Original Article
ICAM-1 +469 A/G polymorphism and cancer risk: a meta-analysis involving 9375 subjects

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Received October 17, 2013; Accepted November 21, 2013; Epub January 15, 2014; Published January 30, 2014

Abstract: Background: The ICAM-1 +469 A/G polymorphism has been implicated in susceptibility to cancer, but the results were inconclusive. The present meta-analysis aimed to investigate the association between the ICAM-1 +469 A/G polymorphism and cancer risk. Methods: We searched PubMed, Embase to identify studies that evaluated the association between the ICAM-1 +469 A/G polymorphism and cancer risk. Data were extracted and statistical analysis was performed by using the software Revman 5.1 and STATA 12.0. Results: A total of 14 studies involving 9375 subjects were included. The results suggested that ICAM-1 +469 A/G polymorphism had no associated with cancer risk (OR=0.91, 95% CI: 0.76-1.08, P=0.27 for GG+AG vs. AA). Subgroup analysis by cancer type indicated the there was no associated between this polymorphism and breast cancer (OR=0.91, 95% CI: 0.72-1.15, P=0.43 for GG+AG vs. AA), but it was associated with decreased risk of colorectal cancer (OR=0.59, 95% CI: 0.41-0.85, P=0.005 for GG+AG vs. AA). Subgroup analysis by ethnicity revealed a decreased risk of cancer among Caucasians (OR=0.88, 95% CI: 0.78-0.99, P=0.03 for GG+AG vs. AA). Conclusion: The evidence from current meta-analysis doesn’t support the ICAM-1 +469 A/G polymorphism as a risk factor for cancer. Further studies are needed to validate these findings.

Keywords: Cancer, ICAM-1, polymorphism, meta-analysis

Introduction
Cancer is a major public health problem all over the world regardless of age, sex, and race/ethnicity, it is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [1]. The global burden of cancer is increasing, as a result of the aging and growth of the world population and an increasing adoption of cancer-causing behaviors, particularly smoking, within economically developing countries [1-3]. The pathogenesis of cancer is complex and has not been fully understood, recent studies suggest that genetic factors play critical roles in the pathogenic process of cancer [4]. Quite a lot studies have investigated the association of genetic variants with cancer susceptibility, and among them, the ICAM-1 +469 A/G polymorphism has been highlighted.

Intercellular adhesion molecule-1 (ICAM-1), a cell adhesion molecule with a key role in inflammation and immune surveillance, has been implicated in carcinogenesis by facilitating instability of the tumor environment [5, 6]. Several studies have indicated the ICAM-1 plays roles in a serial of cancers, including lung cancer, gastric cancer, breast cancer, colorectal cancer, and prostate cancer. For example, ICAM-1 is overexpressed in gastric cancer tissues, and this could be related to the aggressive nature of the tumor, and has a poor prognostic effect on gastric cancer [7]. ICAM-1 is also significantly elevated in patients with breast cancer compared with controls, and its expression is associated with a more aggressive tumor phenotype [8, 9]. A number of studies have investigated the association between ICAM-1 +469 A/G polymorphism and cancer risks, however, the results were inconclusive and inconsistent. Since meta-analysis is a useful tool to synthesize data from different studies on the same topic, and it is also widely used to synthesize data on different topics, thus, the
present meta-analysis aimed to clarify the relationship between ICAM-1 +469 A/G polymorphism and cancer risks based on all eligible case-control studies.

**Method**

**Literature search**

Two independent reviewers searched in Pubmed and Embase databases to identify studies involving the possible association between cancer risk and ICAM-1 +469 A/G gene polymorphism (Last updated on August 15, 2013). The search terms were as follows: “Intercellular adhesion molecule-1 or ICAM-1” in combination with “cancer or carcinoma or neoplasms” and “polymorphism or variant or mutation”. The reference lists of identified original studies and review articles were also manually searched to find additional relevant publications.

**Study selection**

We set the inclusion criteria for the eligible studies as follows: (1) the study should evaluate the association between ICAM-1 +469 A/G gene polymorphism and cancer (2) they should be case-control studies, (3) genotype distributions in both cases and controls were available for estimating an odds ratio (OR) with 95% confi-
ICAM-1 +469 A/G polymorphism and cancer risk

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Cancer Type</th>
<th>Cases</th>
<th>Control</th>
<th>Genotyping method</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arandi N</td>
<td>2008</td>
<td>Iran</td>
<td>Asian</td>
<td>Breast cancer</td>
<td>264</td>
<td>200</td>
<td>PCR-RFLP</td>
<td>Y</td>
</tr>
<tr>
<td>Cai G</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>Prostate cancer</td>
<td>405</td>
<td>515</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Chen H</td>
<td>2006</td>
<td>USA</td>
<td>African-American</td>
<td>Ovarian cancer</td>
<td>286</td>
<td>391</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Cox DG</td>
<td>2006</td>
<td>USA</td>
<td>Caucasian</td>
<td>Breast cancer</td>
<td>1169</td>
<td>1635</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Howell WM</td>
<td>2005</td>
<td>UK</td>
<td>Caucasian</td>
<td>Melanoma</td>
<td>151</td>
<td>224</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Kammerer S (1)</td>
<td>2004</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Breast cancer</td>
<td>242</td>
<td>265</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Kammerer S (2)</td>
<td>2004</td>
<td>Germany</td>
<td>Caucasian</td>
<td>Breast cancer</td>
<td>178</td>
<td>142</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Kammerer S (3)</td>
<td>2004</td>
<td>Australia</td>
<td>Caucasian</td>
<td>Breast cancer</td>
<td>167</td>
<td>170</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Lin CW</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>Oral cancer</td>
<td>595</td>
<td>561</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Thanopoulos E</td>
<td>2012</td>
<td>Greece</td>
<td>Caucasian</td>
<td>Lung cancer</td>
<td>203</td>
<td>175</td>
<td>PCR-RFLP</td>
<td>Y</td>
</tr>
<tr>
<td>Theodoropoulos G</td>
<td>2006</td>
<td>Greece</td>
<td>Caucasian</td>
<td>Colorectal cancer</td>
<td>222</td>
<td>200</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Tian MM</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>Gastric cancer</td>
<td>332</td>
<td>380</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Vinceti M</td>
<td>2006</td>
<td>Italy</td>
<td>Caucasian</td>
<td>Melanoma</td>
<td>57</td>
<td>57</td>
<td>PCR</td>
<td>Y</td>
</tr>
<tr>
<td>Wang QL</td>
<td>2009</td>
<td>China</td>
<td>Asian</td>
<td>Colorectal cancer</td>
<td>87</td>
<td>102</td>
<td>PCR-SSP</td>
<td>Y</td>
</tr>
</tbody>
</table>

PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; SSP: Single strand polymorphism; HWE: Hardy-Weinberg equilibrium; Y: Yes.

Confidence interval (CI 95%). (4) genotype distribution of control subjects must be consistent with Hardy-Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: (1) abstracts and reviews, (2) genotype frequency not reported, (3) repeat or overlapping publications.

Data extraction

The final set of publications was assessed independently by two reviewers, who were blinded to the article details, and the differences between them were solved by consensus. The following items were extracted from each study if available: first author, year of publication, country of origin, ethnicity, sample size, type of cancer, genotyping method, and genotype number in cancer cases and controls. In publications containing both a “discovery group” and a “replication group”, each group was treated as a single study in the meta-analysis.

Statistical analysis

The strength of the association between the ICAM-1 +469 A/G gene polymorphism and the risk of cancer was measured by OR and 95% CI. The significance of the pooled OR was determined by the Z-test and P<0.05 was considered statistically significant. Firstly, we evaluated with the dominant model (GG+AG vs. AA) and recessive model (GG vs. AG+AA) and then evaluated variant genotype GG and compared with the wild-type AA homozygote (GG vs. AA). In addition, we also estimated the risks of AG vs. AA and A vs. G. To evaluate ethnicity-specific and cancer type-specific effects, subgroup analyses were performed by ethnic group and cancer type.

Heterogeneity was evaluated by a $\chi^2$-based Q statistic and was considered statistically significant at $P<0.10$. When the $P$ value is greater than 0.10, the pooled OR of each study was calculated by the fixed-effects model; otherwise, a random-effects model was used. Publication bias was analyzed by Begg’s funnel plots and Egger’s test [10, 11]. All statistical tests were performed by using the Revman 5.1 software and STATA 12.0 software.

Results

After independent review, 12 publications with 14 case-control studies containing 9,375 subjects (4,358 cancers cases and 5,017 controls) on the evaluation of the association between ICAM-1 +469 A/G gene polymorphism and the risk of cancer were considered eligible for inclusion in present meta-analysis [12-23]. One publication was excluded because of the HWE problem of controls [24]. There were five case-controls of Asians [12, 13, 18, 21, 23], eight of Caucasians [15-17, 19, 20, 22]. Of the included publications, five reported breast cancer, two reported colorectal cancer, two reported melanoma, Prostate cancer, lung cancer, oral cancer, ovarian cancer and gastric cancer were also reported. The genotype frequencies for control group were all consistent with HWE in included studies. The flow diagram of included
ICAM-1 +469 A/G polymorphism and cancer risk

and excluded studies was showed in Figure 1. The characteristics of each case-control studies are summarized in Table 1. Genotype and allele distributions for each case-control studies are listed in Table 2.

Quantitative data synthesis

Firstly, we analyzed the heterogeneity of GG+AG vs. AA to choose calculation model. For included 14 studies, the value of $\chi^2$ was 44.06 with $P<0.01$ in a random-effects model, thus, we chose the random-effects model to synthesize the data. Overall, the pooled OR was 0.91 (95% CI: 0.76-1.08) and the test for overall effect Z value was 1.11 ($P=0.27$) (Figure 2). The results suggested that the GG homozygote and AG heterozygote carriers don’t have an increased risk of cancer compared with those individuals with the AA homozygote, on the contrast, it may be protective factor for cancer. For recessive model, we didn’t find an obvious association between the GG homozygote carriers and risk of cancer with an OR of 0.99 (95% CI: 0.83-1.19, $P=0.94$). The result of allelic genetic model suggested that that the G allele carriers may have a decreased risk of cancer compared with those individuals with the A allele (Figure 3), but without statistical significance. Summary of the results of other genetic comparisons are listed in Table 3.

Subgroup analysis

Next, we carried out subgroup analysis to determine the effect of ICAM-1 +469 A/G gene polymorphism on specific cancer type and the ethnicity. In the subgroup analysis by cancer type, ICAM-1 +469 A/G gene polymorphism showed no association with breast cancer risk (OR=0.91, 95% CI=0.72-1.15, $P=0.43$ for GG+AG vs. AA), and ICAM-1 +469 A/G gene polymorphism may be a protective factor for melanoma and colorectal cancer, as shown in Table 3. In the subgroup analysis by ethnicity, ICAM-1 +469 A/G gene polymorphism was associated a low cancer risk in Caucasians (OR=0.88, 95% CI=0.78-0.99, $P=0.03$ for GG+AG vs. AA), no associations were found among Asians (OR=1.06, 95% CI=0.75-1.52, $P=0.73$ for GG+AG vs. AA).

Publication bias

Begg’s funnel plot and Egger’s test were used to assess publication bias. The shape of the funnel plots seemed symmetrical in the GG+AG vs. AA comparison genetic model, suggesting the absence of publication bias (Figure 4). Then, the Egger’s test was performed to provide statistical evidence of funnel plots asymmetry. The results indicated a lack of publication bias of the current meta-analysis ($P=0.167$), suggesting the reliability of our results.

Discussion

Cancer remains a leading cause of mortality worldwide and it places heavy health burden, while the pathogenesis of cancer has not been well understood [1-3]. Genetic factors may alter
protein function and individual’s susceptibility to disease, thus, may play a role in pathogenesis of cancer [4]. ICAM-1 is involved in cell adhesion and inflammation, might play an important role in the development a serial of cancers. The +469 A/G polymorphism in the gene ICAM-1 might interact with environmental factors in the development of cancer, correlation of this polymorphism and with cancer risk has been studied, but the results remain controversial.
### Table 3. Summary of different comparative results

<table>
<thead>
<tr>
<th></th>
<th>GG+AG vs. AA</th>
<th>GG vs. AG+AA</th>
<th>GG vs. AA</th>
<th>AG vs. AA</th>
<th>G vs. A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P*</td>
<td>OR (95% CI)</td>
<td>P*</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>0.91 (0.76-1.08)</td>
<td>0.27</td>
<td>0.99 (0.83-1.19)</td>
<td>0.94</td>
<td>0.93 (0.73-1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.96 (0.83-1.08)</td>
<td>0.28</td>
<td>0.94 (0.83-1.07)</td>
</tr>
<tr>
<td><strong>Subgroup by Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.91 (0.72-1.15)</td>
<td>0.43</td>
<td>0.89 (0.76-1.04)</td>
<td>0.14</td>
<td>0.88 (0.74-1.05)</td>
</tr>
<tr>
<td>Melanoma</td>
<td><strong>0.64 (0.44-0.94)</strong></td>
<td><strong>0.02</strong></td>
<td>0.93 (0.58-1.47)</td>
<td>0.74</td>
<td>0.71 (0.42-1.18)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.59 (0.41-0.85)</td>
<td><strong>0.005</strong></td>
<td>0.72 (0.50-1.04)</td>
<td>0.08</td>
<td><strong>0.55 (0.35-0.88)</strong></td>
</tr>
<tr>
<td><strong>Subgroup by Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td><strong>0.88 (0.78-0.99)</strong></td>
<td><strong>0.03</strong></td>
<td>0.88 (0.77-1.02)</td>
<td>0.08</td>
<td><strong>0.83 (0.71-0.97)</strong></td>
</tr>
<tr>
<td>Asian</td>
<td>1.06 (0.75-1.52)</td>
<td>0.73</td>
<td>1.35 (1.08-1.68)</td>
<td>0.009</td>
<td>1.37 (0.96-1.97)</td>
</tr>
</tbody>
</table>

The bold values mean that their association is significant, *P* value for Z test.
Therefore, we performed this meta-analysis to clarify the relationship between this polymorphism and susceptibility to cancer. To our knowledge, it is the most comprehensive meta-analysis regarding the ICAM-1 +469 A/G polymorphism and cancer risk. A total of 14 case-control studies were included in this meta-analysis. The strength of the present analysis was based on the accumulation of published data giving information to detect more precise conclusion. In this study, the effect of dominant/recessive models and the effect of additive genetic model were all estimated. What’s more, the consistency of genetic effects across populations from different ethnicities was investigated. For present meta-analysis, research findings do not support a role for the ICAM-1 +469 A/G gene polymorphism in the development of cancer in the total combined analysis, on the contrast, it may be a protective factor for cancer. In addition, we also observed an effect modification of cancer risk was observed by ethnicity and cancer type for the +469 A/G gene polymorphism.

Although evidences suggested that ICAM-1 may play a role in breast cancer [8, 9], our meta-analysis did not support the role of ICAM-1 +469 A/G gene polymorphism in breast cancer risk. Since the genetic-protein interaction is complicated, there is no surprise that no association between ICAM-1 +469 A/G gene polymorphism in breast cancer risk. To consistent with our findings, a recent published article suggested ICAM-5 V301I and rs281439 variants, but not ICAM-1 +469 A/G variant, might be complicated with breast cancer risk [25], suggesting a complicate interaction between gene polymorphism and cancer. The contributions of genetic factors to breast cancer are quite complex, except for current known gene polymorphisms, uncommon polymorphisms may also contribute to breast cancer. Our study also identified that ICAM-1 +469 A/G gene polymorphism may be a risk factor for melanoma and colorectal cancer, another three studies also support +469 A/G gene polymorphism as a risk factor for prostate cancer lung cancer and gastric cancer, in addition, the +469 A/G polymorphism of ICAM-1 gene is associated with the prognosis of lung cancer and gastric cancer, thus, to detect the +469 A/G polymorphism of ICAM-1 gene may be helpful for the comprehensive management of cancer patients. These data support that the effect of ICAM-1 +469 A/G gene polymorphism on cancer risk may be tumor origin specific.

Our study also carried out a detailed sub-group analysis to the effect of ICAM-1 +469 A/G gene polymorphism on a specific ethnicity. Our results revealed that the ICAM-1 +469 A/G gene polymorphism is associated with decreased cancer risk in Caucasians, while there was no association between this polymorphism and Asians. Considering the ethnic difference, there may be differences in the genes involved in different populations, different polymorphisms within a specific locus, different loci within the same gene, and environmental factors may even play a role in the expression of these changes. To take a consideration of population differences will be particularly informative, susceptibility genes identified in cancer patients with different ethnicities provide an opportunity to explore new mechanisms of disease that are specific in different population. In addition, the effects of gene-gene and gene-environment interactions remain questions. The identification of human cancer susceptibility genes and discovery of their roles in carcinogenesis, and a comprehen-
sive understanding of genetic, epigenetic, environmental, and clinical factors will ultimately be important for the development of methods for prediction of risk, diagnosis, prognosis, prevention and therapy for human cancers [4, 26].

Our study also had several limitations that should be concerned. First of all, the number of studies and subjects included in this meta-analysis were small, which may not have enough power to explore the association between the +469 A/G gene polymorphism and cancer risk, thus, larger multicenter random control investigations are warranted for further confirmation our findings; Secondly, the twelve included studies were performed mainly in Asian or Caucasian populations, more studies are needed in other ethnic population such as Latino because of possible ethnic differences of the +469 A/G gene polymorphism. Thirdly, although we didn’t set language limit, only English publications were identified in selected electronic databases for present meta-analysis, it is possible that some unpublished studies which had null outcomes or relevant published studies in other languages were not included, which might bias the results.

Conclusion

To our knowledge, this is the first and most comprehensive meta-analysis to assess the relationship between the ICAM-1 +469 A/G gene polymorphism and cancer risk. The evidence from our study does not support ICAM-1 +469 A/G gene polymorphism as a risk factor for cancer. In the future, large well-designed and multi-center epidemiological studies in different ethnic population should be performed to assess these associations.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China #81230001 and 31171103 to Dr. Fuqiang Wen, #81300032 to Dr. Yongchun Shen.

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References

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