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# Ovarian Cancer Susceptibility Alleles and Risk of Ovarian Cancer in *BRCA1* and *BRCA2* Mutation Carriers

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## Abstract

Germline mutations in *BRCA1* and *BRCA2* are associated with increased risks of breast and ovarian cancer. A genome-wide association study (GWAS) identified six alleles associated with risk of ovarian cancer for women in the general population. We evaluated four of these loci as potential modifiers of ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Four single-nucleotide polymorphisms (SNPs), rs10088218 (at 8q24), rs2665390 (at 3q25), rs717852 (at 2q31), and rs9303542 (at 17q21), were genotyped in 12,599 *BRCA1* and 7,132 *BRCA2* carriers, including 2,678 ovarian cancer cases. Associations were evaluated within a retrospective cohort approach. All four loci were associated with ovarian cancer risk in *BRCA2* carriers; rs10088218 per-allele hazard ratio (HR) = 0.81 (95% CI: 0.67–0.98) P-trend = 0.033, rs2665390 HR = 1.48 (95% CI: 1.21–1.83) P-trend = $1.8 \times 10^{-4}$, rs717852 HR = 1.25 (95% CI: 1.10–1.42) P-trend = $6.6 \times 10^{-4}$, rs9303542 HR = 1.16 (95% CI: 1.02–1.33) P-trend = 0.026. Two loci were associated with ovarian cancer risk in *BRCA1* carriers; rs10088218 per-allele HR = 0.89 (95% CI: 0.81–0.99) P-trend = 0.029, rs2665390 HR = 1.25 (95% CI: 1.10–1.42) P-trend = $6.1 \times 10^{-4}$. The HR estimates for the remaining loci were consistent with odds ratio estimates for the general population. The identification of multiple loci modifying ovarian cancer risk may be useful for counseling women with *BRCA1* and *BRCA2* mutations regarding their risk of ovarian cancer.

### Keywords

ovarian cancer; BRCA1; BRCA2; association; SNP

## Introduction

Pathogenic mutations in the *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 600185) genes confer high risks of ovarian and breast cancer [Miki et al., 1994; Wooster et al., 1995]. Breast cancer risks by age 70 have been estimated to range between 40% and 87% for *BRCA1* and 40–84% for *BRCA2* mutation carriers, whereas ovarian cancer risk estimates range between 16–68% and 11–27% for *BRCA1* and *BRCA2* mutation carriers, respectively [Antoniou et al., 2003; Antoniou et al., 2008; Begg et al., 2008; Chen et al., 2006; Ford et al., 1998; Hopper et al., 1999; Milne et al., 2008; Simchoni et al., 2006; Struewing et al., 1997; Thompson et al., 2001; Thompson et al., 2002]. Recent genome-wide association studies (GWAS) have identified common alleles associated with risk of breast, ovarian, and other cancers [reviewed Easton and Eeles, 2008; McCarthy and Hirschhorn, 2008; Song et al., 2009]. These common variants are plausible candidates for modifiers of disease risk for mutation carriers. The Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) has provided convincing evidence that variants identified through GWAS of breast cancer are also associated with the risk of developing breast cancer for *BRCA1* and/or *BRCA2*

mutation carriers [Antoniou et al., 2008a; Antoniou et al., 2009; Antoniou et al., 2010b; Antoniou et al., 2011].

Similarly, CIMBA has investigated the influence of ovarian cancer GWAS variants on ovarian cancer risk in *BRCA1* and *BRCA2* carriers. The first ovarian cancer susceptibility locus identified by a GWAS was rs3814113 at 9p22.2. The minor C allele was associated with a decreased risk of ovarian cancer (odds ratio (OR) = 0.82, 95% confidence interval (CI): 0.79–0.86, $P = 5.1 \times 10^{-19}$) [Song et al., 2009]. A previous CIMBA study showed that the minor allele of rs3814113 was also associated with a reduced risk of ovarian cancer for both *BRCA1* and *BRCA2* carriers (HR = 0.78 for both *BRCA1* and *BRCA2* mutation carriers) [Ramus et al., 2011].

A breast cancer GWAS in *BRCA1* mutation carriers found that locus 19p13 is associated with breast cancer risk for *BRCA1* mutation carriers. Two alleles on 19p13, rs8170C>T and rs2363956G>T, showed independent associations with breast cancer risk [Antoniou et al., 2010a]. Analysis of the associations of these SNPs with ovarian cancer risk in 843 ovarian cancer cases showed no evidence that this locus modifies ovarian cancer risk for *BRCA1* mutation carriers. However, the same two alleles were identified at the same time as ovarian cancer susceptibility alleles in a population-based ovarian cancer GWAS - rs8170 (OR = 1.12, 95% CI: 1.07–1.17, P-trend = $3.6 \times 10^{-6}$, serous OR = 1.18, 95% CI: 1.12–1.25, P-trend = $2.7 \times 10^{-9}$) and rs2363956 (OR = 1.1, 95% CI: 1.06–1.15, P-trend = $1.2 \times 10^{-7}$, serous OR = 1.16, 95% CI: 1.11–1.21, P-trend = $3.8 \times 10^{-11}$) [Bolton et al., 2010]. Subsequent genotyping of SNPs rs8170 and rs67397200 (an SNP correlated with both rs8170 and rs2363956 and identified via imputation), in a larger series of *BRCA1* and *BRCA2* mutation carriers from CIMBA, confirmed that both SNPs are associated with breast cancer risk. This analysis, which included 1,399 *BRCA1* ovarian cancer cases and 428 *BRCA2* ovarian cancer cases, also found that the 19p13 SNPs were associated with ovarian cancer risk in both *BRCA1* and *BRCA2* carriers in an analysis of the simultaneous breast and ovarian cancer associations in *BRCA1* carriers [Couch et al., in press].

Four additional ovarian cancer susceptibility loci were identified in a GWAS of more than 10,000 cases and 17,000 controls: rs2072590G>T (2q31) OR = 1.16 (95% CI: 1.12–1.21) P-trend = $4.5 \times 10^{-14}$, rs2665390T>C (3q25) OR = 1.19 (95% CI: 1.11–1.27) P-trend = $3.2 \times 10^{-7}$, rs10088218G>A (8q24) OR = 0.84 (95% CI: 0.80–0.89) P-trend = $3.2 \times 10^{-9}$, and rs9303542A>G (17q21) OR = 1.11 (95% CI: 1.06–1.16) P-trend = $1.4 \times 10^{-6}$ [Goode et al., 2010]. All these associations were stronger for serous ovarian cancer, the most common histology observed in BRCA-related ovarian cancer, than for all histologies. To investigate whether these SNPs are associated with risk of ovarian and breast cancer for mutation carriers, we genotyped these SNPs (or, in the case of rs2072590, a surrogate SNP, rs717852A>G, $r^2 = 0.96$) for 12,599 *BRCA1* and 7,132 *BRCA2* mutation carriers from 40 studies that were part of CIMBA.

## Materials and Methods

### Subjects

All subjects were female carriers of pathogenic mutations in *BRCA1* or *BRCA2* from 40 studies from Europe, North America, South Africa, and Australia (Supp. Table S1). Pathogenic mutations were defined as protein-truncating mutations or mutations listed on the Breast Cancer Information Core (BIC) http://research.nhgri.nih.gov/bic/ as described previously [Antoniou et al., 2007]. All subjects were 18 years or older at recruitment. The majority of carriers (>97%) were recruited through cancer genetics clinics offering genetic testing, and enrolled into national or regional studies. Some carriers were identified by population-based sampling of cases, and some by community recruitment. Only women of

self-reported white, European ancestry were included in the analysis. Subjects were excluded if they were from a country other than the country in which the study is conducted, or if they carried mutations in both genes. If a woman was enrolled in two different studies, only one of the samples was included in the analysis. These duplicate samples were identified by dates of birth and diagnosis and from available genotyping data. Subject information included year of birth; age at last follow-up; ages at breast and/or ovarian cancer diagnosis; and age at bilateral prophylactic mastectomy or oophorectomy. Related subjects were identified through a unique family identifier. *BRCA1* mutations were classified based on their predicted functional consequence. Class 1 was comprised of loss of function mutations subject to nonsense-mediated decay whereas class 2 mutations were those expected to generate a stable protein (details described previously [Antoniou et al., 2008a]). Subjects participated in clinical or research studies at the host institutions under ethically-approved protocols. Further details about CIMBA are described elsewhere [Chenevix-Trench et al., 2007].

## Genotyping

The DNA samples from 12,599 *BRCA1* and 7,132 *BRCA2* carriers from 40 studies were genotyped for SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) using the iPLEX (Sequenom, San Diego, CA) Mass Array platform (Supp. Table S1) at four genotyping centers. We used a correlated SNP ($r^2 = 0.96$), rs717852, to replace a failed assay for rs2072590. All genotyping data were subjected to a standard set of quality control criteria. Samples from affected and unaffected subjects were randomly arrayed within plates. No template controls were included on every 384-well plate and at least 2% of the samples were tested in duplicate. Samples were excluded if they consistently failed genotyping, defined as a pass rate of < 80% for all SNPs in this genotyping round. For a study to be included in the analysis, the genotype data were required to attain or exceed a call-rate threshold of 95% and a concordance between duplicates of 98%. We also evaluated the deviation from Hardy-Weinberg equilibrium (HWE) for unrelated subjects. For none of these studies was HWE rejected at a predefined threshold of $P = 0.001$. An additional quality control criterion was consistent results for 95 DNA samples from a standard test plate (Coriell Institute, Camden, NJ) genotyped at all centers. If the genotyping was inconsistent for more than one sample in the test plate, the study was excluded. A total of 19,731 carriers with genotype data were eligible for inclusion in the analysis (12,599 *BRCA1* and 7,132 *BRCA2* carriers) (Supp. Table S1). Three studies failed quality control for rs717852 and one for rs2665390.

## Statistical Analysis

The primary aim of this study was to evaluate the association between each genotype and ovarian cancer risk. The primary endpoint was therefore the age at diagnosis of ovarian cancer. For this purpose, individuals were censored at the age of the ovarian cancer diagnosis, or risk-reducing salpingo-oophorectomy (RRSO) or the age at last observation. Breast cancer was not considered as a censoring event in this analysis, and mutation carriers who developed ovarian cancer after a breast cancer diagnosis were considered as affected in the ovarian cancer analysis. To address the fact that mutation carriers were not sampled at random with respect to their disease phenotype, analysis was conducted by modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes as previously described [Antoniou et al., 2007; Barnes et al., In Press]. This method has been shown to provide unbiased estimates of the risk ratios within the present sampling frame [Barnes et al., In Press]. The effect of each SNP was modeled either as a per-allele hazard ratio (HR) (multiplicative model) or as separate HRs for heterozygotes and homozygotes, and these were estimated on the logarithmic scale. The HRs were assumed to be independent of age (i.e., we used a Cox proportional-hazards model). The assumption of proportional

hazards was tested by adding a "genotype × age" interaction term to the model in order to fit models in which the HR changed with age. Analyses were carried out with the pedigree-analysis software MENDEL [Lange et al., 1988] and details of this approach have been described previously [Antoniou et al., 2007; Barnes et al., In Press]. We examined between study/country heterogeneity by comparing the models that allowed for study-specific log HRs against models in which the same log HR was assumed to apply to all studies.

To investigate whether our results were influenced by any of our assumptions, we performed additional sensitivity analyses. If any of the SNPs were associated with disease survival, the inclusion of prevalent cases may influence the HR estimates. We therefore repeated our analysis by excluding mutation carriers diagnosed more than 5 years prior to the age at recruitment into the study. We also examined whether SNP associations differed by type of *BRCA1* mutations as described above.

The associations of these SNPs with breast cancer risk were assessed within a competing risk analysis framework [Barnes et al., In Press; Ramus et al., 2011] by estimating HRs simultaneously for breast and ovarian cancers. In this model, each individual was at risk of developing either breast or ovarian cancer, and the probabilities of developing each disease were assumed to be independent conditional on the underlying genotype. A different censoring process was used in this case, whereby individuals were followed up to the age of the first breast or ovarian cancer diagnosis and were considered to have developed the corresponding disease. No follow-up was considered after the first cancer diagnosis. Individuals were censored for breast cancer at the age of bilateral prophylactic mastectomy and for ovarian cancer at the age of bilateral oophorectomy and in such circumstances 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.

To ensure a sufficiently large number of mutation carriers within each stratum, we grouped studies from the same country. All analyses were stratified and used calendar year and cohort-specific cancer incidences for *BRCA1* and *BRCA2* [Antoniou et al., 2008b]. For sensitivity analyses, strata with small numbers of mutation carriers were grouped. We used a robust variance-estimation approach to allow for the nonindependence among related carriers [Boos, 1992].

## Results

In total, 12,599 *BRCA1* and 7,132 *BRCA2* carriers were eligible for analysis of associations between ovarian cancer risk and rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21). The primary analysis included 2,678 mutation carriers who were followed up to the age at diagnosis of invasive ovarian cancer (cases) and 17,053 carriers who were censored as unaffected (Table 1).

The minor allele of rs2665390 (3q25) was associated with a significantly increased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = $6.1 \times 10^{-4)}$) and *BRCA2* carriers (per allele HR = 1.48, 95% CI: 1.21–1.83, P-trend = $1.8 \times 10^{-4}$) (Table 2). The minor allele of rs10088218 (8q24) was associated with a significantly decreased risk of ovarian cancer for both *BRCA1* carriers (per-allele HR = 0.89, 95% CI: 0.81–0.99, P-trend = 0.029), and *BRCA2* carriers (per allele HR = 0.81, 95% CI: 0.67–0.98, P-trend = 0.033). The two remaining SNPs, rs717852 (2q31) and rs9303542 (17q21), were associated with ovarian cancer risk for *BRCA2* carriers (rs717852-per allele HR = 1.25, 95% CI: 1.10–1.42, P-trend = $6.6 \times 10^{-4}$; rs9303542-per allele HR = 1.16, 95% CI: 1.02–1.33, P-trend = 0.026). The estimated HRs in *BRCA1* carriers for these two SNPs were also >1 but not significantly different from 1, nor did they differ significantly from the HRs in

*BRCA2* carriers. There was no evidence that the HRs varied by age for either *BRCA1* or *BRCA2* mutation carriers (*BRCA1*-rs10088218 $P = 0.34$, rs2665390 $P = 0.24$, rs717852 $P = 0.09$, rs9303542 $P = 0.58$; *BRCA2*-rs10088218 $P = 0.66$, rs2665390 $P = 0.95$, rs717852 $P = 0.88$, rs9303542 $P = 0.67$). The country-specific HRs are shown in Figure 1. There was no evidence of heterogeneity in HRs across the studies/countries (*BRCA1*-rs10088218 $P = 0.27$, rs2665390 $P = 0.59$, rs717852 $P = 0.60$, rs9303542 $P = 0.10$; *BRCA2* -rs10088218 $P = 0.16$, rs2665390 $P = 0.32$, rs717852 $P = 0.75$, rs9303542 $P = 0.49$).

To determine if any survival bias was introduced by including long-term survivors, we excluded all ovarian cancer cases recruited 5 or more years after diagnosis (Supp. Table S2). All HR estimates were similar to those from the primary analysis although only three were significant in the reduced sample set.

We examined the associations between the SNPs and ovarian cancer risk by the *BRCA1* mutation-type based on the predicted functional consequence (Supp. Table S2). We found no evidence of a difference in the per-allele HR by *BRCA1* mutation type for rs10088218 (8q24) (P for difference in HR = 0.99). For rs2665390 (3q25) the estimated HR for class 1 mutations was somewhat higher (per-allele HR = 1.34 [95% CI: 1.15-1.56] P-trend = $2.2 \times 10^{-4}$) compared to class 2 mutations (HR = 1.08 (95% CI: 0.78–1.36), P-trend = 0.85), but the difference in HRs was not significant ($P = 0.06$). Similar patterns in the HRs between class 1 and class 2 mutations were seen for rs9303542 (17q21) and rs717852 (2q31), but none of the differences were significant ($P = 0.20$ and $P = 0.36$, respectively).

To determine whether these four SNPs were also associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers, we performed an analysis in which we estimated HRs for breast and ovarian cancer simultaneously within a bivariate outcome model (Table 3). There was no evidence of association between these SNPs and breast cancer risk for mutation carriers. The estimated HRs for ovarian cancer risk under this analysis were similar to those estimated in the main analysis. However, some of the results were no longer significant due to the fact that mutation carriers diagnosed with ovarian cancer after a breast cancer diagnosis are censored at breast cancer, which results in a reduced number of ovarian cancer cases. The 3q25 SNP, rs2665390, was significantly associated with ovarian cancer risk for both *BRCA1* and BRCA2 carriers (per-allele HR = 1.23, 95% CI: 1.06-1.44, P-trend = $8.5 \times 10^{-3}$ and per-allele HR = 1.59, 95% CI: 1.25–2.02, P-trend = $1.9 \times 10^{-4}$, respectively). As in the primary analysis, rs717852 (2q31) was only associated with an increased ovarian cancer risk in *BRCA2* carriers (HR = 1.31, 95% CI: 1.12–1.53, P-trend = $8.5 \times 10^{-4}$). The magnitude of the association between SNP rs10088218 (8q24) and ovarian cancer risk in *BRCA2* carriers was somewhat larger than in the primary analysis (HR = 0.72, 95% CI: 0.57–0.91, P-trend = $5.7 \times 10^{-3}$).

## Discussion

Recent studies have shown that common genetic variants identified from ovarian cancer GWAS are associated with susceptibility to ovarian cancer for *BRCA1* and/or *BRCA2* mutation carriers [Couch et al., in press; Ramus et al., 2011]. In the present study, we genotyped four SNPs, rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) that were found to be associated with ovarian cancer in women from the general population. We found that all SNPs were associated with ovarian cancer risk for *BRCA2* mutation carriers. There was significant evidence that two of the SNPs (rs10088218 at 8q24 and rs2665390 at 3q25) were also associated with ovarian cancer risk for *BRCA1* mutation carriers. For the remaining two SNPs at 2q31 and 17q21, the associations with ovarian cancer risk in *BRCA1* mutations did not reach statistical significance. However, the estimated HRs were still consistent with both the estimated HRs in *BRCA2* carriers, and the

estimated ORs in the general population. Thus these data, combined with those for the previously detected ovarian cancer risk SNPs at 9p22.2 [Ramus et al., 2011] and 19p13 [Couch et al, in press], indicate that all six known common susceptibility loci for ovarian cancer, are also associated with the ovarian cancer risk in *BRCA1* and *BRCA2* carriers, and moreover that the relative risk of ovarian cancer is generally similar to that in the general population.

In the general population, the magnitude of the associations with ovarian cancer risk were stronger for cases with the serous histological subtype for rs2072590 (2q31) $P_{heterogeneity} = 2.9 \times 10^{-4}$, rs10088218 (8q24) $P_{heterogeneity} = 1.1 \times 10^{-7}$, and rs2665390 (3q25) $P_{heterogeneity} = 0.02$ [Goode et al., 2010]. However, we were not able to assess this interaction in the *BRCA1* and *BRCA2* carriers, due to small numbers and incomplete pathology data for histological subtype.

When the data were analyzed within a competing risks framework, we observed no evidence that these SNPs were associated with breast cancer risk for *BRCA1* or *BRCA2* mutation carriers. None of the published breast cancer GWAS using women from the general population [Ahmed et al., 2009; Easton et al., 2007; Gold et al., 2008; Hunter et al., 2007; Thomas et al., 2009] have reported associations for these SNPs at the strict genome-wide levels of significance. These results indicate that, for both groups of mutation carriers and for the general population, the predominant association is with ovarian cancer risk and that the association with breast cancer risk, if any, is very weak.

The fine-mapping and functional follow-up of the risk alleles from the ovarian cancer GWAS are currently being performed. Therefore, the gene most likely to be driving the ovarian cancer risk in each region has not yet been identified but the closest genes to each SNP and the genes in the linkage disequilibrium block provide some insight to the potential candidates. The rs2665390 SNP is located at 3q25, and is intronic to the *TIPARP* gene, a member of the poly (ADP-ribose) polymerase (PARP) superfamily. *BRCA1-BRCA2*–deficient cells can use the *PARP1* alternative DNA repair mechanism to survive, and synthetic inhibition of *PARP1* has been developed as a new therapy for breast and ovarian cancer patients with mutations in these genes [Fong et al., 2009]. There are no other candidate genes within 200 kb of this SNP and the five other genes within the linkage disequilibrium block (*LEKR1, LOC730091, PA2G4P4, SSR3*, and *KCNAB1*) are not known to have functions that suggest a role in cancer [www.genecards.org; Safran et al., 2010].

The rs717852 SNP is located at 2q31 in a region containing a family of homeobox (*HOX*) genes; *HOXD10, HOXD11, HOXD12, HOXD13, HOXD3, HOXD4, HOXD8, HOXD9*, and *HOXD1. HOX* genes are involved in regulating embryogenesis and organogenesis and altered expression of *HOX* genes has been reported in many cancers [Buzzai and Licht, 2008; Shiraishi et al., 2002.]. The other genes in this region, *KIAA1715, EVX2*, and *MTX2*, do not have a reported role in cancer [www.genecards.org; Safran et al., 2010]. The ovarian cancer risk-associated SNP rs2072590 is downstream of *HOXD3* and upstream of *HOXD1*, and it tags SNPs in the *HOXD3* 3′ untranslated region. The genotyped SNP rs717852 is intronic of *HOXD3*.

Common variants that confer susceptibility to multiple cancer phenotypes, including prostate, colorectal, breast, and bladder cancers have been identified in a 500-kb region of a gene desert at 8q24, approximately 200 kb 5′ of *MYC* [Jia et al., 2009]. Functional studies have suggested that transcriptional regulation of *MYC* may explain these associations [Jia et al., 2009; Pomerantz et al., 2009]. In contrast, rs10088218 is >700 kb 3′ of *MYC*. Variants in this region may also be capable of distant regulation of *MYC*. However, *PVT1*, a

noncoding RNA which is an MYC protein target, is another plausible candidate in this region. *PVT1* is amplified in breast and ovarian tumors, and is overexpressed in transformed cells [Guan et al., 2007]. A prostate cancer risk variant at the 8q24 locus, located 0.5 Mb upstream of the *PVT1* gene has recently been shown to be associated with increased expression of the *PVT1* gene rather than affecting MYC expression [Meyer et al., 2011].

The final SNP, rs9303542 at 17q21, is intronic to *SKAP1*, a src kinase-associated phosphoprotein, which regulates mitotic progression [Fang et al., 2009]. SKAP1 has been shown to suppress activation of *RAS* and *RAF1* genes that may have a role in the early-stage development of ovarian cancer [Kosco et al., 2008]. The region also contains 10 *HOXB* genes and, as described earlier, altered expression of *HOX* genes has been reported in many cancers. Of the other 12 genes in this region, the only ones with a suggested role in cancer are, *PRAC*, encoding a small nuclear protein which is a prostate cancer susceptibility candidate, *CBX1*, which may play an important role in the epigenetic control of chromatin structure and gene expression, and *CDK5RAP3* that may be involved in cell proliferation [www.genecards.org; Safran et al., 2010].

We have previously demonstrated that common risk alleles for breast cancer increase the risk of breast cancer to a similar relative extent in *BRCA1* and *BRCA2* carriers (once estrogen receptor status is taken into account). These results demonstrate that the same holds true for ovarian cancer loci identified through GWAS, and provides a general model in which common susceptibility loci and *BRCA1* and *BRCA2* mutations interact multiplicatively on the risk of developing ovarian cancer [Wacholder et al., 2011]. Although the HR conferred by each locus is modest, the HRs are much larger in combination. These translate to small differences in absolute risk between different genotypes for the vast majority of women at low risk of this disease, but the absolute risk differences for mutation carriers will be much greater. As more genetic modifiers of ovarian cancer risk are identified, in the future, such information combined with other risk factors such as parity and oral contraceptive use could be incorporated into risk prediction algorithms such as BOADICEA [Antoniou et al., 2008b]. This could enable the stratification of mutation carriers into different ovarian cancer risk categories and could potentially be used for guiding the clinical management of mutation carriers with respect to screening or prophylactic surgery.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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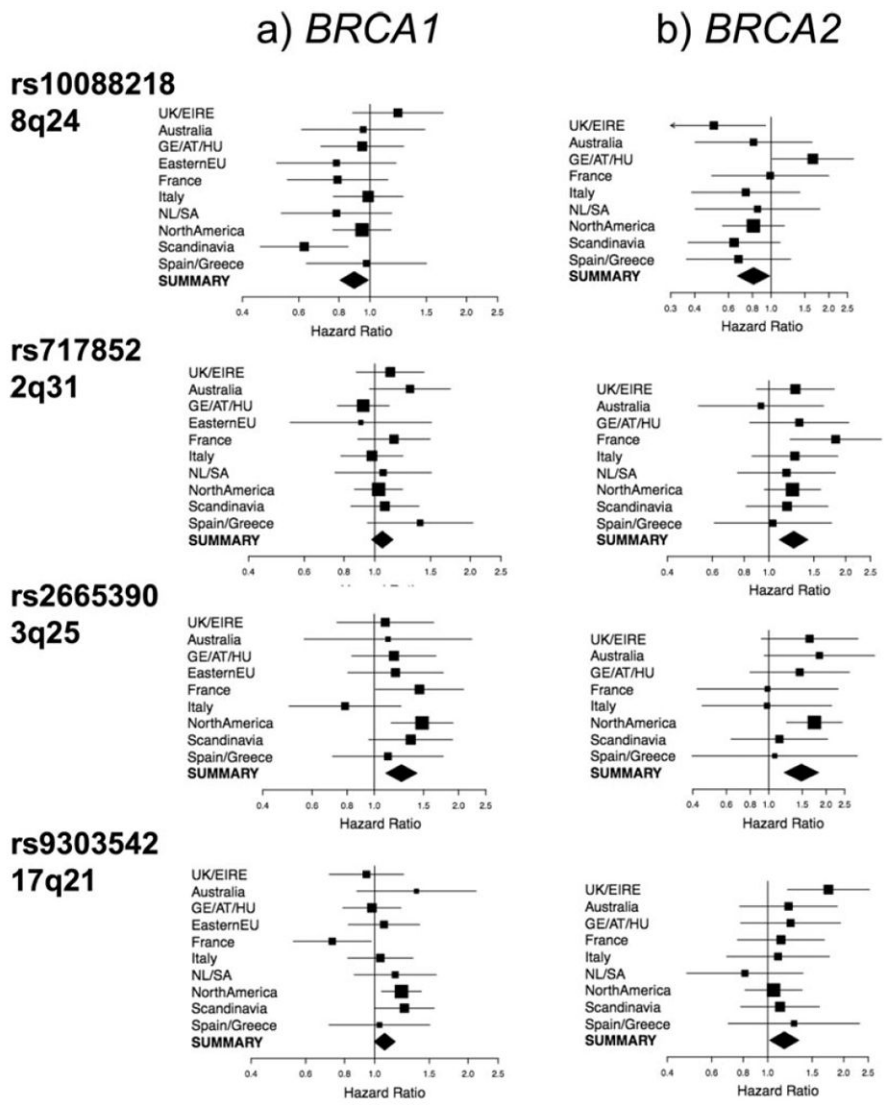


**Figure 1.**

Forest plots of study-specific HRs for ovarian cancer risk in (a) *BRCA1* mutation carriers, (b) *BRCA2* mutation carriers. Country-specific per-allele HR estimates for the SNPs rs10088218 (8q24), rs2665390 (3q25), rs717852 (2q31), and rs9303542 (17q21) in *BRCA1* and *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. Diamonds indicate the summary HR estimates for all of the CIMBA. For *BRCA2,* some of the smaller studies have been combined with others from the same country. GE/AT/HU denotes the stratum for Germany, Austria, and Hungary. NL/SA denotes the stratum for the Netherlands and South Africa.

## Table 1

Summary Characteristics for the 19,731 Eligible *BRCA1* and *BRCA2* Carriers[a] Used in the Analysis

| | *BRCA1* | | *BRCA2* | |
|---|---|---|---|---|
| **Characteristic** | **Unaffected** | **Ovarian cancer** | **Unaffected** | **Ovarian cancer** |
| Number | 10,535 | 2,064 | 6,518 | 614 |
| Person-years follow-up | 459,178 | 104,942 | 304,789 | 34,605 |
| Median age at censure (IQR) | 42 (35–50) | 50 (45–56) | 45 (38–55) | 56 (49–63) |
| Age at censure, N (%) | | | | |
| < 30 | 1,536 (14.6) | 93 (4.5) | 796 (12.2) | 24 (3.9) |
| 30–39 | 2,945 (28.0) | 171 (8.3) | 1,402 (21.5) | 15 (2.4) |
| 40–49 | 3,375 (32.0) | 760 (36.8) | 2,017 (31.0) | 129 (21.0) |
| 50–59 | 1,721 (16.3) | 707 (34.8) | 1,297 (19.9) | 217 (35.3) |
| 60–69 | 656 (6.2) | 269 (13.0) | 667 (10.2) | 175 (28.5) |
| 70+ | 302 (2.9) | 64 (3.1) | 339 (5.2) | 54 (8.8) |
| Year of birth, N (%) | | | | |
| <1920 | 50 (0.5) | 8 (0.4) | 56 (0.9) | 11 (1.8) |
| 1920–1929 | 204 (1.9) | 123 (6.0) | 199 (3.1) | 67 (10.9) |
| 1930–1939 | 548 (5.2) | 337 (16.3) | 499 (7.7) | 163 (26.6) |
| 1940–1949 | 1,495 (14.2) | 678 (32.9) | 1,122 (17.2) | 323 (37.8) |
| 1950–1959 | 2,757 (26.2) | 641 (31.1) | 1,736 (26.6) | 115 (18.7) |
| 1960–1969 | 3,113 (29.6) | 256 (12.4) | 1,747 (26.8) | 23 (3.8) |
| 1970+ | 2,368 (22.5) | 21 (1.0) | 1,159 (17.8) | 3 (0.5) |
| Mutation class, N (%) | | | | |
| Class 1[b] | 6,460 (61.3) | 1,481 (71.8) | 6,058 (92.9) | 576 (93.8) |
| Class 2[b] | 3,294 (31.3) | 459 (22.2) | 163 (2.5) | 9 (1.5) |
| Other | 781 (7.4) | 124 (6.0) | 297 (4.6) | 29 (4.7) |

[a] Carriers of self-reported white European ancestry only

[b] See methods for definitions.

IQR, interquartile range.

**Table 2**

SNP Genotype Distributions and Associations with Ovarian Cancer Risk

| Mutation | Genotype | Unaffected N (%) | Affected[a] N (%) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| 8q24–rs10088218 | | | | | | |
| *BRCA1* | GG | 7,978 (76.1) | 1,574 (76.3) | 1 | | |
| | AG | 2,325 (22.2) | 461 (22.4) | 0.93 | 0.83–1.05 | |
| | AA | 176 (1.7) | 27 (1.3) | 0.61 | 0.41–0.91 | |
| | 2-df test | | | | | 0.032 |
| | per allele | | | 0.89 | 0.81–0.99 | 0.029 |
| *BRCA2* | GG | 4,865 (74.7) | 485 (79.0) | 1 | | |
| | AG | 1,537 (23.6) | 116 (18.9) | 0.73 | 0.59–0.91 | |
| | AA | 113 (1.7) | 13 (2.1) | 1.12 | 0.61–2.04 | |
| | 2-df test | | | | | 0.014 |
| | per allele | | | 0.81 | 0.67–0.98 | 0.033 |
| 3q25–rs2665390 | | | | | | |
| *BRCA1* | TT | 8,242 (85.6) | 1,623 (83.1) | 1 | | |
| | TC | 1,330 (13.8) | 314 (16.1) | 1.25 | 1.08–1.44 | |
| | CC | 58 (0.6) | 17 (0.9) | 1.57 | 0.91–2.69 | |
| | 2-df test | | | | | $2.7 \times 10^{-3}$ |
| | per allele | | | 1.25 | 1.10–1.42 | $6.1 \times 10^{-4}$ |
| *BRCA2* | TT | 5,226 (85.3) | 449 (78.6) | 1 | | |
| | TC | 862 (14.1) | 118 (20.7) | 1.58 | 1.26–1.98 | |
| | CC | 38 (0.6) | 4 (0.7) | 1.20 | 0.34–4.19 | |
| | 2-df test | | | | | $3.2 \times 10^{-4}$ |
| | per allele | | | 1.48 | 1.21–1.83 | $1.8 \times 10^{-4}$ |
| 2q31–rs717852 | | | | | | |
| *BRCA1* | TT | 4,134 (47.0) | 863 (45.3) | 1 | | |
| | CT | 3,807 (43.2) | 862 (45.3) | 1.11 | 0.99–1.23 | |
| | CC | 864 (9.8) | 179 (9.4) | 1.06 | 0.88–1.27 | |
| | 2-df test | | | | | 0.18 |
| | per allele | | | 1.06 | 0.98–1.14 | 0.16 |

| Mutation | Genotype | Unaffected N (%) | Affected[a] N (%) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| *BRCA2* | TT | 3,029 (48.6) | 245 (42.0) | 1 | | |
| | CT | 2,645 (42.4) | 272 (46.6) | 1.30 | 1.08–1.56 | |
| | CC | 558 (9.0) | 67 (11.5) | 1.51 | 1.13–2.01 | |
| | 2-df test | | | | | $3.2 \times 10^{-3}$ |
| | per allele | | | 1.25 | 1.10–1.42 | $6.6 \times 10^{-4}$ |
| 17q21–rs9303542 | | | | | | |
| *BRCA1* | TT | 5,695 (54.2) | 1,076 (52.3) | 1 | | |
| | TC | 4,085 (38.9) | 826 (40.1) | 1.08 | 0.98–1.20 | |
| | CC | 729 (6.9) | 157 (7.6) | 1.15 | 0.95–1.40 | |
| | 2-df test | | | | | 0.17 |
| | per allele | | | 1.08 | 1.00–1.17 | 0.06 |
| *BRCA2* | TT | 3,445 (53.0) | 296 (48.3) | 1 | | |
| | TC | 2,593 (39.9) | 264 (43.1) | 1.19 | 1.00–1.42 | |
| | CC | 462 (7.1) | 53 (8.7) | 1.31 | 0.95–1.81 | |
| | 2-df test | | | | | 0.082 |
| | per allele | | | 1.16 | 1.02–1.33 | 0.026 |

[a]Ovarian cancer.

Analysis restricted to mutation carriers of white European ancestry.

**Table 3**

Competing Risk Analysis

| | | | | | Breast cancer | | | Ovarian cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Unaffected N (%) | Breast cancer N (%) | Ovarian cancer N (%) | HR | 95% C.I. | *P*-value | HR | 95% C.I. | *P*-value |
| 8q24—rs10088218 | | | | | | | | | | |
| *BRCA1* | GG | 3,661 (77.0) | 4,772 (75.5) | 1,119 (76.4) | 1 | | | 1 | | |
| | AG | 1,025 (21.5) | 1,431 (22.6) | 330 (22.5) | 1.03 | 0.94–1.11 | | 0.96 | 0.83–1.11 | |
| | AA | 70 (1.5) | 117 (1.9) | 16 (1.1) | 1.08 | 0.84–1.38 | | 0.55 | 0.32–0.94 | |
| | 2-df test | | | | | | 0.72 | | | 0.083 |
| | per allele | | | | 1.03 | 0.96–1.10 | 0.44 | 0.91 | 0.80–1.03 | 0.13 |
| *BRCA2* | GG | 2,123 (73.9) | 2,861 (75.3) | 366 (80.6) | 1 | | | 1 | | |
| | AG | 699 (24.3) | 877 (23.1) | 77 (17.0) | 0.91 | 0.82–1.02 | | 0.60 | 0.46–0.78 | |
| | AA | 53 (1.8) | 62 (1.6) | 11 (2.4) | 0.85 | 0.61–1.18 | | 1.17 | 0.60–2.27 | |
| | 2-df test | | | | | | 0.17 | | | $7.7 \times 10^{-4}$ |
| | per allele | | | | 0.92 | 0.84–1.00 | 0.061 | 0.72 | 0.57–0.91 | $5.7 \times 10^{-3}$ |
| 3q25–rs2665390 | | | | | | | | | | |
| *BRCA1* | TT | 3,716 (85.2) | 4,995 (85.7) | 1,151 (82.8) | 1 | | | 1 | | |
| | TC | 614 (14.1) | 801 (13.7) | 229 (16.4) | 1.00 | 0.90–1.11 | | 1.27 | 1.06–1.51 | |
| | CC | 31 (0.7) | 33 (0.6) | 11 (0.8) | 0.80 | 0.53–1.19 | | 1.22 | 0.62–2.41 | |
| | 2-df test | | | | | | 0.54 | | | 0.028 |
| | per allele | | | | 0.98 | 0.89–1.08 | 0.70 | 1.23 | 1.06–1.44 | $8.5 \times 10^{-3}$ |
| *BRCA2* | TT | 2,282 (85.5) | 3,067 (85.1) | 326 (76.8) | 1 | | | 1 | | |
| | TC | 368 (13.8) | 517 (14.4) | 95 (22.5) | 1.02 | 0.89–1.16 | | 1.75 | 1.34–2.27 | |
| | CC | 19 (0.7) | 20 (0.6) | 3 (0.7) | 0.72 | 0.39–1.35 | | 1.02 | 0.21–5.10 | |
| | 2-df test | | | | | | 0.57 | | | $1.6 \times 10^{-4}$ |
| | per allele | | | | 0.99 | 0.87–1.12 | 0.82 | 1.59 | 1.25–2.02 | $1.9 \times 10^{-4}$ |
| 2q31–rs717852 | | | | | | | | | | |
| *BRCA1* | TT | 1,817 (47.3) | 2,576 (46.5) | 606 (45.5) | 1 | | | 1 | | |
| | CT | 1,667 (43.5) | 2,400 (43.3) | 602 (45.1) | 1.01 | 0.94–1.09 | | 1.10 | 0.96–1.25 | |
| | CC | 356 (9.3) | 562 (10.2) | 125 (9.4) | 1.13 | 0.99–1.29 | | 1.10 | 0.87–1.40 | |
| | 2-df test | | | | | | 0.18 | | | 0.32 |

| | | | | | Breast cancer | | | Ovarian cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Unaffected N (%) | Breast cancer N (%) | Ovarian cancer N (%) | HR | 95% C.I. | *P*-value | HR | 95% C.I. | *P*-value |
| | per allele | | | | 1.04 | 0.99–1.10 | 0.14 | 1.08 | 0.98–1.19 | 0.15 |
| *BRCA2* | TT | 1,345 (49.8) | 1,752 (47.5) | 177 (41.4) | 1 | | | 1 | | |
| | CT | 1,112 (41.2) | 1,603 (43.5) | 202 (47.2) | 1.08 | 0.98–1.19 | | 1.39 | 1.11–1.74 | |
| | CC | 244 (9.0) | 331 (9.0) | 50 (11.5) | 1.03 | 0.87–1.21 | | 1.60 | 1.13–2.26 | |
| | 2-df test | | | | | | 0.30 | | | $3.8 \times 10^{-3}$ |
| | per allele | | | | 1.04 | 0.97–1.12 | 0.30 | 1.31 | 1.12–1.53 | $8.5 \times 10^{-4}$ |
| 17q21–rs9303542 | | | | | | | | | | |
| *BRCA1* | TT | 2,537 (53.1) | 3,470 (54.8) | 764 (52.3) | 1 | | | 1 | | |
| | TC | 1,891 (39.6) | 2,434 (38.5) | 586 (40.1) | 0.98 | 0.91–1.05 | | 1.08 | 0.95–1.23 | |
| | CC | 349 (7.3) | 426 (6.7) | 111 (7.6) | 0.95 | 0.82–1.09 | | 1.10 | 0.87–1.40 | |
| | 2-df test | | | | | | 0.70 | | | 0.44 |
| | per allele | | | | 0.98 | 0.92–1.03 | 0.41 | 1.06 | 0.97–1.17 | 0.22 |
| *BRCA2* | TT | 1,517 (52.8) | 2,012 (53.1) | 212 (46.7) | 1 | | | 1 | | |
| | TC | 1,136 (39.6) | 1,520 (40.1) | 203 (44.9) | 0.98 | 0.89–1.08 | | 1.26 | 1.02–1.55 | |
| | CC | 218 (7.6) | 259 (6.8) | 38 (8.4) | 0.87 | 0.73–1.05 | | 1.17 | 0.79–1.74 | |
| | 2-df test | | | | | | 0.35 | | | 0.099 |
| | per allele | | | | 0.96 | 0.89–1.03 | 0.22 | 1.16 | 0.99–1.35 | 0.075 |

Associations with breast and ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. Analysis restricted to mutation carriers of European ancestry.

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