

The effect of XRCC3 rs861539 polymorphism on the risk of head and neck squamous cell carcinoma: a systematic review and meta-analysis.

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Abstract

Background: Some studies suggested that XRCC3 rs861539 polymorphism might change the risk of Head and Neck Squamous Cell Carcinoma (HNSCC). However, other studies have reported negative results. Therefore, we did this meta-analysis to investigate the role of XRCC3 rs861539 polymorphism on HNSCC risk.

Methods and materials: Online electronic databases (PubMed, EMBASE and Wangfang database) were searched. The strength of association was assessed by calculating Odds Ratio (OR) with 95% Confidence Interval (CI).

Results: A total of 5 studies with 868 cases and 1477 controls on the association between XRCC3 rs861539 polymorphism and HNSCC risk were included in this meta-analysis. Individuals with XRCC3 rs861539 polymorphism had an increased HNSCC risk (OR=1.65; 95% CI, 1.03-2.64; P=0.04). Subgroup analysis was performed according to smoking status. Light smokers with XRCC3 rs861539 polymorphism did not have an increased HNSCC risk (OR=3.73; 95% CI, 0.87-16.07; P=0.08). However, moderate smokers (OR=3.20; 95% CI, 1.79-5.70; P<0.0001) and heavy smokers (OR=3.69; 95% CI, 1.56-8.77; P=0.003) showed increased risk of HNSCC, respectively.

Conclusions: In conclusion, this study suggested that XRCC3 rs861539 polymorphism was associated with HNSCC risk.

Keywords: Head and neck squamous cell carcinoma (HNSCC), XRCC3, Meta-analysis.

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Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is one of the most common malignancies in the developing world, accounting worldwide for more than 500,000 new cases each year [1]. Surgical and chemoradiation treatments have been met with modest success. However, understanding of genetic drivers of HNSCC has been limited.

X-ray repair cross-complementing group 3 (XRCC3) belongs to the *RAD51* gene family. XRCC3 involved in the Homologous Recombination Repair (HRR) of DNA double-strand break repair and cross-links [2].

Shen et al. identified a C to T substitution in exon 7 at position 18067 of XRCC3, which results in an amino acid substitution (threonine to methionine) at codon 241 [3]. Some studies suggested that XRCC3 rs861539 polymorphism might change the risk of HNSCC.

However, other studies have reported negative results [4-9]. Therefore, we did this meta-analysis to investigate the role of XRCC3 rs861539 polymorphism on HNSCC risk.

Materials and Methods

Search for publications

Online electronic databases (PubMed, EMBASE, and Wangfang database) were searched using the search terms: (XRCC3 or 'X-ray repair cross-complementation group 3') and (polymorphism or mutation or variation) and (head and neck squamous cell carcinoma or HNSCC). Reference lists of articles retained for review were inspected for relevant publications.

Inclusion and exclusion criteria

Two authors independently evaluated all of the studies. The study had to meet the following criteria: (1) Evaluation of XRCC3 rs861539 polymorphism on HNSCC risk; (2) Using a case-control design; (3) Genotype distributions in both cases and controls should be available for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if one of the following existed: (1) Genotype frequencies or number not offered; (2) Animal studies; (5) Editorials, reviews and abstracts. If more than one study used

the same cases, the one with the most comprehensive population were included.

Data extraction and qualitative assessment

The following data was extracted: first author, year of publication, country, ethnicity, age, gender, tumor location, and the numbers of subjects. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality.

Statistical analysis

Hardy-Weinberg Equilibrium (HWE) was tested using the chi-square test. A statistical test for heterogeneity was performed based on the Q statistic. The $P > 0.10$ of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model. Stratified analysis was performed by smoking status. Potential publication bias was examined by funnel plot and Egger's test. All statistical tests were performed with the software Revman version 5.1 and STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value < 0.05 was considered statistically significant.

Results

Characteristics of studies

A total of 5 studies with 868 cases and 1477 controls on the association between XRCC3 rs861539 polymorphism and HNSCC risk were included in this meta-analysis. All studies included Caucasian population. All the HWE results were not statistically significant. The characteristics of each study are presented in Tables 1 and 2.

Meta-analysis results

As shown in Figure 1, individuals with XRCC3 rs861539 polymorphism had an increased HNSCC risk (OR=1.65; 95% CI, 1.03-2.64; $P=0.04$). Subgroup analysis was performed according to smoking status. Light smokers with XRCC3 rs861539 polymorphism did not had an increased HNSCC risk (OR=3.73; 95% CI, 0.87-16.07; $P=0.08$) (Figure 2). However, moderate smokers (OR=3.20; 95% CI, 1.79-5.70; $P<0.0001$) and heavy smokers (OR=3.69; 95% CI, 1.56-8.77; $P=0.003$) showed increased risk of HNSCC, respectively. Funnel plot was performed to assess the publication bias of literatures. The

Table 1. Characteristics of included studies.

Author	Year	Country	Ethnicity	Tumor location	No. of cases	No. of controls	Age	Female (%)	HWE
Werbrouck	2008	Belgium	Caucasian	Mixed	152	157	59.5 ± 10.5	11.5	Yes
Sliwinski	2010	Poland	Caucasian	NA	288	353	56	22	Yes
Gugatschka	2011	Austria	Caucasian	NA	169	463	65 ± 12	11.8	Yes
Kostrzewska-Poczekaj	2013	Poland	Caucasian	Mixed	90	160	42 ± 5.2	15.6	Yes
Farnebo	2015	Sweden	Caucasian	Mixed	169	344	NA	34	Yes

shape of the funnel plot showed symmetry (Figure 3). Egger's test found no evidence of publication bias ($P=0.8$) (Table 3).

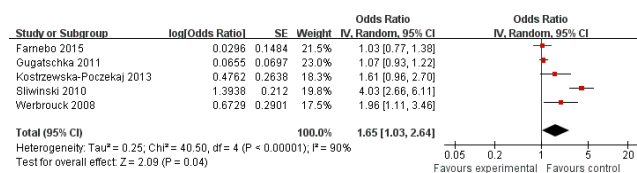


Figure 1. The association between XRCC3 rs861539 polymorphism and HNSCC risk.

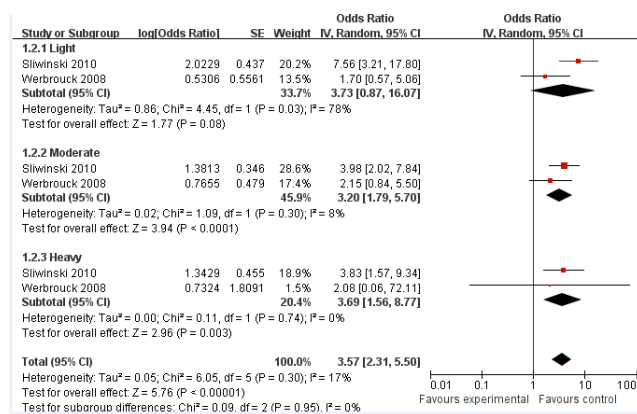


Figure 2. Subgroup analysis of XRCC3 rs861539 polymorphism and HNSCC risk by smoking status.

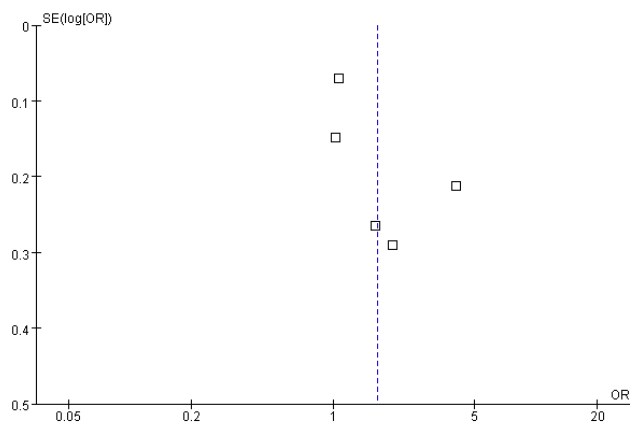


Figure 3. Funnel plot between XRCC3 rs861539 polymorphism and HNSCC risk.

Table 2. Quality scores of studies using Newcastle-Ottawa Scale.

Study	Selection	Comparability	Outcome	Overall quality
Werbrouck	3	2	2	7
Sliwinski	3	3	2	8
Gugatschka	3	1	2	7
Kostrzewska-Poczekaj	3	3	2	8
Farnebo	3	2	3	8

Table 3. Results of the meta-analysis.

	OR (95% CI)	P	I ²
Overall	1.65 (1.03-2.64)	0.04	90
Smoking status			
Light smokers	3.73 (0.87-16.07)	0.08	78
Moderate smokers	3.20 (1.79-5.70)	<0.0001	8
Heavy smokers	3.69 (1.56-8.77)	0.003	0

Discussion

To our knowledge, this was the first meta-analysis to investigate the role of XRCC3 rs861539 polymorphism on HNSCC risk. This meta-analysis included 5 studies with 868 cases and 1477 controls. We found that individuals with XRCC3 rs861539 polymorphism had an increased HNSCC risk. Subgroup analysis was performed according to smoking status. Light smokers with XRCC3 rs861539 polymorphism did not have an increased HNSCC risk. However, moderate smokers and heavy smokers showed increased risk of HNSCC, respectively.

Carriers of the variant allele of XRCC3 rs861539 polymorphism had different DNA adduct levels in lymphocyte DNA, and the Met variant was significantly associated with higher DNA adduct levels, indicating that this polymorphism was associated with the DNA repair capacity [9]. This polymorphism has been studied in many other diseases. Lu et al. concluded that the XRCC3 Thr241Met polymorphism is associated with an increased risk of thyroid cancer in the overall population [10]. Chai et al. suggested that XRCC3 Thr241Met polymorphism might be associated with breast cancer risk, especially in Asian populations [11]. Cheng et al. suggested that XRCC3 gene rs861539 polymorphism was associated with the risk for gastric cancer in Asian populations [12]. Bei et al. did not find a significant correlation between XRCC3 Thr241Met polymorphism and lung cancer risk [13]. Feng et al. also suggested that XRCC3 T241M polymorphism did not confer glioma risk [14].

Some limitations of this meta-analysis should be acknowledged. First, the number of published studies was not sufficiently large for a comprehensive analysis. Second, the sample size was relatively small. Third, there was clinical and statistical heterogeneity among included studies

In conclusion, this meta-analysis suggested that XRCC3 rs861539 polymorphism was significantly associated with HNSCC risk.

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