Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

# 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 nine 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) $\geq$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. *Cancer Epidemiol Biomarkers Prev; 22(3); 467–9. ©2013 AACR.*

## 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.

## Materials and 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 the 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 among Han Chinese was assessed using SNAP (5). Independence of loci was defined using an $r^2 \geq 0.6$. Genotyping and imputation methods and quality control have been previously described (3). Briefly, genotyping data were from the Affymetrix Genome-Wide Array (6.0); only variants with quality control values of 0.95 or more were included. Imputation was conducted using MACH; only data with quality scores [r-squared correlation coefficient (RSQ)] >0.3 (mean 0.98, median 1.00) were included. Furthermore, only common genetic variants [minor allele frequency (MAF) $\geq$0.05] were evaluated.

### Statistical analysis

Multivariate logistic regression was used to estimate ORs and 95% confidence intervals (CI) for associations between breast cancer risk and genetic variants using additive effect models that included adjustment for age and education. Effect measure modification was

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/)..

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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.). All statistical tests were two-tailed, and statistical significance was defined by a P value 0.05 or less.

## Results

As shown in Fig. 1, in addition to the 10 original ovarian cancer susceptibility variants in the GWAS catalog, 353 additional variants in linkage disequilibrium ($r^2 \geq 0.6$) among Han Chinese were identified. Genotyped ($N = 51$) or imputed ($N = 141$) data were available for 192 variants; however, 89 were excluded from analysis (MAF < 0.05). Thus, 25 genotyped and 78 imputed common (MAF $\geq$ 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 S1; summary findings in Table 1). These 103 variants represent 5 of 9 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 1 variant (*rs8170*), for which neither genotyping nor imputed data were available. However, according to HapMap, this variant also has a very low MAF among Han Chinese (0.004).

Stratified analyses by menopausal status, estrogen receptor (ER), progesterone receptor (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, whereas 1 variant in locus 5 (*rs1416745*) was associated

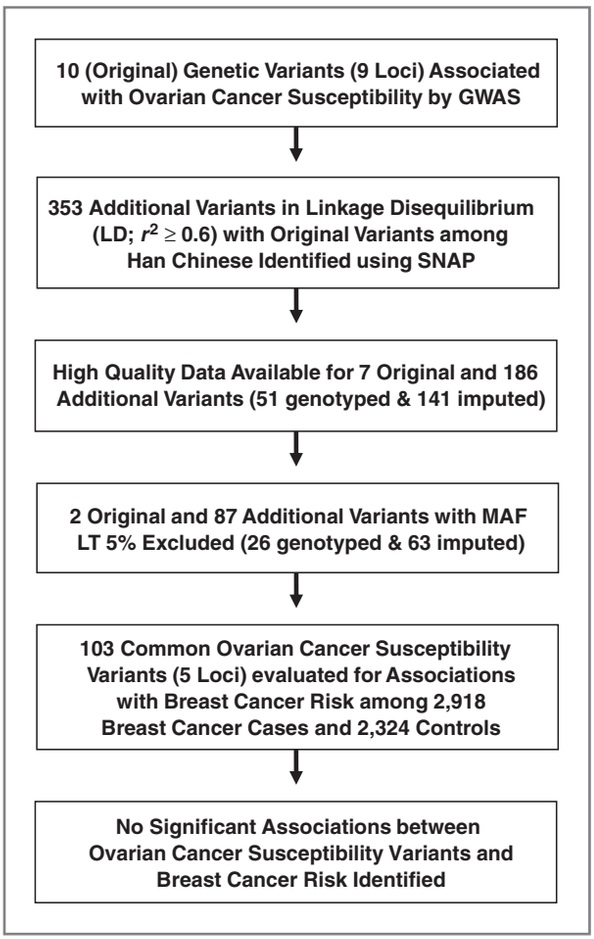


**Figure 1.** Study overview.

**Table 1.** Ovarian cancer susceptibility variants and breast cancer risk

| | | | | | | Breast cancer risk | |
|---|---|---|---|---|---|---|---|
| **Locus** | **Variant[a]** | **Location (HG18)** | **Data[b]** | **Alleles[c]** | **MAF[c]** | **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[d] | 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[e] | NA | NA |
| 9 | **rs2363956** | ch19: 17255124 | Imputed | T/g | 31.3 | 0.97 (0.88–1.05) | 0.423 |

[a]Original GWAS variants in bold.
[b]Imputed by MACH 1.0 or genotyped by Affymetrix Genome-Wide Array (6.0) among 5,242 Chinese women.
[c]Major and minor alleles and minor allele frequency (MAF) based on genotypes among 2,324 controls.
[d]Four SNPs in perfect linkage disequilibrium ($r^2$, $D' = 1$) had MAF LT 5%.
[e]MAF LT 5% in CHB according to HapMap; no variants in linkage disequilibrium identified by SNAP.

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; ref. 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 10 original ovarian cancer susceptibility variants, 4 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 10 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.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

### Authors' Contributions

**Conception and design:** X. Ma, X.-O. Shu, W. Lu, Y.-T. Gao, W. Zheng, A. Beeghly-Fadiel
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**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** X. Ma, R.J. Delahanty, B. Zhang, J. Long, A. Beeghly-Fadiel
**Writing, review, and/or revision of the manuscript:** X. Ma, Q. Cai, X.-O. Shu, Y.-T. Gao, W. Zheng, A. Beeghly-Fadiel
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** Y.-T. Gao, W. Zheng
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