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No Association between Ovarian Cancer Susceptibility Variants and Breast Cancer Risk among Chinese Women

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Abstract

Background—As breast and ovarian cancers may have similar etiologies, this study aimed to evaluate the hypothesis that breast cancer shares common genetic susceptibility variants with ovarian cancer.

Methods—Ten genetic variants in 9 loci were previously identified to be associated with ovarian cancer risk among Caucasian women; an additional 353 variants in high linkage disequilibrium ($r^2 \geq 0.6$) among Han Chinese were identified. Data were available from the Affymetrix Genome Wide Array (6.0) or MACH imputation for 25 and 78 common genetic variants (minor allele frequency (MAF) ≥ 0.05), respectively. Associations with breast cancer risk were evaluated by additive logistic regression models among 2,918 breast cancer cases and 2,324 controls.

Results—No associations with breast cancer risk were evident for 103 ovarian cancer susceptibility variants in five loci. Four loci were not evaluated, as they included only rare variants (MAF < 0.05).

Conclusions—Ovarian cancer susceptibility variants identified in Caucasian women were not associated with breast cancer risk among 5,242 Chinese women.

Impact—These findings suggest that breast and ovarian cancer may not share common susceptibility variants among Chinese women.

Keywords

Genetic Variants; Breast Cancer; Ovarian Cancer

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Introduction

Breast and ovarian cancer are hormonally driven, and have similar etiologies, including inherited mutations in *BRCA1* or *BRCA2* (1). We hypothesized that these cancers may share common genetic susceptibility variants. To date, genome-wide association studies (GWAS) have identified 10 ovarian cancer susceptibility variants; these studies have included only Caucasian women (2). To the best of our knowledge, no previous studies have evaluated the association between ovarian cancer susceptibility variants and breast cancer risk.

Methods

Study population

This analysis included a total of 2,918 breast cancer cases from the Shanghai Breast Cancer Study (SBCS), Shanghai Breast Cancer Survival Study (SBCSS), and the Shanghai Women's Health Study (SWHS), and 2,324 controls from SBCS and SWHS. Detailed study design and data collection procedures have been described previously (3, 4). Study protocols were approved by the relevant review boards of all institutions, and informed consent was obtained from all participants.

Variant Selection, Genotyping, and Imputation

Genetic variants associated with ovarian cancer susceptibility were identified in the GWAS catalog (2). Linkage disequilibrium (LD) among Han Chinese was assessed using SNAP (5). Independence of loci was defined using an $r^2 \leq 0.6$. Genotyping and imputation methods and quality control have been previously described (3). Briefly, genotyping data was from the Affymetrix Genome Wide Array (6.0); only variants with quality control values ≥ 0.95 were included. Imputation was conducted using MACH; only data with quality scores (RSQ > 0.3 (mean 0.98, median 1.00) were included. Further, only common genetic variants (MAF ≥ 0.05) were evaluated.

Statistical Analysis

Multivariate logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between breast cancer risk and genetic variants using additive effect models that included adjustment for age and education. Effect measure modification was evaluated with stratified analyses and the likelihood ratio test. Quanto was used for power calculations (6). All other analyses were conducted with SAS version 9.2 (SAS institute Inc., Cary, North Carolina). All statistical tests were two-tailed, and statistical significance was defined by a p-value ≤ 0.05 .

Results

As shown in Figure 1, in addition to the 10 original ovarian cancer susceptibility variants in the GWAS catalog, 353 additional variants in linkage disequilibrium (LD; $r^2 \leq 0.6$) among Han Chinese were identified. Genotyped (N=51) or imputed (N=141) data was available for 192 variants; however, 89 were excluded from analysis (MAF < 0.05). Thus, 25 genotyped and 78 imputed common (MAF ≥ 0.05) variants, including 5 original and 98 additional ovarian cancer susceptibility variants were evaluated. No associations with breast cancer risk in additive effect models adjusted for age and education were identified (Full results in Supplementary Table 1; summary findings in Table 1). These 103 variants represent five of the nine loci identified. Three loci were not evaluated as they included only uncommon variants (MAF < 0.05). One locus was not evaluated as it included only one variant (*rs8170*),

for which neither genotyping nor imputed data was available. However, according to HapMap, this variant also has a very low MAF among Han Chinese (0.004).

Stratified analyses by menopausal status, ER, PR, and tumor stage were conducted to evaluate effect measure modification. Two variants in locus 7 (*rs7207826* and *rs136870*) were associated with increased risk among ER+ tumors, while one variant in locus 5 (*rs1416745*) was associated with a decreased risk among late stage tumors. However, these nominally significant associations did not withstand correction for multiple comparisons.

Discussion

In this large, population-based, case-control study, we did not observe any significant associations between ovarian cancer susceptibility variants and breast cancer risk. To the best of our knowledge, this is the first study aimed to evaluate the association between ovarian cancer susceptibility variants and breast cancer risk. Two studies have evaluated the association between breast cancer susceptibility variants and ovarian cancer risk (7, 8). The first included 7 variants and found no association (7). The second included 11 variants, and found a significant association between *rs4954956* and ovarian cancer risk (OR: 1.07; 95% CI: 1.01–1.13) (8).

Strengths of this study include the large study population, the use of both genotyped and imputed data to maximize genetic coverage, and sufficient power to detect associations for common genetic variants. For a variant with a MAF of 20%, this study had greater than 78% power to detect an OR of 1.15. A limitation of this study is that rare variants (MAF<5%) were not evaluated, as very large studies are needed for adequate power. Notably, of the ten original ovarian cancer susceptibility variants, four had low MAFs among Han Chinese (*rs2665390* *rs10088218* *rs12794435* and *rs8170*). Therefore, differences in the genetic architecture of ovarian cancer between Chinese and Caucasian populations may influence our results. Notably, all ten ovarian cancer susceptibility variants identified to date are from studies of Caucasian women.

In conclusion, we found no evidence for an association between ovarian cancer susceptibility variants and breast cancer risk among Chinese women. Resequencing and fine-mapping of ovarian cancer susceptibility loci for evaluation of rare variants may be necessary to fully evaluate associations with breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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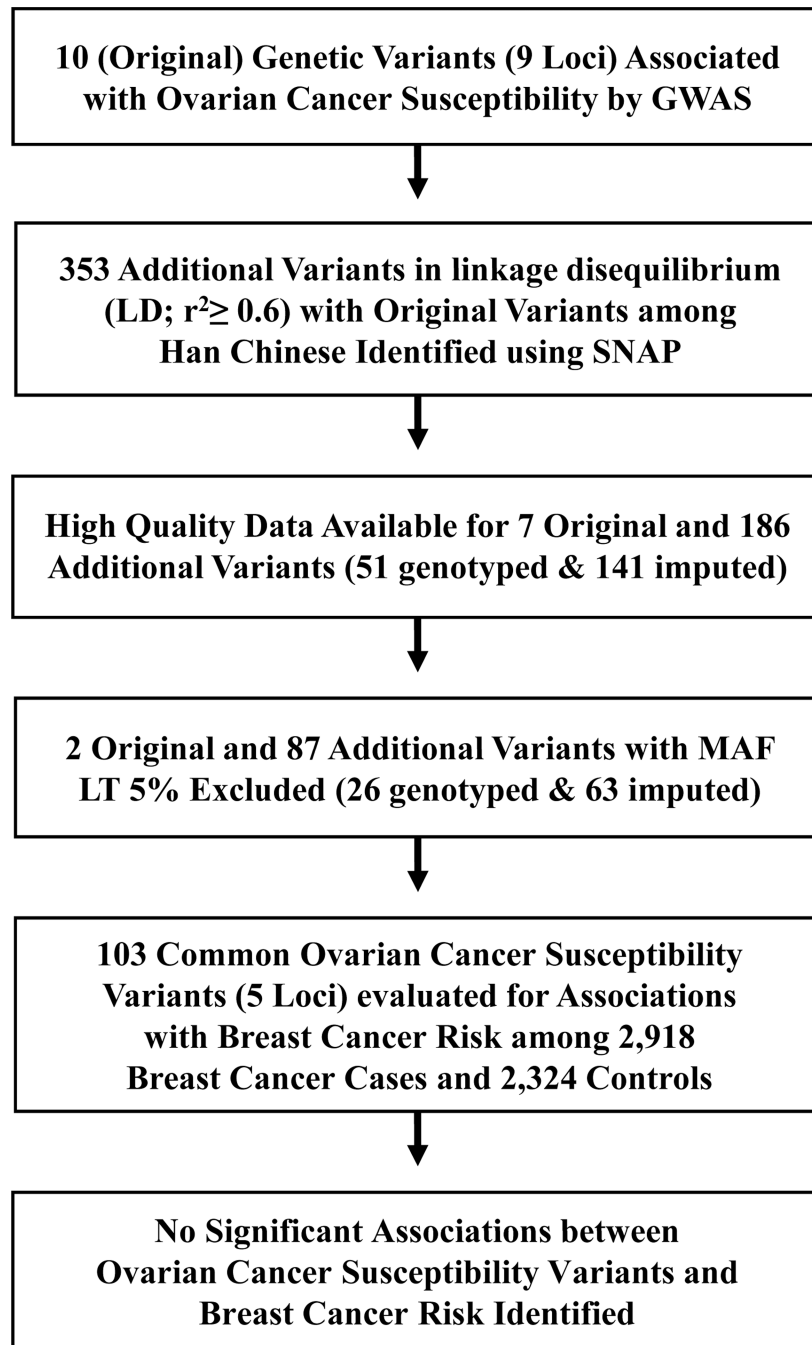


Figure 1.
Study Design Schematic

Table 1

Ovarian Cancer Susceptibility Variants and Breast Cancer Risk

Locus	Variant ¹	Location (HG18)	Data ²	Alleles ³	MAF ³	Breast Cancer Risk	
						OR (95% CI)	P value
1	rs7521902	ch1: 22363311	Imputed	A/c	47.9	1.01 (0.93–1.09)	0.883
2	rs2072590	ch2: 176750879	Imputed	C/a	25.2	1.07 (0.98–1.17)	0.153
3	rs2665390	ch3: 157880443	Imputed	T/c	LT 5%	NA	NA
4	rs10088218	ch8: 129613131	Genotyped	G/a	LT 5%	NA	NA
5	rs3814113	ch9: 16905021	Not Available	T/c	NA	NA	NA
5	rs7032221	ch9: 16904895	Genotyped	A/g	26.1	0.99 (0.90–1.08)	0.745
6	rs12794435	ch11: 25164280	Not Available	A/g	NA *	NA	NA
7	rs2084881	ch17: 43712119	Imputed	G/a	13.7	1.06 (0.94–1.18)	0.345
7	rs9303542	ch17: 43766499	Imputed	A/g	14.7	0.95 (0.85–1.07)	0.416
8	rs8170	ch19: 17389704	Not Available	A/g	NA **	NA	NA
9	rs2363956	ch19: 17255124	Imputed	T/g	31.3	0.97 (0.88–1.05)	0.423

¹Original GWAS Variants in Bold

²Imputed by MACH 1.0 or Genotyped by Affymetrix Genome Wide Array (6.0) among 5,242 Chinese women

³Major and minor (M/m) alleles and minor allele frequency (MAF) based on genotypes among 2,324 controls

* Four SNPs in perfect LD (r^2 , $D' = 1$) had MAF LT 5%

** MAF LT 5% in CHB according to HapMap; no variants in LD identified by SNAP