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Review

# Association between *BRCA1* rs799917 polymorphism and breast cancer risk: A meta-analysis of 19,878 subjects

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ABSTRACT

Studies investigating the association between the *BRCA1* rs799917 polymorphism and breast cancer risk have reported controversial results. In order to derive a more precise estimation of the relationship, we performed a comprehensive meta-analysis. A total of 8 articles comprising 19,878 subjects were included in this meta-analysis. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated by Stata 11 software. Heterogeneity tests were conducted by Q test with $I^2$ value, and publication bias assessment was performed by Begg's funnel plot and Egger's test. The pooled results did not show any sufficient evidence approving the association between the *BRCA1* rs799917 polymorphism and breast cancer risk in total population (T vs C: OR = 1.01, 95% CI = 0.97–1.06; TT vs CC: OR = 1.03, 95% CI = 0.93–1.13; CT vs CC: OR = 1.04, 95% CI = 0.92–1.16; TT + CT vs CC: OR = 1.04, 95% CI = 0.94–1.15; TT vs CT + CC: OR = 1.03, 95% CI = 0.94–1.12). In the further subgroup analyses, no significant associations were found in any comparison models according to ethnicity and source of controls. No publication bias was observed in this meta-analysis. In summary, based on the overall results, this meta-analysis strongly suggests that the *BRCA1* rs799917 polymorphism is not associated with breast cancer risk.


## 1. Introduction

Breast cancer is the most common cancer occurred in females, and usually behaves extremely aggressively. Besides, breast cancer is the main reason of cancer mortality all over the word in women [1]. What is more, its incidence has been reported to increase by up to 5% annually in developing countries [2–4]. Considering its position as the leading health problem for women, breast cancer has been one of the most appealing cancer types in gene studies since last century [5]. Like most human cancers, breast cancer is also caused by environmental and genetic factors [6]. Previous studies have demonstrated that complicated genetic, epidemiological and epigenetic factors contribute to breast cancer etiology [7]. Twin studies indicated that approximately 27% of breast cancer risk is due to genetic predisposition [8].

*BRCA1*, belonging to tumor suppressor genes, is known as the first human familial breast and ovarian cancer susceptibility gene. It is on chromosome band 17q21, first cloned in 1994 [9]. The protein translated from the *BRCA1* gene function to prevent cells from proliferating and growing in an uncontrolled way. Previous studies have proven that, as a cancer suppressor, the *BRCA1* gene works by multifarious mechanisms, including transcription repression, DNA damage repair, cell cycle checkpoint and transcription repression [10].

To date, researches from many countries have been carried out to validate the relationship between the rs799917 polymorphism and breast cancer susceptibility. However, the results remain controversial and inconclusive. Possible reasons bringing about the conflicting results are ethnic difference and single study without enough subjects. With increasing studies conducted among different populations, it is still need to synthesize current data. Hence, we performed a systematic meta-analysis to investigate the association between the rs799917 polymorphism and breast cancer risk.

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## 2. Materials and methods

### 2.1. Publication search

We searched the PubMed and Embase databases for all case-control studies, which investigated the association between the rs799917 polymorphism and breast cancer risk up to May 17, 2014. The following keywords and terms were used for the search: "BRCA1", "breast cancer/carcinoma" and "polymorphism/variation". In addition, references of retrieved publications were also screened by hand-searched. All enrolled studies in the meta-analysis must meet the following criteria:

- case-control study;
- evaluation of the association between the rs799917 polymorphism and breast cancer risk;
- written in English;
- at least two comparison groups (breast cancer group vs control group).

And the major exclusion criteria were:

- not case-control study;
- no sufficient data;
- reviews, comments and abstracts.

### 2.2. Data extraction

Two of the authors extracted all data independently, complying with the selection criteria and reached a consensus on all items. In case of disagreement, another author reassessed these articles. The following items were collected: first author's name, year of publication, ethnicity of study population, genotyping methods, source of controls, total number of cases and controls and genotype distributions in cases and controls.

### 2.3. Statistical analysis

We first analyzed Hardy–Weinberg Equilibrium (HWE) in the controls for each study using goodness-of-fit test (chi$^2$ or Fisher's exact test), and contravention of HWE was determined by $P < 0.05$. Then, crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the rs799917 polymorphism and breast cancer susceptibility. The pooled ORs were performed under allele genetic model (T vs C), homozygote model (TT vs CC), heterozygote model (CT vs CC), dominant model (TT + CT vs CC) and recessive model (TT vs CT + CC). T represents the mutant type while C represents the wild type allele. Stratified analyses were also conducted with respect to ethnicity.

Exist of heterogeneity between all eligible comparisons was tested by $\chi^2$-based Q test. The degree of heterogeneity was assessed by calculating the $I^2$ (inconsistency index) value, respectively representing low, moderate and high while $< 25\%$, 25–75% and $> 75\%$ [11]. If the result of the Q test was $P > 0.10$, the pooled ORs was analyzed by a fixed effects model with the Mantel–Haenszel method, which indicated that the between-study heterogeneity was not significant [12]. Otherwise, a random-effects model with the Der-Simonian and Laird method was used [13].

To estimate the stability of the result, sensitivity analysis was carried out by removing each study at a time. Additionally, to evaluate the potential publication bias, Begg's test and Egger's linear regression test were carried out by inspecting the shape of the funnel plot, and $P < 0.05$ represents significant publication bias [14]. All statistical analyses were performed by using the STATA software (version 11; Stata Corporation, College Station, Texas), and all tests were two-sided.

## 3. Results

### 3.1. Characteristics of the studies

A total of 79 studies were obtained by search from the PubMed and Embase database to evaluate the relationship between the rs799917 polymorphism and breast cancer risk, using various combinations of key terms. A total of 47 eligible studies were retrieved for further evaluation. We excluded 39 studies (18 not focused on *BRCA1* gene, 13 not for rs799917 polymorphism and 8 not present usable data) (Fig. 1). Finally, a total of 8 case-control articles met our inclusion criteria [15–22], including 19,878 subjects. And detailed characteristics of these studies were presented in Table 1. The distribution of genotypes in the controls was in agreement with HWE for all except for one study ($P = 0.005$) [22], and omission of this individual study did not change the result substantially (data not shown).

### 3.2. Quantitative synthesis

The results of overall meta-analysis did not suggest any associations between the rs799917 polymorphism and breast cancer susceptibility for all genetic models (for T vs C: OR = 1.01, 95% CI = 0.97–1.06, $P_{heterogeneity} = 0.176$; for TT vs CC: OR = 1.03, 95% CI = 0.93–1.13, $P_{heterogeneity} = 0.497$; for CT vs CC: OR = 1.04, 95% CI = 0.92–1.16, $P_{heterogeneity} = 0.023$; for TT + CT vs CC: OR = 1.04, 95% CI = 0.94–1.15, $P_{heterogeneity} = 0.037$; for TT vs CT + CC: OR = 1.03, 95% CI = 0.94–-1.12, $P_{heterogeneity} = 0.621$) (Table 2 and Fig. 2). When stratified according to ethnicity, we found that the rs799917 polymorphism was not associated with increased breast cancer risk among Caucasians in dominant model (TT + CT vs CC: OR = 1.02, 95% CI = 0.89–1.17, $P_{heterogeneity} = 0.026$) and recessive model (TT vs CT + CC: OR = 1.05, 95% CI = 0.95–1.15, $P_{heterogeneity} = 0.471$). In addition, the same result happened among Asians in dominant model (TT + CT vs CC: OR = 1.11, 95% CI = 0.96–1.28,

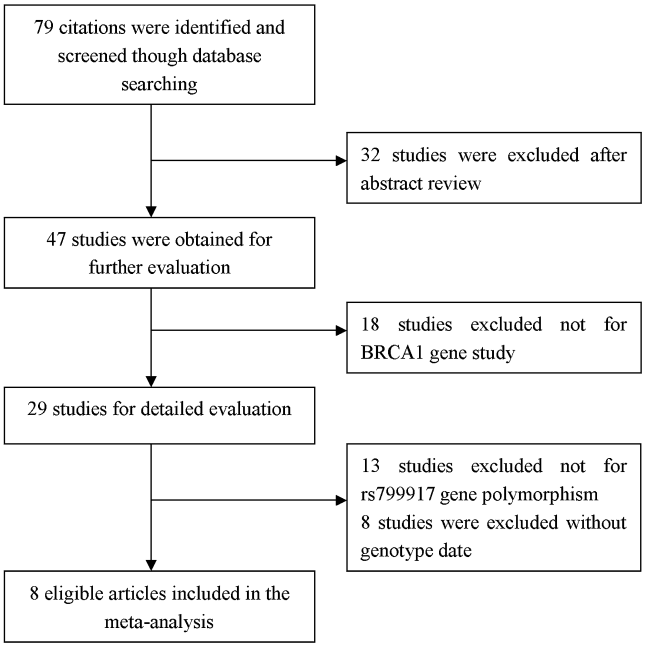


**Fig. 1.** Study identification diagram.