Five Polymorphisms and Breast Cancer Risk: Results from the Breast Cancer Association Consortium

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Abstract

Previous studies have suggested that minor alleles for ERCC4 rs744154, TNF rs361525, CASP10 rs13010627, PGR rs1042838, and BID rs8190315 may influence breast cancer risk, but the evidence is inconclusive due to their small sample size. These polymorphisms were genotyped in more than 30,000 breast cancer cases and 30,000 controls, primarily of European descent, from 30 studies in the Breast Cancer Association Consortium. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) as a measure of association. We found that the minor alleles for these polymorphisms were not related to invasive breast cancer risk overall in women of European descent: ECCR4 per-allele OR (95% CI) = 0.99 (0.97-1.02), minor allele frequency = 27.5%; TNF 1.00 (0.95-1.06), 5.0%; CASP10 1.02 (0.98-1.07), 6.5%; PGR 1.02 (0.99-1.06), 15.3%; and BID 0.98 (0.86-1.12), 1.7%. However, we observed significant between-study heterogeneity for associations with risk for single-nucleotide polymorphisms (SNP) in CASP10, PGR, and BID. Estimates were imprecise for women of Asian and African descent due to small numbers and lower minor allele frequencies (with the exception of BID SNP). The ORs for each copy of the minor allele were not significantly different by estrogen or progesterone receptor status, nor were any significant interactions found between the polymorphisms and age or family history of breast cancer. In conclusion, our data provide persuasive evidence against an overall association between invasive breast cancer risk and ERCC4 rs744154, TNF rs361525, CASP10 rs13010627, PGR rs1042838, and BID rs8190315 genotypes among women of European descent. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1610–6)

Introduction

Results from genome-wide scans have confirmed common genetic variants with very small effects on breast cancer risk; however, this approach likely misses clinically and functionally important cancer susceptibility alleles because of false negatives and poor coverage in some regions. Therefore, examination of candidate genes still provides a useful, complementary approach. The Breast Cancer Association Consortium, a collaborative data pooling effort of more than 60,000 subjects, was initiated to validate reported genetic associations with breast cancer risk. At least one member group had reported associations between breast cancer risk and *ERCC4* rs744154 (1), *TNF* rs361525 (2), and *CASP10* rs13010627 (3). Here, we also follow up on the Breast Cancer Association Consortium's previously published evidence of a suggestive association between *PGR* rs1042838 and breast cancer risk based on five studies that are also included in this report (4). In addition, *BID* rs8190315 was significantly associated with elevated breast cancer risk [per minor G allele, odds ratio (OR), 1.91; 95% confidence intervals (95% CI), 1.17-3.19] in the Sheffield Breast Cancer Study of 1,021 cases and 1,115 controls.[31] To precisely estimate the hypothesized weak effects of these polymorphisms, we assessed their association with breast cancer risk using more than 30,000 breast cancer cases and 30,000 controls in the Breast Cancer Association Consortium.

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Table 1. Summary ORs and 95% CIs for five polymorphisms and invasive breast cancer risk among women of European descent, based on data from ~30,000 cases and 30,000 controls from the Breast Cancer Association Consortium

Gene, SNP description, and rs no.	No. of studies	Genotype	No. of cases	No. of controls	MAF	Pooled OR* (95% CI)	P †	Between-study heterogeneity ‡
ECCR4, IVS1−807G>C, rs744154		*GG*	13,585	15,267		1.00		
		GC	10,280	11,616		1.00 (0.97-1.04)		
		CC	1,878	2,191		0.97 (0.91-1.04)		
	27	per allele			27.5	0.99 (0.97-1.02)	0.62	0.36
TNF, −417A>G, rs361525		*GG*	25,623	28,815		1.00		
		GA	2,616	2,993		0.99 (0.94-1.05)		
		AA	94	93		1.14 (0.85-1.52)		
	28	per allele			5.0	1.00 (0.95-1.06)	0.93	0.65
CASP10, Ex9−188G>A, rs13010627		*GG*	23,456	26,597		1.00		
		GA	3,352	3,706		1.03 (0.98-1.09)		
		AA	109	126		0.94 (0.72-1.22)		
	28	per allele			6.5	1.02 (0.98-1.07)	0.33	0.008
PGR, Ex4+72G>T, rs1042838		*GG*	16,506	19,746		1.00		
		GT	6,040	7,097		1.02 (0.98-1.06)		
		TT	583	664		1.04 (0.93-1.17)		
	24	per allele			15.3	1.02 (0.99-1.06)	0.26	0.04
BID, S56G, rs8190315		*AA*	13,211	13,711		1.00		
		AG	452	478		0.99 (0.87-1.14)		
		GG	1	4		N/E		
	11	per allele			1.7	0.98 (0.86-1.12)	0.81	0.05

Abbreviation: N/E, not estimated.
*Unconditional logistic regression models were adjusted for study and included genotypes using indicator variables with homozygotes of the major allele as the reference category.
† We assumed a log-linear association with the number of minor alleles to calculate the P value for a linear trend.
‡ The P value for "between study heterogeneity" was calculated using an interaction variable with study and genotypes, which was tested for deviation from a multiplicative interaction model using the log likelihood ratio test to compare the fit of logistic models with and without an interaction term.

Materials and Methods

Study Populations. Thirty case-control studies (described in Supplementary Table S1) contributed data to these analyses. Studies were conducted in Europe, the United States, and Australia, among women of primarily European descent, with the exception of the two Southeast Asian studies. Most studies (exceptions listed in Supplementary Table S2) provided information on disease status, age at diagnosis/enrollment, ethnic group (European, Asian, other), and first-degree history of breast cancer. All studies received approval from their institutional review committees and participants provided informed consent or were analyzed under specific coding procedures (Amsterdam Breast Cancer Study).

Genotyping. Genotyping platforms are detailed in Supplementary Table S1. Case and control counts, minor allele frequencies, tests for Hardy-Weinberg equilibrium, and completion proportions by study and locus can be found in Supplementary Table S3. Data on specific genotypes from studies with gross deviations from Hardy-Weinberg equilibrium ($P > 10^{-4}$) were excluded from analyses (Norwegian Breast Cancer Study for *ERCC4* rs744154, Bavarian Breast Cancer Cases and Controls for *TNF* rs361525, Norwegian Breast Cancer Study and Taiwanese Breast Cancer Study for *CASP10* rs13010627; data not shown). A total of 4,819 subjects with >20% failed genotypes for the five single-nucleotide polymorphisms (SNP) in this analysis (6.2% overall—7.2% of invasive cases, 16.6% of *in situ* cases, and 5.0% of controls) were excluded from analyses (data not shown). Although numbers for each SNP varied based on study participation in genotyping efforts, 34,239 invasive breast cancer cases, 1,092 *in situ* cases, and 37,214 controls were the maximum numbers of subjects available for statistical analysis. Call rates for these cases and controls were >94% for all assays in each study (Supplementary Table S3).

Statistical Analyses. Multivariate, random-effects models were weighted for each study by the within-study and between-study variances (5). For *BID* rs8190315, a Cochran-Mantel-Haenszel meta-analysis was done using Genie (6, 7) to account for familial relationships present in the Utah Breast Cancer Study. The presence of between-study heterogeneity was assessed by the Q test (5). Women of Asian and African descent, comprising ≥10% of the study population, were treated separately in statistical models.

We also used unconditional logistic regression models to estimate pooled ORs and 95% CIs for the association between individual SNPs and breast cancer risk for all studies combined (8). All models were adjusted for race and study, but not age, because age was missing for more than half of participants from seven studies (Supplementary Table S2). However, the inclusion of age did not alter OR estimates in analyses of data from studies with available information (data not shown). Exclusion of studies with Hardy-Weinberg equilibrium P values between 10^{-4} and 0.05 did not substantially alter overall ORs (data not shown). All analyses were done with STATA (version 10.0) or Genie (6, 7) when the Utah Breast Cancer Study was included.

Results

Most invasive breast cancer cases were diagnosed with ductal carcinomas (73.1%), were stage I (50.5%) or stage

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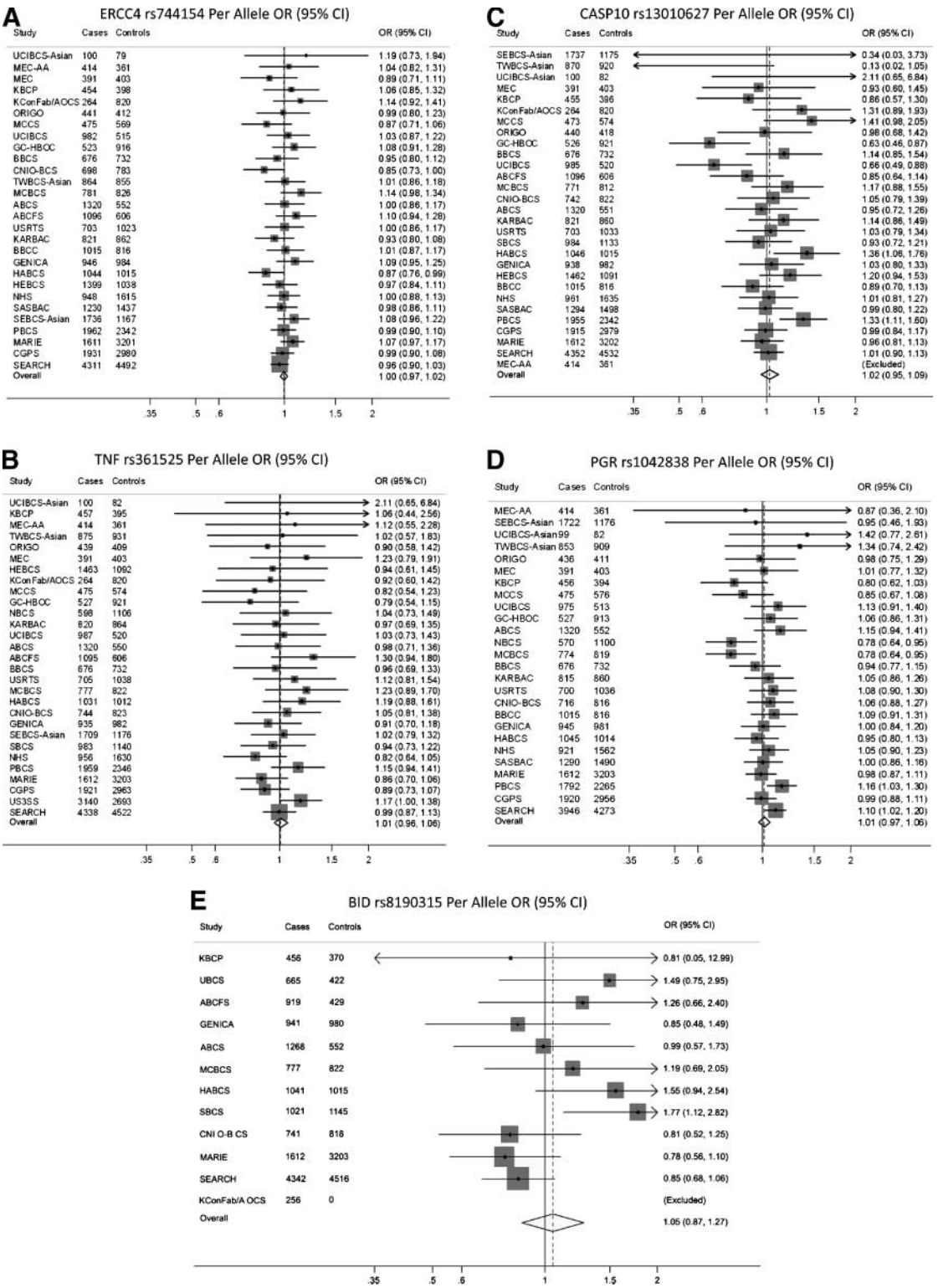

Figure 1. Per-allele ORs and 95% CIs for breast cancer risk by study are shown for *ERCC4* rs744154 (**A**), *TNF* rs361525 (**B**), *CASP10* rs13010627 (**C**), *PGR* rs1042838 (**D**), and *BID* rs8190315 (**E**), based on data from ~30,000 cases and 30,000 controls from the Breast Cancer Association Consortium. Studies are weighted and ranked according to the inverse of the variance of the log OR estimate. The size of the box is inversely proportional to the variance of the log OR estimate. The solid line is drawn where OR is equal to 1.0, and the dotted line is at the OR estimate for all studies combined. Estimates were calculated separately for women of European, Asian (labeled as "Asian"), and African (labeled as "AA") descent. Study acronyms are defined in Supplementary Table S1.

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II (42.3%) disease, and were moderately differentiated (49.2%). The mean (± SD) age was 54.9 (± 11.6) years for invasive cases, 55.7 (± 10.7) years for *in situ* cases, and 56.5 (± 12.5) years for controls. A larger proportion of invasive and *in situ* cases (16.3% and 23.7%, respectively) had a family history of breast cancer than controls (5.0%). Most subjects were of European descent (90.0% of invasive cases, 96.3% of *in situ* cases, and 92.4% of controls). Other women were of African descent (1.9%, 1.4%, and 1.5%, respectively), Asian descent (8.0%, 2.0%, and 5.9%, respectively), and unknown ancestry (0.1%, 0.3%, and 0.1%, respectively). Among controls of European descent, pooled estimates for the minor allele frequencies of *ERCC4* rs744154, *TNF* rs361525, *CASP10* rs13010627, *PGR* rs1042838, and *BID* rs8190315 ranged from 1.7% to 27.5% (Table 1). Minor allele frequencies were slightly lower for controls of African and Asian descent with the exception of *CASP10* rs13010627 (Supplementary Table S4).

Figure 1 displays the random effects OR for the association between genotype and overall breast cancer risk by study and ethnic group, whereas Table 1 displays the ORs for the association between genotype and invasive breast cancer risk among women of European descent only. In both models, none of the SNPs were associated with invasive breast cancer risk with per-allele ORs close to unity (Table 1; Fig. 1). Among women of European descent (Table 1), there was some evidence for between-study differences for *CASP10* rs13010627 (between-study heterogeneity, $P = 0.008$), *PGR* rs1042838 ($P = 0.04$), and *BID* rs8190315 ($P = 0.05$), but not for *ERCC4* rs744154 ($P = 0.36$) and *TNF* rs361525 ($P = 0.65$). Genotypes were also not associated with *in situ* breast cancer risk with the possible exception of *BID* rs8190315 (Supplementary Table S5).

The genotype-invasive breast cancer risk association was not modified by age (Supplementary Table S6) or family history of breast cancer (Supplementary Table S7). Given the compelling association previously found for *CASP8* rs1045485 and breast cancer risk (9) and the functional interaction of *CASP8* and *BID* in the apoptosis pathway, we also tested for an interaction between *CASP8* rs1045485 and *BID* rs8190315. Assuming dominance for the high-risk allele at each locus, we found no evidence of departure from multiplicative effects ($P = 0.75$).

Discussion

In a pooled study of more than 30,000 cases and 30,000 controls, the minor alleles of *ERCC4* rs744154, *TNF* rs361525, *CASP10* rs13010627, *PGR* rs1042838, and *BID* rs8190315 were not associated with risk of invasive breast cancer. We observed significant between-study heterogeneity for results of *CASP10* rs13010627, *PGR* rs1042838, and *BID* rs8190315. Outlier studies for the three SNPs did not differ from other studies with respect to genotyping quality, study population characteristics, or study design. The source of observed between study heterogeneity is thus unknown and could be due to chance.

Despite previous epidemiologic results (1-4, 10-17) and, in some cases, biological plausibility (18-20), it is unlikely that there are weak associations between the genetic polymorphisms under study and breast cancer risk. The narrow confidence intervals excluded log-additive relative risks >1.1 for ''risk'' variants (or <0.9 for ''protective'' variants) and even smaller risks for some variants. Larger sample sizes would be needed to evaluate moderate recessive effects, particularly for *TNF* rs361525. It is possible that other genetic variations conferring elevated breast cancer risk might exist in or around these genes. Further, although we did not comprehensively examine interaction between these SNPs and other breast cancer risk factors, the identification of strong, common modifiers is unlikely based on the persuasive lack of main effects. We found no evidence of interaction with age, family history of breast cancer, or, in the case of *BID* rs8190315, with *CASP8* rs1045485.

This analysis of selected candidate polymorphisms and breast cancer risk in 30 studies further supports the utility of large consortia. We have shown compelling evidence of no overall association with breast cancer risk for *ERCC4* rs744154, *TNF* rs361525, *CASP10* rs13010627, *PGR* rs1042838, and *BID* rs8190315, although they may be associated with breast cancer risk for small subgroups of women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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