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 Wang fang 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 show 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.

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.
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 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.](image1)

![Figure 2. Subgroup analysis of XRCC3 rs861539 polymorphism and HNSCC risk by smoking status.](image2)

![Figure 3. Funnel plot between XRCC3 rs861539 polymorphism and HNSCC risk.](image3)

**Table 1. Characteristics of included studies.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Tumor location</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Age</th>
<th>Female (%)</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werbroeck</td>
<td>2008</td>
<td>Belgium</td>
<td>Caucasian</td>
<td>Mixed</td>
<td>152</td>
<td>157</td>
<td>59.5±10.5</td>
<td>11.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Siwiński</td>
<td>2010</td>
<td>Poland</td>
<td>Caucasian</td>
<td>NA</td>
<td>288</td>
<td>353</td>
<td>56</td>
<td>22</td>
<td>Yes</td>
</tr>
<tr>
<td>Gugatschka</td>
<td>2011</td>
<td>Austria</td>
<td>Caucasian</td>
<td>NA</td>
<td>169</td>
<td>463</td>
<td>65±12</td>
<td>11.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Kostrzewska-Poczekaj</td>
<td>2013</td>
<td>Poland</td>
<td>Caucasian</td>
<td>Mixed</td>
<td>90</td>
<td>160</td>
<td>42±5.2</td>
<td>15.6</td>
<td>Yes</td>
</tr>
<tr>
<td>Farnebo</td>
<td>2015</td>
<td>Sweden</td>
<td>Caucasian</td>
<td>Mixed</td>
<td>169</td>
<td>344</td>
<td>NA</td>
<td>34</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 2. Quality scores of studies using Newcastle-Ottawa Scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werbrouck</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Sliwinski</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Gugatschka</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Kostrzewska-Poczekaj</td>
<td>3</td>
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<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Farnebo</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3. Results of the meta-analysis.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.65 (1.03-2.64)</td>
<td>0.04</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light smokers</td>
<td>3.73 (0.87-16.07)</td>
<td>0.08</td>
</tr>
<tr>
<td>Moderate smokers</td>
<td>3.20 (1.79-5.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heavy smokers</td>
<td>3.69 (1.56-8.77)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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.

References


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