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A locus on 19p13 modifies risk of breast cancer in *BRCA1* mutation carriers and is associated with hormone receptor–negative breast cancer in the general population

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AUTHOR CONTRIBUTIONS

F.J.C., A.C.A. and D.F.E. designed the study and obtained financial support. G.C.-T. founded CIMBA in order to provide the infrastructure for the *BRCA1* GWAS. F.J.C. and X.W. coordinated collection of samples. A.C.A. directed the statistical analysis. D.F.E. advised on the statistical analysis. C.K., Z.S.F. and T.L. carried out analyses. Z.S.F., R.T., J.M., L.M. and D.B. provided bioinformatics and database support. F.J.C., H. Hakonarson and X.W. directed the genotyping of the *BRCA1* carrier and triple-negative samples. M.G. directed the genotyping of the UK case-control samples. A.C.A., F.J.C. and D.F.E. drafted the manuscript. F.J.C. was the overall project leader.

O.M.S. and S.H. coordinated the *BRCA1* mutation classification. T.K., J.V., M.M.G., D.A. and C.G. were involved in the *BRCA2* GWAS genotyping and coordination. K.O. led the *BRCA2* GWAS.

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Abstract

Germline *BRCA1* mutations predispose to breast cancer. To identify genetic modifiers of this risk, we performed a genome-wide association study in 1,193 individuals with *BRCA1* mutations who were diagnosed with invasive breast cancer under age 40 and 1,190 *BRCA1* carriers without breast cancer diagnosis over age 35. We took forward 96 SNPs for replication in another 5,986 *BRCA1* carriers (2,974 individuals with breast cancer and 3,012 unaffected individuals). Five SNPs on 19p13 were associated with breast cancer risk ($P_{trend} = 2.3 \times 10^{-9}$ to $P_{trend} = 3.9 \times 10^{-7}$), two of which showed independent associations (rs8170, hazard ratio (HR) = 1.26, 95% CI 1.17–1.35; rs2363956 HR = 0.84, 95% CI 0.80–0.89). Genotyping these SNPs in 6,800 population-based breast cancer cases and 6,613 controls identified a similar association with estrogen receptor–negative breast cancer (rs2363956 per-allele odds ratio (OR) = 0.83, 95% CI 0.75–0.92, $P_{trend} = 0.0003$) and an association with estrogen receptor–positive disease in the opposite direction (OR = 1.07, 95% CI 1.01–1.14, $P_{trend} = 0.016$). The five SNPs were also associated with triple-negative breast cancer in a separate study of 2,301 triple-negative cases and 3,949 controls ($P_{trend} = 1 \times 10^{-7}$ to $P_{trend} = 8 \times 10^{-5}$; rs2363956 per-allele OR = 0.80, 95% CI 0.74–0.87, $P_{trend} = 1.1 \times 10^{-7}$).

Pathogenic *BRCA1* and *BRCA2* mutations confer high risks of breast and ovarian cancer. Variation in risk estimates by degree of family history suggests that these risks are modified by other genetic variants[1–5]. Recent studies from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) have demonstrated that common breast cancer susceptibility alleles, identified through genome-wide association studies (GWAS) in the general population[6–9], are also associated with the risk of developing breast cancer in *BRCA1* or *BRCA2* mutation carriers[10,11]. However, although five of six alleles were associated with risk of breast cancer for *BRCA2* mutation carriers, only two polymorphisms (in the *TOX3* and 2q35 regions) were associated with risk for *BRCA1* carriers. These findings are consistent with the distinct pathology of breast cancer in *BRCA1* tumors[12,13] and suggest that the genetic variants that modify breast cancer risk for *BRCA1* mutation carriers may differ from the modifiers of risk for *BRCA2* carriers or for non-carriers.

To search for genetic loci associated with breast cancer in *BRCA1* carriers, we conducted a two-stage GWAS. In stage 1, we genotyped 2,500 *BRCA1* carriers using the Illumina

Infinium 610K array, which included 620,901 SNPs. Mutation carriers were selected on the basis of an invasive breast cancer diagnosis at under 40 years of age (n = 1,250) or the absence of breast cancer when 35 years of age or older (n = 1,250). After quality control exclusions, 2,383 carriers (1,193 unaffected and 1,190 affected) from 20 centers in 11 different countries and 555,616 SNPs were available for analysis (Supplementary Tables 1 and 2). Genotype associations were evaluated using a 1 degree-of-freedom (d.f.) score test for trend, based on modeling the retrospective likelihood of the observed genotypes conditional on the disease phenotypes, stratified by country of residence. A kinship-adjusted version of the score test statistic was used to allow for the dependence between related individuals.

There was little evidence for inflation in the test statistic of association (inflation factor (λ) = 1.036; Supplementary Fig. 1). Ninety-six SNPs were significant at the $P < 10^{-4}$ level compared with 55.6 SNPs which were expected by chance. In stage 2, we genotyped 86 of these SNPs, seven surrogate SNPs (within 10 kb of the significant SNPs and pair-wise $r^2 > 0.90$) and three additional SNPs in 6,332 *BRCA1* carriers. After quality control exclusions, 89 SNPs and 5,986 *BRCA1* mutation carriers (3,012 unaffected and 2,974 affected) were used in the stage 2 analysis. The most significant associations were for five SNPs on 19p13 ($P < 0.002$), which had hazard ratios in the same direction as in stage 1 (Table 1 and Supplementary Table 3). In the combined analysis of stage 1 and 2, there was strong evidence of association[14] with breast cancer for these SNPs ($P = 2.3 \times 10^{-9}$ to $P = 3.9 \times 10^{-7}$).

The minor alleles of rs8170 and rs4808611 were associated with an increased breast cancer risk for *BRCA1* carriers (per allele HR = 1.26, 95% CI 1.17–1.35 for both SNPs). In contrast, SNPs rs8100241, rs2363956 and rs3745185 were associated with decreased breast cancer risk (HR = 0.84, 95% CI 0.80–0.89 for rs8100241 and rs2363956; HR = 0.86, 95% CI 0.81–0.91 for rs3745185) (Table 1). The HR estimates for rs8170 and rs4808611 were similar in stages 1 and 2, but for rs8100241, rs2363956 and rs3745185, the HRs were stronger in stage 1; this may be due to the sample selection criteria for stage 1 or a 'winner's curse' effect[15]. There was no evidence of heterogeneity in the HR estimates among the countries of residence in stages 1 and 2 combined (Fig. 1; rs8170, $P = 0.10$; rs4808611, $P = 0.14$; rs8100241, $P = 0.18$; rs2363956, $P = 0.17$; and rs3745185, $P = 0.48$).

The strength of the association with breast cancer could also be affected by the inclusion of prevalent cases if these SNPs were associated with breast cancer survival. To address this possibility, we excluded breast cancer cases diagnosed with the disease >5 years before study entry. The HR estimates were similar to the overall analysis after this exclusion (Supplementary Table 4). This indicates that the inclusion of prevalent breast cancer cases was unlikely to have influenced the overall results.

To investigate whether any of these SNPs were associated with ovarian cancer risk for *BRCA1* carriers, we analyzed the data within a competing risks framework and estimated HR simultaneously for breast and ovarian cancer. There was no evidence of association with ovarian cancer risk for any of the SNPs, and the breast cancer associations were virtually identical to the primary analysis both in terms of significance and in the HR estimates (Table 2). We repeated the breast cancer association analysis after excluding all individuals who developed ovarian cancer either before or after a breast cancer diagnosis. Despite the sample size reduction, the top four SNPs remained significant at $P < 10^{-7}$ and the HR estimates were identical to the analysis which included individuals with ovarian cancer as unaffected individuals (Supplementary Table 4). We also evaluated ovarian cancer associations after excluding individuals with ovarian cancer who were recruited >3 years after their cancer diagnosis in order to account for a potential survival bias. No significant associations were

observed after this exclusion (P_{trend} = 0.44 to P_{trend} = 0.96 using competing risk analysis). We conclude that the associations with breast cancer were not confounded by the competing risk of ovarian cancer.

We evaluated the SNP associations by the predicted functional consequences of *BRCA1* mutation type[16–18]. Class 1 mutations correspond to loss-of-function mutations and are expected to result in a reduced transcript or protein level due to nonsense-mediated RNA decay, whereas class 2 mutations are likely to generate stable proteins with potential residual or dominant negative function[18–20]. Among class 1 mutation carriers (combined stage 1 and 2, n = 5,732), the five most significant associated SNPs included rs6994019, an intronic SNP in *MMP16* on chromosome 8 ($P_{trend} = 2.9 \times 10^{-6}$) and four SNPs in the 19p13 region ($P_{trend} = 7.6 \times 10^{-6}$ to $P_{trend} = 1.6 \times 10^{-4}$). The *MMP16* SNP rs6994019 was the ninth most significant SNP in the primary analysis of all mutations combined ($P_{trend} = 2.7 \times 10^{-4}$ in stage 1 and 2 combined; Supplementary Table 3). The strongest association with breast cancer risk for carriers of class 2 mutations was at the five SNPs in the 19p13 region ($P_{trend} = 1.8 \times 10^{-6}$ to $P_{trend} = 1.2 \times 10^{-4}$; Supplementary Table 3). The HR estimates for the five SNPs in 19p13 were larger for class 2 mutations, but the differences between class 1 and class 2 mutations were significant for only rs8170 and rs3745185 (P = 0.03 and P = 0.004, respectively). These differences might reflect a stronger modifying effect on breast cancer risk for tumors retaining residual or dominant negative BRCA1 function.

Tumor estrogen or progesterone receptor status was available for 1,197 breast cancer cases in stage 1 and 2 combined. A case-only analysis revealed significant differences in the associations for the 19p13 SNPs between estrogen receptor–positive and estrogen receptor–negative disease and between estrogen receptor– or progesterone receptor–positive and estrogen receptor– and progesterone receptor–negative disease, particularly for SNPs rs8100241, rs2363956 and rs3745185 (P = 0.002 to P = 0.04; Supplementary Table 5). The OR estimates suggest that these SNPs are more strongly associated with estrogen receptor–negative disease.

The two most significant SNPs (rs8170 and rs4808611) were strongly correlated (r^2 = 0.87) in the *BRCA1* samples but displayed a low correlation with the other associated SNPs (r^2 < 0.23). rs8100241 and rs2363956 were perfectly correlated (r^2 = 1), whereas the least significant SNP, rs3745185, had weaker correlations with both sets of SNPs (r^2 = 0.17 and r^2 = 0.74 with rs8170 and rs8100241, respectively).

To evaluate the contribution of the 19p13 locus to breast cancer risk in the general population, we genotyped rs8170 and rs2363956 in 6,800 breast cancer cases and 6,613 controls from the SEARCH (Studies of Epidemiology and Risk Factors in Cancer Heredity) study in the UK. Neither SNP was associated with overall breast cancer risk (P = 0.65 and P = 0.79; Table 3). However, stratification of tumors by estrogen receptor status indicated that both SNPs were associated with estrogen receptor–negative breast cancer (rs8170, per-allele OR = 1.21, 95% CI 1.07–1.37, P = 0.0029 and rs2363956, OR = 0.83, 95% CI 0.75–0.92, P = 0.0003; Table 3). These effect sizes were similar to the estimated HRs for *BRCA1* carriers, consistent with the observation that *BRCA1* mutations predispose predominately to estrogen receptor–negative disease. Weaker associations were observed in the opposite direction for estrogen receptor–positive disease (rs8170, per-allele OR = 0.91, 95% CI 0.84–0.98, P = 0.011 and rs2363956, OR = 1.07, 95% CI 1.01–1.14, P = 0.016). Similar patterns were observed when tumors were stratified by progesterone receptor status or estrogen receptor and progesterone receptor status combined (Table 3).

The majority of breast tumors in *BRCA1* carriers exhibit a triple-negative (estrogen receptor, progesterone receptor and HER2 negative) phenotype. To evaluate the association of the

19p13 locus with triple-negative disease in the general population, we obtained genotype data for the five SNPs from up to 2,301 cases from 15 centers in six countries involved in the triple-negative breast cancer consortium (TNBCC). Genotype data from up to 3,949 geographically matched controls were also available (Supplementary Table 5). All SNPs were associated with triple-negative breast cancer, and the ORs were comparable to the HRs seen in the *BRCA1* carriers and the ORs for estrogen receptor–negative breast cancer seen in the SEARCH population-based study (rs2363956, per-allele OR = 0.80, 95% CI 0.74–0.87, $P = 1.1 \times 10^{-7}$ and rs8170, OR = 1.28, 95% CI 1.16–1.41, $P = 1.2 \times 10^{-6}$; Table 3 and Supplementary Table 5).

Two of the SNPs (rs8170 and rs2366956) were genotyped in 2,486 *BRCA2* mutation carriers as part of an ongoing GWAS. Neither SNP was associated with breast cancer risk for *BRCA2* carriers ($P_{trend} = 0.17$ and $P_{trend} = 0.07$), but the HR estimates were in line with the ORs estimated for estrogen receptor–positive disease in the SEARCH study (Table 3).

All five SNPs were located in a region that spans 39 kb on 19p13 (Fig. 2). In an analysis for the joint effect of these SNPs on breast cancer risk for *BRCA1* carriers, it was not possible to distinguish between rs8170 and rs4808611, as neither SNP improved the model fit significantly when the other was included ($P = 0.11$ and $P = 0.22$ for rs8170 and rs4808611, respectively). rs8100241 was retained in preference to rs3745185 (P for inclusion of rs3745185 in model = 0.79). Thus, the most parsimonious model included SNPs rs8170 and either rs8100241 or rs2363956 (P for inclusion = 7.7×10^{-5} and $P = 6.7 \times 10^{-5}$ for rs8170 and rs8100241, respectively) and had a 2 d.f. $P = 6.3 \times 10^{-13}$ for inclusion of both SNPs. This suggests that these associations may be driven by a single causative variant that is partially correlated with all five SNPs. To investigate this further, we evaluated the associations for SNPs identified through the 1000 Genomes Project using imputation. 1,055 SNPs in a 300-kb interval with a minor allele frequency >0.01 in samples of European ancestry, were evaluated. Thirty-one SNPs, none of which were genotyped in stage 1, displayed $P < 1.76 \times 10^{-9}$ (Fig. 2 and Supplementary Table 3). The most significant associations with the imputed genotypes in stage 1 and 2 combined were for eight perfectly correlated SNPs within a 13-kb region (the most significant SNP was rs4808075, $P = 9.4 \times 10^{-12}$; Supplementary Table 3). These SNPs were correlated with the four genotyped SNPs ($r^2 = 0.37$ to $r^2 = 0.58$ based on the 1000 Genomes Project data; Supplementary Fig. 2). This suggests that one or more of these imputed SNPs may be causally associated with breast cancer risk. However, some rare SNPs may have been missed because the 1000 Genome Project data used were based on the resequencing of only 56 individuals. Therefore, the possibility that the association is driven by a rarer variant, or a more cryptic common variant not detected in the resequencing, cannot yet be ruled out.

Of the five genotyped SNPs in the region and the eight most significant imputed SNPs, only rs8170 and rs2363956 were located in coding regions. The smaller 13-kb region, defined by the most strongly associated SNPs, contains three genes: *ABHD8* (encoding abhydrolase domain containing 8), *ANKLE1* (encoding ankyrin repeat and LEM domain containing 1) and *C19orf62*. The eight most significant imputed SNPs were clustered in and around *ANKLE1*, which encodes a protein of undefined function. However, *C19orf62*, which encodes MERIT40 (Mediator of Rap80 Interactions and Targeting 40 kD), is a more plausible genetic modifier of breast cancer in *BRCA1* carriers because MERIT40 interacts with BRCA1 in a protein complex. MERIT40 is a component of the BRCA1 A complex containing BRCA1-BARD1, Abraxas1, RAP80, BRCC36 and BRCC45 that is required for recruitment and retention of the BRCA1-BARD1 ubiquitin ligase and the BRCC36 deubiquitination enzyme at sites of DNA damage[21–23]. Thus, a variant that modifies MERIT40 function or expression might influence BRCA1-dependent DNA repair and checkpoint activity in mammary epithelial cells of *BRCA1* carriers sufficiently, before loss

of the wildtype BRCA1 allele, to increase the risk of breast cancer. However, until the SNPs that increase risk of cancer have been definitively linked to MERIT40, it remains possible that the other genes in the region or genes influenced by long range chromatin remodeling or by transcriptional events account for the breast cancer association.

Genetic variation at this locus, in combination with other risk modifiers, may prove useful in individual cancer risk assessment for breast cancer in *BRCA1* carriers. In addition, understanding the functional basis of this association may provide important insights into the etiology of *BRCA1*-associated breast cancer and hormone receptor–negative breast cancer in the general population. Our results suggest that GWAS in *BRCA1* mutation carriers or GWAS restricted to specific breast cancer subtypes may identify further breast cancer susceptibility variants.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

URLs

1000 Genomes Project, http://www.1000genomes.org; MACH software, http://www.sph.umich.edu/csg/yli/mach/index.html/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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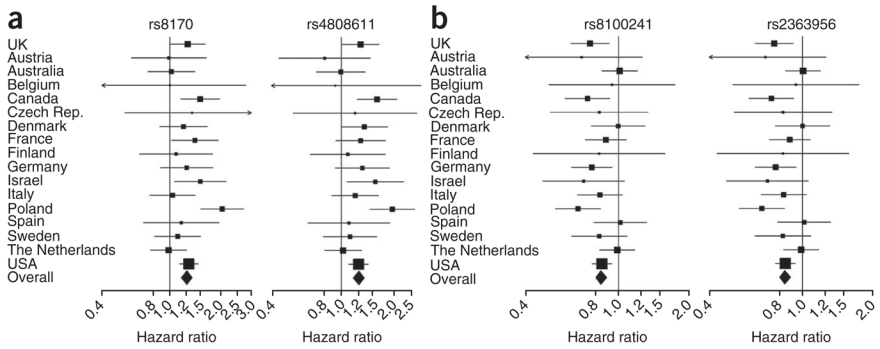

Figure 1.

Forest plots of the associations by country of residence of *BRCA1* mutation carriers in the combined stage 1 and stage 2 samples. (**a**,**b**) Squares indicate the country specific per-allele HR estimates for SNPs rs8170, rs4808611 (**a**) and rs8100241, rs2363956 (**b**). The area of the square is proportional to the inverse of the variance of the estimate. Horizontal lines indicate 95% CIs.

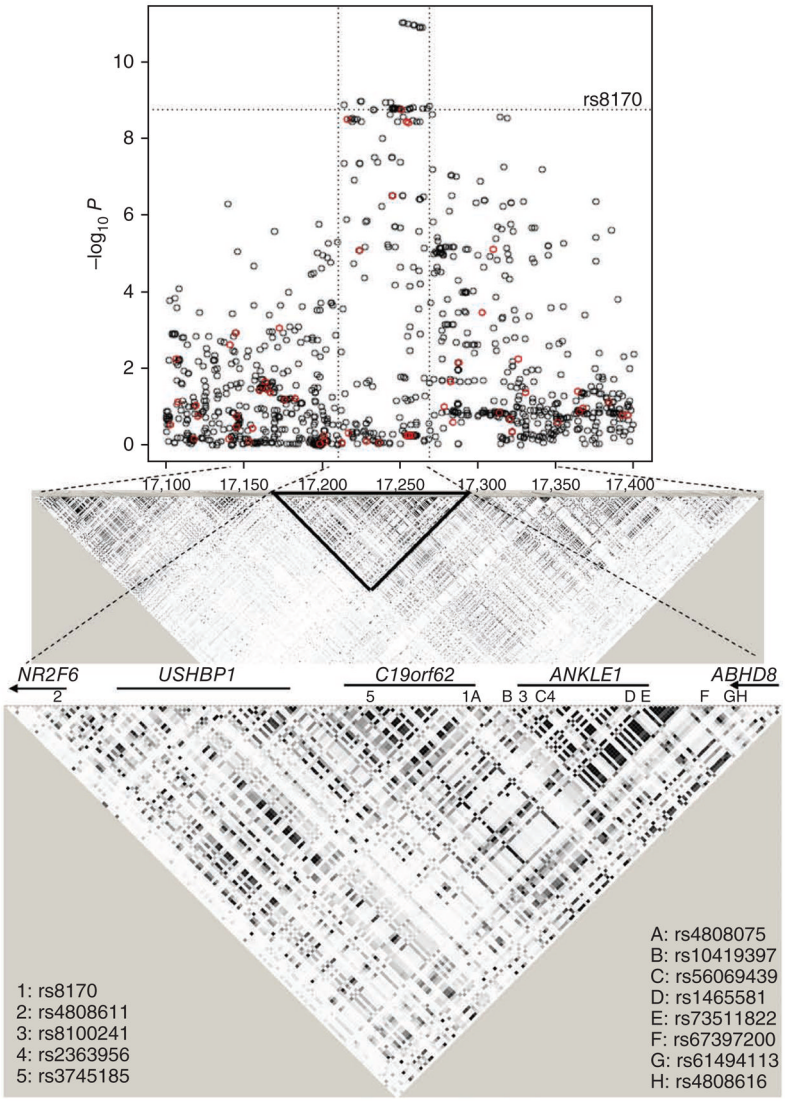

Figure 2.

Above, results of the kinship-adjusted score test statistic (1 d.f.) by position (kb) in stage 1 and 2 samples combined for genotyped and imputed SNPs in the associated region (chromosome 19, positions 17,100–17,400 kb). Genotyped SNPs in stages 1 or 2 are shown in red and imputed SNPs are shown in black. The horizontal dotted line indicates the *P* values for the strongest association among genotyped SNPs (rs8170). At middle, the linkage disequilibrium (LD) blocks around the top five associated SNPs (chromosome 19, positions 17,150–17,350 kb) in the combined analysis of stage 1 and stage 2 samples based on the 1000 Genomes Project data for the samples of European ancestry. Squares in the LD blocks indicate pairwise correlations between the SNPs (r^2) by grayscale (darker symbols indicate correlations closer to 1). Below, details of the region containing the most significantly associated genotyped and imputed SNPs (chromosome 19, positions 17,210–17,268 kb). Location of genotyped SNPs shown by numbers 1–5 and the eight most significantly associated imputed SNPs are shown in letters A–H ($P = 9.0 \times 10^{-12}$ to $P = 1.0 \times 10^{-11}$).

Table 1

Associations with breast cancer risk in *BRCA1* mutation carriers for the five most significant sNPs on 19p13

		Number		Allele 2 frequency		HR (95% CI)[b]			
SNP, position, allele 1/allele 2	Stage	Unaffected[a]	Affected[a]	Unaffected	Affected	Per allele[c]	Heterozygote	Homozygote[d]	P_{trend}[e]
rs8170	Stage 1	1,193	1,190	0.16	0.20	1.25 (1.12–1.39)	1.23 (1.08–1.41)	1.61 (1.13–2.30)	1.1×10^{-4}
17,250,704	Stage 2	3,010	2,970	0.17	0.20	1.26 (1.15–1.38)	1.28 (1.14–1.43)	1.54 (1.17–2.03)	4.1×10^{-6}
G/A	Combined	4,203	4,160	0.17	0.20	1.26 (1.17–1.35)	1.26 (1.16–1.37)	1.57 (1.26–1.95)	2.3×10^{-9}
rs4808611	Stage 1	1,191	1,190	0.16	0.19	1.26 (1.13–1.41)	1.23 (1.08–1.41)	1.72 (1.21–2.45)	7.9×10^{-5}
17,215,825	Stage 2	3,000	2,964	0.16	0.19	1.26 (1.15–1.39)	1.30 (1.16–1.46)	1.43 (1.06–1.92)	6.4×10^{-6}
G/A	Combined	4,191	4,154	0.16	0.19	1.26 (1.17–1.35)	1.27 (1.17–1.39)	1.53 (1.22–1.93)	2.7×10^{-9}
rs8100241	Stage 1	1,191	1,189	0.53	0.47	0.81 (0.74–0.88)	0.82 (0.71–0.95)	0.65 (0.55–0.77)	1.8×10^{-6}
17,253,894	Stage 2	3,008	2,972	0.51	0.49	0.86 (0.80–0.92)	0.93 (0.82–1.05)	0.74 (0.65–0.85)	1.1×10^{-4}
G/A	Combined	4,199	4,161	0.52	0.48	0.84 (0.80–0.89)	0.88 (0.81–0.97)	0.71 (0.63–0.79)	3.9×10^{-9}
rs2363956	Stage 1	1,193	1,190	0.53	0.47	0.81 (0.74–0.88)	0.82 (0.71–0.95)	0.65 (0.55–0.77)	1.5×10^{-6}
17,255,124	Stage 2	3,006	2,970	0.51	0.49	0.87 (0.81–0.93)	0.92 (0.82–1.04)	0.75 (0.65–0.86)	1.7×10^{-4}
A/C	Combined	4,199	4,160	0.52	0.48	0.84 (0.80–0.89)	0.88 (0.80–0.97)	0.71 (0.64–0.79)	5.5×10^{-9}
rs3745185	Stage 1	1,193	1,190	0.46	0.40	0.83 (0.76–0.90)	0.81 (0.71–0.93)	0.69 (0.57–0.82)	2.3×10^{-5}
17,245,267	Stage 2	3,009	2,972	0.44	0.41	0.88 (0.82–0.95)	0.89 (0.80–1.00)	0.77 (0.67–0.89)	1.2×10^{-3}
G/A	Combined	4,202	4,162	0.44	0.41	0.86 (0.81–0.91)	0.86 (0.81–0.91)	0.74 (0.66–0.83)	3.9×10^{-7}

[a] Affected, unaffected with breast cancer.

[b] Estimated hazard ratio and 95% CI.

[c] Per copy of allele 2.

[d] Two copies of allele 2.

[e] Kinship-adjusted score test.

Table 2

Competing risk analysis; associations with breast and ovarian cancer risk for *BRCA1* mutation carriers in the combined stage 1 and 2 samples

					Ovarian cancer			Breast cancer		
SNP	**Genotype**	**Unaffected (%)**	**Breast cancer (%)**	**Ovarian cancer (%)**	**HR**	**95% CI**	P^a	**HR**	**95% CI**	P^a
rs8170	GG	2,306 (68.4)	2,631 (63.4)	584 (69.3)	1.00			1.00		
	GA	973 (28.9)	1,360 (32.8)	238 (28.2)	1.10	0.92–1.31		1.27	1.17–1.39	
	AA	91 (2.7)	159 (3.8)	21 (2.5)	1.06	0.68–1.66		1.58	1.27–1.97	
	Per allele				1.07	0.93–1.24	0.33	1.27	1.18–1.36	1.5×10^{-10}
rs4808611	GG	2,353 (70.0)	2,696 (65.1)	593 (70.7)	1.00			1.00		
	GA	923 (27.5)	1,307 (31.5)	229 (27.3)	1.14	0.96–1.36		1.29	1.18–1.41	
	AA	86 (2.6)	141 (3.4)	17 (2.0)	0.99	0.58–1.69		1.54	1.22–1.94	
	Per allele				1.10	0.94–1.27	0.34	1.27	1.18–1.37	1.6×10^{-10}
rs8100241	GG	793 (23.6)	1,100 (26.5)	188 (22.4)	1.00			1.00		
	GA	1,676 (49.8)	2,118 (51.0)	428 (50.9)	1.01	0.83–1.23		0.89	0.81–0.98	
	AA	899 (26.7)	933 (22.5)	225 (26.8)	0.89	0.71–1.11		0.70	0.62–0.78	
	Per allele				0.94	0.84–1.05	0.28	0.84	0.79–0.88	1.6×10^{-10}
rs2363956	AA	793 (23.6)	1,100 (26.5)	188 (22.3)	1.00			1.00		
	AC	1,678 (49.8)	2,116 (51.0)	429 (51.0)	1.01	0.83–1.23		0.89	0.80–0.97	
	CC	896 (26.6)	934 (22.5)	225 (26.7)	0.89	0.71–1.12		0.70	0.63–0.78	
	Per allele				0.94	0.85–1.05	0.30	0.84	0.79–0.88	2.4×10^{-10}
rs3745185	GG	1,051 (31.2)	1,423 (34.3)	245 (29.1)	1.00			1.00		
	GA	1,675 (49.7)	2,048 (49.3)	437 (51.8)	1.03	0.85–1.23		0.86	0.79–0.94	
	AA	643 (19.1)	681 (16.4)	161 (19.1)	0.92	0.73–1.15		0.73	0.65–0.82	
	Per allele				0.97	0.86–1.08	0.54	0.86	0.81–0.91	7.1×10^{-8}

[a] Robust Wald statistic.

Table 3

Associations with breast cancer risk in the seArCH study overall and by tumor subtype, associations with triple negative breast cancer in the tNBCC study and associations with overall breast cancer risk for *BRCA2* mutation carriers

	rs8170				rs2363956			
Study/subtype		**Controls (%)**	**Cases (%)**	**OR/HR[a] (95% CI)**	***P***	**Controls (%)**	**Cases (%)**	**OR/HR[a] (95%CI)**	***P***
SEARCH									
All cases									
	GG	4,288 (65.8)	4,227 (66.5)	1.00		AA	1,628 (24.7)	1,556 (24.3)	1.00	
	GA	1,999 (30.7)	1,885 (29.7)	0.96 (0.89–1.03)		AC	3,261 (49.4)	3,174 (49.7)	1.02 (0.93–1.11)	
	AA	229 (3.5)	241 (3.8)	1.07 (0.89–1.29)		CC	1,714 (26.0)	1,660 (26.0)	1.01 (0.92–1.12)	
	Per allele			0.99 (0.93–1.05)	0.65	Per allele			1.01 (0.96–1.06)	0.79
Estrogen receptor status										
Estrogen receptor positive										
	GG	4,288 (65.8)	2,437 (68.7)	1.00		AA	1,628 (24.7)	817 (22.7)	1.00	
	GA	1,999 (30.7)	988 (27.9)	0.87 (0.79–0.95)		AC	3,261 (49.4)	1,791 (49.8)	1.09 (0.99–1.21)	
	AA	229 (3.5)	123 (3.5)	0.95 (0.75–1.18)		CC	1,714 (26.0)	992 (27.6)	1.15 (1.03–1.29)	
	Per allele			0.91 (0.84–0.98)	0.011	Per allele			1.07 (1.01–1.14)	0.016
Estrogen receptor negative										
	GG	4,288 (65.8)	503 (61.4)	1.00		AA	1,628 (24.7)	240 (28.8)	1.00	
	GA	1,999 (30.7)	272 (33.2)	1.16 (0.99–1.36)		AC	3,261 (49.4)	421 (50.5)	0.88 (0.74–1.04)	
	AA	229 (3.5)	44 (5.4)	1.64 (1.17–2.29)		CC	1,714 (26.0)	172 (20.7)	0.68 (0.55–0.84)	
	Per allele			1.21 (1.07–1.37)	0.0029	Per allele			0.83 (0.75–0.92)	0.0003
	Heterogeneity[b]				2.9×10^{-5}					1.6×10^{-6}
Progesterone receptor status										
Progesterone receptor positive										
	GG	4,288 (65.8)	1,087 (68.1)	1.00		AA	1,628 (24.7)	368 (23.3)	1.00	
	GA	1,999 (30.7)	447 (28.0)	0.88 (0.78–1.00)		AC	3,261 (49.4)	759 (48.0)	1.03 (0.90–1.18)	
	AA	229 (3.5)	62 (3.9)	1.07 (0.80–1.43)		CC	1,714 (26.0)	454 (28.7)	1.17 (1.01–1.37)	
	Per allele			0.94 (0.85–1.04)	0.21	Per allele			1.08 (1.00–1.17)	0.038
Progesterone receptor negative										
	GG	4,288 (65.8)	451 (62.4)	1.00		AA	1,628 (24.7)	199 (27.5)	1.00	

	rs8170					rs2363956				
Study/subtype		**Controls (%)**	**Cases (%)**	**OR/HR[a] (95% CI)**	***P***		**Controls (%)**	**Cases (%)**	**OR/HR[a] (95%CI)**	***P***
	GA	1,999 (30.7)	237 (32.8)	1.13 (0.95–1.33)		AC	3,261 (49.4)	375 (51.7)	0.94 (0.78–1.13)	
	AA	229 (3.5)	35 (4.8)	1.45 (1.01–2.10)		CC	1,714 (26.0)	151 (20.8)	0.72 (0.58–0.90)	
	Per allele			1.16 (1.01–1.33)	0.031	Per allele			0.85 (0.77–0.95)	0.004
	Heterogeneity[b]				0.0088					0.0002
Estrogen receptor and progesterone receptor status										
Estrogen receptor or progesterone receptor positive										
	GG	4,288 (65.8)	2,515 (68.6)	1.00		AA	1,628 (24.7)	848 (22.8)	1.00	
	GA	1,999 (30.7)	1,019 (27.8)	0.87 (0.79–0.95)		AC	3,261 (49.4)	1,838 (49.5)	1.08 (0.98–1.20)	
	AA	229 (3.5)	130 (3.6)	0.97 (0.78–1.21)		CC	1,714 (26.0)	1,026 (27.6)	1.15 (1.03–1.29)	
	Per allele			0.91 (0.85–0.98)	0.014	Per allele			1.07 (1.01–1.13)	0.017
Estrogen receptor and progesterone receptor negative										
	GG	4,288 (65.8)	280 (59.5)	1.00		AA	1,628 (24.7)	134 (28.3)	1.00	
	GA	1,999 (30.7)	169 (35.9)	1.29 (1.07–1.58)		AC	3,261 (49.4)	256 (54.0)	0.95 (0.77–1.19)	
	AA	229 (3.5)	22 (4.7)	1.47 (0.93–2.32)		CC	1,714 (26.0)	84 (17.7)	0.60 (0.45–0.79)	
	Per allele			1.26 (1.07–1.48)	0.0054	Per allele			0.79 (0.69–0.90)	0.0004
	Heterogeneity[b]				0.0002					8.3×10^{-6}
TNBCC										
Estrogen receptor, progesterone receptor and HER2 negative										
	GG	2,610 (66.2)	1,388 (60.7)	1.00		AA	890 (22.6)	614 (26.9)	1.00	
	GA	1,200 (30.5)	791 (34.6)	1.30 (1.15–1.47)		AC	1,938 (49.3)	1,115 (48.9)	0.83 (0.72–0.95)	
	AA	131 (3.3)	106 (4.6)	1.55 (1.16–2.07)		CC	1,103 (28.1)	550 (24.1)	0.65 (0.55–0.76)	
	Per allele			1.28 (1.16–1.41)	1.2×10^{-6}	Per allele			0.80 (0.74–0.87)	1.1×10^{-7}
BRCA2										
	GG	784 (65.1)	864 (69.5)	1.00		AA	302 (24.9)	297 (23.8)	1.00	
	GA	373 (31.0)	337 (27.1)	0.86 (0.71–1.04)		AC	608 (50.2)	599 (47.9)	1.03 (0.82–1.28)	
	AA	47 (3.9)	43 (3.5)	0.92 (0.58–1.46)		CC	301 (24.9)	354 (28.3)	1.25 (0.98–1.61)	
	Per allele			0.90 (0.77–1.05)	0.17[c]	Per allele			1.12 (0.99–1.27)	0.07[c]

[a] OR estimates for the SEARCH and TNBCC studies and HR estimates for the *BRCA2* associations.

[b] Difference in OR between hormone receptor–positive and hormone receptor–negative breast cancer tumors.

[c]Based on the kinship-adjusted score test statistic.