

RESEARCH ARTICLE

Lack of Influence of an XRCC3 Gene Polymorphism on Oral Cancer Susceptibility: Meta-analysis

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Abstract

Background: To systematically summarize the association between the X-ray repair cross complementing 3 (XRCC3) gene polymorphism and oral cancer susceptibility by meta-analysis. **Materials and Methods:** Databases including PubMed, EMBase, CNKI, VIP and WanFang Data were searched to identify case-control studies concerning the association between an XRCC3 gene polymorphism and the risk of oral cancer from the inception to June 2014. Two reviewers independently screened the literature according to the criteria, extracted the data and assessed the quality. Then meta-analysis was performed using Stata 11.0 software. **Results:** Seven published case-control studies including 775 patients with oral cancer and 1922 controls were selected. Associations between the rs861539 polymorphism and overall oral cancer risk were not statistically significant in all kinds of comparison models (CT vs CC: OR=0.94, 95% CI=0.74-1.18; TT vs CC: OR=0.94, 95% CI=0.64-1.38; dominant model: OR=0.95, 95% CI=0.76-1.18; recessive model: OR=0.94, 95% CI=0.69-1.29; allele T vs C: OR=0.97, 95% CI=0.84-1.11). In the stratified analysis by ethnicity, no significant associations were found among Asians and Caucasians. On stratification by tumor type, no significant associations were found for cancer and oral premalignant lesions. **Conclusions:** The XRCC3 gene polymorphism was not found to be associated with the risk of oral cancer. Considering the limited quality of the included case-control studies, more high quality studies with large sample size are needed to verify the above conclusion.

Keywords: XRCC3 - Single nucleotide polymorphism - oral cancer - oral premalignant lesions - susceptibility

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Introduction

Oral cancer is the sixth most frequent cancer worldwide and an estimated 263,900 new cases and 128,000 deaths from oral cavity cancer (including lip cancer) occurred in 2008 worldwide (Jemal et al., 2011). Both environmental risk factors and genetic factors play important roles in the development of oral cancer. Environmental carcinogens contained in air pollution or tobacco smoking fumes, which are suggested to be important risk factors for oral cancer, could cause many types of DNA damages. Unrepaired DNA damage can result in cell apoptosis or unregulated cell growth and may eventually lead to cancer. The capacity for DNA repair is essential in maintaining cellular functions and homeostasis; however, this capacity can be altered based on DNA sequence variations in DNA repair genes, which may contribute to the onset of cancer. The DNA repair pathways play important roles in the genomic stability, thus defending against carcinogenesis. There has been increasing evidence that DNA damage plays a critical role in the carcinogenesis of most cancers and DNA

repair genes are considered key genes associated with the onset of cancer (Berwick et al., 2000; Poirier, 2012; Jin et al., 2013). Some repair genes have been reported to be associated with oral cancer (Sugimura et al., 2006; Bau, 2012), including the X-ray repair cross complementing 3 (XRCC3) gene (Flores-Obando et al., 2010).

Recent genetic association studies on cancer risk have focused on the effects of single-nucleotide polymorphisms in some genes. Several of these genes have included DNA repair genes, which are increasingly studied because they have a critical role in maintaining genomic integrity. Although these polymorphisms are only slightly associated with cancer risk at the level of the individual, the polymorphisms are prevalent at the population level and may contribute to the risk of a given population for cancer (Matullo et al., 2001). Two recent meta-analysis confirmed the associations between DNA repair gene variants in different types of cancers (Vineis et al., 2009) and the association between the DNA damage repair genes with oral, pharyngeal and laryngeal cancer (Flores-Obando et al., 2010).

A common variant of XRCC3 comprises a threonine

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to methionine substitution at amino acid 241 (Thr241Met, rs861539). This change may affect the function of the enzyme or influence its interaction with other proteins involved in DNA repair pathways (Matullo et al., 2001). XRCC3 gene is involved in the repair of DNA double-strand breaks (DSB), which is important to prevent chromosomal fragmentation, translocations and deletions (Kanaar et al., 1998).

To date, there are studies reporting the association between polymorphisms of XRCC3 codon 241 with oral cancer risk but these published data were contradictory (Benhamou et al., 2004; Majumder et al., 2005; Matullo et al., 2006; Kietthubthewa et al., 2006; Yang et al., 2008; Yen et al., 2008; Dos Reis et al., 2013). Until now, there was no meta-analysis or systematic review on the risk of oral cancer with XRCC3 polymorphism. So we perform an updated meta-analysis on all available case-control studies to investigate the relationship between rs861539 polymorphism in XRCC3 gene and the susceptibility of oral cancer.

Materials and Methods

Data sources

We retrieved the articles using the following terms “XRCC3” and “oral cancer or oral carcinoma” from PubMed, EMBASE, CNKI, VIP and WanFang Datasets (Last search was updated on May 2014). We evaluated potentially relevant publications by examining their titles and abstracts and all studies matching the eligible criteria were retrieved.

Study selection and data extraction

Eligible studies were selected according to the following explicit inclusion criteria: (a) evaluation of the rs861539 polymorphism and oral cancer or oral carcinoma susceptibility, (b) using the method of a case-control study, (c) There was sufficient published data for the computation of odds ratios (ORs) with 95% confidence intervals (95% CIs).

Duplicate and obviously unrelated articles were eliminated at first. Two authors (E.Z. and Z.C.) read the abstracts even whole articles independently to decide whether the articles should be excluded. The following information was obtained from each publication: first author’s name, publication year, country origin, ethnicity, case characteristics, total number of cases and controls, and numbers of each group with rs861539 genotypes, respectively.

Statistical methods

The Hardy-Weinberg equilibrium in control groups for each included study was analyzed by chi-squared tests. We assessed the between-study heterogeneity by Cochran’s Q test and quantified by I² (a significance level of $p < 0.05$ and/or $I^2 \geq 50\%$). If the heterogeneity was not significant, the summary OR estimates were calculated by the fixed-effect model. Otherwise, the random-effect model was used. Pooled ORs and their 95% CIs were calculated to assess the association between XRCC3 polymorphism and cancer risks. ORs were calculated from combination of each study by heterozygote comparison (CT vs CC), homozygote comparison (TT vs CC), dominant model (CT+TT vs CC), recessive model (TT vs CT+CC) and allelic model (T vs C), respectively. For each genetic comparison model, subgroup analysis according to ethnicity was investigated to estimate ethnic-specific ORs for Asian population and Caucasian population. Meanwhile, stratified analyses by tumor type were also applied for each genetic comparison model.

Results

Characteristics of included studies

A total of 15 articles were eligible after searching. One study on cancer prognosis and two studies about cell line were excluded. Five studies were excluded because of no cancer risk and data missing. Finally 7 articles were included and used in quantitative synthesis for systematic review. Flow chart

Table 1. Characteristics of All Studies in Meta-analysis

Author, year	Country	Ethnicity type	Cancer	Genotyping Method	SNP	Control Characteristicse	No.		Case				Control				HWE(P)
							(case/control)	CC/AA	CT/AG	TT/GG	CC/AA	CT/AG	TT/GG	CC/AA	CT/AG	TT/GG	
Benhamou(2004)	France	Caucasian	OSCC	PCR	rs861539	HB	65/166	23	32	10	47	89	30	0.56			
Majumder(2005)	Kolkata,India	Asian	OSCC	PCR	rs861539	HB	128/109	0	120	8	0	97	12	-			
Majumder(2005)	Kolkata,India	Asian	OPL	PCR	rs861539	HB	72/109	0	64	8	0	97	12	-			
Matullo(2006)	European	Caucasian	UADC	TaqMan and PE/DHPLC	rs861539	PB	82/1094	29	39	14	383	544	167	0.51			
Kietthubthewa(2006)	Thailand	Asian	OSCC	PCR	rs861539	PB	106/164	83	22	1	140	23	1	0.99			
Kietthubthewa(2006)	Thailand	Asian	OPL	PCR	rs861539	PB	147/147	63	63	21	66	65	16	1			
Yen(2008)	Taiwan	Asian	OSCC	PCR	rs861539	PB	103/98	96	7	0	89	9	0	0.89			
Dos Reis(2013)	Brazil	Caucasian	OSCC	RFLP-PCR	rs861539	PB	144/144	63	72	9	52	78	14	0.14			

*HB: hospital-based, PB: population-based

of the study selection process was shown in Figure 1.

Characteristics of all studies in meta-analysis are shown in Table 1. There were four studies of Caucasian population and three studies of Asians. Seven published case-control studies including 775 patients with oral cancer and 1922 controls were selected. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was the most common technique used for analyzing the genotype frequencies of the two SNPs. The distributions of genotypes in the controls were all in Hardy-Weinberg equilibrium (HWE).

XRCC3 rs861539 SNP and overall oral cancer risks

There was no significant between-study heterogeneity. The associations between rs861539 polymorphism and overall oral cancer risk were not statistically significant (CT vs CC: OR=0.94, 95%CI=0.74-1.18, $p=0.503$ for heterogeneity, $I^2=0.0\%$; TT vs CC: OR=0.94, 95%CI=0.64-1.38, $p=0.485$ for heterogeneity, $I^2=0.0\%$;

dominant model TT+CT vs CC: OR=0.95, 95%CI=0.76-1.18, $p=0.375$ for heterogeneity, $I^2=6.4\%$; recessive model TT vs CT+CC: OR=0.94, 95%CI=0.69-1.29, $p=0.674$ for heterogeneity, $I^2=0.0\%$; allele T vs C: OR=0.97, 95%CI=0.84-1.11, $p=0.549$ for heterogeneity, $I^2=0.0\%$). Meta-analysis results of the association under the heterozygote comparison model (CT versus CC), the homozygote comparison model (TT versus CC), the dominant model (CT+TT versus CC), the recessive model (TT versus CT+CC), and the allelic model (T versus C) were also shown in Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6, respectively.

Sensitivity analyses suggested that the present results were stable. Every one single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. This procedure did not change the pooled ORs supporting the robustness of our findings.

No publication bias was detected by either the inverted funnel plot or Begg's test. The shapes of the funnel plot

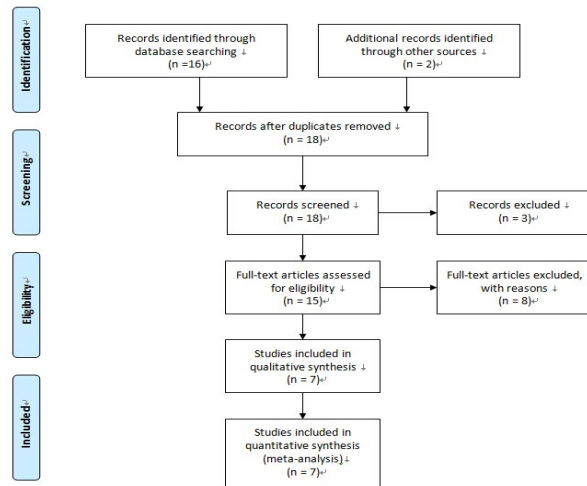


Figure 1. Flow Chart of the Study Selection Process

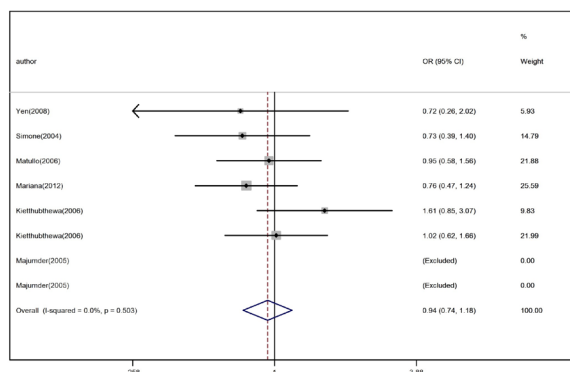


Figure 2. Meta-analysis of the Association between XRCC3 Polymorphism and Oral Cancer Risk Under the Heterozygote Comparison Model (CT versus CC)

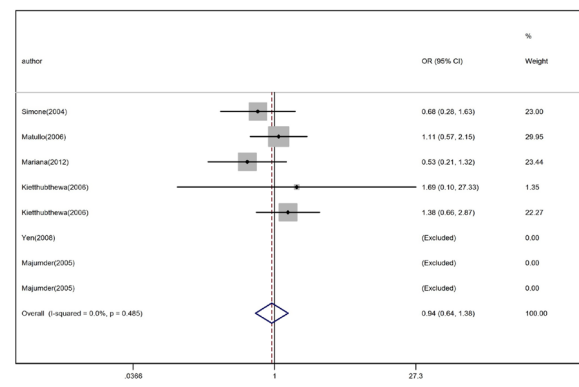


Figure 3. Meta-analysis of the Association between XRCC3 Polymorphism and oral Cancer Risk Under the Homozygote Comparison Model (TT versus CC)

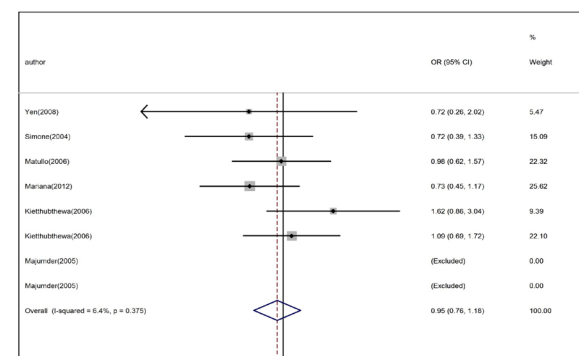


Figure 4. Meta-analysis of the Association between XRCC3 Polymorphism and Oral Cancer Risk Under the Dominant Model (CT+TT versus CC)

Table 2. Association between XRCC3 Polymorphism and Oral Cancer Risks

	Data set number	Fixed effect	Random effect	Phet	I-squared (%)
rs861539					
CT vs CC	6	0.94[0.74,1.18]	0.94[0.74,1.18]	0.503	0
TT vs CC	5	0.94[0.64,1.38]	0.95[0.64,1.39]	0.485	0
TT+CT vs CC	6	0.95[0.76,1.18]	0.95[0.75,1.20]	0.375	6.4
TT vs CT+CC	7	0.94[0.69,1.29]	0.94[0.69,1.29]	0.674	0
T vs C	7	0.97[0.84,1.11]	0.97[0.84,1.11]	0.549	0

*Phet: P value for heterogeneity test

for the comparison of rs861539 polymorphism seemed approximately symmetrical and P value of the Egger' test was not statistical significant.

Stratified analyses by ethnicity and tumor type

Stratified analyses were conducted for rs861539 polymorphism by ethnicity and tumor type. In the stratified analysis by ethnicity, no significant associations were found among Asians and Caucasians. (For Asian: CT vs CC: OR=1.13, 95%CI=0.78-1.62, p=0.352 for heterogeneity, I²=4.3%; TT vs CC: OR=1.39, 95%CI=0.68-2.84, p=0.889 for heterogeneity, I²=0.0%; dominant model TT+CT vs CC: OR=1.17, 95%CI=0.82-1.66, p=0.377 for heterogeneity, I²=0.0%; recessive model TT vs CT+CC: OR=1.00, 95%CI=0.63-1.59, p=0.466 for heterogeneity, I²=0.0%; allele T vs C: OR=1.05, 95%CI=0.86-1.28, p=0.559 for heterogeneity, I²=0.0% For Caucasian: CT vs CC: OR=0.82, 95%CI=0.64-1.11, p=0.771 for heterogeneity, I²=0.0%; TT vs CC: OR=0.80, 95%CI=0.51-1.67, p=0.401 for heterogeneity, I²=0.0%; dominant model TT+CT vs CC: OR=0.82, 95%CI=0.61-1.09, p=0.606 for heterogeneity, I²=0.0%; recessive model

TT vs CT+CC: OR=0.90, 95%CI=0.59-1.37, p=0.504 for heterogeneity, I²=0.0%; allele T vs C: OR=0.88, 95%CI=0.76-1.08, p=0.473 for heterogeneity, I²=0.0%) In the stratified analysis by tumor type, no significant associations were found to cancer and oral premalignant lesions (OPL). Table 3 showed the meta-analysis results of the association between XRCC3 rs861539 polymorphism and oral cancer susceptibility stratified by ethnicity and cancer type under the allele model (T versus C).

Discussion

The individual susceptibility plays important role in the development of cancers. Polymorphisms of genes involved in carcinogenesis may account for the susceptibility. Therefore, genetic susceptibility to cancer, especially single nucleotide polymorphism (SNP), has become a research focus in scientific field. Understanding the genetic background and etiology of oral cancer would be important in both the risk assessment and the findings of effective methods for cancer prevention and treatment. Although a large number of studies have been undertaken

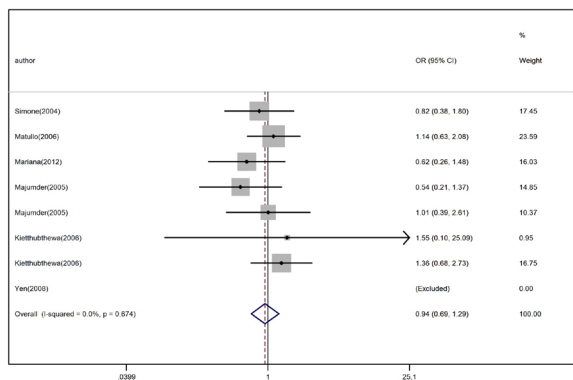


Figure 5. Meta-analysis of the Association between XRCC3 Polymorphism and Oral Cancer Risk Under the Recessive Model (TT versus CT+CC)

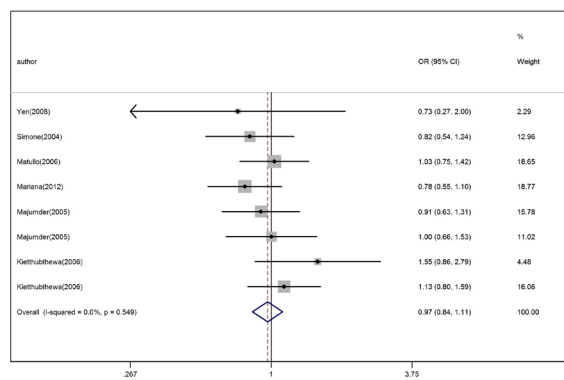


Figure 6. Meta-analysis of the Association between XRCC3 Polymorphism and Oral Cancer Risk Under the Allelic Model (T versus C)

Table 3. Pooled ORs and 95% CIs of Stratified Meta-analysis

Subgroup	Genotype	No of Studies	Test of Association			Test of Heterogeneity			
			OR(95%CI)	Z	P-value	Model	X ²	P-value	I ² (%)
Asian	CT vs CC	3	1.13[0.78,1.62]	0.63	0.526	F	2.09	0.352	4.3
	TT vs CC	2	1.39[0.68,2.84]	0.91	0.362	F	0.02	0.889	0
	TT+CT vs CC	3	1.17[0.82,1.66]	0.87	0.386	F	1.95	0.377	0
	TT vs CT+CC	4	1.00[0.63,1.59]	0.01	0.992	F	2.55	0.466	0
	T vs C	5	1.05[0.86,1.28]	0.48	0.629	F	2.99	0.559	0
Caucasian	CT vs CC	3	0.82[0.64,1.11]	1.27	0.204	F	0.52	0.771	0
	TT vs CC	3	0.80[0.51,1.67]	0.94	0.346	F	1.83	0.401	0
	TT+CT vs CC	3	0.82[0.61,1.09]	1.36	0.173	F	1	0.606	0
	TT vs CT+CC	3	0.90[0.59,1.37]	0.5	0.617	F	1.37	0.504	0
	T vs C	3	0.88[0.76,1.08]	1.19	0.234	F	1.5	0.473	0
cancer	CT vs CC	5	0.91[0.70,1.19]	0.64	0.522	F	4.19	0.381	4.5
	TT vs CC	4	0.82[0.52,1.28]	0.87	0.382	F	2.09	0.554	0
	TT+CT vs CC	5	0.91[0.70,1.17]	0.75	0.452	F	4.89	0.299	0
	TT vs CT+CC	5	0.83[0.57,1.22]	0.94	0.349	F	2.55	0.636	18.2
	T vs C	6	0.92[0.78,1.09]	0.91	0.36	F	4.85	0.435	0/0
OPL	CT vs CC	-	-	-	-	-	-	-	-
	TT vs CC	-	-	-	-	-	-	-	-
	TT+CT vs CC	-	-	-	-	-	-	-	-
	TT vs CT+CC	2	1.23[0.70,2.15]	0.72	0.468	F	0.25	0.616	0
	T vs C	2	1.08[0.83,1.40]	0.55	0.584	F	0.18	0.669	0

to identify strategies to prevent oral cancer, few studies have been performed to assess the clinical significance of SNPs in DNA repair genes and their possible roles as tools for identifying high risk subgroups.

Studies of allelic variants in repair genes are of great importance because they are responsible for correcting damaged nucleotides generated by exposure to carcinogens, which is necessary to maintain cellular functions and homeostasis (Dos Reis et al., 2013).

In this study, we analyzed the allelic variants of genes involved in DNA damage repair (XRCC3) because many studies have indicated that some allelic variants in this kind of genes are associated with cancers related to exposure to environmental carcinogens (Sturgis et al., 1999). We did not find statistically significant association between the SNP in XRCC3 gene and cancer susceptibility. XRCC3 gene participates in the repair of DNA double-strand breaks, which is the most common lesion in the genome and can occur as a result of multiple damaging agents, such as ionizing radiation or chemical exposure (Ataian et al., 2006). The accurate functioning of DNA repair proteins is a crucial step in maintaining genomic homeostasis and preventing carcinogenesis (Werbrouck et al., 2008), and polymorphisms in repair genes could alter an individual susceptibility to cancer.

XRCC3 gene encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage and is thought to play a major role in double-strand break repair and in maintaining genomic stability. Very possibly, defective double-strand break repair of cells can lead to carcinogenesis. This gene functionally complements Chinese hamster irs1SF, a repair-deficient mutant that exhibits hypersensitivity to a number of different DNA-damaging agents and is chromosomally unstable. A rare microsatellite polymorphism in this gene is associated with cancer in patients of varying radiosensitivity. This gene is involved in the repair of DNA double-strand breaks (DSB) through the process of homologous recombination (HR) (Liu et al., 1998), and this repair mechanism is important to prevent chromosomal fragmentation, translocations and deletions.

Rs861539 polymorphism of XRCC3 comprises a threonine to methionine substitution at amino acid 241 (Thr241Met). This change may influence their protein activity, resulting in differences of individual DNA repair capacity (DRC) that may affect the susceptibility of oral cancer. Growing number of studies have been done to examine the relationship between this SNP and the risks of oral cancer (Benhamou et al., 2004; Majumder et al., 2005; Matullo et al., 2006; Kietthubthaw et al., 2006; Yang et al., 2008; Yen et al., 2008; Dos Reis et al., 2013). However, the results are inconclusive. For the associations of XRCC3 polymorphisms with cancers, the negative findings may result from the low statistical power of available studies now. To better understanding of the association between these polymorphisms and oral cancer risk, a meta-analysis with larger sample and subgroup analysis is necessary. In the present meta-analysis, the statistical power was increased by combining the results of seven included studies.

The current study is the first meta-analysis of the association between XRCC3 rs861539 polymorphism with the susceptibility of oral cancer. Although this meta-analysis did not show the significant association between XRCC3 rs861539 polymorphism and oral cancer risks, the present results also provided new evidence for the susceptibility and etiology of oral cancer. In recent years, there are some meta-analyses about XRCC3 polymorphisms and cancer risks, which comprised breast cancer, cervical cancer, colorectal cancer, gliomas and head and neck cancer published in the journal *Asian Pac J Cancer Prev* and the results are not concordant, suggesting this polymorphism plays different role in diverse types of cancer (Yin et al., 2012; Jiang et al., 2013; Nassiri et al., 2013; Qin et al., 2013; Mao et al., 2014). It is well known that systematic review and meta-analyses are considered the highest level of evidence in Evidence-based Medicine. The quality of meta-analyses may be an important problem or pitfall in this field. So it has a certain positive significance to publish more and more high-level meta-analyses.

Despite our efforts in performing a comprehensive analysis, some limitations exist in our meta-analysis. First, our analysis used published studies, which could bring publication bias, although the results for publication bias in the present meta-analyses were not statistically significant. Second, lack of the original data of available studies limited our further evaluation of potential interactions, such as age, gender, family history, environmental factors and lifestyle. Third, there was no study in African population.

In conclusion, our meta-analysis suggested that the rs861539 polymorphism in XRCC3 gene might not associated with the risk of oral cancer. Considering the limited quality of the included case-control studies, future well-designed and larger population studies, especially in other ethnic populations are of great value to confirm these findings. Moreover, combination of genetic factors together with environmental exposures should also be considered.

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