

Original Article

Association between *RAD51* polymorphism and breast cancer susceptibility: a meta analysis

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Abstract: Background: *RAD51* interacting with *BRCA1* and *BRCA2* could modulate the penetrance of *BRCA1/BRCA2* mutations, which may increase susceptibility for breast cancer by inhibiting DNA repair and genome stability. The purpose of this study was to provide refined statistical evidence for the association between *RAD51* polymorphism and breast cancer risk. Design and results: We conducted a meta-analysis of 15 publications with a total of 11,766 cancer cases and 11,227 controls. We summarized the data on the association of *RAD51* polymorphism with breast cancer risk and performed subgroup analyses by ethnicity and control source. The pooled ORs based on fixed-effects model did not indicate a modified risk of breast cancer associated with *RAD51* polymorphism in the overall population. Nor did we find a significant association in any stratified analysis. Conclusions: This meta-analysis suggested that *RAD51* polymorphism did not appear to represent a significant risk factor for breast cancer.

Keywords: *RAD51*, breast cancer, polymorphism, susceptibility

Introduction

Breast cancer incidences have increased steadily worldwide in recent years and it remains the major cause of cancer-related deaths among women [1, 2]. Several lines of evidence implicate that exposure to radiation is a risk factor for breast cancer, due to its capability of inducing double-strand DNA damage that may consequently contribute to the occurrence of this disease [3-5]. The mutations of *BRCA1* and *BRCA2* genes involved in double-strand break repair should be responsible for approximately 45% to 65% of all breast cancer cases [6]. DNA double-strand breaks repair gene *RAD51* is able to modulate cancer risk through interaction with *BRCA1* and *BRCA2*, two critical genes in response to ionizing radiation and genome stability [7, 8]. Genetic polymorphisms of DNA repair genes have been reported to play an important role in DNA damage repair [9]. The most commonly studied has been a polymorphism in the 5' untranslated region of the *RAD51* gene.

A number of previous investigations have focused on the role of *RAD51* polymorphism in

the susceptibility to breast cancer [10-24]. The results, however, are highly controversial. This controversy stimulated great interest of several investigators to carry out a meta-analysis. The initial study by Wang et al. [25] suggested that the *RAD51* polymorphism may contribute to breast cancer susceptibility. In the following meta-analyses, the reported associations are also inconsistent: *RAD51* polymorphism as a protective factor [26], as a cancer promoter [27, 28], and even no association [29]. These results are probably biased on account of the inclusion of repeated data and failure to identify all usable data [30].

In this study, we rigorously reviewed the eligibility of studies included in previous analyses and identified newly published articles to provide compelling statistical evidence for the association between *RAD51* polymorphism and breast cancer risk.

Materials and methods

Search strategy

Potentially relevant studies were identified by searching the electronic databases of PubMed,

RAD51 polymorphism and breast cancer susceptibility

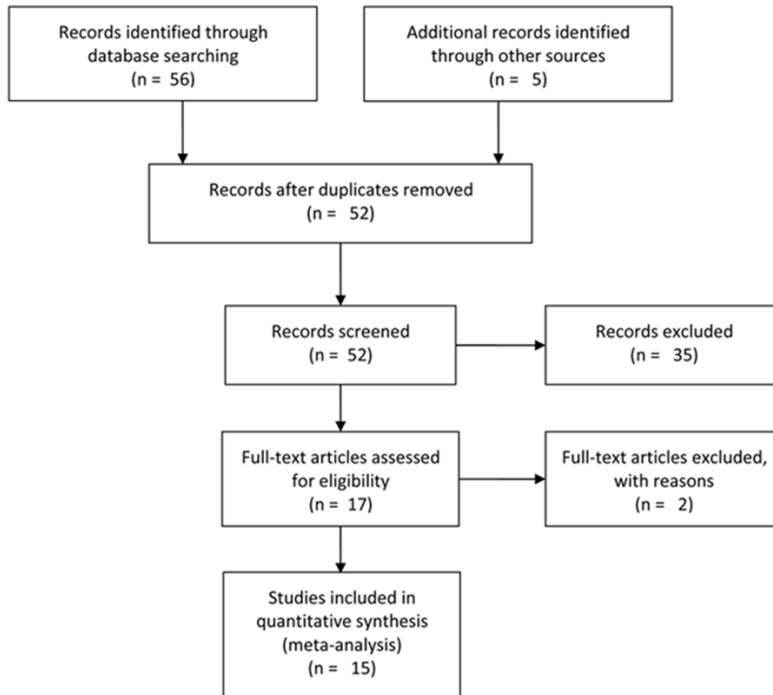


Figure 1. Flow diagram of included studies for this meta-analysis.

EMBASE and CNKI from March 2008 to March 2014 using the following key words: “RAD51”, “polymorphism” and “breast cancer”. To obtain additional articles that may have been missed in the electronic search, we scanned the references cited in all extracted publications. If the same case series was included in multiple studies published in the name of the same authors, the most informative study with the largest number of subjects was finally selected.

Inclusion criteria

We defined the following criteria to select the studies eligible for the current meta-analysis: (1) the case population was composed of breast cancer patients and cancer-free healthy individuals were used as controls, (2) the association of RAD51 G135C polymorphism with breast cancer risk was investigated, and (3) published as a full-length article with detailed genotyping data that could help to estimate the odds ratios (ORs) with 95% confidence intervals (CIs).

Data extraction

Two authors independently collected data on the following items for each study: first author’s

surname, publication date, location where the study was conducted, ethnicity of study population, total numbers of cases and controls, allele and genotype frequency in cancer cases and control subjects. When several ethnic groups were investigated in a single article, they were classified into Asian, European or American category and the data were separately extracted. Discrepancies were handled by consensus involving a third author.

Statistical methods

The association between RAD51 polymorphism and breast cancer risk was assessed by calculating ORs with 95% CIs using five genetic models (GG vs. CC, GG

+ GC vs. CC, GG vs. GC + CC, G vs. C, GC vs. CC). Significance of the summary ORs was assessed by the Z-test, and $P < 0.05$ was considered significant. Subgroup analyses were performed by ethnicity and source of controls.

A Chi square based ‘Q’ test defined by Cochran was applied to evaluate the between-study heterogeneity in the meta-analysis [31]. A P value lower than 0.05 was deemed statistically significant. Combined effect sizes were measured by a fixed-effects model (the Mantel-Haenszel method) [32] when there was no indication of substantial heterogeneity ($P > 0.05$). Otherwise, a random-effects model (the DerSimonian and Laird method) that includes assumptions on potential variance across studies was used [33]. Violation of Hardy-Weinberg equilibrium (HWE) was determined by χ^2 test using genotype data in control groups.

Publication bias was determined by Begg’s funnel plots and Egger’s test [34], which uses a weighted regression method to investigate the relationship between outcome effects (log odds ratio) and its standard error in each study. We considered a p value less than 0.05 as statistically significant. All statistical analyses were performed with STATA 12.0 (StataCorp, College Station, TX).

Table 1. Characteristics of studies included in the meta-analysis

First author	Year	Source of control	Genotyping method	Sample size		Country of study	Ethnicity
				Cases	controls		
Lee	2005	HB	MassARRAY	782	587	Korea	Asian
Sliwinski	2005	NA	PCR-RFLP	150	150	Poland	European
Webb	2005	PB	TaqMan	1295	660	Australia	European
Dufloth	2005	PB	PCR-RFLP	78	119	Brazil	American
Tarasov	2006	PB	PCR-RFLP	151	191	Russia	European
Costa	2007	PB	PCR-RFLP	265	435	Portugal	European
Antoniou	2007	NA	TaqMan	4443	4069	UK	European
Pharoah	2007	NA	TaqMan	2160	2266	UK	European
Hu	2008	NA	PCR	71	85	China	Asian
Brooks	2008	PB	PCR-RFLP	606	611	USA	American
Jakubowska	2009	PB	Simple Probe	1007	1069	Poland	European
Akisik	2010	NA	PCR-RFLP	147	120	Turkey	Asian
Jara	2010	HB	PCR-RFLP	267	500	Chili	American
Hosseini	2012	PB	PCR-RFLP	294	315	Poland	European
Smolarz	2013	NA	PCR-RFLP	50	50	Iran	Asian

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; NA: not available; HB: hospital-based; PB: population-based; HWE: Hardy-Weinberg equilibrium.

Results

Selection of studies

We initially identified a total of 61 relevant articles by a systematic literature search. Among them, 26 studies appeared to meet the pre-designed inclusion criteria and were singled out for further examination. After screening the full texts, 11 articles were excluded for the following reasons: (a) using the same patient population as the studies included [8, 35-42]; (b) presenting no or insufficient data [43, 44]. Therefore, our final data set consisted of 15 studies, providing 11,766 cancer cases and 11,227 controls (**Figure 1**).

Characteristics of included studies

The main characteristics of the eligible studies are summarized in **Table 1**. All studies were based on a case-control design, of which three were conducted among Americans [13, 19, 22], four among Asians [10, 18, 21, 24] and eight among Europeans [11, 12, 14-17, 20, 23]. For genotyping method, most studies used the typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Genotype distribution in all control groups did not deviate from values predicted by HWE except for four studies [12, 13, 19, 21].

Quantitative synthesis

In the meta-analysis including a total of 11,766 cancer cases and 11,227 controls, we examined the association of *RAD51* polymorphism with breast cancer risk. As shown in **Table 2**, overall, the *RAD51* polymorphism was not found to be associated with either an increased or a decreased risk of breast cancer (GG vs. CC: OR = 1.00, 95% CI = 0.96-1.04, *P* for heterogeneity = 0.987; GG + GC vs. CC: OR = 1.00, 95% CI = 0.96-1.03, *P* for heterogeneity = 0.946; GG vs. GC + CC: OR = 1.00, 95% CI = 0.96-1.04, *P* for heterogeneity = 0.769; G vs. C: OR = 1.00, 95% CI = 0.97-1.03, *P* for heterogeneity = 0.656; GC vs. CC: OR = 0.98, 95% CI = 0.89-1.07, *P* for heterogeneity = 0.778). Similarly, no major effects were revealed in subsequent stratification analyses by ethnicity and source of controls. To test reliability of the obtained results, we excluded the studies that disobeyed HWE. The primary pooled ORs were not significantly altered (**Figure 2**).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence conferred by the independent studies on the association of *RAD51* polymorphism with risk of breast cancer. The combined ORs were not obviously affected by excluding

RAD51 polymorphism and breast cancer susceptibility

Table 2. Meta-analysis of the association between *RAD51* G135C polymorphism and breast cancer risk

Subgroups (No. Of studies)	GG vs. CC		GG + GC vs. CC		GG vs. GC + CC		G vs. C		GC vs. CC	
	OR (95% CI)	<i>P</i> -het	OR (95% CI)	<i>P</i> -het	OR (95% CI)	<i>P</i> -het	OR (95% CI)	<i>P</i> -het	OR (95% CI)	<i>P</i> -het
Ethnicity										
Asian (n = 4)	0.96 (0.83, 1.12)	0.203	0.96 (0.84, 1.09)	0.101	1.07 (0.93, 1.24)	0.080	1.01 (0.91, 1.11)	0.015	0.83 (0.64, 1.08)	0.075
European (n = 8)	1.00 (0.96, 1.04)	1.000	1.00 (0.96, 1.04)	1.000	1.00 (0.96, 1.04)	0.952	1.00 (0.97, 1.03)	0.998	1.00 (0.90, 1.11)	0.990
American (n = 3)	1.01 (0.88, 1.15)	0.988	1.01 (0.89, 1.14)	0.990	1.00 (0.89, 1.14)	0.979	1.01 (0.92, 1.10)	0.970	1.05 (0.76, 1.45)	0.939
Source of control										
Hospital (n = 2)	0.99 (0.86, 1.13)	0.956	0.99 (0.88, 1.12)	0.959	1.01 (0.88, 1.15)	0.806	1.00 (0.91, 1.09)	0.904	0.94 (0.70, 1.25)	0.933
Population (n = 7)	1.00 (0.93, 1.08)	1.000	1.00 (0.94, 1.07)	1.000	0.98 (0.91, 1.05)	0.943	0.99 (0.95, 1.04)	0.994	1.04 (0.89, 1.22)	0.984
Total (n = 15)	1.00 (0.96, 1.04)	0.987	1.00 (0.96, 1.03)	0.946	1.00 (0.96, 1.04)	0.769	1.00 (0.97, 1.03)	0.656	0.98 (0.89, 1.07)	0.778

CI: confidence interval; OR, odds ratio.

RAD51 polymorphism and breast cancer susceptibility

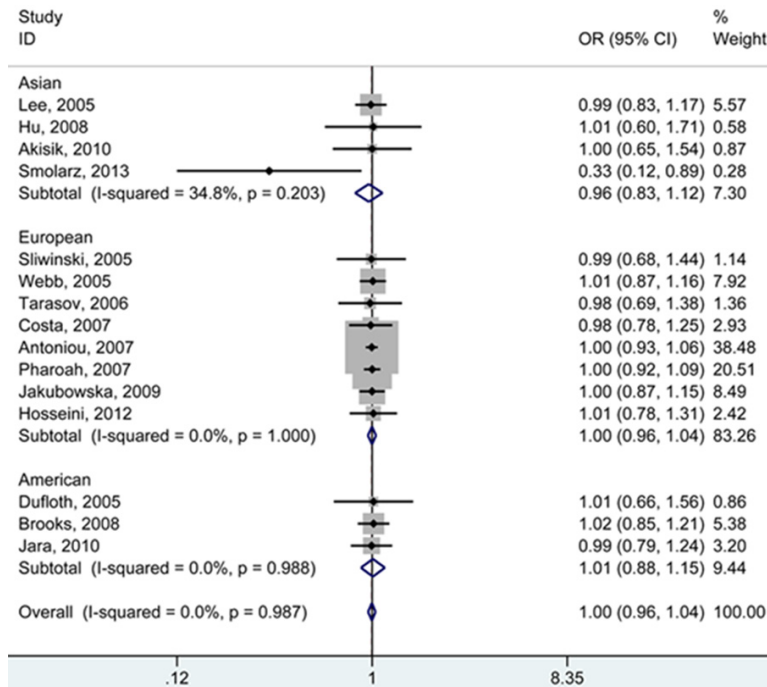


Figure 2. Forest plot (fixed-effects model) describing the association of the *RAD51* G135C polymorphism with risk of breast cancer. The *RAD51* G135C polymorphism was not associated with breast cancer under GG vs. CC.

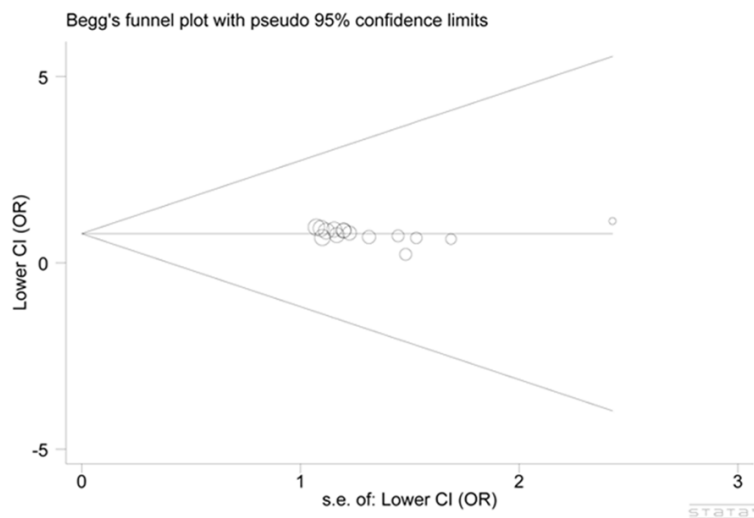


Figure 3. Funnel plot analysis to detect publication bias. Each point represents an individual study for the indicated association (Egger's test: $P = 0.364$ for GG vs. GC + CC).

each study. Therefore, our results were reliable.

Bias diagnostics

Begg's funnel plots and Egger's test were performed to determine the publication bias in the

meta-analysis. The symmetrical shape of each funnel plot and Egger's test did not reveal any evidence of publication bias (Egger's test: $P = 0.364$ for GG vs. GC + CC) (**Figure 3**).

Discussion

Genetic instability and reduced DNA repair capacity may result in the breast carcinogenesis [45]. Harmful mutations in *BRCA1* and *BRCA2* prevent reconstruction of damaged DNA and thereby increase susceptibility for breast cancer. *RAD51* is a homologue of bacterial RecA protein, playing a key role in meiotic and mitotic recombination and homology-dependent recombinational repair of DNA double-strand breaks. *RAD51* could modulate the penetrance of *BRCA1/BRCA2* mutations by interacting with *BRCA1* and *BRCA2* [46]. These results suggested that the *RAD51* gene is a potential susceptibility locus for breast cancer. Therefore, investigating and establishing the role of single nucleotide polymorphisms within the region are substantially important to identify the populations at higher risk of the malignancy.

The G135C polymorphism in the *RAD51* gene has been investigated in a number of genetic association studies in different ethnic groups with conflicting findings, making it important to perform a meta-analysis, a statistical method that is different from a single study tending to achieve a less precise measure of interest and contributes to a higher statistical power for the measure. In the present study, we failed to find statistical evidence for an increased risk of breast cancer associated with *RAD51* polymorphism, an observation supported by Yu et al. [29], who identified 12 studies involving 7,065 cases and 6,981 controls, showing that the

G135C polymorphism is not a risk factor for breast cancer. Inconsistent with former findings, Zhou et al. [27] demonstrated that *RAD51* G135C polymorphism is associated with an elevated risk of breast cancer. While data from the study by Sun et al. [26] suggested that the polymorphism of interest is a low-penetrant risk factor for developing breast cancer. Lack of accuracy in data and inclusion of studies with overlapped information may result in decreases in the precision of reported associations and thus make the results less credible [30].

In the subgroup analysis by ethnicity, none of the ethnic groups showed a significant association with breast cancer, even though we excluded all repeated data and included new subjects into the meta-analysis. Interestingly, Gao et al. found an increased breast cancer risk in European populations [28] and Sun et al. reported a statistically decreased risk in Asians [26]. Ethnicity is a crucial host-related factor that may modify the association between polymorphism and cancer, because different genetic backgrounds may result in potential gene/gene and gene/environment interactions. A second possibility is that the *RAD51* polymorphism is common among Europeans and Asians and functions biologically in both ethnic groups, thus modulating the risk of developing this cancer. In addition to the aforementioned explanations, another reason may again relate to data inaccuracy, a cause of false positive and false negative findings.

Although we attempted to avoid the shortcomings mentioned by He et al. [30], our results need to be interpreted with caution because of some limitations. First, significant HWE deviation was tested in several studies and this deviation may have more or less influenced the results despite no change in combined results was observed when the outlier were excluded. Second, *RAD51* G135C polymorphism might be a low-penetrance risk factor for breast cancer, and the exact genetic association merits further investigations. Third, gene/gene and gene/environment interactions were not considered in this work. Further, the real association for Americans and Asians may have been masked as a result of the relatively sample sizes.

In conclusion, our study provided some evidence for lack of an association between

RAD51 G135C polymorphism and risk of breast cancer. Subgroup analysis by ethnicity likewise did not implicate a statistically significant association. Further studies with a much larger number are needed to establish the *RAD51*-breast cancer relationship. As human diseases are a result of both environmental and genetic factors, the effects of exogenous and endogenous mutagens are expected to be considered in future.

Disclosure of conflict of interest

None.

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RAD51 polymorphism and breast cancer susceptibility

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