Association of OPN rs11730582 polymorphism with cancer risk: a meta-analysis

Lanlan He1,*
Yong Wang2,∗

1Emergency Department, Zhenjiang First People’s Hospital, Zhenjiang, People’s Republic of China; 2Department of Interventional Radiology and Vascular Surgery, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, People’s Republic of China

*Both authors contributed equally to this work

Purpose: Several molecular epidemiological studies have investigated the association between OPN rs11730582 C>T polymorphism and cancer risk, but the results are inconsistent. Hence, a meta-analysis was conducted to determine the association of this polymorphism with cancer risk.

Materials and methods: The related articles were searched in PubMed, Embase, and Chinese National Knowledge Infrastructure databases. Pooled odds ratios and 95% confidence intervals were calculated to evaluate the strength of the associations. A random-effects model or fixed-effects model was employed depending on the heterogeneity.

Results: A total of ten case-control studies involving 2,749 cancer cases and 3,398 controls were included in the meta-analysis. In overall analysis, OPN rs11730582 C>T polymorphism was not associated with cancer risk. In a stratified analysis by cancer type, no significant association was found between OPN rs11730582 C>T polymorphism and the risk of glioma, gastric cancer, and other cancers.

Conclusion: This meta-analysis suggests that OPN rs11730582 C>T polymorphism is not associated with cancer susceptibility.

Keywords: osteopontin, polymorphism, cancer, risk

Introduction

Cancer has become one of the leading causes of mortality worldwide. Results from GLOBOCAN showed that there were approximately 8.2 million cancer-related deaths in 2012.1 According to cancer incidence trend, the number of new cancer cases worldwide is expected to reach 22.2 million in 2030.2 However, the exact mechanism of carcinogenesis remains largely unknown. With the developing of epidemiology, it is becoming clear that genetic variation plays an important role in the development of cancer.3

OPN is a secreted, integrin-binding phosphoprotein with chemotactic and cell-adhesive properties both in vitro and in vivo.4 OPN mainly contributes to host defense, wound healing, and bone formation, by stimulating macrophage migration as well as protecting against viral and bacterial infections through its pro-Th1 effect.5–7 Furthermore, OPN plays critical roles in various aspects of malignancy, such as invasion and metastasis.8–9 The human OPN gene has been mapped to chromosome 4q24-q25, and several potential functional polymorphisms in the OPN gene have been identified and noticeably affect its expression.10 For example, the variant -443 C>T (rs11730582) in the promoter region of OPN gene was found to be located in the transcriptional factor binding site regions, which regulates the transcription of the OPN gene.10,11 Recently, the associations between OPN rs11730582 polymorphism and cancer risk have been extensively studied. However, previous literature about the
associations between the OPN rs11730582 polymorphism and risk of cancer has provided inconsistent results.\textsuperscript{12–21}
For instance, significant associations have been found in nasopharyngeal carcinoma,\textsuperscript{13} papillary thyroid cancer,\textsuperscript{15} and gastric cancer.\textsuperscript{16} However, similar results were not found in intrahepatic cholangiocarcinoma,\textsuperscript{10} lung cancer,\textsuperscript{17} and gastric cancer.\textsuperscript{18} The objective of this meta-analysis is to broadly evaluate the available evidence of the OPN rs11730582 polymorphism and risk of cancer, to derive a more reliable assessment.

Materials and methods

Search strategy

Eligible publications were retrieved by searching PubMed, Embase, and Chinese National Knowledge Infrastructure (CNKI) databases up to August 1, 2015. The search strategy was based on combinations of “osteonopin”, “OPN”, or “SPP1”; “polymorphism”, “variant”, or “SNP”; “cancer”, “carcinoma”, “tumor”, or “malignance”. Furthermore, we also searched the additional publications from the reference lists of the retrieved articles or reviews which had been previously missed.

Inclusion criteria

All studies selected had to fulfill the following four criteria: 1) case-control study of the OPN rs11730582 C>T polymorphism and cancer risk; 2) the genotype distribution in cases and controls described in detail; 3) genotype distributions of controls consistent with Hardy–Weinberg equilibrium (HWE); 4) when multiple publications reported on the same or overlapping data, only the largest or most recent publication was included.

Data extraction

Data extraction was carried out independently by two reviewers. The following information was extracted from each included publication: the first author’s name, year of publication, ethnicity, cancer type, genotyping method, sample size, and numbers of different genotype in all subjects. Discrepancies were adjudicated by discussion.

Statistical analysis

HWE among controls for each study was assessed using Pearson chi-square test and $P_{HWE} \geq 0.05$ was deemed to conform to HWE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations. Five models were conducted: dominant model (CC+CT vs TT), recessive model (CC vs CT+TT), heterozygote comparison (TC vs TT), homoyzgote comparison (CC vs TT) and allele model (C vs T). Summary ORs and corresponding 95% CIs were estimated by the fixed-effects model or the random-effects model which was employed depending on the heterogeneity. The heterogeneity among studies was evaluated by a chi-square-based Q test and $I^2$ statistic. When heterogeneity was absent ($P_{h} > 0.05$ and $I^2 < 50\%$), a fixed-effects model was applied; otherwise, a random-effects model was employed. Sensitivity analysis was conducted to assess the stability of the combined results by the omission of every single study each time. Finally, the Begg’s funnel plot and Egger’s test were used to estimate the possible publication bias. $P_{E} < 0.05$ indicated the presence of potential publication bias. All the analyses were performed using STATA (version 12.0) software (StataCorp LP, College Station, TX, USA).

Results

Characteristics of studies

As shown in Figure 1, a total of 31 records were identified from PubMed, Embase, and CNKI. After reviewing the titles and abstracts of articles, 15 articles were excluded, mainly due to no relevance, being reviews, or functional studies. Sixteen full-text articles that met the crude inclusion criteria were further evaluated for eligibility. Finally, ten eligible studies were included in the meta-analysis. The main characteristics of eligible studies are summarized in Table 1. All selected studies containing 2,749 cases and 3,398 controls were carried out in Asian countries. The studied cancer types included intrahepatic cholangiocarcinoma, nasopharyngeal carcinoma, glioma, papillary thyroid cancer, gastric cancer, lung cancer, cervical cancer, and oral carcinogenesis. In addition, genotype distributions in the controls of all selected studies are in agreement with HWE.

Figure 1 Flow chart of study selection in the meta-analysis.
Table 2 Meta-analysis of the association of OPN rs11730582 polymorphism with cancer risk

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Test of heterogeneity</th>
<th>Test of association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P&lt;sub&gt;h&lt;/sub&gt;, %</td>
<td>P&lt;sub&gt;n&lt;/sub&gt;, %</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs TT</td>
<td>91.0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CT vs TT</td>
<td>91.0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CC+CT vs TT</td>
<td>93.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CC vs CT+TT</td>
<td>85.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C vs T</td>
<td>94.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs TT</td>
<td>91.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CT vs TT</td>
<td>64.6%</td>
<td>0.09</td>
</tr>
<tr>
<td>CC+CT vs TT</td>
<td>86.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>CC vs CT+TT</td>
<td>89.5%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C vs T</td>
<td>92.9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs TT</td>
<td>85.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>CT vs TT</td>
<td>3.1%</td>
<td>0.31</td>
</tr>
<tr>
<td>CC+CT vs TT</td>
<td>65.8%</td>
<td>0.09</td>
</tr>
<tr>
<td>CC vs CT+TT</td>
<td>82.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>C vs T</td>
<td>82.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>Other cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs TT</td>
<td>93.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CT vs TT</td>
<td>94.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CC+CT vs TT</td>
<td>95.7%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CC vs CT+TT</td>
<td>89.0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C vs T</td>
<td>96.3%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: P<sub>h</sub>, P-value of heterogeneity test; P<sub>n</sub>, P-value of Z test; R, random-effects model; F, fixed-effects model; OR, odds ratio; CI, confidence interval.

Quantitative synthesis
The pooled results of meta-analysis for the association between OPN rs11730582 polymorphism and cancer risk are shown in Table 2 and Figure 2. In overall analysis, OPN rs11730582 C>T polymorphism was not associated with cancer risk (CC vs TT: OR, 0.96; 95% CI, 0.54–1.72; CT vs TT: OR, 0.85; 95% CI, 0.58–1.26; CC vs TT: OR, 1.00; 95% CI, 0.66–1.53; C vs T: OR, 0.93; 95% CI, 0.66–1.30). In a stratified analysis by cancer type, no significant association was found between OPN rs11730582 C>T polymorphism and the risk of glioma (CC vs TT: OR, 1.44; 95% CI, 0.50–4.14; CT vs TT: OR, 1.08; 95% CI, 0.73–1.60; CC+CT vs TT: OR, 1.21; 95% CI, 0.65–2.24; CC vs CT+TT: OR, 1.34; 95% CI, 0.50–4.14; C vs T: OR, 0.93; 95% CI, 0.66–1.30). In a stratified analysis by cancer type, no significant association was found between OPN rs11730582 C>T polymorphism and the risk of glioma (CC vs TT: OR, 1.44; 95% CI, 0.50–4.14; CT vs TT: OR, 1.08; 95% CI, 0.73–1.60; CC+CT vs TT: OR, 1.21; 95% CI, 0.65–2.24; CC vs CT+TT: OR, 1.34; 95% CI, 0.50–4.14; C vs T: OR, 0.93; 95% CI, 0.66–1.30).
95% CI, 0.60–3.01; C vs T: OR, 1.21; 95% CI, 0.70–2.09),
gastric cancer (CC vs TT: OR, 1.33; 95% CI, 0.30–5.84; CT
vs TT: OR, 1.08; 95% CI, 0.79–1.49; CC+CT vs TT: OR,
1.14; 95% CI, 0.67–1.94; CC vs CT+TT: OR, 1.25; 95% CI,
0.34–4.69; C vs T: OR, 1.14; 95% CI, 0.65–1.99) and other
cancer (CC vs TT: OR, 0.74; 95% CI, 0.30–1.86; CT vs TT:
OR, 0.71; 95% CI, 0.36–1.39; CC+CT vs TT: OR, 0.73; 95%
CI, 0.36–1.49; CC vs CT+TT: OR, 0.84; 95% CI, 0.44–1.61;
C vs T: OR, 0.79; 95% CI, 0.45–1.38).

Sensitivity analysis and publication bias
A single study involved in the meta-analysis was deleted each
time to reflect the influence of the individual data set on the
pooled ORs. As shown in Figure 3, no single study influenced
the overall results qualitatively, which indicates that our results
were statistically robust. Begg’s funnel plot and Egger’s test
were performed to assess the publication bias of literature. As
shown in Figure 4, the shapes of the funnel plots did not reveal
any evidence of obvious asymmetry. The statistical results of
Egger’s test still did not show publication bias ($P_{E} = 0.51$ for
CC vs TT, $P_{E} = 0.91$ for CT vs TT, $P_{E} = 0.83$ for CC+CT vs TT,
$P_{E} = 0.25$ for CC vs CT+TT, $P_{E} = 0.63$ for C vs T).

Discussion
Previous studies have reported an inconsistent association
between OPN rs11730582 polymorphism and cancer risk. Although the inconsistent results of OPN rs11730582
polymorphism and cancer risk cannot be clarified, it might
be due to studies with inadequate statistical power, and
different cancer types; and because a single study might
be underpowered to explain the role of OPN rs11730582
polymorphism in cancer risk. Furthermore, a meta-analysis
is a very powerful tool for analyzing cumulative data of
studies where the individual sample sizes are small and the
statistical power low. Thus, we performed this meta-analysis
attempting to acquire a more accurate result. To the best of
our knowledge, this is the largest and most comprehensive
meta-analysis for the association of interest. In the current
meta-analysis, we included all the studies investigating the
association between OPN rs11730582 polymorphism and
cancer risk. We did not find any association between OPN
rs11730582 polymorphism and cancer risk.

Although our result is suggestive, some limitations of
our meta-analysis should be considered in interpreting the
results. Firstly, the present conclusion was drawn based
on unadjusted estimates, while a more precise analysis should be conducted by adjusting other covariates including age, lifestyle, and environmental factors. Secondly, the number of cases and controls in the included studies was not enough. Therefore, further large and well-designed studies are required for confirmation. Finally, all studies were from an Asian population, and studies based on other ethnic groups should be performed to re-evaluate the association.

In conclusion, our investigations suggested that the OPN rs11730582 polymorphism might not contribute to the susceptibility of cancer risk.

Disclosure
The authors report no conflicts of interest in this work.

References