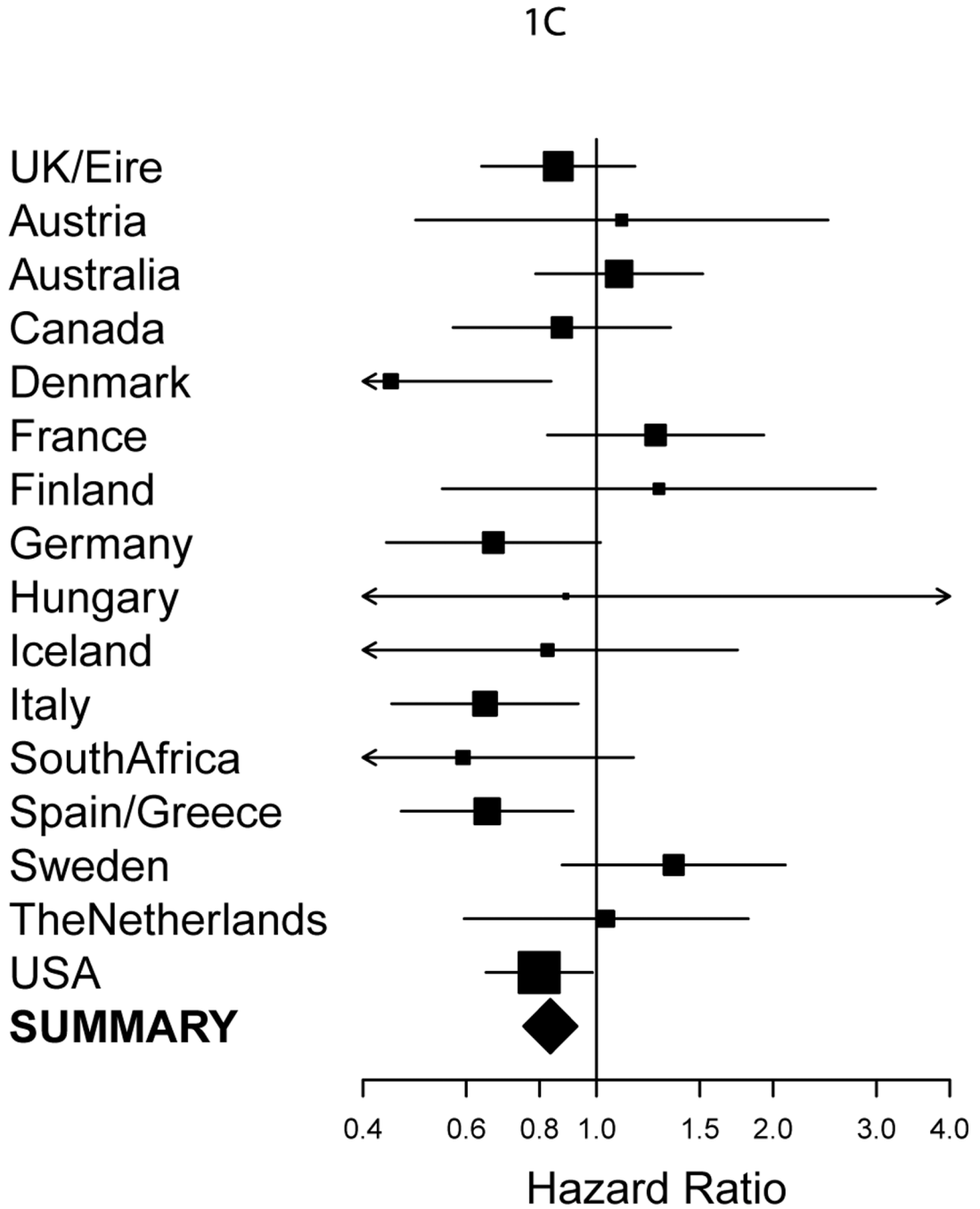


Figure 1. Forest plots of the associations by country of residence of *BRCA1* and *BRCA2* mutation carriers with breast cancer risk overall

(A–C) Squares indicate the country specific per-allele HR estimates for SNPs (A) rs8170 for *BRCA1* mutation carriers, (B) rs67397200 for *BRCA1* mutation carriers and (C) rs16917302 for *BRCA2* mutation carriers. The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% Confidence Intervals (CIs).

Table 1Summary characteristics for the 19,731 eligible *BRCA1* and *BRCA2* mutation carriers* used in the analysis

Characteristic	<i>BRCA1</i>		<i>BRCA2</i>	
	Unaffected	Breast Cancer	Unaffected	Breast Cancer
Number	6209	6390	3322	3810
Person-Years follow-up	264903	263068	147053	168201
Median Age at Censure (IQR ¹)	42 (34–50)	40 (34–47)	43 (34–53)	43 (37–50)
Age at Censure, N (%)				
<30	1189 (19.2)	691 (10.8)	611 (18.4)	306 (8.0)
30–39	1661 (26.8)	2445 (38.3)	834 (25.1)	1141 (30.0)
40–49	1765 (28.4)	2191 (34.3)	865 (26.0)	1394 (36.6)
50–59	1058 (17.0)	812 (12.7)	566 (17.0)	687 (18.0)
60–69	380 (6.1)	198 (3.1)	302 (9.1)	226 (5.9)
70+	156 (2.5)	53 (0.8)	144 (4.3)	56 (1.5)
Year of birth, N (%)				
<1920	28 (0.5)	30 (0.5)	23 (0.7)	44 (1.2)
1920–29	131 (2.1)	196 (3.1)	99 (3.0)	167 (4.4)
1930–39	369 (5.9)	516 (8.1)	232 (7.0)	430 (11.3)
1940–49	832 (13.4)	1341 (21.0)	458 (13.8)	896 (23.5)
1950–59	1409 (22.7)	1989 (31.1)	691 (20.8)	1160 (30.5)
1960–69	1703 (27.4)	1666 (26.1)	902 (27.2)	868 (22.8)
1970+	1737 (28.0)	652 (10.2)	917 (27.6)	245 (6.4)
Mutation Class, N (%)				
Class 1 ²	4063 (65.4)	3878 (60.7)	3114 (93.7)	3520 (92.4)
Class 2 ²	1780 (28.7)	1973 (30.9)	72 (2.2)	100 (2.6)
Other	366 (5.9)	539 (8.4)	136 (4.1)	190 (5.0)

¹IQR: Interquartile range²See methods for definitions

* Carriers of self reported European ancestry only.

Table 2

Evaluation of associations between SNPs and breast cancer risk among *BRCA1* and *BRCA2* mutation carriers of European ancestry

SNP/ Mutation	Genotype	Unaffected N (%)	Affected ^a N (%)	HR	95% CI	p-value
rs8170 – 19p13.1						
<i>BRCA 1</i>	GG	3870 (67.5)	3755 (63.3)	1.00		
	AG	1689 (29.4)	1950 (32.9)	1.22	1.14 – 1.31	
	AA	178 (3.1)	227 (3.8)	1.35	1.13 – 1.62	
	per allele			1.20	1.13 – 1.28	8.7×10 ⁻⁹
<i>BRCA 2</i>						
	GG	2047 (66.3)	2501 (68.2)	1.00		
	AG	931 (30.2)	1026 (28.0)	0.93	0.84 – 1.03	
	AA	108 (3.5)	138 (3.8)	1.16	0.89 – 1.52	
	per allele			0.98	0.90 – 1.07	0.67
rs67397200 – 19p13.1						
<i>BRCA 1</i>	CC	2536 (51.0)	2455 (46.0)	1.00		
	GC	2022 (40.6)	2397 (44.9)	1.24	1.16 – 1.34	
	GG	415 (8.4)	487 (9.1)	1.25	1.10 – 1.43	
	per allele			1.17	1.11 – 1.23	2.4×10 ⁻⁸
<i>BRCA 2</i>						
	CC	1553 (49.8)	1871 (50.7)	1.00		
	GC	1302 (41.7)	1494 (40.5)	0.95	0.87 – 1.04	
	GG	265 (8.5)	323 (8.8)	1.07	0.91 – 1.27	
	per allele			1.00	0.93 – 1.07	0.97
rs311499 – 20q13.3						
<i>BRCA 1</i>	GG	5346 (86.2)	5484 (85.9)	1.00		
	AG	816 (13.2)	873 (13.7)	1.03	0.94 – 1.13	
	AA	41 (0.7)	28 (0.4)	0.67	0.42 – 1.08	
	per allele			1.00	0.91 – 1.09	0.94
<i>BRCA 1</i>	GG	2873 (86.6)	3312 (87.0)	1.00		
	AG	429 (13.0)	475 (12.5)	0.94	0.82 – 1.07	
	AA	16 (0.5)	21 (0.6)	0.97	0.60 – 1.57	
	per allele			0.95	0.84 – 1.07	0.36

SNP/ Mutation	Genotype	Unaffected N (%)	Affected ^a N (%)	HR	95% CI	p-value
rs16917302 - 10q21.2						
<i>BRCA 1</i>	AA	4913 (79.3)	5084 (79.7)	1.00		
	CA	1216 (19.6)	1222 (19.2)	0.96	0.88 – 1.01	
	CC	71 (1.1)	73 (1.1)	0.94	0.69 – 1.27	
	per allele			0.96	0.89 – 1.03	0.27
<i>BRCA 2</i>	AA	2583 (77.9)	3101 (81.5)	1.00		
	CA	691 (20.8)	674 (17.7)	0.82	0.74 – 0.92	
	CC	41 (1.2)	32 (0.8)	0.78	0.49 – 1.23	
	per allele			0.83	0.75 – 0.93	7.0×10 ⁻⁴

^aBreast cancer

Table 3

Associations between SNPs and breast cancer risk by estrogen receptor (ER) status of breast cancer cases among women with *BRCA1* and *BRCA2* mutations

SNP/	Unaff	Affected ^a (N)		ER+		ER-		Case het	
Mutation	N	ER-	ER+	HR	95% CI	p-trend	HR	95% CI	p-trend
rs8170 – 19p13.1									
<i>BRCA1</i>	4483	1820	541	1.12	0.96 – 1.29	0.15	1.23	1.14 – 1.33	2.0×10 ⁻⁷
<i>BRCA2</i>	2738	401	1343	0.94	0.85 – 1.05	0.26	1.18	0.99 – 1.40	0.058
rs67397200 – 19p13.1									
<i>BRCA1</i>	4486	1821	542	1.14	1.01 – 1.30	0.040	1.22	1.14 – 1.30	4.4×10 ⁻⁹
<i>BRCA2</i>	2733	401	1349	0.92	0.85 – 1.01	0.074	1.29	1.11 – 1.49	8.7×10 ⁻⁴
rs311499 – 20q13.3									
<i>BRCA1</i>	4898	1890	559	1.07	0.87 – 1.31	0.51	0.95	0.85 – 1.06	0.35
<i>BRCA2</i>	2930	406	1372	0.95	0.82 – 1.09	0.48	0.83	0.63 – 1.10	0.19
rs16917302 - 10q21.2									
<i>BRCA1</i>	4897	1888	558	0.77	0.62 – 0.95	0.016	1.01	0.92 – 1.11	0.85
<i>BRCA2</i>	2927	406	1372	0.86	0.75 – 0.97	0.016	0.79	0.62 – 1.00	0.048

^aBreast cancer

^bp-value for heterogeneity in the associations with ER+positive and ER–negative breast cancer

ER+: ER positive, ER–: ER negative, Unaff: Unaffected

Table 4

Associations with SNPs and breast and ovarian cancer risk using a competing risk analysis model among *BRCA1* and *BRCA2* mutation carriers of European ancestry

SNP/	Unaffected		Breast Cancer		Ovarian Cancer		Breast Cancer		Ovarian Cancer	
Mutation	Genotype	N (%)	N (%)	HR	95% CI	p-value	HR	95% CI	p-value	
rs8170 – 19p13.1										
<i>BRCA1</i>	GG	2972 (67.9)	3730 (63.3)	923 (66.0)	1.00		1.00			
	AG	1269 (29.0)	1936 (32.9)	434 (31.0)	1.26	1.17 – 1.36	1.23	1.08 – 1.42		
	AA	139 (3.2)	224 (3.8)	42 (3.0)	1.34	1.10 – 1.63	1.04	0.72 – 1.50		
	per allele				1.22	1.14 – 1.30	2.1 × 10 ⁻⁹	1.15	1.03 – 1.29	0.015
<i>BRCA2</i>	GG	1788 (67.0)	2494 (68.2)	266 (62.2)	1.00		1.00			
	AG	796 (29.9)	1024 (28.0)	137 (32.0)	0.95	0.85 – 1.05	1.17	0.93 – 1.47		
	AA	83 (3.1)	138 (3.8)	25 (5.8)	1.37	1.05 – 1.80	2.72	1.65 – 4.48		
	per allele				1.02	0.94 – 1.12	0.62	1.12 – 1.62		1.9 × 10 ⁻³
rs67397200 – 19p13.1										
<i>BRCA1</i>	CC	1903 (51.5)	2436 (46.0)	652 (49.7)	1.00		1.00			
	GC	1498 (40.5)	2381 (44.9)	540 (41.2)	1.28	1.18 – 1.38	1.16	1.01 – 1.33		
	GG	298 (8.1)	484 (9.1)	120 (9.2)	1.33	1.16 – 1.53	1.36	1.07 – 1.73		
	per allele				1.20	1.13 – 1.27	4.5 × 10 ⁻¹⁰	1.16	1.05 – 1.29	3.8 × 10 ⁻⁴
<i>BRCA2</i>	CC	1363 (50.5)	1866 (50.7)	194 (45.2)	1.00		1.00			
	GC	1123 (41.6)	1489 (40.5)	184 (42.9)	0.96	0.87 – 1.06	1.15	0.92 – 1.44		
	GG	214 (7.9)	323 (8.8)	51 (11.9)	1.18	0.99 – 1.41	1.95	1.37 – 2.77		
	per allele				1.03	0.96 – 1.11	0.39	1.10 – 1.52		1.8 × 10 ⁻³
rs311499 – 20q13.3										
<i>BRCA1</i>	GG	4115 (86.0)	5442 (85.9)	1273 (86.9)	1.00		1.00			
	AG	637 (13.3)	869 (13.7)	183 (12.5)	1.01	0.92 – 1.12	0.88	0.74 – 1.05		
	AA	32 (0.7)	28 (0.4)	9 (0.6)	0.70	0.42 – 1.17	1.16	0.47 – 2.87		
	per allele				0.99	0.90 – 1.08	0.77	0.91	0.77 – 1.07	0.25
<i>BRCA2</i>	GG	2492 (86.7)	3303 (87.0)	390 (86.1)	1.00		1.00			
	AG	372 (12.9)	474 (12.5)	58 (12.8)	0.93	0.82 – 1.07	0.92	0.68 – 1.26		
	AA	11 (0.4)	21 (0.6)	5 (1.1)	1.09	0.68 – 1.74	2.23	0.80 – 6.22		

SNP/	Unaffected		Breast Cancer		Ovarian Cancer		Breast Cancer		Ovarian Cancer		
Mutation	Genotype	N (%)	N (%)	N (%)	N (%)	HR	95% CI	p-value	HR	95% CI	p-value
	per allele					0.95	0.84 – 1.08	0.44	1.02	0.76 – 1.37	0.88
rs16917302 - 10q21.2											
<i>BRCA1</i>	AA	3784 (79.2)	5044 (79.7)	1169 (79.8)	1.00				1.00		
	CA	937 (19.6)	1216 (19.2)	285 (19.5)	0.96	0.88 – 1.04			0.97	0.84 – 1.13	
	CC	60 (1.3)	73 (1.2)	11 (0.8)	0.86	0.62 – 1.19			0.47	0.25 – 0.92	
	per allele				0.95	0.88 – 1.03		0.21	0.92	0.80 – 1.05	0.20
<i>BRCA2</i>	AA	2237 (77.9)	3094 (81.5)	353 (78.1)	1.00				1.00		
	CA	601 (20.9)	671 (17.7)	93 (20.6)	0.81	0.72 – 0.92			0.93	0.72 – 1.21	
	CC	35 (1.2)	32 (0.8)	6 (1.3)	0.80	0.50 – 1.30			1.21	0.46 – 3.18	
	per allele				0.83	0.74 – 0.92		5.8×10 ⁻⁴	0.96	0.76 – 1.22	0.76