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Review Article

Lack of association of BRCA1 gene rs799917 polymorphism with cancer risk

Hui Zhao[1], Zhijun Kong[2]

[1]*Department of General Surgery, Third Affiliated Hospital of Nantong University, Wuxi, China;* [2]*Department of General Surgery, Affiliated Hospital of Nanjing Medical University, Changzhou Second People's Hospital, Changzhou, China*

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Abstract: Several studies identified the BRCA1 gene rs799917 polymorphism as a susceptibility locus for cancer with contradictory results. Therefore, we conducted this meta-analysis to derive a more precise estimation of the effects of BRCA1 gene rs799917 polymorphism on cancer risk. A total of 13 eligible case-control studies were identified by searching the databases of PubMed and EMBASE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to describe the strength of the associations. The overall analysis (10,231 cases and 15,993 controls) indicated that there was no significant association between the BRCA1 rs799917 polymorphism and overall cancer risk under the five genetic models. However, in the subgroup analysis of ethnicity, BRCA1 rs799917 polymorphism showed a positive correlation with the decreased risk of cancer among Asians. Stratification analysis by types of cancer suggested that BRCA1 rs799917 polymorphism was associated with the reduced risk of non-breast cancer (Non-BC) in the allelic, dominant, recessive and homozygous models. In conclusion, BRCA1 rs799917 polymorphism decreases the risk of Non-BC. Further studies should confirm these findings.

Keywords: BRCA1, cancer, polymorphism, meta-analysis

Introduction

The incidence of cancer is increasing with the growth and aging of the population as well as an increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development [1]. According to the American Cancer Society estimates, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in 2017 [2]. Cancer is the result of complex interactions between inherited and environmental factors [3]. Inherited genetic factors make contributions to susceptibility to most types of cancer [4]. For example, highly penetrant variants in the breast cancer associated gene 1 (BRCA1) account for less than 20% of the genetic risk of breast cancer (BC) [5].

BRCA1 is located on chromosome 17q21, which is the first identified high penetrance but low frequent BC susceptibility gene [6]. It contributes to maintaining genomic stability through critical roles in DNA repair, cell-cycle arrest, and transcriptional control [7]. Mutations in BRCA1 have been found in approximately 90% of familial breast and ovarian cancers [8]. Mori reported that there is a frequent loss of heterozygosity in the region including BRCA1 in esophageal squamous cell carcinoma (ESCC), even in tumors at early stage [9]. In addition, DNA methylation profile in diffuse-type gastric cancer showed that hypermethylation of the BRCA1 promoter region and decreased BRCA1 expression are also involved in early-onset gastric carcinogenesis [10]. BRCA1 may bind to p53 (a tumor suppressor protein) and acts as a co-activator of p53-mediated transcription [11]. These observations led to a hypothesis that BRCA1 gene may be significantly associated with the pathogenesis of cancer.

Single nucleotide polymorphisms (SNPs) can influence the gene expression and function, participating in carcinogenesis [12]. Zhang found that BRCA1 functional rs799917 polymorphism is involved in susceptibility to devel-

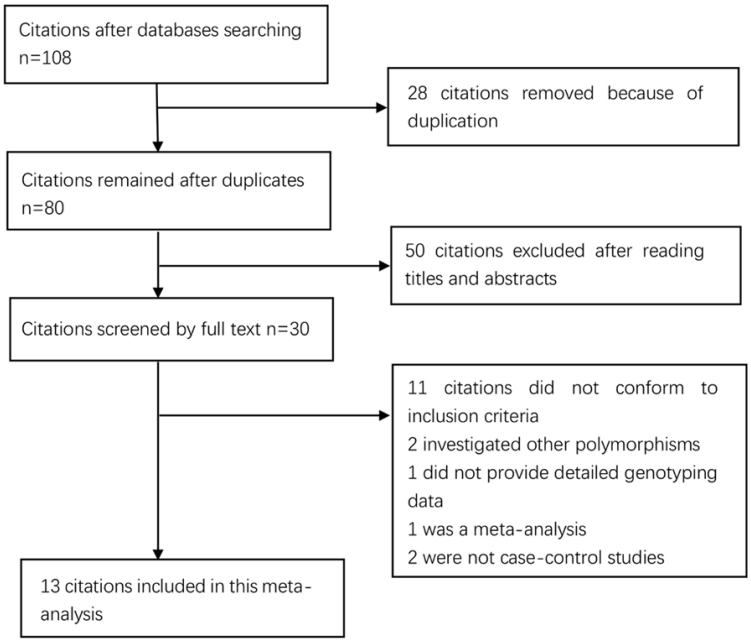

Figure 1. Selection for eligible citations included in this meta-analysis.

oping ESCC [9]. However, the associations between BRCA1 rs799917 polymorphism and the risk of other cancers remains obscure because of contradictory and inconclusive findings of these studies [10, 13-23]. The clinical heterogeneity, small sample sizes of these studies, and different ethnic populations may contribute to these disparities. To overcome these limitations and provide a more precise evaluation of such unsettled association, we performed this meta-analysis to assess whether BRCA1 rs799917 polymorphism was associated with overall cancer susceptibility or not.

Materials and methods

Literature search and criteria of inclusion

Two investigators carried out a systematic electronic search independently in PubMed and EMBASE to identify relevant studies using the following key words: "Breast cancer associated gene 1", "BRCA1", "polymorphism", "single nucleotide polymorphism", "SNP", "cancer", "neoplasm", "tumor", "neoplasia". No restrictions were placed on the search. Additional initially omitted studies (such as reference lists of identified studies) have been identified by hand screening.

Eligible studies conformed to the following criteria: (1) evaluating the relationship between BRCA1 rs799917 polymorphism and cancer risk; (2) sufficient data for calculating the pooled odds ratio (ORs) with 95% confidence interval (CI); (3) case-control studies; (4) studied on human beings; (5) articles published in English.

Data extraction and quality assessment

Two investigators reviewed and extracted data independently in accordance with the inclusion criteria. From each study, the following information was extracted: surname of the first author, publication year, country of origin, ethnicity, numbers of cases and controls, and types of cancer. Authors were contacted to provide supplemental data if data were not available in the relevant articles. When studies included subjects of more than one ethnicity, genotype data were extracted separately.

The quality of the selected studies were assessed by using the Newcastle-Ottawa Scales (NOS) [24]. Total NOS scores ranged from 0 to 9. A score ranging from 5 to 9 stars is considered to be a generally high methodological quality while a score ranging from 0 to 4 is regarded as a relatively poor quality. The discrepancies were resolved by discussion or consulting with a third reviewer.

Statistical analysis

Our meta-analysis was conducted according to the PRISMA checklists and followed their guidelines [25]. Pooled ORs with corresponding 95% CIs were calculated to evaluate the strength of the relationship between BRCA1 rs799917 polymorphism and overall cancer risk. Stratification analyses were carried out by ethnicity, types of cancer, Hardy-Weinberg Equilibrium (HWE) and source of controls (SOC). Cochran's Q-statistics was used to assess the null hypothesis that all studies were evaluating the same effect. A P value greater than 0.10 or values of I^2 exceeding 50% was considered as

Table 1. Characteristics of included studies

Author and year	SOC	Cancer types	Study design	Country	Ethnicity	Genotyping method	Case			Control			HWE	NOS
							CC	CT	TT	CC	CT	TT		
Dunning 1997	PB	BC	Case-control	UK	Caucasian	ASO	342	370	89	266	250	56	Y	8
Dunning 1997	PB	OC	Case-control	UK	Caucasian	ASO	102	94	27	266	250	56	Y	8
Chang 2008	PB	GBM	Case-control	USA	Caucasian	ParAllele SNP panel	51	51	10	55	38	19	N	8
Wang 2009	PB	BC	Case-control	China	Asian	PCR-RFLP	381	483	140	403	463	142	Y	8
Huo 2009	PB	BC	Case-control	China	Asian	PCR-RFLP	215	283	70	255	285	84	Y	7
Zhou 2009	PB	CC	Case-control	China	Asian	PCR-RFLP	166	196	42	158	183	63	Y	7
Dombernowsky 2009	PB	BC	Case-control	Denmark	Caucasian	TaqMan	550	496	155	1756	1896	467	Y	8
Abbas 2010	PB	BC	Case-control	Germany	Caucasian	MALDI-TOF MS	1395	1393	348	2412	2441	617	Y	7
Nicoloso 2010	PB	BC	Case-control	Italy	Caucasian	BigDye Terminator Reaction Chemistry v3.1	90	118	39	90	75	20	Y	7
Zhang 2013	PB	ESCC	Case-control	China	Asian	PCR-RFLP	482	530	116	444	524	182	Y	8
Wu 2013	PB	BC	Case-control	USA	Caucasian	BioTrove OpenArray™ system	108	164	63	120	211	77	Y	8
Hasan 2013	HB	BC	Case-control	Saudi Arabia	Caucasian	TaqMan	31	37	32	30	36	34	N	6
Wang 2015	PB	GC	Case-control	China	Asian	PCR-RFLP	286	313	61	302	365	133	Y	7
Gutierrez 2016	PB	CML	Case-control	Mexico	Caucasian	TaqMan	147	129	36	200	210	59	Y	6

BC, breast cancer; OC, ovarian cancer; GC, gastric cancer; GBM, glioblastoma; CC, Cervical cancer; ESCC, esophageal squamous cell carcinoma; CML, chronic myeloid leukemia; SOC, source of controls; PB, population-based controls; HB, hospital-based controls; HWE, Hardy-Weinberg Equilibrium; NOS, Newcastle-Ottawa Scales; ASO, allele-specific oligonucleotides.

Table 2. Meta-analysis of association between BRCA1 rs799917 polymorphism and cancer risk

Comparison	OR (95% CI)	*P*-value	*P* for heterogeneity	I^2 (%)	Model
T vs. C	0.96 (0.90, 1.03)	0.287	0.001	62.7	Random
TT+CT vs. CC	0.98 (0.90, 1.06)	0.542	0.030	46.0	Random
TT vs. CC+CT	0.89 (0.76, 1.05)	0.160	< 0.001	69.1	Random
TT vs. CC	0.90 (0.76, 1.06)	0.200	< 0.001	68.6	Random
CT vs. CC	0.99 (0.92, 1.08)	0.898	0.091	35.6	Random

an indicator of significant heterogeneity. When no heterogeneity was found with $P > 0.10$ or $I^2 < 50\%$, a fixed-effect model was used for this meta-analysis. Otherwise, a random-effects model was applied [26]. In order to detect between-study heterogeneity, meta-regression was conducted using the following covariates: ethnicity, types of cancer, SOC and HWE. Sensitivity analysis was conducted to determine the effect on the test of heterogeneity and evaluate the stability of the results by omitting each study in turn. A X^2 test was used to determine whether the observed genotype frequencies conformed to the HWE. Publication bias was evaluated by visual inspection of symmetry of Begg's funnel plot and assessment of Egger's test [27]; $P < 0.05$ was regarded as statistical significance. All statistical analyses were performed using Stata 11.0 software (StataCorp, College Station, TX, USA).

Results

Characteristics of the included studies

108 citations were retrieved after the initial search, and 30 full citations were identified for possible inclusion. 17 citations were excluded due to the following reasons: two citations investigated other polymorphisms; one citation did not provide detailed genotyping data; eleven citations did not conform to the inclusion criteria; one citation was a meta-analysis and two were not case-control studies. In total, 13 eligible citations [9, 10, 13-23] involving 10,231 cases and 15,993 controls remained. Selection for eligible studies included in this meta-analysis was presented in **Figure 1**. The detailed characteristics of all the selected studies were presented in **Table 1**. Most of the studies were population-based studies and conformed to HWE. Moreover, the NOS scores of all included studies ranged from 6 to 8 stars, suggesting that they were studies of high methodological quality.

Quantitative synthesis of data

The overall results of this meta-analysis are shown in **Table 2**. BRCA1 rs799917 polymorphism exhibited negative associations with overall cancer risk (T vs. C: OR = 0.96, 95% CI = 0.90-1.03, $P = 0.289$, $I^2 = 62.7\%$, **Figure 2**). Further, we evaluated the effects of BRCA1 rs799917 polymorphism according to ethnicity, cancer types, HWE and SOC. As shown in **Table 3**, BRCA1 rs799917 polymorphism was associated with the decreased risk of cancer in the recessive model (TT vs. CC+CT: OR, 0.71; 95% CI, 0.55-0.92, $P = 0.010$, **Figure 3**) and homozygous model (TT vs. CC: OR, 0.72; 95% CI, 0.53-0.98, $P = 0.036$) among Asian populations. In addition, BRCA1 rs799917 polymorphism showed a strongly positive correlation with the risk of other types of cancer except for BC and could be viewed as a protective factor of cancer in Allelic model, dominant model, recessive model and homozygous model (T vs. C: OR = 0.85, 95% CI = 0.77-0.93, $P < 0.001$; TT+CT vs. CC: OR = 0.87, 95% CI = 0.78-0.96, $P = 0.006$, **Figure 4**; TT vs. CC+CT: OR = 0.69, 95% CI = 0.53-0.90, $P = 0.005$; TT vs. CC: OR = 0.67, 95% CI = 0.52-0.87, $P = 0.003$). Finally, no significant associations were observed among the stratification analyses of HWE and SOC.

High between-study heterogeneity was observed under the allelic model, recessive model and homozygous model. Meta-regression suggested that ethnicity ($p = 0.116$), SOC ($p = 0.924$) and HWE ($p = 0.797$) had no significant impact on the heterogeneity in ORs with BRCA1 rs79917 polymorphism. However, types of cancer ($p = 0.005$) showed a positive correlation with heterogeneity. Sensitivity analysis was conducted to assess the effect of each study on the pooled ORs by the omission of individual study at a time. The pooled ORs did not change significantly, suggesting that our results were credible and stable. Pub-

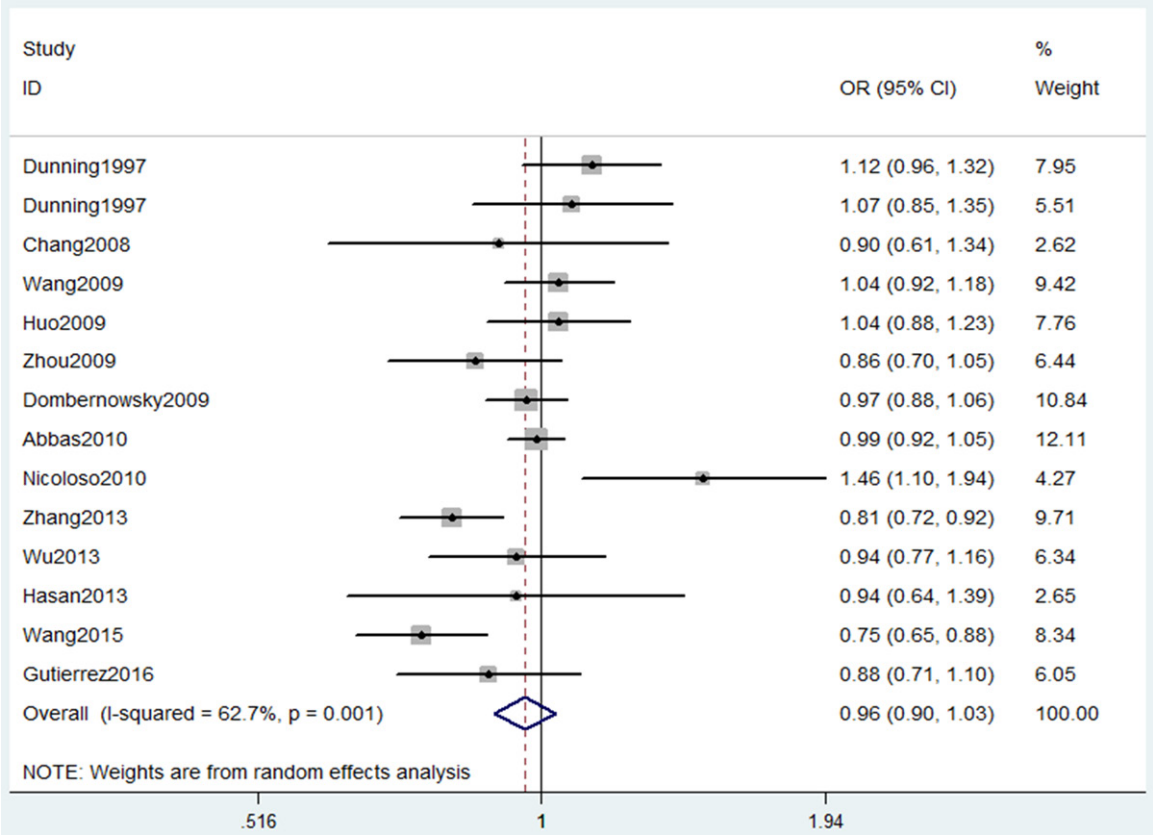

Figure 2. Forest plot shows odds ratio for the association between BRCA1 rs799917 polymorphism and cancer risk (T vs. C).

lication bias was assessed by Begg's funnel plot and quantitative Egger's test (TT+CT vs. CC, **Figure 5**). Our data revealed that there was no obvious publication bias for BRCA1 rs799917 polymorphism (data not shown).

Discussion

In this current meta-analysis, no significant association was obtained between BRCA1 gene rs799917 polymorphism and overall cancer risk. However, stratification analysis of ethnicity indicated that BRCA1 rs799917 polymorphism was associated with the decreased risk of cancer among Asians, but not for Caucasians. Stratification analysis by types of cancer also observed an association between the rs799917 polymorphism and non-BC risk.

BRCA1, a cancer suppressor, contains several functional domains that interact directly or indirectly with a variety of molecules, including tumor suppressors, oncogenes, DNA damage repair proteins, cell cycle regulators, transcriptional activators and repressors and others [8]. In vitro experiments indicate that miR-638 could negatively regulate BRCA1 expression and lower BRCA1 expression may lead to the higher risk of cancer [9]. Remarkably, Nicoloso showed that T allele of rs799917 polymorphism was associated with a weaker miR-638-dependent BRCA1 reduction [17]. Many studies attached importance to the association between BRCA1 rs799917 polymorphism and cancer risk recently. Dunning firstly reported that BRCA1 rs799917 polymorphism was not associated with the risk of breast and ovarian cancer in the United Kingdom [20]. Subsequent studies also failed to obtain a significant association between the BRCA1 rs799917 polymorphism and the risk of BC [14-16, 18, 19, 21] and other types of cancer, such as glioblastoma and chronic myeloid leukemia [22, 23]. However, some studies revealed that this SNP was significantly associated with a decreased risk of esophageal squamous cell carcinoma [9] and gastric cancer [10]. In addition, Nicoloso found that BRCA1 gene rs799917

Table 3. Summary of the subgroup analyses in this meta-analysis

Comparison	Category	Category	Studies	OR (95% CI)	*P*-value	P for heterogeneity
T vs. C	Ethnicity	Caucasian	9	1.01 (0.94, 1.08)	0.840	0.167
		Asian	5	0.89 (0.78, 1.02)	0.101	0.003
	Type	BC	8	1.02 (0.96, 1.09)	0.488	0.174
		Non-BC	6	0.85 (0.77, 0.93)	< 0.001	0.234
	HWE	Yes	12	0.97 (0.89, 1.04)	0.358	< 0.001
		No	2	0.92 (0.70, 1.22)	0.570	0.884
	SOC	PB	13	0.96 (0.89, 1.04)	0.816	< 0.001
		HB	1	0.94 (0.90, 1.39)	0.934	N/A
TT+CT vs. CC	Ethnicity	Caucasian	9	1.00 (0.90, 1.11)	0.976	0.073
		Asian	5	0.94 (0.82, 1.09)	0.430	0.055
	Type	BC	8	1.04 (0.93, 1.15)	0.497	0.036
		Non-BC	6	0.87 (0.78, 0.96)	0.006	0.641
	HWE	Yes	12	0.97 (0.89, 1.06)	0.532	0.014
		No	2	1.06 (0.72, 1.58)	0.762	0.640
	SOC	PB	13	0.98 (0.90, 1.06)	0.574	0.020
		HB	1	0.95 (0.52, 1.74)	0.878	N/A
TT vs. CC+CT	Ethnicity	Caucasian	9	1.05 (0.94, 1.16)	0.406	0.369
		Asian	5	0.71 (0.55, 0.92)	0.010	0.006
	Type	BC	8	1.03 (0.94, 1.13)	0.475	0.657
		Non-BC	6	0.69 (0.53, 0.90)	0.005	0.030
	HWE	Yes	12	0.91 (0.77, 1.07)	0.260	< 0.001
		No	2	0.71 (0.38, 1.31)	0.270	0.210
	SOC	PB	13	0.89 (0.76, 1.05)	0.174	< 0.001
		HB	1	0.91 (0.51, 1.65)	0.764	N/A
TT vs. CC	Ethnicity	Caucasian	9	1.03 (0.91, 1.17)	0.632	0.310
		Asian	5	0.72 (0.53, 0.98)	0.036	0.003
	Type	BC	8	1.03 (0.94, 1.13)	0.537	0.515
		Non-BC	6	0.67 (0.52, 0.87)	0.003	0.054
	HWE	Yes	12	0.91 (0.76, 1.09)	0.291	< 0.001
		No	2	0.75 (0.44, 1.29)	0.306	0.401
	SOC	PB	13	0.90 (0.75, 1.07)	0.215	< 0.001
		HB	1	0.91 (0.45, 1.83)	0.793	N/A
CT vs. CC	Ethnicity	Caucasian	9	0.99 (0.88, 1.11)	0.863	0.051
		Asian	5	1.01 (0.92, 1.12)	0.792	0.394
	Type	BC	8	1.03 (0.92, 1.16)	0.596	0.023
		Non-BC	6	0.94 (0.85, 1.05)	0.290	0.660
	HWE	Yes	12	0.99 (0.91, 1.07)	0.778	0.074
		No	2	1.24 (0.80, 1.92)	0.331	0.406
	SOC	PB	13	1.00 (0.92, 1.06)	0.928	0.064
		HB	1	0.99 (0.50, 1.96)	0.988	N/A

BC, breast cancer; Non-BC, non-breast cancer; SOC, source of controls; PB, population-based controls; HB, hospital-based controls.

polymorphism increased the risk of BC [17]. To overcome these limitations of individual studies, we conducted this meta-analysis to investigate the role of BRCA1 rs799917 polymorphism in overall cancer risk. Our data showed that there was no significant association between

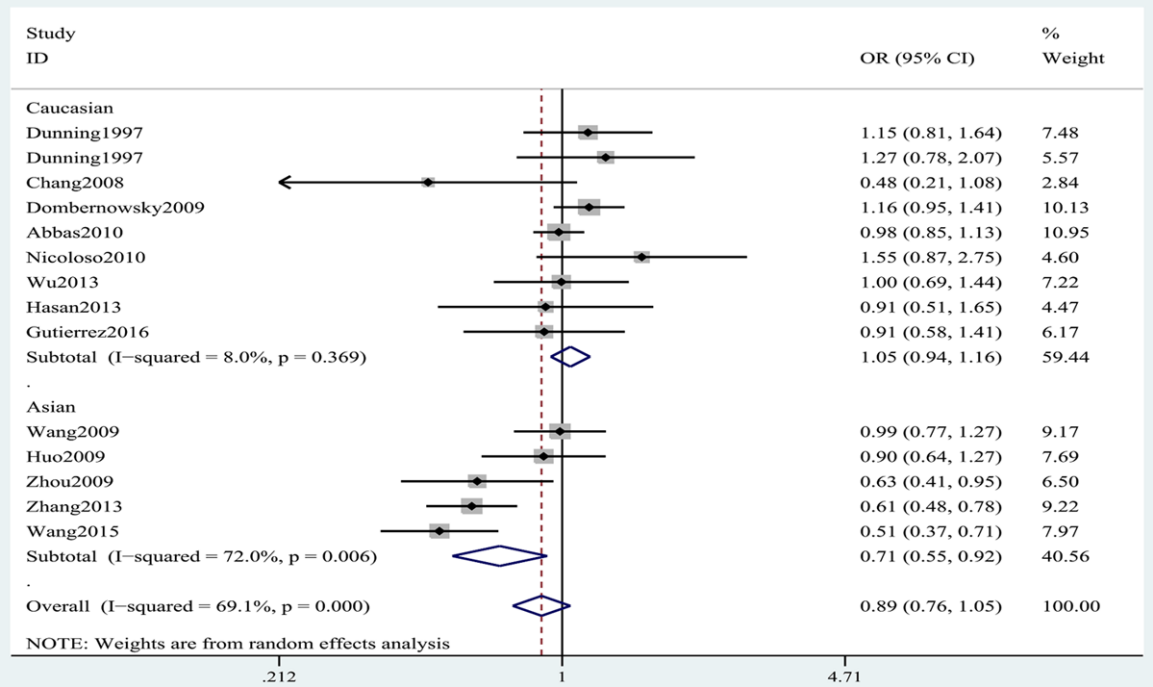

Figure 3. Stratification analyses by ethnicity shows odds ratio for the association between BRCA1 rs799917 polymorphism and cancer risk (TT vs. CC+CT).

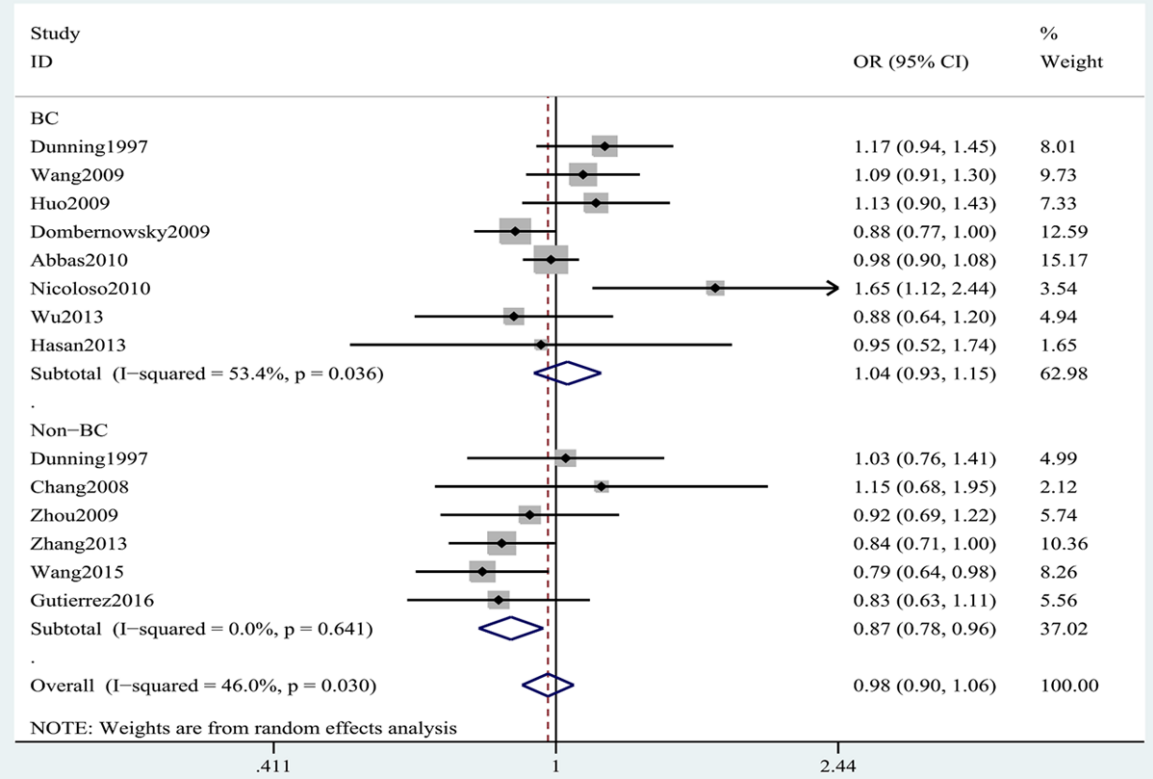

Figure 4. Stratification analyses of cancer types shows odds ratio for the association between BRCA1 rs799917 polymorphism and cancer risk (TT+CT vs. CC).

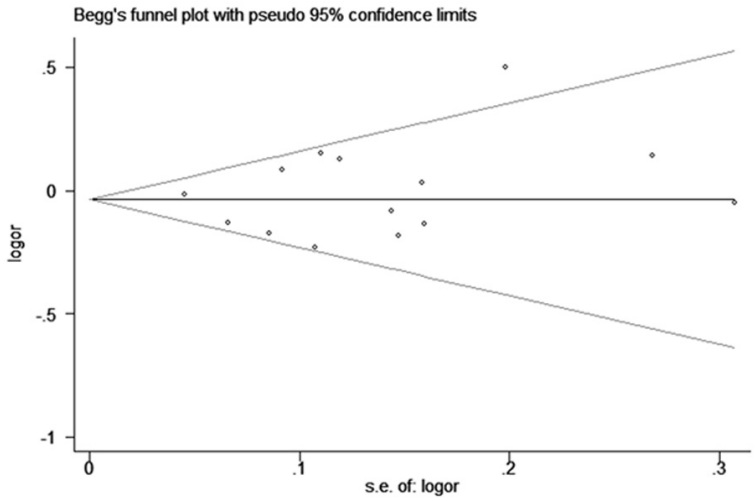

Figure 5. Begg's tests between BRCA1 rs799917 polymorphism and cancer risk (TT+CT vs. CC).

the BRCA1 rs799917 polymorphism and overall cancer risk.

In the subgroup analysis of ethnicity, this meta-analysis found that BRCA1 gene rs799917 polymorphism exerted a protective role against cancer among Asians, but not among Caucasians. A possible explanation for the contradict findings between Asian populations and Caucasian populations was that rs799917 polymorphism may have an ethnicity-specific effect. However, we could not exclude the following assumptions: one, Firstly, genetic heterogeneity for diverse cancers may exist in different populations. Secondly, clinical heterogeneity of every individual study existed among different populations. Finally, the different genotyping methods, different sample sizes, and random errors may account for different conclusions between Asians and Caucasians. In the subgroup analysis by types of cancer indicated that rs799917 polymorphism was not associated with BC risk, which was in accordance with the finding of a previous meta-analysis [28]. However, BRCA1 rs799917 polymorphism was correlated to the decreased risk of Non-BC under the allelic model, dominant model, recessive model and homozygous model. We hypothesized that this SNP may not be a susceptibility loci for BC patients, which needs future studies to confirm it.

The potential limitations need to be taken into consideration. First, cancer is a multifactorial disease and may be affected by several factors, such as smoking and family history of cancer. Thus, the function of a single SNP is limited. Second, different types of cancer were included in our meta-analysis, but the majority only contained one or two studies; therefore, the subgroup analyses were not fully implemented for each type of cancer. Third, only Caucasian and Asian population were included in this meta-analysis and the results may be not applied to other ethnic groups. Fourth, the number of the eligible studies included in this study is relatively small, which might increase the probability of false positives or false negatives. Finally, heterogeneity of all genetic models in this meta-analysis was somewhat high; therefore, we should interpret the data with caution.

In conclusion, our meta-analysis confirms that BRCA1 rs799917 polymorphism is a protective factor of Non-BC. Stratification analysis by ethnicity obtained a significant association between BRCA1 rs799917 polymorphism and cancer risk among Asians. Further multi-center, well-designed studies with larger sample sizes are warranted to confirm our findings.

Disclosure of conflict of interest

None.

Abbreviations

BRCA1, breast cancer associated gene 1; ESCC, esophageal squamous cell carcinoma; NOS, Newcastle-Ottawa Scale; OR, odds ratios; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism.

Address correspondence to: Zhijun Kong, Department of General Surgery, Affiliated Hospital of Nanjing Medical University, Changzhou Second People's Hospital, 68 Gehu Road, Wujin District, Changzhou City, China. Tel: +86-510-86362576; Fax: +86-519-88345560; E-mail: kongzhijun623@sina.com

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