

## 19p13.1 Is a Triple-Negative-Specific Breast Cancer Susceptibility Locus

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## Abstract

The 19p13.1 breast cancer susceptibility locus is a modifier of breast cancer risk in *BRCA1* mutation carriers and is also associated with the risk of ovarian cancer. Here, we investigated 19p13.1 variation and risk of breast cancer subtypes, defined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status, using 48,869 breast cancer cases and 49,787 controls from the Breast Cancer Association Consortium (BCAC). Variants from 19p13.1 were not associated with breast cancer overall or with ER-positive breast cancer but were significantly associated with ER-negative breast cancer risk [rs8170 OR, 1.10; 95% confidence interval (CI), 1.05–1.15;  $P = 3.49 \times 10^{-5}$ ] and triple-negative (ER-, PR-, and HER2-negative) breast cancer (rs8170: OR, 1.22; 95% CI, 1.13–1.31;  $P = 2.22 \times 10^{-7}$ ). However, rs8170 was no longer associated with ER-negative breast cancer risk when triple-negative cases were excluded (OR, 0.98; 95% CI, 0.89–1.07;  $P = 0.62$ ). In addition, a combined analysis of triple-negative cases from BCAC and the Triple Negative Breast Cancer Consortium (TNBCC;  $N = 3,566$ ) identified a genome-wide significant association between rs8170 and triple-negative breast cancer risk (OR, 1.25; 95% CI, 1.18–1.33;  $P = 3.31 \times 10^{-13}$ ). Thus, 19p13.1 is the first triple-negative-specific breast cancer risk locus and the first locus specific to a histologic subtype defined by ER, PR, and HER2 to be identified. These findings provide convincing evidence that genetic susceptibility to breast cancer varies by tumor subtype and that triple-negative tumors and other subtypes likely arise through distinct etiologic pathways. *Cancer Res*; 72(7); 1795–803. ©2012 AACR.

## Introduction

It is becoming increasingly apparent that genetic susceptibility to breast cancer varies by expression levels of estrogen receptor (ER) in breast tumors. Studies of genetic loci identified in genome-wide association studies (GWAS) have shown that variants in 5p12, 8q24, 1p11.2, 9p21.3, 10q21.2, and 11q13

are associated with ER-positive breast cancer (1–8) but not ER-negative breast cancer, whereas variants in *FGFR2*, *2q35*, *TOX3*, *LSP1*, *MAP3K1*, *TGFB1*, *RAD51L1*, and *ESR1* are associated with both ER-positive and ER-negative disease (8–10). In addition, only a subset of these genetic risk factors for overall breast cancer (*TOX3*, *2q35*, *5q11*, *LSP1*, *RAD51L1*, and *ESR1*) have been

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**Note:** Supplementary data for this article are available at Cancer Research Online (<http://cancerres.aacrjournals.org/>).

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associated with triple-negative breast cancer, defined by ER, progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) expression levels (10–12). To date, no variants have been specifically associated with ER-negative or triple-negative disease.

The 19p13.1 breast cancer susceptibility locus was first identified in a GWAS of *BRCA1* carriers as a modifier of breast cancer risk (9). Single-nucleotide polymorphisms (SNP), rs8170 and either rs8100241 or rs2363956 ( $r^2 = 1$ ), from 19p13.1 were associated with risk of breast cancer (rs8170: HR, 1.27,  $P = 1.5 \times 10^{-10}$ ; rs8100241: HR, 0.84,  $P = 1.6 \times 10^{-10}$ ; and rs2363956: HR, 0.84,  $P = 2.4 \times 10^{-10}$ ). The same variants have also been associated with the risk of ovarian cancer in the general population (13). In addition, replication studies have suggested associations between these SNPs and ER-negative and ER-positive breast cancer (9, 12) and also with triple-negative disease (9, 12). The 19p13.1 locus contains the genes *c19orf62* (MERIT40), *ANKLE1*, and *ABHD8*, but the causal variants underlying these associations with breast and ovarian cancer risk have yet to be identified.

Here, we present a study of the 19p13.1 locus and breast cancer risk in the Breast Cancer Association Consortium (BCAC), an international consortium that has identified or confirmed genome-wide significant associations between commonly inherited variants in several loci and breast cancer risk. We investigated associations between rs8170 from the 19p13.1 locus and breast cancer risk using 48,869 breast cancer cases and 49,787 controls and associations between rs8100241 and rs2363956 from 19p13.1 and breast cancer in a subset of the BCAC cohort. We also directly assessed differences in breast cancer risk by tumor subtype, defined by ER, PR, and HER2 status, and showed that 19p13.1 variants are associated specifically with risk of triple-negative breast cancer.

## Materials and Methods

### Ethics statement

Study subjects were recruited on protocols approved by the Institutional Review Boards at each participating institution, and all subjects provided written informed consent.

### BCAC studies

Thirty-nine studies from the BCAC contributed genotype data (rs8170, rs8100241, and/or rs2363956) to this study (Supplementary Tables S1 and S2). Women of white European ancestry were included from 37 BCAC studies based in Europe, North America, and Australia (49,897 cases and 48,306 controls). Asian women were included from 2 BCAC studies based in Thailand and Taiwan (1,198 cases and 1,481 controls). BCAC studies are described in detail in Supplementary Table S2. Study participants were recruited under protocols approved by the Institutional Review Board at each institution, and all subjects provided written informed consent.

### TNBCC studies

Thirteen studies from the Triple Negative Breast Cancer Consortium (TNBCC) were included in the triple-negative-specific analysis of rs8170 (Supplementary Tables S1 and S2). These studies included 1,350 triple-negative breast cancer

cases and 3,852 controls of women of white European ancestry. Samples included from the 5 TNBCC studies that are also involved in BCAC (BBCC, KARBAC, MCCS, SBCS, and POSH) are unique to the TNBCC analysis and were not included in the BCAC analyses presented in this article. TNBCC studies are described in detail in Supplementary Table S2. Study participants were recruited under protocols approved by the Institutional Review Board at each institution, and all subjects provided written informed consent.

### Genotyping

Genotyping of rs8170, rs8100241, and rs2363956 in BCAC was conducted using a TaqMan allelic discrimination assay or the Sequenom iPLEX platform (Sequenom) via standard protocols. Robust quality control criteria, established by BCAC, were applied as detailed in previous consortium studies (4). Briefly, the genotyping concordance was verified with internal duplicates and overall data quality was ensured using independent genotyping of 96 CEU samples by each genotyping center. We excluded all samples from any study with more than 2 discordant genotypes on the CEU plate. All studies met the specified criteria for call rate (>95%).

rs8170 and rs8100241 genotyping in TNBCC samples was conducted using a single multiplex on the iPLEX Mass Array platform (Sequenom) as part of a larger 22-SNP genotyping project. Samples were plated by study as random mixtures of cases and controls with no-template and CEPH controls in every plate. Genotyping quality for SNPs and samples was evaluated using an iterative quality control process. SNPs and samples were excluded on the basis of the following criteria: SNP call rate < 95%, Hardy-Weinberg equilibrium (HWE)  $P$  value < 0.01 among controls, and sample call rate < 95%.

### Pathology and tumor markers

Pathology analyses of BCAC data were conducted using studies of white European women only. All studies except CTS, GC-HBOC, and UKBGS provided data on ER and PR status of tumors and 25 studies provided data on HER2 (Supplementary Table S3). The collection of pathology and tumor marker information for BCAC has been described previously (14). Briefly, studies provided information on histopathologic subtype, grade of differentiation, tumor size, nodal involvement, and stage at diagnosis of breast tumors. ER/PR status was most commonly defined using data from medical records. ER- and PR-negative status was defined as less than 10% of the tumor cells stained. HER2-negative status was typically defined as a score of 0 or 1+ on a HER2 immunohistochemistry (IHC) scale of 0 to 3+.

TNBCC cases were defined as individuals with an ER-, PR-, and HER2-negative breast cancer. Definition of ER- and PR-negative status were <1% cells stained positive for DEMOKRITOS, DFCI, FCCC, and MCCS; <10% cells stained positive for BBCC, KARBAC; intensity score (0–3) percentage of cells stained (0%–100%) <50 for SBCS; or an Allred score <3 for RPCI and POSH. Definition of HER2-negative status was score 0 or 1+ by IHC for BBCC, DEMOKRITOS, FCCC, MCCS, POSH, RCPI, SBCS; or IHC score 0, 1+, or 2+ and FISH negative for DFCI and KARBAC. Cytokeratin 5/6

(CK5/6) and EGF receptor (EGFR) IHC data for identification of basal tumors were not available.

### Statistical methods

Departure from HWE was assessed in controls using a goodness-of-fit test. Evidence of departure was not observed in any of the participating studies (HWE,  $P \geq 0.001$ ). Single SNP analyses were conducted using unconditional logistic regression separately for white Europeans and Asians. Analyses using only BCAC case-control studies were adjusted for study, and analyses using all BCAC studies (case-control and case-only studies) were adjusted for country. SNP associations were tested in a log-additive model. To obtain additional information, we also used a 2 degree of freedom test, calculating ORs and 95% confidence intervals (CI) separately for heterozygotes and rare homozygotes. Consideration of age made no substantial difference to the results, assessed by both the exclusion of studies for which the age of controls was not known and the adjustment for age in 5-year categories and as a continuous covariate. Subtype-specific associations defined by ER, PR, and HER2 status were estimated for white Europeans with invasive breast cancer using polytomous logistic regression with control status as the reference outcome, adjusting for country or study where appropriate. SNP associations were tested in a log-additive model. Heterogeneity in the OR by subtypes was tested by applying polytomous logistic regression to cases-only, treating the number of minor alleles as the outcome. Triple-negative-specific analyses were conducted among cases with known ER, PR, and HER2 status using polytomous logistic regression with ER-negative (excluding triple negative) and triple-negative cases compared with controls as the reference outcome, adjusting for country. BCAC and TNBCC analyses were conducted in a combined data set using raw genotype data for rs8170 and rs8100241 from each consortium, and analyses were adjusted for country and consortium. Interaction and haplotype analyses were conducted using the combined BCAC and TNBCC data set adjusting for country. Haplotype analyses were conducted using the haplo.glm function from the haplo.stats package in R with default parameters.

### Results

We first evaluated 3 SNPs in the 19p13.1 locus—rs8170, rs8100241, and rs2363956—for associations with overall risk of invasive breast cancer in BCAC studies of white European women. The rs8170 was genotyped in all 37 studies (47,671 cases and 48,306 controls), whereas only a subset of studies genotyped rs8100241 (21,645 cases and 21,521 controls) or rs2363956 (17,857 cases and 20,648 controls; Supplementary Table S1). Neither rs8170 nor rs2363956 was associated with the risk of overall invasive breast cancer. However, the A allele of rs8100241 was associated with a small increased risk of breast cancer (OR, 1.04; 95% CI, 1.01–1.08;  $P = 2.88 \times 10^{-3}$ ; Table 1). Results were very similar when excluding 4 case-only studies (Supplementary Table S4). No associations were observed between rs8170, rs8100241, or rs2363956 and risk of ductal carcinoma *in situ* (DCIS). Similarly, no association was observed between rs8170 or rs8100241 and risk of invasive breast cancer in 2 BCAC studies of Asian women including

1,198 breast cancer cases and 1,481 controls, although power to detect an association with rs8170 was limited because of a very low minor allele frequency of 0.20% in this population (Supplementary Table S5). Adjustment for age did not change the magnitude or significance of our results.

Given that the 19p13.1 susceptibility locus was first identified as a modifier of breast cancer risk in *BRCA1* mutation carriers (9), who predominantly develop tumors with an ER-negative or triple-negative phenotype, we next evaluated associations between these 3 SNPs and the risk of invasive breast cancer subtypes as defined by ER, PR, and HER2 status (Table 2). Because genotype data were available for rs8170 in the entire BCAC data set, we focused on this SNP in the analyses of breast cancer subtypes. When considering ER status alone, rs8170 was associated with risk of ER-negative breast cancer (OR, 1.09; 95% CI, 1.05–1.14;  $P = 6.69 \times 10^{-5}$ ), but not with ER-positive breast cancer (OR, 0.99; 95% CI, 0.96–1.02;  $P = 0.38$ ;  $P_{\text{Het}} = 1.61 \times 10^{-5}$ ; Table 2). A similar pattern was observed for PR status (PR-negative: OR, 1.05; 95% CI, 1.01–1.10;  $P = 7.39 \times 10^{-3}$ ;  $P_{\text{Het}} = 6.52 \times 10^{-3}$ ; Table 2). When considering both ER and PR status, rs8170 was associated only with tumors negative for both markers (OR, 1.10; 95% CI, 1.05–1.16;  $P = 4.10 \times 10^{-5}$ ; Table 2). Incorporation of HER2 status showed that the 19p13.1 locus was associated with risk of triple-negative breast cancer (OR, 1.21; 95% CI, 1.13–1.31;  $P = 2.97 \times 10^{-7}$ ), but not any other combination of ER, PR, and HER2 status ( $P_{\text{Het}} = 1.32 \times 10^{-5}$ ). In particular, rs8170 was not associated with risk of developing HER2-negative tumors that were ER-positive or PR-positive (OR, 1.00; 95% CI, 0.97–1.04;  $P = 0.80$ ), indicating that rs8170 is associated with triple-negative rather than HER2-negative disease. The estimate of effect for rs8170 was stronger among triple-negative breast cancers (OR, 1.21) than all ER-negative breast cancers (OR, 1.09). Analysis of rs8170 among cases-only was consistent with the case-control analyses (Supplementary Table S6). Similar patterns by subtype were observed for rs8100241 and rs2363956 (Supplementary Table S7). Exclusion of the 4 case-only BCAC studies did not substantially alter these findings (Supplementary Table S8).

We next investigated whether variants in the 19p13.1 locus were associated specifically with risk of triple-negative disease by comparing triple-negative cases (ER<sup>-</sup>, PR<sup>-</sup>, HER2<sup>-</sup>) to non-triple-negative, ER-negative cases (ER<sup>-</sup>, PR<sup>+</sup> or HER2<sup>+</sup>) in an analysis of ER-negative breast cancers with known ER, PR, and HER2 status (Table 3). The rs8170 was not associated with the risk of ER-negative breast cancer when excluding triple-negative cases (OR, 0.98; 95% CI, 0.89–1.07;  $P = 0.63$ ) but remained strongly associated with risk of triple-negative breast cancer (OR, 1.21; 95% CI, 1.13–1.31;  $P = 2.94 \times 10^{-7}$ ;  $P_{\text{Het}} = 9.07 \times 10^{-5}$ ). Given that basal-like tumors account for approximately 80% of triple-negative tumors (15), we also evaluated the influence of CK5/6 and EGFR basal tumor marker status on the 19p13.1 association with breast cancer risk. Because of limited data for these markers (Supplementary Table S3), we focused on rs8170 to maximize power to detect differences by basal status. The rs8170 was significantly associated with risk of basal-like triple-negative tumors (OR, 1.27; 95% CI, 1.07–1.50;  $P = 0.0069$ ) but was not associated with risk of non-basal triple-negative tumors (OR, 1.03; 95% CI, 0.79–1.34;  $P = 0.83$ ;

$P_{\text{Het}} = 0.026$ ; Supplementary Table S9). Furthermore, rs8170 was not associated with either ER-positive basal tumors ( $n = 301$ ; OR, 0.90; 95% CI, 0.73–1.10;  $P = 0.30$ ) or ER-negative, non-basal triple-negative tumors ( $n = 122$ ; OR, 0.89; 95% CI, 0.64–1.23;  $P = 0.48$ ;  $P_{\text{Het}} = 0.80$ ). This suggests that the 19p13.1 locus is exclusively associated with triple-negative basal-like tumors. However, because of the small sample size and potential misclassification of CK5/6 and EGFR, these results need to be confirmed in larger studies of breast cancer subtypes.

We next extended our evaluation of 19p13.1 variants to nonoverlapping subjects (1,350 triple-negative cases and 3,852 controls) from the TNBCC (Supplementary Table S1; ref. 12). Among the TNBCC studies alone, rs8170 was associated with an increased risk of triple-negative breast cancer (OR, 1.26; 95% CI, 1.13–1.40;  $P = 3.02 \times 10^{-5}$ ; Table 3). Importantly, the combined rs8170 genotype data from BCAC and TNBCC ( $n = 3,566$  triple-negative cases) yielded a genome-wide significant association with the risk of triple-negative breast cancer (OR, 1.25; 95% CI, 1.18–1.33;  $P = 4.24 \times 10^{-13}$ ; Table

3). There was no evidence for heterogeneity of the ORs by country for either triple-negative or non-triple-negative, ER-negative breast cancer in the combined analysis (Fig. 1). The difference in effect estimates between triple-negative and non-triple-negative, ER-negative breast cancer was highly significant ( $P_{\text{Het}} = 2.51 \times 10^{-6}$ ), indicating that rs8170 is a triple-negative-specific risk variant. A similar pattern was observed for rs8100241, which was inversely associated only with triple-negative disease (OR, 0.81; 95% CI, 0.76–0.86;  $P = 1.91 \times 10^{-12}$ ) and not with non-triple-negative, ER-negative disease (OR, 0.94; 95% CI, 0.86–1.03;  $P = 0.19$ ) in the combined data set ( $P_{\text{Het}} = 3.30 \times 10^{-3}$ ; Supplementary Table S10).

To better understand the influence of 19p13.1 variants on risk of triple-negative breast cancer, we included both rs8170 and rs8100241 in a multivariate model in the combined BCAC and TNBCC data set. Both rs8170 (OR, 1.16; 95% CI, 1.07–1.26;  $P = 6.14 \times 10^{-4}$ ) and rs8100241 (OR, 0.85; 95% CI, 0.79–0.91;  $P = 5.10 \times 10^{-6}$ ) remained significantly associated with risk of triple-negative breast cancer with only slight attenuation of the ORs. However, when considering the association of one SNP

**Table 1.** 19p13.1 single SNP associations with breast cancer among white European women

	Cases	Controls	OR (95% CI)	$P_{\text{trend}}$
<i>Invasive breast cancer</i>				
rs8170				
CC	31,083	31,673	1.00	
CT	14,807	14,917	0.99 (0.96–1.02)	
TT	1,781	1,716	0.95 (0.89–1.02)	
	Log-additive		0.98 (0.96–1.01)	0.17
rs8100241				
GG	5,128	4,968	1.00	
GA	10,848	10,711	1.05 (1.01–1.10)	
AA	5,669	5,842	1.09 (1.03–1.15)	
	Log-additive		1.04 (1.01–1.08)	$2.88 \times 10^{-3}$
rs2363956				
TT	4,396	5,315	1.00	
TG	8,876	10,215	1.01 (0.96–1.06)	
GG	4,585	5,298	1.02 (0.96–1.07)	
	Log-additive		1.01 (0.98–1.04)	0.59
<i>DCIS</i>				
rs8170				
CC	1,523	28,349	1.00	
CT	699	13,412	1.02 (0.93–1.12)	
TT	83	1,548	0.95 (0.75–1.19)	
	Log-additive		1.00 (0.93–1.09)	0.90
rs8100241				
GG	346	4,276	1.00	
GA	722	9,123	1.01 (0.88–1.15)	
AA	390	4,900	1.03 (0.88–1.20)	
	Log-additive		1.01 (0.93–1.10)	0.75
rs2363956				
TT	141	5,066	1.00	
TG	317	10,039	0.99 (0.81–1.22)	
GG	159	5,225	0.93 (0.74–1.19)	
	Log-additive		0.97 (0.85–1.09)	0.60

**Table 2.** Risk of invasive breast cancer associated with rs8170 among white Europeans defined by ER, PR, and HER2 tumor status

	N	rs8170: OR (95% CI)	$P_{\text{trend}}$	Case-only ( $P_{\text{het}}$ )
<b>ER status</b>				
Controls	48,306	1.00	—	$1.61 \times 10^{-5}$
ER <sup>+</sup>	25,649	0.99 (0.96–1.02)	0.38	
ER <sup>-</sup>	7,641	1.09 (1.05–1.14)	$6.69 \times 10^{-5}$	
<b>PR status</b>				
Controls	48,306	1.00	—	$6.52 \times 10^{-3}$
PR <sup>+</sup>	19,996	0.99 (0.96–1.03)	0.71	
PR <sup>-</sup>	10,444	1.05 (1.01–1.10)	$7.39 \times 10^{-3}$	
<b>ER/PR status</b>				
Controls	48,306	1.00	—	$3.68 \times 10^{-4}$
ER <sup>+</sup> /PR <sup>+</sup>	18,811	0.99 (0.96–1.02)	0.60	
ER <sup>+</sup> /PR <sup>-</sup>	4,294	0.99 (0.93–1.05)	0.66	
ER <sup>-</sup> /PR <sup>+</sup>	1,102	1.04 (0.93–1.16)	0.47	
ER <sup>-</sup> /PR <sup>-</sup>	6,092	1.10 (1.05–1.16)	$4.10 \times 10^{-5}$	
<b>ER, PR and HER2 status</b>				
Controls	45,684	1.00	—	$1.32 \times 10^{-5}$
(ER <sup>+</sup> or PR <sup>+</sup> )/HER2 <sup>-</sup>	11,774	1.00 (0.97–1.04)	0.80	
(ER <sup>+</sup> or PR <sup>+</sup> )/HER2 <sup>+</sup>	1,918	1.02 (0.94–1.11)	0.62	
ER <sup>-</sup> /PR <sup>-</sup> /HER2 <sup>-</sup>	2,216	1.21 (1.13–1.31)	$2.97 \times 10^{-7}$	
ER <sup>-</sup> /PR <sup>-</sup> /HER2 <sup>+</sup>	1,109	0.94 (0.85–1.05)	0.31	

Abbreviations: +, positive; -, negative;  $P_{\text{het}}$ , case-only heterogeneity  $P$  value.

stratified by the genotype of the other, we found that the effect of rs8170 was restricted to individuals with the rs8100241 "GA" genotype (OR, 1.29; 95% CI, 1.14–1.45;  $P = 3.13 \times 10^{-5}$ ) and that the effect of rs8100241 was restricted to individuals with the rs8170 "CC" genotype (OR, 0.82; 95% CI, 0.76–0.89;  $P = 9.90 \times 10^{-7}$ ; Supplementary Table S11a). This is reflected by a significant interaction between these SNPs (interaction OR, 1.21; 95% CI, 1.06–1.37;  $P = 0.0036$ ; Supplementary Table S11b). A haplotype analysis for these 2 SNPs found that the C-G and T-G haplotypes (rs8170–rs8100241) were both associated with risk of triple-negative breast cancer compared with the C-A

haplotype (C-G: OR, 1.17; 95% CI, 1.09–1.25;  $P = 1.00 \times 10^{-5}$  and T-G: OR, 1.35; 95% CI, 1.25–1.46;  $P = 2.51 \times 10^{-14}$ ), whereas the T-A haplotype was not observed at all (Supplementary Table S12), suggesting that both SNPs tag the causal variant. No interactions were observed between these SNPs among other subtypes defined by any combination of ER, PR, and HER2 status.

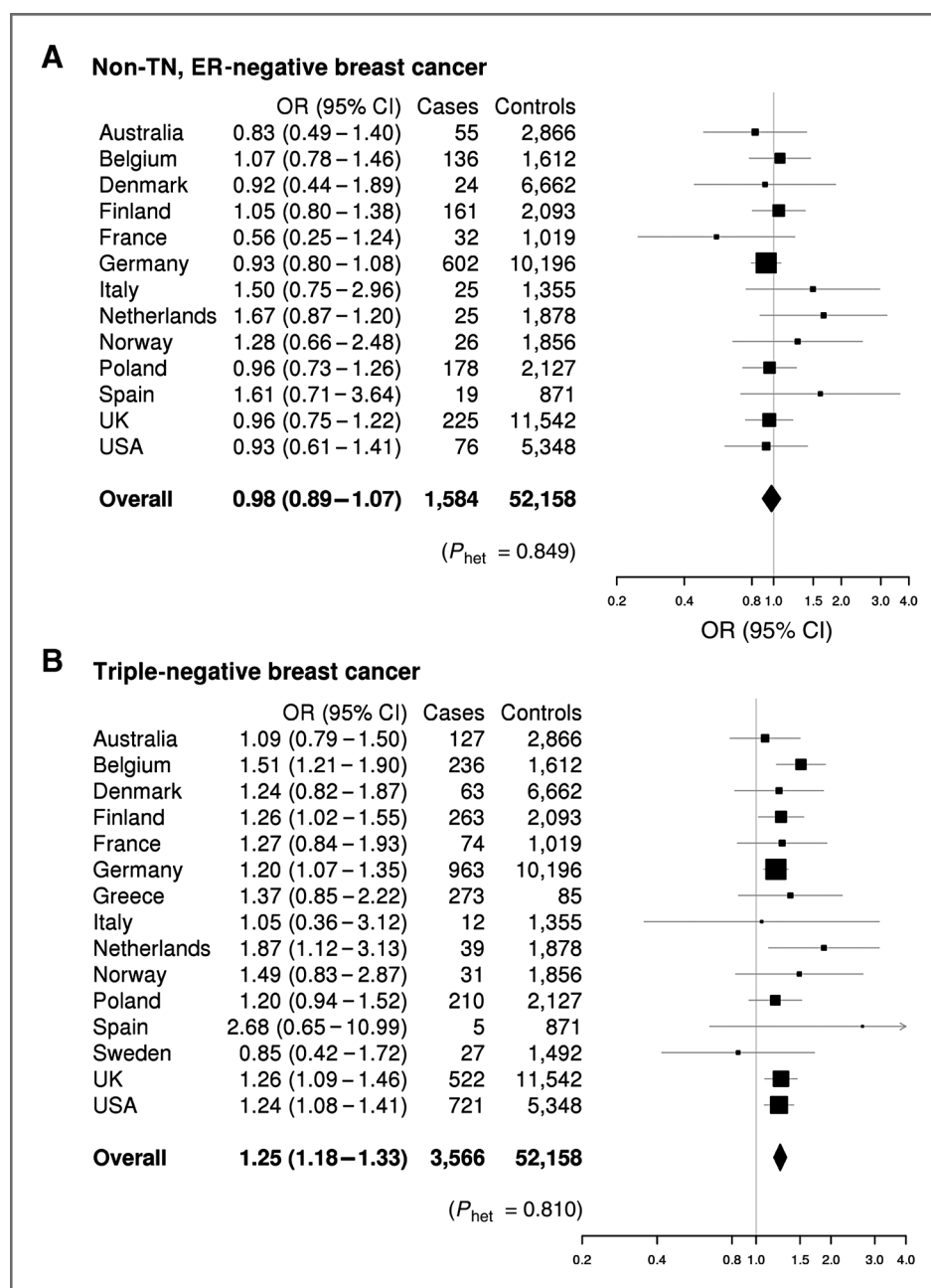
Because of the overlap between the BCAC samples in this analysis and a subset of those in SEARCH and the TNBCC, which were previously examined in an initial generalization of 19p13.1 SNP associations with *BRCA1*-related tumors (9), we

**Table 3.** Triple-negative-specific risk associated with rs8170

	N	OR (95% CI)	$P_{\text{trend}}$	Case-only ( $P_{\text{het}}$ )
<b>All BCAC studies</b>				
Controls	45,684	1.00		
ER <sup>-</sup> (non-TN)	1,584	0.98 (0.89–1.07)	0.63	
TN	2,216	1.21 (1.13–1.31)	$2.94 \times 10^{-7}$	$1.77 \times 10^{-4}$
<b>TNBCC studies</b>				
Controls	3,852	1.00		
TN	1,350	1.26 (1.13–1.40)	$3.02 \times 10^{-5}$	NA
<b>BCAC + TNBCC studies</b>				
Controls	52,158	1.00		
ER <sup>-</sup> (non-TN)	1,584	0.98 (0.89–1.07)	0.60	
TN	3,566	1.25 (1.18–1.33)	$4.24 \times 10^{-13}$	$2.51 \times 10^{-6}$

Abbreviations: -, negative; TN, triple-negative.

**Figure 1.** 19p13.1 (rs8170) association with risk of non-triple-negative, ER-negative and triple-negative (TN) breast cancer. Forest plots for rs8170 and risk of (A) non-triple-negative, ER-negative breast cancer and (B) triple-negative breast cancer are shown by country. Country-specific ORs (95% CIs) are denoted by black boxes (black lines). Overall OR estimates are represented by black diamonds, where diamond width corresponds to 95% CI bounds. Box and diamond heights are inversely proportional to precision of the OR estimate.  $P$  values for heterogeneity ( $P_{\text{het}}$ ) of ORs by country are shown.



conducted a sensitivity analysis removing these studies from the ER and ER/PR/HER2 subtype analyses. The effect estimates in this sensitivity analysis were very similar to those from the complete BCAC analysis, with only slight attenuation of significance (Supplementary Table S13).

## Discussion

Here, we report on the identification of the first triple-negative breast cancer-specific susceptibility locus at 19p13.1. We found that rs8170 was strongly associated with the risk of triple-negative breast cancer (OR, 1.25;  $P = 4.24 \times 10^{-13}$ ) but was not associated with ER-positive (OR, 0.99;  $P =$

0.38) or non-triple-negative, ER-negative (OR, 0.98;  $P = 0.63$ ) breast cancer. Further analyses based on basal tumor markers suggested that the 19p13.1 variants are associated specifically with basal-like TN tumors (OR, 1.27;  $P = 0.0069$ ). Ongoing histopathology studies in BCAC involving characterization of the CK5/6 and EGFR status of tumors may increase the numbers of triple-negative basal cases and allow reevaluation of this finding in the future. We were well powered to detect an association between 19p13.1 variants and these breast cancer subtypes in more than 32,000 cases and 48,000 controls. Importantly, our ability to evaluate risk of breast cancer across histologic subtypes in a single, large consortium strengthens

the validity of the findings. Heterogeneity in hormone receptor and basal marker status across studies may influence our ability to detect associations with breast tumor subtypes at 19p13.1. However, in a sensitivity analysis including only cases from studies with the most stringent criteria for defining hormone receptor status (<1% of cells stained positive for ER, PR, and HER2: 0 or 1+ on IHC), the effect estimates were very similar to those from the complete analysis of the ER-negative, non-triple-negative and triple-negative subtypes. These findings have important implications for understanding genetic susceptibility to breast cancer because they suggest that additional susceptibility variants for specific subtypes of breast cancer remain to be identified.

Triple-negative breast cancer accounts for approximately 15% of all breast cancer among women of European descent and differs substantially from other subtypes of breast cancer by expression and genomic profiles and by epidemiologic characteristics (15). Women with triple-negative breast cancer are more likely to be younger, have an earlier age at menarche, higher body mass index during premenopausal years, higher parity, and a lower lifetime duration of breast feeding and in the United States are more likely to be African-American or Latina (16–18), and triple-negative tumors are associated with more aggressive disease and poorer survival (15, 19, 20). The biologic and clinical distinctions between biologic and other breast cancer subtypes are concordant with the identification of triple-negative-specific genetic risk factors and provide additional evidence for a distinct triple-negative tumor etiology. This highlights the importance of additional subtype-specific breast cancer studies and studies of breast cancer in additional populations such as African-Americans and Latinas, as it is not known whether similar associations with the SNPs described here exist in these populations.

The 3 19p13.11 variants measured in this study are located in the genes *C19orf62* and *ANKLE1* and are approximately 13 kb from the gene *ABHD8*. *C19orf62*, which encodes the MERIT40 protein, is currently hypothesized to be the most likely cancer susceptibility gene in this region because of the known interaction between MERIT40 and BRCA1. MERIT40 is integral to the localization of the BRCA1-A complex during DNA double-strand break repair, specifically through the recruitment and retention of the BRCA1-BARD1 ubiquitin ligase and the BRCC36 deubiquitination enzyme (21–24). However, both *ANKLE1* (ankyrin repeat and LEM domain containing 1) and *ABHD8* (abhydrolase domain containing 8) encode proteins of uncharacterized functions, making conjecture about the involvement of these proteins in cancer-related processes difficult.

It is unknown whether a single causal variant or multiple rare variants underlie the 19p13.1 association, affecting triple-negative risk through dysregulation of these or other nearby genes. Conversely, the causal variant at 19p13.1 may lie in a regulatory element that confers risk to triple-negative disease through long-range effects on distant genes. Although the biology underlying this association is unknown, it is likely that the functional consequences of variants at 19p13.1 are to modify genes or proteins that cooperate with other factors in signaling pathways critical to the development of the triple-negative phenotype. One can speculate that the causal 19p13.1 variants directly initiate

and promote triple-negative tumor development, or alternatively that the 19p13.1 causal variants act to change the morphology of an existing malignant breast lesion to a triple-negative phenotype early in tumorigenesis. Resequencing and fine-mapping efforts in triple-negative breast cancer cases will be important for identification of the causal variants in the 19p13.1 locus and the mechanism by which these variants specifically influence risk of triple-negative breast cancer.

In conclusion, our study provides convincing evidence that the 19p13.1 locus is specifically associated with risk of triple-negative disease, confirming that some breast cancer susceptibility loci differ by histologic breast tumor subtype defined by ER, PR, and HER2 status. This report provides further evidence that triple-negative tumors and other subtypes likely arise through distinct etiologic pathways. Genetic and functional studies of triple-negative breast cancer will be necessary to identify the mechanism underlying the 19p13.1 association and to identify additional triple-negative-specific susceptibility loci.

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No potential conflicts of interests were disclosed.

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