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Original Article

Association between RAD51 polymorphisms and susceptibility of head and neck cancer: a meta-analysis

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Abstract: Background: The associations between RAD51 gene polymorphisms (G135C and G172T) and risk of head and neck cancer (HNC) have been investigated, but the results are controversial. The aim of this study was to provide a more precise estimation of its relationship with HNC using a meta-analysis. Methods: Relevant studies were retrieved from the PubMed, Excerpta Medica Database, and China National Knowledge Infrastructure. Strict selection and exclusion criteria were determined, and the odds ratio (OR) with a 95% confidence interval (CI) was used to assess the strength of the association between RAD51 polymorphisms and HNC risk. Results: Six studies were eligible for RAD51 G135C (1593 cases and 1719 controls), and three studies were eligible for RAD51 G172T (997 cases and 979 controls). In the overall population, significant association between RAD51 G135C polymorphism and HNC risk was observed under allele model (C vs G: OR = 1.21, 95% CI = 1.04-1.41, *P* = 0.015). In the subgroup analysis by smoking status, a significant association was found among smokers (C vs G: OR = 1.59, 95% CI = 1.25-2.04; GC vs GG: OR = 2.29, 95% CI = 1.29-4.05; GC + CC vs GG: OR = 2.08, 95% CI = 1.56-2.78). When stratified based on drinking status, a significant association was found among drinkers(C vs G: OR = 1.60, 95% CI = 1.21-2.11; GC vs GG: OR = 2.50, 95% CI = 1.16-5.38; GC + CC vs GG: OR = 2.17,95% CI = 1.56-3.01). However, no significant association with HNC risk was demonstrated when stratified based on source of control and ethnicity. For G172T polymorphism, the results showed no significant risk association in overall analysis. In the subgroup analysis by ethnicity, the result suggested that a decreased HNC risk was found among Caucasians (T vs G: OR = 0.82, 95% CI = 0.72-0.95; TT vs GG: OR = 0.62, 95% CI = 0.46-0.84; TT vs GT + GG: OR = 0.64, 95% CI = 0.49-0.84). Conclusion: This meta-analysis suggested that RAD51 G135C is associated with increased HNC risk, especially among smokers and drinkers, while G172T polymorphism may play a protective role against HNC among Caucasians. Larger-scale and well-designed studies are needed to further clarify the association.

Keywords: Head and neck cancer, meta-analysis, polymorphism, RAD51

Introduction

Head and neck cancer (HNC) is now the fifth most common type of cancer in the world [1], with approximately 434,000 new patients diagnosed annually worldwide [2]. HNC is considered to be a complex disease because both genetic and environmental risk factors contribute to its etiology [3]. Several environmental risk factors such as tobacco use, alcohol consumption, and viral infection, have been reported to be associated with HNC [4, 5]. Nevertheless, only a small proportion of the people exposed to these environmental factors eventually develop HNC, indicating that genetic susceptibility may also contribute to its development [6]. Recent data imply that the environmental risk factors may be modified by polymorphisms in the carcinogen metabolizing genes i.e. gene-environment interactions.

RAD51 gene is located on chromosome 15q15.1 in humans [7]. The RAD51 protein encoding by RAD51 gene is essential for the repair of DNA damage. Growing evidences show that RAD51 has an irreplaceable role in the

maintenance of genomic stability and the repair of DNA double-strand breaks [8]. Two commonly studied polymorphisms of RAD51 gene are G135C (rs1801320), a G to C transversion at position +135, and G172T (rs1801321), a G to T transversion in the 172 position. These two polymorphisms were shown to affect mRNA stability or translational efficiency, leading to altered polypeptide product levels and altering the function of encoding RAD51 protein, and influenced the DNA repair capacity to some extent [9, 10].

Several original studies have reported the role of RAD51 gene polymorphisms (G135C and G172T) in HNC risk, but the results are inconclusive. Considering that small sample size might have inadequate power to explore genetic association of complex multifactorial disease such as cancer, we performed a meta-analysis to derive a more precise estimation of this association.

Methods

Search strategy

We conducted a comprehensive literature search in PubMed, Excerpta Medica Database, and China National Knowledge Infrastructure (up to 5 January 2015) using the following search strategy: "RAD51", "polymorphism" and "head and neck cancer or oral cancer or pharynx cancer or larynx or nasopharynx cancer". In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies.

Inclusion and exclusion criteria

The studies included in the meta-analysis must meet the following criteria. They (a) have case-control designs, (b) evaluated the effect of RAD51 gene polymorphisms (G135C and G172T) on HNC risk, and (c) supplied sufficient reported genotypic frequencies in both cases and controls for estimating an odds ratio (OR) with its 95% confidence interval (CI). Exclusion criteria were as follows: They are (a) not case-control studies; (b) case reports, reviews, or letters; (c) control population including patients; and (d) studies contained overlapping data.

Data extraction

From each eligible study, the following information were extracted by two investigators independently with the standard protocol: the first author's name, year of publication, country of origin, ethnicity, source of control, method of genotyping and the frequency of genotypes in both cases and controls. The results were compared and disagreement was resolved by discussion.

Statistical analysis

ORs with 95% CI were calculated to assess the strength of the association between the RAD51 gene polymorphisms and HNC risk. The Hardy-Weinberg equilibrium (HWE) was determined using the chi-square test in the control groups [11]. The pooled ORs for RAD51 G135C polymorphism were performed under allele model (C vs G), homozygote model (CC vs GG), heterozygote model (GC vs GG), recessive model (CC vs GC + GG) and dominant model (GC + CC vs GG). The same methods were applied to the analysis of the RAD51 G172T polymorphism. Stratified analyses were conducted with respect to source of control, ethnicity, smoking status and drinking status.

Heterogeneity assumption was checked by the chi-square-based *Q*-test. In addition, the percentage of total variation due to heterogeneity was quantified by the I^2 value [12]. If $P \geq 0.1$ and $I^2 < 50$ %, we used the fixed-effects model (the Mantel-Haenszel method) to pool the results [13]. Otherwise, the random effects model (the DerSimonian Laird method) was used [14]. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias [15]. All of the statistical tests were performed using STATA version 12.0 (Stata Corporation, College Station, TX). A *P*-value less than 0.05 was considered statistically significant.

Results

Literature search and characteristics in the meta-analysis

Based on the search criteria, a total of 6 case-control studies were identified in the current meta-analysis [16-21], among which 6 studies with 1593 cases and 1719 controls for RAD51 G135C polymorphism and 3 studies with 997 cases and 979 controls for G172T polymorphism. The genotype distributions of the controls in one study [18] did not conform to HWE. The main characteristics of the eligible studies are listed in **Tables 1** and **2**.

Table 1. Characteristics of the studies included on RAD51 G135C polymorphism

First author	Year	Country	Ethnicity	Source of control	Genotyping method	Case			Control			HWE
						GG	GC	CC	GG	GC	CC	
Lu	2007	USA	Caucasian	HCC	PCR- RFLP	624	91	1	622	96	1	0.17
Werbrouck	2008	Belgium	Caucasian	HCC	PCR	136	15	1	134	23	0	0.322
Sliwinski	2010	Poland	Caucasian	HCC	PCR- RFLP	101	88	2	258	64	32	< 0.001
Gresner	2012	Poland	Caucasian	PCC	PCR	67	13	1	71	14	2	0.217
Romanowicz-Makowska	2012	Poland	Caucasian	PCC	PCR-RFLP	174	69	10	190	58	5	0.816
Kayani	2014	Pakistan	Asian	HCC	PCR-RFLP	120	70	10	106	41	3	0.674

HWE: Hardy-Weinberg equilibrium; HCC: hospital-based case-control; PCC: population-based case-control; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism.

Table 2. Characteristics of the studies included on RAD51 G172T polymorphism

First author	Year	Country	Ethnicity	Source of control	Genotyping method	Case			Control			HWE
						GG	GT	TT	GG	GT	TT	
Lu	2007	USA	Caucasian	HCC	PCR- RFLP	261	351	104	240	335	144	0.169
Gresner	2012	Poland	Caucasian	PCC	PCR	36	43	2	43	54	13	0.524
Kayani	2014	Pakistan	Asian	HCC	PCR-RFLP	83	90	27	99	49	2	0.132

HWE: Hardy-Weinberg equilibrium; HCC: hospital-based case-control; PCC: population-based case-control; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism.

Meta-analysis result

The pooled results of meta-analysis for the association between RAD51 polymorphisms (G135C and G172T) and HNC susceptibility are shown in **Tables 3** and **4**.

As for G135C polymorphism, a total of 6 case-control studies with 1593 cases and 1719 controls were identified. Meta-analysis showed that there was significant association between RAD51 G135C and HNC risk under allele model among the overall population (C vs G: OR = 1.21, 95% CI = 1.04-1.41, *P* = 0.015, **Figure 1**), while there was no significant association in these four genetic models (CC vs GG: OR = 1.06, 95% CI = 0.35-3.27, *P* = 0.914; GC vs GG: OR = 1.31, 95% CI = 0.81-2.13, *P* = 0.278;GC + CC vs GG: OR = 1.27, 95% CI = 0.88-1.83, *P* = 0.200;CC vs GC + GG: OR = 0.94, 95% CI = 0.27-3.31, *P* = 0.921). The heterogeneity was significant in all genetic models except for allele model and the detailed data are shown in **Table 3**. These eligible studies were analyzed by stratified analysis. In the subgroup analysis by smoking status, the G135C polymorphism was associated with smokers (C vs G: OR = 1.59, 95% CI = 1.25-2.04; GC vs GG: OR = 2.29, 95% CI = 1.29-4.05; GC + CC vs GG: OR = 2.08, 95% CI = 1.56-2.78), no significant association was found under all models among non-smokers. When stratified based on drinking status, the G135C polymorphism was associated with drinkers (C vs G: OR = 1.60, 95% CI = 1.21-2.11; GC vs GG: OR = 2.50, 95% CI = 1.16-5.38; GC + CC vs GG: OR = 2.17, 95% CI = 1.56-3.01), but not with non-drinkers. However, no significant association with HNC risk was demonstrated when stratified based on source of control and ethnicity (**Table 3**).

With respect to G172T polymorphism, a total of 3 case-control studies with 997 cases and 979 controls were selected. As shown in **Table 4**, the pooled results revealed no significant associations between G172T polymorphism and HNC susceptibility in all genetic models (T vs G: OR = 1.16, 95% CI = 0.55-2.43, *P* = 0.914, **Figure 2**; TT vs GG: OR = 1.22, 95% CI = 0.15-9.98, *P* = 0.914; GT vs GG: OR = 1.26, 95% CI = 0.73-2.16, *P* = 0.278;GT + TT vs GG: OR = 1.24, 95% CI = 0.58-2.66, *P* = 0.200; TT vs GT + GG: OR = 0.11, 95% CI = 0.17-7.23, *P* = 0.921). The heterogeneity was significant in all genetic models. We also analyzed these eligible studies by stratified analysis. When stratified by ethnicity, the G172T polymorphism had a decreased HNC risk among Caucasians (T vs G: OR = 0.82, 95% CI = 0.72-0.95; TT vs GG: OR = 0.62, 95% CI = 0.46-0.84; TT vs GT + GG: OR = 0.64, 95% CI = 0.49-0.84). However, no significant association with HNC risk was demon-

Table 3. Meta-analysis of the association of RAD51 G135C polymorphism with HNC risk

Analysis	Allele model (C vs G)		Homozygote model (CC vs GG)		Heterozygote model (GC vs GG)		Dominant model (GC + CC vs GG)		Recessive model (CC vs GC + GG)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Overall (6)	1.21 (1.04-1.41)	0.116	1.06 (0.35-3.27)	0.038	1.31 (0.81-2.13)	0.000	1.27 (0.88-1.83)	0.001	0.94 (0.27-3.31)	0.011
Source of control										
HCC (4)	1.18 (0.87-1.59)	0.056	0.96 (0.17-5.62)	0.023	1.37 (0.67-2.79)	0.000	1.30 (0.76-2.20)	0.000	0.84 (0.12-6.05)	0.007
PCC (2)	1.27 (0.93-1.73)	0.279	1.70 (0.65-4.45)	0.296	1.23 (0.86-1.77)	0.554	1.27 (0.90-1.80)	0.386	1.61 (0.62-4.22)	0.32
Ethnicity										
Caucasian (5)	1.15 (0.97-1.36)	0.142	0.80 (0.21-3.02)	0.055	1.26 (0.70-2.29)	0.000	1.20 (0.77-1.87)	0.001	0.72 (0.16-3.32)	0.016
Smoking status										
Smokers (3)	1.59 (1.25-2.04)	0.597	1.08 (0.17-6.74)	0.019	2.29 (1.29-4.05)	0.041	2.08 (1.56-2.78)	0.310	0.85 (0.11-6.40)	0.008
Non-smokers (3)	1.25 (0.85-1.84)	0.542	1.85 (0.61-5.66)	0.409	1.25 (0.78-2.00)	0.435	1.28 (0.81-2.01)	0.688	1.63 (0.55-4.81)	0.356
Drinking status										
Drinkers (2)	1.60 (1.21-2.11)	0.584	0.78 (0.06-10.51)	0.009	2.50 (1.16-5.38)	0.030	2.17 (1.56-3.01)	0.321	0.60 (0.03-10.82)	0.003
Non-drinkers (2)	1.06 (0.67-1.65)	0.460	0.23 (0.03-1.83)	0.719	1.75 (0.59-5.24)	0.038	1.36 (0.82-2.26)	0.138	0.18 (0.02-1.39)	0.594

P value of *Q*-test for heterogeneity, Random-effects model was used when *P* value for heterogeneity test < 0.10; otherwise, fixed-effects model was used. HCC, hospital-based case-control study; OR, odds ratio; CI, confidence interval.

Table 4. Meta-analysis of the association of RAD51 G172T polymorphism with HNC risk

Analysis	Allele model (T vs G)		Homozygote model (TT vs GG)		Heterozygote model (GT vs GG)		Dominant model (GT + TT vs GG)		Recessive model (TT vs GT + GG)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Overall (3)	1.16 (0.55-2.43)	0.000	1.22 (0.15-9.98)	0.000	1.26 (0.73-2.16)	0.006	1.24 (0.58-2.66)	0.000	1.11 (0.17-7.23)	0.000
Source of control										
HCC (2)	1.48 (0.48-4.48)	0.000	3.02 (0.12-76.61)	0.000	1.42 (0.63-3.17)	0.002	1.52 (0.50-4.65)	0.000	2.56 (0.15-44.46)	0.000
Ethnicity										
Caucasian (2)	0.82 (0.72-0.95)	0.502	0.62 (0.46-0.84)	0.111	0.96 (0.78-1.19)	0.969	0.86 (0.71-1.06)	0.788	0.64 (0.49-0.84)	0.103
Smoking status										
Smokers (2)	1.22 (0.29-5.08)	0.057	1.36 (0.01-149.5)	0.000	1.26 (0.47-3.33)	0.041	1.26 (0.31-5.11)	0.002	0.90 (0.16-5.11)	0.000
Non-smokers (2)	1.68 (0.52-5.41)	0.000	3.23 (0.20-53.27)	0.101	2.36 (1.23-4.55)	0.294	2.19 (0.71-6.75)	0.142	1.35 (0.25-7.21)	0.027

P value of *Q*-test for heterogeneity, Random-effects model was used when *P* value for heterogeneity test < 0.10; otherwise, fixed-effects model was used. HCC, hospital-based case-control study; OR, odds ratio; CI, confidence interval.

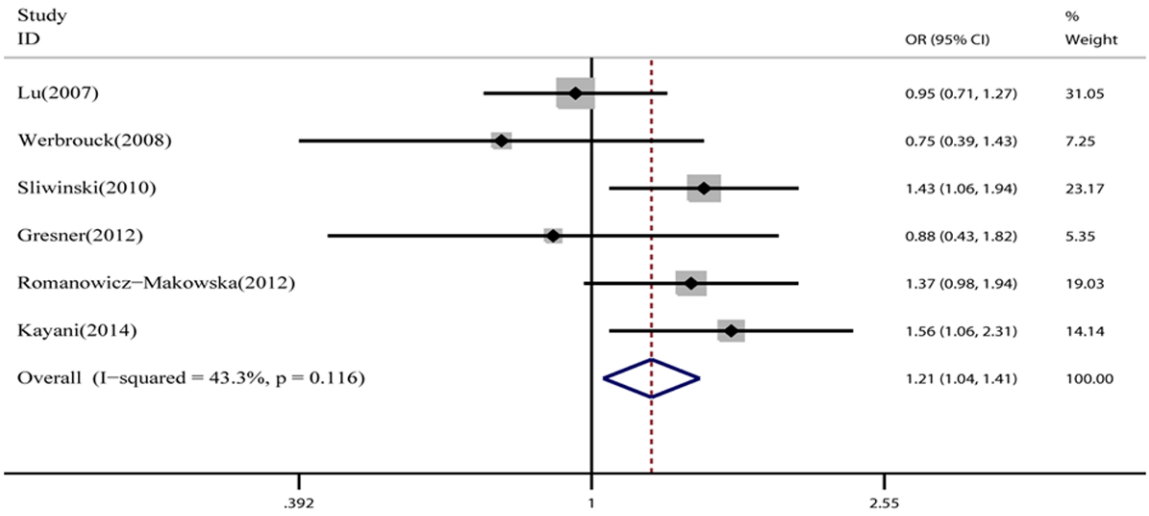

Figure 1. Meta-analysis of the association between the RAD51 G135C polymorphism and HNC risk (C vs G).

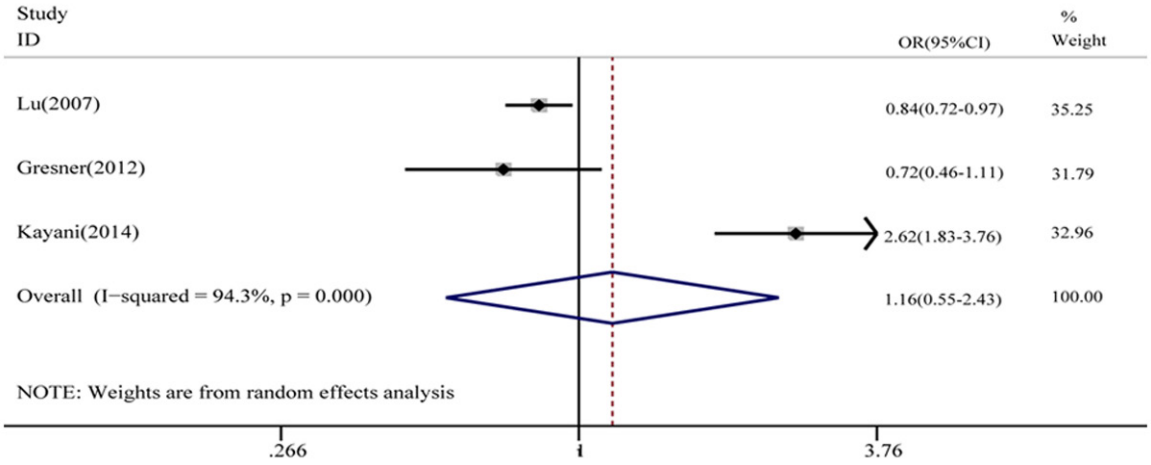

Figure 2. Meta-analysis of the association between the RAD51 G172T polymorphism and HNC risk (T vs G).

strated when stratified based on source of control and smoking status (**Table 4**).

Publication bias

We further identify the potential publication biases of literatures by Egger's test and funnel plot. In all studies, no funnel plot asymmetry was found (**Figure 3**). The results of the Egger's test for RAD51G135C and G172T polymorphisms did not show any evidence of publication bias.

Discussion

RAD51, a kind of ubiquitous strand exchange protein, is known to be a central enzyme involved in DNA double-strand break repair by homologous recombination. It could polymerize onto single-stranded DNA and searches for homology in a duplex donor DNA molecule, usually the sister chromatid [22]. Recent researches have suggested two common polymorphisms (G135C and G172T) located in the 59 untranslated region seems to be of functional relevance. In addition, the association of RAD51 variants (G135C and G172T) and risk of HNC has been extensively investigated in many studies. In addition, meta-analysis has been recognized as an important way to detect the effect of selected genetic polymorphisms on disease risk precisely. Therefore, we performed this meta-analysis including all published stud-

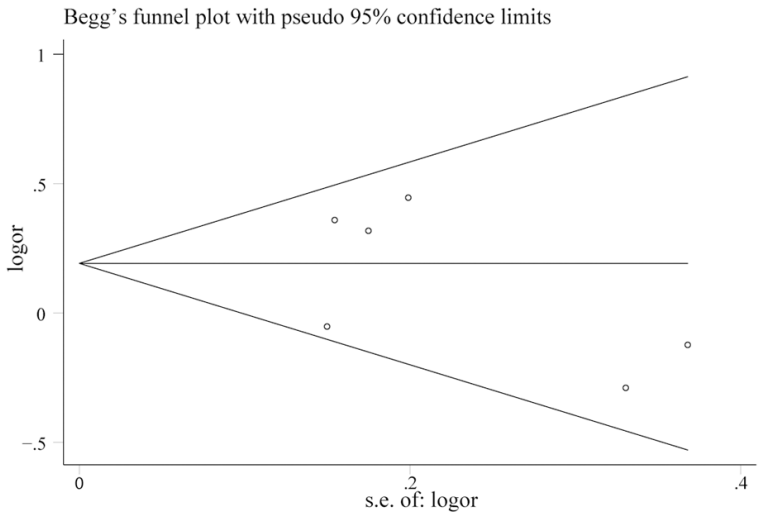

Figure 3. Begg's funnel plot of the meta-analysis of the RAD51 G135C polymorphism and HNC risk(C vs G).

ies to investigate the association between the RAD51 gene polymorphisms and HNC risk. To the best of our knowledge, this is the first meta-analysis of genetics studies on the association between RAD51 gene polymorphisms and HNC risk.

In this meta-analysis, 6 case-control studies (6 for G135C polymorphism, 3 for G172T polymorphism) were performed to provide the most comprehensive assessment of the relationship between RAD51 polymorphisms and HNC risk. In the overall population, the meta-analysis detected significant association between the RAD51 G135C polymorphism and HNC risk under allele model (C vs G: OR = 1.21, 95% CI = 1.04-1.41, *P* = 0.015). However, the pooled results revealed no significant associations between G172T polymorphism and HNC susceptibility in all genetic models. Further, in the subgroup analyses based on source of control, no significant association was found between the RAD51 G135C, and G172T polymorphisms and HNC risk under all genetic models. In the stratified analysis based on ethnicity, RAD51 G172T polymorphism had a decreased HNC risk among Caucasians based on allele, homozygote and recessive models. For G135C polymorphism, there was no significant association among Caucasians in all genetic models.

In the stratified analysis based on smoking status, significant association was found between the RAD51 G135C polymorphism and HNC risk under the allele, heterozygote and dominant models among smokers, no significant association was found under all models among non-smokers. For G172T polymorphism, there was no significant association both among smokers and non-smokers in all genetic models. When stratified based on drinking status, significant association was found between the RAD51 G135C polymorphism and HNC risk under allele, heterozygote and dominant models among drinkers, but not among non-drinkers. Tobacco smoke contains high quantities of chemical carcinogens, such as hydrocarbons, arylamines, nitrosamines and reactive oxygen species (ROS). These chemicals can form bulky adducts after activation by specific enzymes [23], and can induce a variety of oxidative damage[24, 25]. The ethanol in alcoholic beverages is considered to be "the principal ingredient that renders these beverages carcinogenic" [26]. Ethanol induces various reactive oxygen species and oxidative stress, which damage the DNA and affect its repair. Our results indicated that, when tobacco smoking and alcohol consumption were taken into account, the RAD51 G135C polymorphism was associated with increased risk of HNC. Besides the role of genetic variants, smoking and drinking behavior show a major effect on the HNC susceptibility.

Heterogeneity between studies should be noted because it may affect the strengths of the meta-analysis. In the current meta-analysis, significance heterogeneity was observed for both RAD51 G135C and G172T polymorphisms. Thus, random-effect models were used if significant heterogeneity was identified. Meanwhile, to diminish the heterogeneity, we carried out subgroup analysis based on ethnicity, source of control, smoking status and drinking status. The results indicated that heterogeneity reduced or disappeared in subgroups. The publication bias for the association between these two polymorphism and HNC risk was not observed.

There are still some limitations that should be pointed out. First, the numbers of published studies collected in our analysis were not large enough for the comprehensive analysis, especially for the RAD51 G172T polymorphism. Second, due to heterogeneity, the results of the present meta-analysis should be interpreted with some extent caution. Third, in the subgroup analysis, the included studies concerned Caucasians and Asians. For Caucasians and Asians, the number of the included studies was limited and their sample sizes were small. It may be underpowered to explore the real association. Fourth, meta-analysis is just a statistical test that is subject to many methodological restrictions, and it is not able to control for other relevant factors.

In conclusion, this meta-analysis suggested that RAD51 G135C is associated with increased HNC risk, especially among smokers and drinkers. However, the G172T polymorphism may play a protective role against HNC among Caucasians. Further studies with larger sample sizes and rigorous design are still needed, especially for investigating the effects of the gene-gene and gene-environment interaction.

Disclosure of conflict of interest

None.

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