RESEARCH ARTICLE

Association Between the XRCC3 T241M Polymorphism and Head and Neck Cancer Susceptibility: a Meta-analysis of Case-control Studies

Qing-Hua Yin1,2& , Chuan Liu3&, Lian Li1, Xu-Yu Zu4, Ya-Jie Wang5*

Abstract

Background: To evaluate the role of the X-ray repair cross complementing group 3 (XRCC3) T241M polymorphism in head and neck cancer susceptibility. Materials and Methods: We performed a meta-analysis of all available studies, which included 3,191 cases and 5,090 controls. Results: Overall, a significant risk effect of the T241M polymorphism was not found under homologous contrast (MM vs TT: OR=1.293, 95% CI=0.926-1.805; TM vs TT: OR=1.148, 95% CI=0.930-1.418) and recessive models (MM vs TT+TM): OR=1.170, 95% CI=0.905-1.512, but a significantly increased risk was observed under a dominant model (MM+TM vs TT): OR=1.243, 95% CI=1.001-1.544. In stratified analyses, there were no significant associations for Asians or Caucasians. Conclusion: Our meta-analysis suggested the XRCC3 241M allele (MM+TM) might act as a head and neck cancer risk factor among all subjects, and the effect of T241M polymorphism on head and neck susceptibility should be studied with a larger, stratified population.

Keywords: Meta-analysis - head and neck cancer - XRCC3

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Introduction

Head and neck cancers (HNC) including oral, oropharynx, hypopharynx, pharyngeal and larynx are among the most common types of cancer and represent a major health problem, there are approximately 540,000 new cases and 271,000 deaths annually worldwide for a mortality of approximately 50% (Szymańska et al., 2010). Development of HNC is a multi-factorial process associated with a variety of risk factors. The principal risk factors for this disease include tobacco and alcohol use, exposure to the human papillomavirus (HPV) contributes to the development of at least 90% of squamous cell carcinoma of the head and neck (SCCHN) cases (Parkin et al., 2005) in a growing younger population. It has been reported that HNC is much more common in smokers than in non-smokers and most common in males over 50 years of age (Kamangar et al., 2006). Unrepaired or misrepaired DNA results in gene mutations, chromosomal alterations and genomic instability. X-ray repair cross-complementing group 3 (XRCC3) belongs to the RAD51 gene family and encodes a protein that functions in the homologous recombination repair of DNA double strand break and participates in DNA double-strand break/recombination repair and likely participates in homologous recombination repair (HRR) (Tebbs et al., 1995; Brenneman et al., 2000). XRCC3 gene has been found polymorphic in the head and neck cancer; The Thr241Met substitution is the most thoroughly investigated polymorphism in XRCC3 due to a (C>T) transition at exon7 (XRCC3-18067C>T, rs861539), in this study, we called this SNP in the XRCC3 gene “T241M” for short. Another two polymorphisms investigated by a few studies is XRCC3-4541A>G (5’-UTR, rs1799794) and XRCC3 c.562-14 A>G (IVS5-14, rs1799796) (Werbrouck et al., 2008).

In the past decades, molecular epidemiological studies had investigated the relationship between the XRCC3 T241M polymorphism and predisposition to head and
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Materials and Methods

Study identification and selection
We searched for studies in the PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) electronic databases by using the terms “head and neck cancer”, “oral cancer”, “oropharyngeal cancer”, “hypopharynx cancer” “laryngeal cancer”, “pharyngeal cancer”, “XRCC3”, “excision repair cross-complementing group 3” and “polymorphism”. The search was performed without any restrictions on language and was focused on studies that had been conducted in humans.

Inclusion criteria were defined as follows: (1) The articles evaluated the association between XRCC3 T241M polymorphisms and the risk of head and neck cancer; (2) The studies designed as case-control; (3) The sufficient data available to estimate an odds ratio (OR) with its 95% CI.

Data extraction
Information was carefully extracted from all eligible publications independently by two investigators according to the inclusion criteria listed above, discrepancies were adjudicated by a third reviewer until consensus was achieved on every item. The following information was extracted from each included publication: the first author’s name, country or region, year of publication, source of publication, total numbers of cases and controls, and numbers of cases and controls who harbored the XRCC3 T241M polymorphism.

Statistical analysis
We assessed the strength of association between XRCC3 T241M polymorphism and head and neck cancer risk by using ORs with 95% CIs which were obtained from the data given in the eligible studies. Although fixed-effect model and random-effects model yielded similar conclusions, we chose to use the random-effects model with Mantel-Haenszel statistics (DerSimonian et al., 1986; Ades et al., 2005), which assumed that the true underlying effect varied among included individuals. Moreover, many investigators also consider that the random effects model to be a more natural choice than fixed effects model in medical decision-making contexts. First, the pooled ORs were performed for codominant model (MM vs TT, TM vs TT), dominant model (MM+TM vs TT), and recessive model (MM vs TT+TM) respectively. Subgroup analyses were done by ethnicity and source of controls. Heterogeneity assumptions among studies was checked by the Chi square-based Q-statistic. A significant Q-statistic (P < 0.05) indicated heterogeneity across studies (Cochran WG., 1954). Meanwhile, we measured the effect of heterogeneity by another measure, F = 100%×(Q – df)/Q (Higgins et al., 2002). Publication bias was observed with the funnel plot and Egger’s linear regression test (Egger et al., 1997).

Results

Characteristics of studies
Through searching and selection, a final list of 15 eligible studies were collected for meta-analysis (Shen et al., 2002; Benhamou et al., 2004; Huang et al., 2005; Majumder et al., 2005; Rydzanicz et al., 2005; Kietthubthew et al., 2006; Matullo et al., 2006; Wen et al., 2007; Werbrouck et al., 2008; Yen et al., 2008; Kietthubthew et al., 2010; Sliwinski et al., 2010; Gugatschka et al., 2011; Al-Hadyan et al., 2012; Kostrzewska-Poczekaj et al., 2012). In total, the 15 eligible studies provided 3,191 cases and 5,090 controls about the relationship between XRCC3 T241M polymorphism and head and neck cancer risk. The characteristics of selected studies are summarized in Table 1. Almost all of the cases were histologically confirmed. The controls were primarily healthy populations. There were 6 groups of Asians, 9 groups of Caucasians; 10 groups of hospital based; PB, population based; HWE Hardy–Weinberg equilibrium (>0.05 was considered representative of agreement with HWE in the controls)

Table 1. Main Characteristics of All Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Area</th>
<th>Study Design</th>
<th>No. of Cases</th>
<th>No. of Control</th>
<th>HWE TT</th>
<th>HWE TM</th>
<th>HWE MM</th>
<th>Case (genotype)</th>
<th>Control (genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kostrzewska-Poczekaj M</td>
<td>2012</td>
<td>Caucasian</td>
<td>Poland</td>
<td>HB</td>
<td>293</td>
<td>160</td>
<td>0.037</td>
<td>35</td>
<td>138</td>
<td>120</td>
<td>22</td>
</tr>
<tr>
<td>Khaled S</td>
<td>2012</td>
<td>Asian</td>
<td>Saudi Arabia</td>
<td>HB</td>
<td>156</td>
<td>251</td>
<td>0.083</td>
<td>51</td>
<td>86</td>
<td>19</td>
<td>101</td>
</tr>
<tr>
<td>Gugatschka M</td>
<td>2011</td>
<td>Caucasian</td>
<td>Austria</td>
<td>HB</td>
<td>168</td>
<td>461</td>
<td>0.227</td>
<td>61</td>
<td>76</td>
<td>31</td>
<td>186</td>
</tr>
<tr>
<td>Sliwinski T</td>
<td>2010</td>
<td>Caucasian</td>
<td>Poland</td>
<td>PB</td>
<td>191</td>
<td>353</td>
<td>0.9</td>
<td>29</td>
<td>97</td>
<td>65</td>
<td>131</td>
</tr>
<tr>
<td>Kietthubthew S</td>
<td>2010</td>
<td>Asian</td>
<td>Thailand</td>
<td>HB</td>
<td>60</td>
<td>56</td>
<td>-</td>
<td>49</td>
<td>11</td>
<td>49</td>
<td>71</td>
</tr>
<tr>
<td>Werbrouck J</td>
<td>2008</td>
<td>Caucasian</td>
<td>Belgium</td>
<td>PB</td>
<td>152</td>
<td>157</td>
<td>0.014</td>
<td>44</td>
<td>75</td>
<td>33</td>
<td>69</td>
</tr>
<tr>
<td>Yen CY</td>
<td>2008</td>
<td>Asian</td>
<td>China</td>
<td>HB</td>
<td>103</td>
<td>98</td>
<td>0.634</td>
<td>96</td>
<td>7</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>Wen SX</td>
<td>2007</td>
<td>Asian</td>
<td>China</td>
<td>HB</td>
<td>175</td>
<td>525</td>
<td>-</td>
<td>144</td>
<td>31</td>
<td>482</td>
<td>43</td>
</tr>
<tr>
<td>Kietthubthew S</td>
<td>2006</td>
<td>Asian</td>
<td>Thailand</td>
<td>HB</td>
<td>106</td>
<td>164</td>
<td>0.958</td>
<td>83</td>
<td>22</td>
<td>1</td>
<td>140</td>
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<td>Matullo G</td>
<td>2006</td>
<td>Caucasian</td>
<td>European</td>
<td>PB</td>
<td>82</td>
<td>1094</td>
<td>0.249</td>
<td>29</td>
<td>39</td>
<td>14</td>
<td>383</td>
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<tr>
<td>Majumder M</td>
<td>2005</td>
<td>Asian</td>
<td>India</td>
<td>HB</td>
<td>310</td>
<td>348</td>
<td>0.071</td>
<td>201</td>
<td>97</td>
<td>12</td>
<td>220</td>
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<tr>
<td>Rydzanicz M</td>
<td>2005</td>
<td>Caucasian</td>
<td>Poland</td>
<td>PB</td>
<td>266</td>
<td>143</td>
<td>0.247</td>
<td>31</td>
<td>112</td>
<td>123</td>
<td>14</td>
</tr>
<tr>
<td>Huang WY</td>
<td>2005</td>
<td>Caucasian</td>
<td>Maryland</td>
<td>PB</td>
<td>516</td>
<td>760</td>
<td>0.397</td>
<td>232</td>
<td>223</td>
<td>61</td>
<td>329</td>
</tr>
<tr>
<td>Benhamou S</td>
<td>2004</td>
<td>Caucasian</td>
<td>France</td>
<td>PB</td>
<td>246</td>
<td>166</td>
<td>0.281</td>
<td>86</td>
<td>116</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Shen H</td>
<td>2002</td>
<td>Caucasian</td>
<td>USA</td>
<td>HB</td>
<td>367</td>
<td>354</td>
<td>0.45</td>
<td>150</td>
<td>159</td>
<td>58</td>
<td>141</td>
</tr>
</tbody>
</table>
Table 2. Results of Meta-analysis for XRCC3 Thr241Met Polymorphism and Head and Neck Cancer

<table>
<thead>
<tr>
<th>Study group</th>
<th>Homozygous MM vs TT</th>
<th>Heterozygous TM vs TT</th>
<th>Dominant model (MM+TM vs TT)</th>
<th>Recessive model (MM vs TT+TM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>1.293(0.926-1.805)</td>
<td>0</td>
<td>1.148(0.930-1.418)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1.074(0.643-1.793)</td>
<td>0.491</td>
<td>1.179(0.795-1.749)</td>
<td>0.09</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.319(0.893-1.949)</td>
<td>0</td>
<td>1.139(0.874-1.485)</td>
<td>0.001</td>
</tr>
<tr>
<td>Source of controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>1.098(0.868-1.389)</td>
<td>0.715</td>
<td>1.057(0.851-1.312)</td>
<td>0.093</td>
</tr>
<tr>
<td>PB</td>
<td>1.567(0.768-3.200)</td>
<td>0</td>
<td>1.283(0.811-2.029)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

P value of Q test for heterogeneity

hospital-based and 5 groups of population-based. The polymorphisms in the control subjects were calculated in Hardy–Weinberg equilibrium.

Quantitative synthesis

Table 2 listed the main results of the meta-analysis for XRCC3 T241M polymorphisms. Overall, no significant associations were found between XRCC3 T241M polymorphism and head and neck cancer risk when all studies were pooled into the meta-analysis under homologous contrast (MM vs TT: OR=1.293, 95% CI=0.926-1.805, P=0.000 for heterogeneity; TM vs TT: OR=1.148 95% CI=0.930-1.418, P=0.001 for heterogeneity) (Figure 1, 2) and recessive model (OR=1.170, 95% CI=0.905-1.512, P=0.001 for heterogeneity) (Figure 4). However, as shown in Figure 3, significant associations were found for the dominant model (OR=1.243, 95% CI=1.001-1.544 P=0.000 for heterogeneity). In stratified analyses, as showed in Table 2, there was not significant association for Aians nor Caucasians, similarly, there was also not significant association for hospital-based nor population-based subjects.

Heterogeneity and sensitivity analysis

There was substantial heterogeneity among these studies in overall comparisons. Therefore, we assessed the source of heterogeneity by source of controls and ethnicity. It was detected that the systemic results were not affected by these characteristics. The corresponding pooled ORs were not qualitatively altered with or without this study. Publication bias test

We performed funnel plot and Egger’s test to assess the publication bias of literatures. The shape of the funnel
plots did not reveal any evidence of obvious asymmetry in each group (Figure 5). The results of Egger’s test did not suggest any evidence of publication bias.

**Discussion**

To clarify the controversial results from previous reports in the present studies, we identified all available studies and performed a meta-analysis to examine the association between XRCC3 T241M polymorphism and head and neck cancer risk. A total of 15 studies on the T241M genotype (8,281 subjects) were critically reviewed. Nevertheless, our analysis suggested that XRCC3 might play a small role in cancer susceptibility on homologous contrast (MM vs TT: OR=1.293, 95% CI = 0.926-1.805; TM vs TT: OR=1.148 95% CI=0.930-1.418) and the XRCC3 241T allele (OR=1.170, 95% CI=0.905-1.512), which was consistent with the characteristics of low penetrance genes. However, the XRCC3 241M allele might act as a head and neck cancer risk factor among all subjects (OR=1.243, 95% CI=1.001-1.544). In the subgroup analysis, insignificant effects were found for any genetic contrast.

Assessment of effect modification might be particularly beneficial in studies of DNA-repair polymorphisms, because a single polymorphism with likely weak effects on the individual’s phenotype might not be measurable except in the context of some supporting environmental factors, such as tobacco smoke or ionizing radiation. The double-strand break DNA repair pathway had been implicated in maintaining genomic stability and affecting cancer risk. Both biological and biochemical evidences indicated a direct role for XRCC3 in DSBs repair (Bishop et al., 1998; Pierce et al., 1999). Functional data also suggested that the XRCC3 Thr241Met polymorphism might be associated with slightly but not significantly decreased DNA repair capacity (Araujo et al., 2002). HRR was a major mechanism for double-strand break DNA repair. XRCC3 had a multiple function and acted both early and late in the HRR pathway (Tebbs et al., 1995).

The XRCC3 T241M variant has been shown to be functionally defective in suppressing duplication of the genome, which is thought to be important for maintaining genomic stability. Therefore, it seems much reasonable to take polymorphisms in XRCC3 as the low-penetrance variant candidate for cancer susceptibility.

There were still some limitations inherited from the published studies. First, there was the lack of of investigation about the detailed molecular mechanism of the association between XRCC3 T241M polymorphism and head and neck cancer risk. Second, the number of studies involved in the meta-analysis was relatively small, so the subgroup analysis was hard to perform. Third, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other co-variates including age, smoking status, environmental factors, and lifestyle. Therefore, in order to achieve a more convincible conclusion, further analysis using adjusted individual data and larger sample size was required, and further mechanism investigation should also be performed.

In conclusion, supported by a meta-analysis with a total of 3,191 cases and 5,090 controls, our study indicated that the XRCC3 241M allele might act as a head and neck cancer risk factor among all subjects. Although there were some limitations, our meta-analysis can still provided valuable information for studying the relationship between XRCC3 T241M polymorphism and head and neck cancer risk.

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**References**


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Figure 5. Begg’s Funnel Plot of XRCC3 T241M Polymorphism and Head and Neck Cancer Risk


