Breast Cancer Res Treat (2011) 125:529–535
DOI 10.1007/s10549-010-1031-8

EPIDEMIOLOGY

RAD51 135G>C polymorphism and breast cancer risk: a meta-analysis

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Received: 16 April 2010 / Accepted: 30 June 2010 / Published online: 11 July 2010

Abstract Mutations in *RAD51* gene are believed to be associated with elevated breast cancer risk. However, several case–control studies focusing on the association between *RAD51* 135G>C and breast cancer risk failed to achieve consensus. To clarify the effect of *RAD51* 135G>C polymorphism on breast cancer, a meta-analysis was performed. By searching PubMed and EMBASE, a total of 14 case–control studies, containing 12,183 cases and 10,183 controls, were included. The strength of association between *RAD51* 135G>C polymorphism and breast cancer risk was assessed by odds ratio (OR) with the corresponding 95% confidence interval (95% CI). When all the eligible studies were pooled into the meta-analysis, an elevated cancer risk was revealed in additive model (OR, 1.34; 95% CI, 1.01–1.78; $P = 0.044$) and recessive model (OR, 1.37; 95% CI, 1.03–1.82; $P = 0.032$). In subgroup analyses by ethnicity, *BRCA1/2* mutation status, and family history, a significant association was found only among *BRCA2* mutation carriers (additive model: OR, 4.92; 95% CI, 1.11–21.83; $P = 0.036$; recessive model: OR, 4.88; 95% CI, 1.10–21.67; $P = 0.037$). Sensitivity analysis did not perturb the results. In conclusion, this meta-analysis suggests that *RAD51* variant 135C homozygote is associated with elevated breast cancer risk among *BRCA2* mutation carriers.

Keywords *RAD51* · Gene polymorphism · Breast cancer · Meta-analysis

Introduction

Double-strand break (DSB) damage, causing cell death or loss of genetic material, is the most injurious lesion and responsible for cancer development. However, it can be repaired by several DSB repair genes such as *BRCA1/2* in which mutations have been proven to contribute to high risk of cancer in women [1]. *RAD51*, a homolog of *Escherichia coli* RecA, is another important DSB repair gene and can interact with BRCA1 and BRCA2 proteins, functioning through homologous recombination and non-homologous end joining [2, 3]. Mutations in *RAD51* gene have been believed to be associated with an elevated risk of cancer including breast cancer which is the most common cancer in women all over the world.

A functional single-nucleotide polymorphism (SNP) in the 5′ untranslated region (UTR) of *RAD51*, 135G>C (c.-98G>C, rs1801320), has been identified, which is involved in modifying promoter activity and the penetrance of *BRCA1/2* mutations [4, 5], and therefore may be a good candidate for low-penetrance variants that contribute to breast cancer risk. Several case–control studies focusing on

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the association between *RAD51* 135G>C and breast cancer risk have been conducted and suggested that *RAD51* 135G>C modified the breast cancer risk of women only if they had a family history or carried *BRCA2* mutations [5–10]. However, the results have been inconsistent and inconclusive [11–13] owing to the relatively small sample sizes and different patient populations. Meta-analysis is a powerful and rigorous method to resolve these problems. In this study, to clarify the association between *RAD51* 135G>C polymorphism and breast cancer susceptibility, a meta-analysis was performed.

Methods

Study identification and selection

Before the study, inclusion criteria were defined as follows: (a) articles evaluating the association between *RAD51* 135G>C polymorphism and breast cancer risk; (b) study designed as case–control; (c) sufficient data available to estimate an odds ratio (OR) with its 95% confidence interval (95% CI). A literature search of PubMed and EMBASE (updated to 2010/04/10) was conducted using the following terms: '*RAD51*', 'polymorphism(s)', 'breast cancer', or 'breast carcinoma', without restriction on language. The retrieved literatures were then read independently in their entirety to assess their appropriateness for the inclusion in this meta-analysis by the two authors (Zhou and Hu). The reference lists of reviews and retrieved articles were searched simultaneously to find additional eligible studies. If studies had partly overlapped subjects, only the study with a larger sample size was selected. Any disagreement was resolved by discussion between the two authors.

Data extraction

The following variables were extracted from each study if available: first author's surname, publication year, patient ethnicity, matching criteria, sample size, and numbers of cases and controls in different *RAD51* 135G>C genotypes.

Statistical analysis

The strength of association between *RAD51* 135G>C polymorphism and breast cancer risk was assessed by OR with the corresponding 95% CI. The pooled OR was calculated by a fixed-effects model (the Mantel–Haenszel method) when between-study heterogeneity was absent [14]. Otherwise, a random-effects model (the DerSimonian and Laird method) [15] was selected. Statistical between-study heterogeneity was checked by the Q test [16] and was

Table 1 Main characteristics of studies included in this meta-analysis

References	Country	Ethnicity	Source of controls	Matching criteria	Sample size (case/control)	Genotype (case/control)			HWE
						GG	GC	CC	
[30]	UK	Caucasian	Population-based	–	2172/840	1904/722	255/116	13/2	Yes
[6]	Israel	Caucasian	Hospital-based	Age, cancer-free	333/260	290/230	43/30[a]		Yes
[13]	Brazil	Mixed	Hospital-based	Breast cancer-free, family history-free	86/120	68/103	9/13	1/3	Yes
[31]	Korea	Asian	Population-based	Age, education	872/671	611/450	143/123	28/14	Yes
[28]	Poland	Caucasian	Hospital-based	Age, cancer-free	150/150	108/106	38/41	4/3	Yes
[32]	Australia	Caucasian	Population-based	Age	1295/660	1100/575	188/77	7/8	Yes
	Australia	All	Population-based	Age	1456/793	1221/676	212/104	11/8	Yes
[33]	China	Asian	Population-based	Age	189/421	116/284	73/137[a]		Yes
[8]	Multiple	Caucasian	Population-based	–	4443/4069	3838/3485	567/565	38/19	Yes
[10]	Portugal	Caucasian	Hospital-based	Age	285/442	216/381	45/53	4/1	Yes
[34]	USA	Mixed	Population-based	Age, date at blood donation	612/612	516/513	88/88	7/10	Yes
[35]	China	Asian	Population-based	Age	71/85	51/59	18/23	2/3	Yes
[9]	Poland	Caucasian	Population-based	Age, sex, geographically	1100/1100	785/822	207/232	15/15	Yes
[36]	Turkey	Caucasian	Population-based	Age	147/120	125/62	20/57	2/1	No
[29]	Chile	Mixed	Population-based	Age, socioeconomic strata	267/500	232/441	33/58	2/1	Yes

HWE Hardy–Weinberg equilibrium

[a] The number of *RAD51* 135C allele carriers (GC/CC) in case and control groups

considered statistically significant with $P < 0.10$. The OR and its 95% CI in each comparison was assessed in dominant (*GC/CC* versus *GG*), additive (*CC* versus *GG*), and recessive (*CC* versus *GG/GC*) genetic models. In addition, subgroup analyses for ethnicity (Caucasian, Asian, and mixed population), *BRCA1/2* mutation status (*BRCA1* mutation carriers, *BRCA2* mutation carriers, non-carriers, and unselected populations), and family history (familial and sporadic breast cancer) were conducted, and influence analysis was performed by omitting each study to find potential outliers [17]. In the control populations, Hardy–Weinberg equilibrium (HWE) was tested, but a deviation from HWE was allowed in a mixed control population. Sensitivity analysis was also conducted by excluding the HWE-violating studies. Potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested by Egger's test ($P < 0.05$ was considered a significant publication bias) [18]. This meta-analysis was performed using the software STATA version 10.0.

Results

Study characteristics

A total of 26 publications met the inclusion criteria. Of these studies, 12 [5, 11, 12, 19–27] were excluded because of their populations overlapped with another three included studies [8, 28, 29]. As a result, a total of 14 publications [6, 8–10, 13, 28–36] containing 12,183 cases and 10,183 controls were included in this meta-analysis. Table 1 lists the main characteristics of these studies. Among these publications, there were eight studies of Caucasian descent [6, 8–10, 28, 30, 32, 36], three of Asian descent [31, 33, 35], and three of mixed populations [13, 29, 34]. Two studies [6, 8] contained the subjects of *BRCA1/2* mutation carriers, two [6, 29] contained non-carriers, and another ten [10, 13, 28, 30–36] contained unselected populations. In addition, five of these studies [10, 13, 28, 29, 36] presented *RAD51* 135G>C polymorphism genotype distributions according to family history (familial and sporadic breast

Table 2 Genotype frequencies for cases and controls in familial and sporadic breast cancer

First author, year	Familial breast cancer (case/control)			Sporadic breast cancer (case/control)		
	GG	GC	CC	GG	GC	CC
Dufloth, 2005 [13]	42/103	6/13	0/3	26/103	3/13	1/3
Sliwinski, 2005 [28]	–	–	–	108/106	38/41	4/3
Costa, 2007 [10]	64/381	18/53	0/1	152/177	27/33	4/1
Jara, 2010 [29]	232/441	33/58	2/1	–	–	–
Akisik, 2010 [36]	125/62	20/57	2/1	–	–	–

Table 3 Results of meta-analysis for *RAD51* 135G>C polymorphism and breast cancer risk

Analysis	Cases/controls	Additive model (CC versus GG)		Dominant model (CC/GC versus GG)		Recessive model (CC versus GG/GC)	
		OR (95% CI)	P/P_h*	OR (95% CI)	P/P_h	OR (95% CI)	P/P_h
Overall	12183/10183	**1.34 (1.01–1.78)**	**0.044/0.570**	0.95 (0.81–1.11)	0.528/0.000	**1.37 (1.03–1.82)**	**0.032/0.565**
Ethnicity							
Caucasian	9925/7641	1.39 (0.98–1.99)	0.069/0.185	0.90 (0.71–1.15)	0.411/0.000	1.42 (0.99–2.03)	0.055/0.175
Asian	1132/1177	1.37 (0.75–2.52)	0.311/0.514	1.02 (0.84–1.25)	0.834/0.271	1.41 (0.77–2.59)	0.265/0.508
Mixed	965/1232	0.83 (0.37–1.87)	0.647/0.398	1.01 (0.79–1.29)	0.952/0.842	0.83 (0.37–1.86)	0.644/0.401
BRCA1/2 mutation							
BRCA1	3009/2979	1.46 (0.79–2.71)	0.231/–	0.89 (0.77–1.02)	0.098/0.602	1.49 (0.80–2.76)	0.208/–
BRCA2	1632/1202	**4.92 (1.11–21.83)**	**0.036**/–	1.15 (0.92–1.45)	0.218/0.134	**4.88 (1.10–21.67)**	**0.037**/–
Non-carrier	409/655	3.80 (0.34–42.15)	0.277/–	1.12 (0.77–1.64)	0.558/0.960	3.77 (0.34–41.73)	0.280/–
Unselected	5909/4156	1.20 (0.82–1.76)	0.355/0.566	0.91 (0.71–1.17)	0.451/0.000	1.23 (0.84–1.80)	0.292/0.548
Family history							
Familial	933/1331	1.24 (0.36–4.27)	0.739/0.649	0.79 (0.27–2.25)	0.654/0.000	1.39 (0.41–4.69)	0.599/0.672
Sporadic	514/660	1.92 (0.67–5.52)	0.226/0.616	0.99 (0.70–1.41)	0.969/0.945	1.95 (0.68–5.59)	0.214/0.662

A significant association was detected ($P < 0.05$)

* P_h P values for heterogeneity from Q test

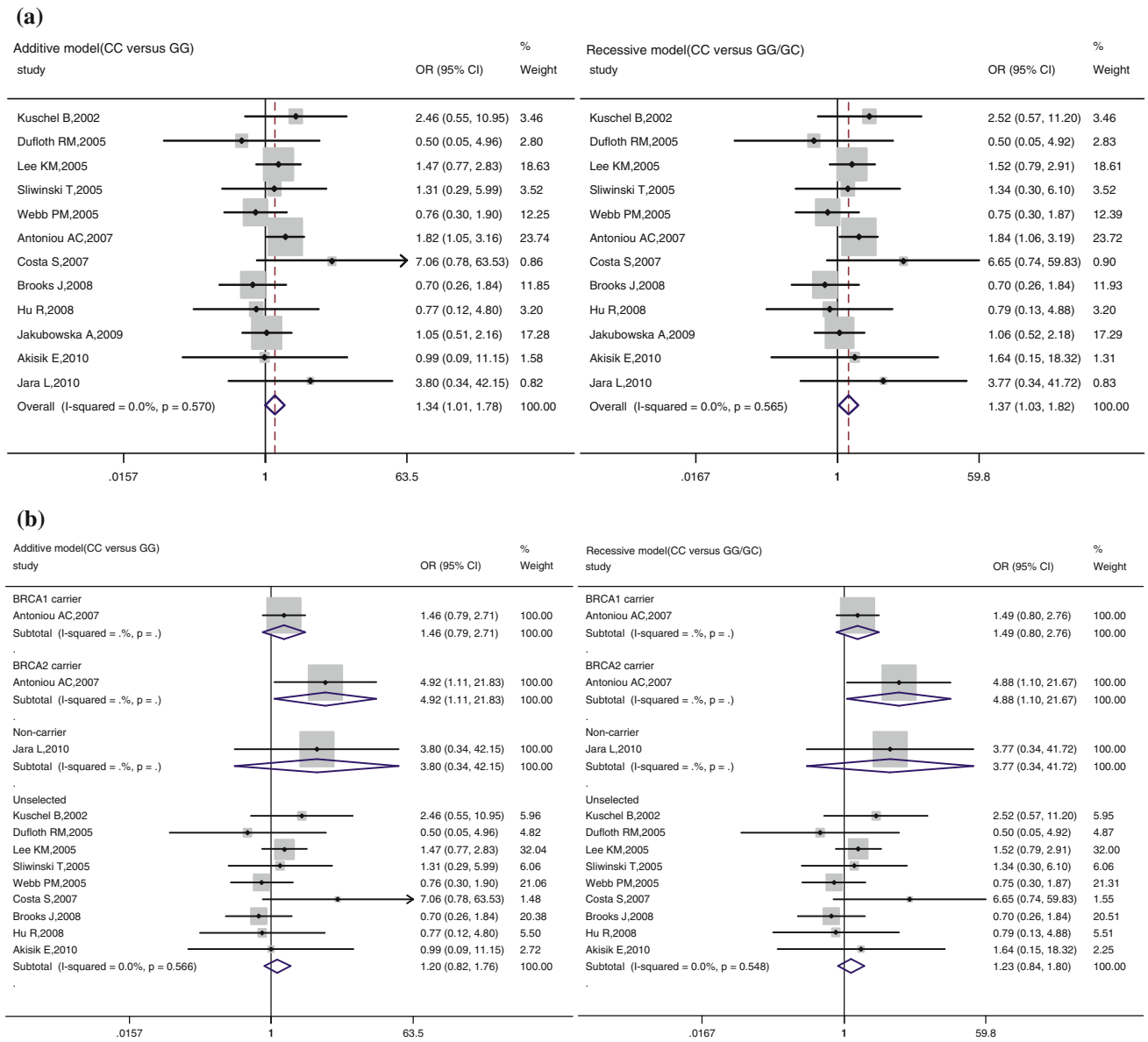

Fig. 1 Meta-analysis of *RAD51* 135G>C polymorphism in breast cancer. **a** Overall meta-analysis, **b** subgroup analysis on *BRCA1/2* mutation status

cancer) (Table 2). All of the cases were histologically confirmed as breast cancer. Controls were mainly healthy populations, and matched with age or cancer-free. Genotype distributions in the controls of all studies were in agreement with HWE except one [36].

Meta-analysis results

As shown in Table 3, no between-study heterogeneity was found in overall comparisons in additive and recessive genetic models. When all the eligible studies were pooled into the meta-analysis, elevated breast cancer risks were revealed in additive model (OR, 1.34; 95% CI, 1.01–1.78; $P = 0.044$) and recessive model (OR, 1.37; 95% CI, 1.03–1.82; $P = 0.032$) (Fig. 1a). Next, the effect of *RAD51* 135G>C polymorphism was evaluated in subgroup analysis according to specific ethnicity, *BRCA1/2* mutation status and family history. A significant association was found only among *BRCA2* mutation carriers (additive model: OR, 4.92; 95% CI, 1.11-21.83; $P = 0.036$; recessive model: OR, 4.88; 95% CI, 1.10-21.67; $P = 0.037$) (Fig. 1b), but not in other subgroups (Table 3).

Sensitivity analysis

Influence analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no

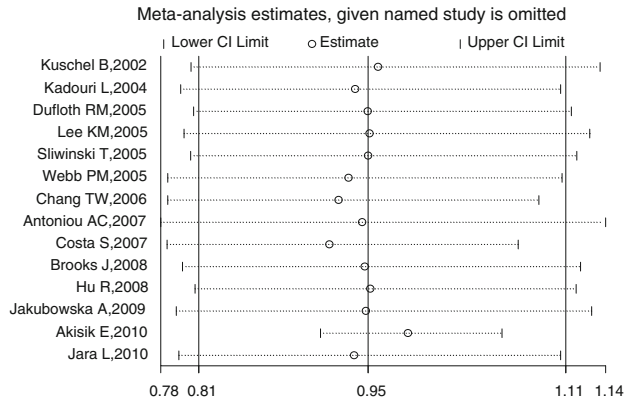

Fig. 2 Influence analysis for GC/CC versus GG in the overall meta-analysis. This figure shows the influence of individual studies on the summary OR. The *middle vertical axis* indicates the overall OR and the two vertical axes indicate its 95% CI. Every *hollow round* indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of every *broken line* represent the 95% CI

individual study significantly affected the pooled ORs (Fig. 2). Sensitivity analysis by excluding HWE-violating study did not perturb the overall results.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias. The shapes of the funnel plot did not indicate any evidence of obvious asymmetry in additive and recessive model (Fig. 3) and the Egger's test suggested the absence of publication bias (additive model: $P = 0.997$; recessive model: $P = 0.906$).

Discussion

RAD51 plays an important role in maintenance of the genomic integrity through DSB repair mechanisms including homologous recombination and non-homologous end joining. However, accumulating evidence supports the hypothesis that genetic polymorphisms in *RAD51* may result in reduced DNA repair capacity and be associated with increased susceptibility to breast cancer [4, 5]. In this meta-analysis, a total of 14 eligible case–control studies were pooled to explore the association between *RAD51* 135G>C polymorphism and breast cancer risk, and the results suggested that carriers with variant *135C* allele homozygote in additive and recessive genetic model had an increased risk of breast cancer. Influence analysis by sequentially removing individual studies did not perturb the results. Neither did sensitivity analysis by excluding the HWE-violating study.

Ethnicity was significantly associated with breast cancer risk and genotype of *RAD51* 135G>C variants ($P < 0.0001$). Asian women had a lower risk of breast cancer than White women. Among Black women, 37.4% had at least one copy of the variant allele *RAD51* 135C, while among non-Jewish White, Jewish White, and other ethnic populations, the frequencies were 15.9, 9.6, and 17.3%, respectively [34]. This may lead to *RAD51* 135G>C polymorphism genotype distribution disequilibrium when all ethnic populations were pooled together. It was essential to conduct a subgroup analysis on ethnicities. In this meta-analysis, all subjects were classified into three ethnic groups (Caucasian (White), Asian, and mixed populations). The results revealed no association between *RAD51* 135G>C variants and breast cancer susceptibility in all ethnic groups.

As described above, the *RAD51* gene product acts together with BRCA1 and BRCA2 proteins in homologous recombination and DSB repair. It is reasonable to assume that *RAD51* and *BRCA1/2* mutations may have interactive effects on breast cancer risk. Some previous studies presented an association of *RAD51* variant allele 135C with an elevated breast cancer risk only in *BRCA2* mutation carrier, but not in *BRCA1* mutation carriers or non-carriers or unselected populations [5–8]. In contrast,

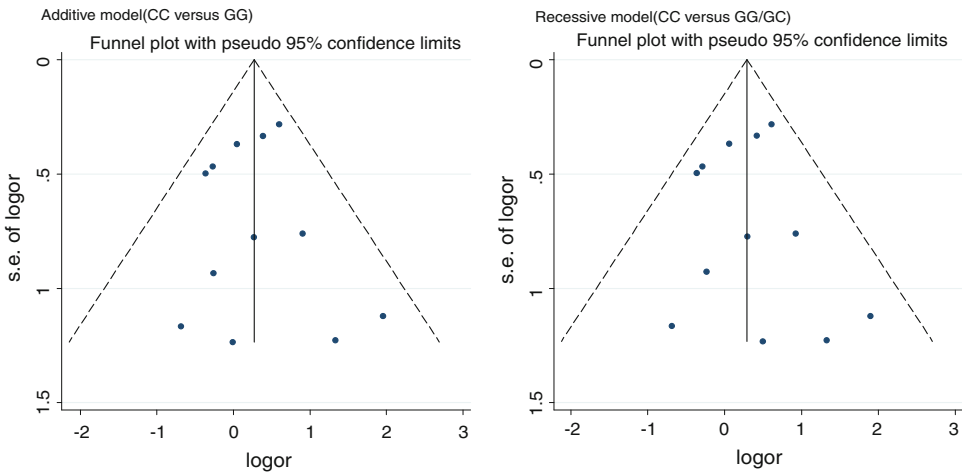

Fig. 3 Funnel plot of *RAD51* 135G>C polymorphism and breast cancer risk for publication bias

Jakubowska et al. [11, 12] observed a significantly reduced risk of breast cancer among Polish female carriers of *RAD51* 135C allele and *BRCA1* founder mutations (5382insC, 4153delA and 300T>G). Subgroup analysis on *BRCA1/2* mutation status in this meta-analysis, however, confirmed the former result.

Furthermore, germline mutations in *BRCA1/2* genes account for fewer than 2% of all breast cancer cases, while for about 20% of the familial breast cancer [37], suggesting that some differences in susceptibility genes may exist between familial and sporadic breast cancer. In order to define whether *RAD51* 135G>C polymorphism played different roles in familial and sporadic breast cancer risks or not, a subgroup analysis based on family history (familial and sporadic breast cancer) was performed. No association was found in both groups as the results suggested.

Although the results of this meta-analysis were powerful, some limitations still exist. First, this study is a study-level but not an individual patient-level meta-analysis. It is known that study-level analysis can lead to biased assessments and use of aggregated summary values has some limitations in explaining the heterogeneity [38]. Second, OR value was obtained without correction. More accurate OR should be corrected by age, menopause status, ethnicity and other exposure factors that are potentially associated with breast cancer risk. Third, of these 14 studies, most subjects were Caucasians and Asians, and no study presented *RAD51* genotype distribution among Africans. Therefore, the conclusion about this association in African populations should be further investigated.

In conclusion, this study suggested that *RAD51* variant 135C homozygote is associated with elevated breast cancer risk among *BRCA2* mutation carriers, but not in *BRCA1* mutation carriers or non-carriers or unselected populations.

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