Original Article

Association between IL-6 -174G>C polymorphism and risk of prostate cancer: a meta-analysis

Xiaobin Gu1, Xian-Shu Gao2, Wei Xiong2, Shaoqian Sun1, Mu Xie1, Ming Cui1, Chuan Peng1, Yun Bai1, Wei Guo3, Linjun Han3

1Department of Radiation Oncology, Peking University First Hospital, Peking University, Beijing, China; 2Tangshan People's Hospital, Hebei 063000, China; 3Graduate School of Medicine, Hebei North University, Zhangjiakou, Hebei 075000, China

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Abstract: The IL-6 -174G>C polymorphism was the most common polymorphism that could directly affect the levels of IL-6. Previous studies have investigated the association between IL-6 -174G>C polymorphism and the risk of prostate cancer (PCa), but the results remained controversial. The current study was designed to comprehensively clarify the association between IL-6 -174G>C polymorphism and PCa susceptibility by the means of meta-analysis. A total of 12 studies from 10 articles with 12,626 cases and 14,672 controls were included in the meta-analysis. Pooled odd ratio (OR) with 95% confidential intervals (95% CI) were calculated to assess the summary effects. Subgroup analysis stratified by ethnicity and source of control were performed. The results showed that there was no association between IL-6 -174G>C polymorphism and PCa risk under all five genetic models: CC vs GG: OR=1.11, 95% CI=0.92-1.33, P_{h}=0.002; GC vs GG: OR=1.02, 95% CI=0.97-1.08, P_{h}=0.253; CC+GC vs GG: OR=1.06, 95% CI=0.95-1.18, P_{h}=0.027; CC vs GC+GG: OR=1.07, 95% CI=0.92-1.24, P_{h}=0.008; and Aelle C vs Aelle G: OR=1.04, 95% CI=0.95-1.14, P_{h}=0.001. Subgroup analysis showed significantly elevated risk in hospital-based populations (CC vs GG: OR=1.2, 95% CI=1.1-1.44, P_{h}=0.699). Our meta-analysis suggested that IL-6 -174G>C polymorphism may not be a risk factor for prostate cancer.

Keywords: IL-6, polymorphism, prostate cancer, risk

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer type and the third leading cause of cancer-related death in man in western countries [1]. In the United States, approximately 220,800 male will be diagnosed with PCa and 27,540 men will die because of PCa annually [2]. Previous studies have revealed a variety of risk factors contributing to the occurrence of PCa, including western lifestyle, dietary, chronic inflammation and family history, among which, chronic inflammation may play pivotal roles in susceptibility to PCa [3-5]. Chronic inflammation can facilitate carcinogenesis through damaging DNA synthesis, enhancing cell proliferation and promoting angiogenesis [6, 7].

As a mainstay in chronic inflammation, Interleukin-6 (IL-6) is a classic inflammatory cytokine regulating various physiological processes including host defense mechanisms, cellular growth and immune response [8]. IL-6 is a positive growth factor for most prostate cells and is upregulated in patients with PCa [9]. IL-6 could also promote prostate carcinogenesis by protecting PCa cells from cell death and induce activation of the androgen receptor (AR) [9]. IL-6 is encoded by IL-6 gene, which is located at chromosome 7p21–24. The promoter polymorphisms in IL-6 gene could directly influence IL-6 production, and several polymorphisms have been reported [10]. The most common polymorphism of IL-6 gene is the -174G>C (rs1800795) variant, which is thought to effect transcriptional regulation and glucocorticoid receptor combination [11, 12]. Various studies have investigated the correlation between IL-6 -174G>C polymorphism and PCa susceptibility [13-17]. However, the results of the previous studies were inconsistent and the
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relative small sample size may limit statistical power of each single study [13-16, 18, 19]. To assess the true association between IL-6 -174G>C polymorphism and the risk of PCa, we collected all available publications and performed a comprehensive meta-analysis.

Materials and methods

Literature search

The relevant studies were searched through Embase, PubMed, ISI Web of Science and China National Knowledge Infrastructure (CNKI) databases updated to Jan 2016. There was no restriction on language, sample size and period time. The search key words were “interleukin-6, IL-6”, “prostate cancer, prostate carcinoma, prostatic neoplasms” and “polymorphism, mutation, variant”. The references of the retrieved articles and reviews were manually examined for other relevant studies. The literature search was carried out by two investigators (Xiaobin Gu and Xian-Shu Gao) independently.

Inclusion and exclusion criteria

Studies included in this meta-analysis needed to meet the following criteria: (1) with a case-control study design; (2) explored the association between IL-6 -174G>C polymorphism and risk of PCa; (3) reported an odds ratio (OR) with 95% confidence interval (CI) or sufficient data to calculate them; and (4) the control group did not contain patients with malignancies. The exclusion criteria were: (1) case reports, reviews, duplicated data or non-human studies; (2) provided no genotype frequency or genotype information; and (3) insufficient information for data extraction.

Data extraction

Data extraction from eligible studies was performed by two independent investigators (Xiaobin Gu and Xian-Shu Gao) and discrepancies were resolved by discussion. The data extracted included: the first author, year of publication, study country, ethnicity, source of control population, genotyping method, numbers of cases and controls, genotype distribution in cases and controls, and Hardy-Weinberg equilibrium (HWE). When a study reported the results on different ethnic subpopulations, we treated it as separate studies in the meta-analysis and the relevant information was extracted separately.

Statistical analysis

Based on the genotype and allele frequencies in cases and controls, we estimated the association between IL-6 -174G>C polymorphism and risk of PCa (OR and 95% CI). ORs were summarized under CC vs GG, GC vs GG, CC+GC vs GG, CC vs GC+GG, and Allele C vs Allele G genetic models. The statistical significance of OR was determined by Z test, and P<0.05 was considered as statistically significant. Stratified analysis was performed by ethnicity and source of control.

The Q test and I² statistics were used to evaluate the statistical heterogeneity among studies [20, 21]. If the result was \( P_0 < 0.1 \) or \( I^2 \geq 50\% \), indicating the presence of significant heterogeneity, and a random-effects model (the...
**Table 1.** Basic characteristics of the studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Source of control</th>
<th>Genotyping method</th>
<th>Case Total</th>
<th>Case GG</th>
<th>Case GC</th>
<th>Case CC</th>
<th>Control Total</th>
<th>Control GG</th>
<th>Control GC</th>
<th>Control CC</th>
<th>HWE</th>
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<tbody>
<tr>
<td>Michaud [26]</td>
<td>2006</td>
<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>Taqman</td>
<td>484</td>
<td>170</td>
<td>223</td>
<td>91</td>
<td>230</td>
<td>293</td>
<td>90</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Kesarwani [27]</td>
<td>2008</td>
<td>India</td>
<td>Asian</td>
<td>HB</td>
<td>ARMS-PCR</td>
<td>200</td>
<td>102</td>
<td>84</td>
<td>14</td>
<td>200</td>
<td>103</td>
<td>87</td>
<td>10</td>
<td>Y</td>
</tr>
<tr>
<td>Moore [16]</td>
<td>2009</td>
<td>USA</td>
<td>Caucasian</td>
<td>HB</td>
<td>Taqman</td>
<td>957</td>
<td>191</td>
<td>485</td>
<td>281</td>
<td>847</td>
<td>196</td>
<td>401</td>
<td>250</td>
<td>Y</td>
</tr>
<tr>
<td>Pierce1 [15]</td>
<td>2009</td>
<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>Taqman</td>
<td>175</td>
<td>48</td>
<td>96</td>
<td>31</td>
<td>1933</td>
<td>696</td>
<td>901</td>
<td>336</td>
<td>Y</td>
</tr>
<tr>
<td>Pierce2 [15]</td>
<td>2009</td>
<td>USA</td>
<td>African-American</td>
<td>PB</td>
<td>Taqman</td>
<td>45</td>
<td>6</td>
<td>34</td>
<td>5</td>
<td>348</td>
<td>50</td>
<td>250</td>
<td>48</td>
<td>N</td>
</tr>
<tr>
<td>Wang [14]</td>
<td>2009</td>
<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>250</td>
<td>91</td>
<td>116</td>
<td>43</td>
<td>252</td>
<td>84</td>
<td>128</td>
<td>40</td>
<td>Y</td>
</tr>
<tr>
<td>Dossus [13]</td>
<td>2010</td>
<td>Germany</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>7937</td>
<td>3594</td>
<td>3218</td>
<td>1125</td>
<td>8508</td>
<td>3832</td>
<td>3402</td>
<td>1274</td>
<td>Y</td>
</tr>
<tr>
<td>Mandal1 [12]</td>
<td>2014</td>
<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>84</td>
<td>50</td>
<td>28</td>
<td>6</td>
<td>26</td>
<td>30</td>
<td>22</td>
<td>Y</td>
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<tr>
<td>Mandal2 [12]</td>
<td>2014</td>
<td>USA</td>
<td>African-American</td>
<td>PB</td>
<td>PCR</td>
<td>80</td>
<td>58</td>
<td>16</td>
<td>6</td>
<td>62</td>
<td>48</td>
<td>14</td>
<td>0</td>
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</tr>
<tr>
<td>Chen [18]</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>HB</td>
<td>PCR-RFLP</td>
<td>212</td>
<td>131</td>
<td>64</td>
<td>17</td>
<td>236</td>
<td>158</td>
<td>67</td>
<td>11</td>
<td>Y</td>
</tr>
<tr>
<td>Winchester [17]</td>
<td>2015</td>
<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>PCR</td>
<td>857</td>
<td>287</td>
<td>404</td>
<td>166</td>
<td>834</td>
<td>287</td>
<td>406</td>
<td>141</td>
<td>Y</td>
</tr>
</tbody>
</table>

Abbreviations: PB: Population-based; HB: Hospital-based; PCR: Polymerase chain reaction; TaqMan: TaqManSNP; ARMS-PCR: Amplification refractory mutation system-PCR; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; Y: Yes; N: No.

**Table 2.** Results of meta-analysis for *IL-6*-174G>C polymorphism and prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of studies</th>
<th>CC vs GG</th>
<th>GC vs GG</th>
<th>CC+GC vs GG</th>
<th>CC vs GC+GG</th>
<th>Aelle C vs Aelle G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12</td>
<td>1.11 (0.92, 1.33)</td>
<td>0.002</td>
<td>1.02 (0.97, 1.08)</td>
<td>0.253</td>
<td>1.06 (0.95, 1.18)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>1.06 (0.88, 1.29)</td>
<td>0.001</td>
<td>1.02 (0.97, 1.08)</td>
<td>0.067</td>
<td>1.04 (0.91, 1.18)</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>1.64 (0.92, 2.94)</td>
<td>0.642</td>
<td>1.06 (0.79, 1.41)</td>
<td>0.572</td>
<td>1.13 (0.86, 1.49)</td>
</tr>
<tr>
<td>African-American</td>
<td>2</td>
<td>2.15 (0.2, 22.94)</td>
<td>0.118</td>
<td>1.03 (0.56, 1.88)</td>
<td>0.773</td>
<td>1.21 (0.67, 2.18)</td>
</tr>
<tr>
<td>Source of control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>8</td>
<td>1.02 (0.78, 1.33)</td>
<td>0.001</td>
<td>1.01 (0.95, 1.07)</td>
<td>0.159</td>
<td>1.01 (0.86, 1.2)</td>
</tr>
<tr>
<td>HB</td>
<td>4</td>
<td>1.12 (1, 1.44)</td>
<td>0.699</td>
<td>1.09 (0.95, 1.25)</td>
<td>0.534</td>
<td>1.12 (0.98, 1.27)</td>
</tr>
</tbody>
</table>

Abbreviations: PB: Population-based; HB: Hospital-based; P: p value of Q test for heterogeneity.
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DerSimonian and Laird method) was used [22], otherwise, a fixed-effects model (Mantel-Haenszel method) was used [23]. Sensitivity analysis was carried out by sequential omission of each study to estimate robustness of the results. HWE of the control groups was determined by the χ² test. Publication bias was assessed using Begg’s funnel plots [24] and Egger’s test [25]. All statistical analyses were conducted by using STATA version 12.0 (Stata Corporation, College Station, TX, USA). P<0.05 was considered as statistically significant.

Results

Study characteristics

The literature selection process was summarized in Figure 1. Of the initial 504 records found, 12 case-control studies with 12,626 cases and 14,672 controls from 10 publications [13-19, 26-28] were ultimately included in the meta-analysis. The basic characteristics of the included studies were presented in Table 1. Eight studies [13-18, 26, 27] were conducted in Caucasians, two studies [19, 28] were conducted in Asians and two studies [13, 16] were conducted in African-Americans. Control groups from all included studies were in accordance with HWE except one [16].

Meta-analysis results

Major results of the meta-analysis were shown in Table 2. Generally, the combined results showed no significant association between IL-6 -174G>C polymorphism and risk of PCa under any of the genetic models: CC vs GG: OR=1.11, 95% CI=0.92-1.33, P=0.002; GC vs GG: OR=1.02, 95% CI=0.97-1.08, P=0.253 (Figure 2); CC+GC vs GG: OR=1.06, 95% CI=0.95-1.18, P=0.027; CC vs GC+GG: OR=1.07, 95% CI=0.92-1.24, P=0.008; and Aelle C vs Aelle G: OR=1.04, 95% CI=0.95-1.14, P=0.001 (Figure 3). Stratified analysis by ethnicity and source of controls

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**Figure 2.** Forest plot of prostate cancer risk associated with *IL-6*-174G>C polymorphism under GC vs GG genetic model.

**Figure 3.** Forest plot of prostate cancer risk associated with *IL-6*-174G>C polymorphism under Allele C vs Allele G genetic model.
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Sensitivity analysis was carried out by removal of the study of Pierce et al. [16] on African-Americans, in which the control populations showed deviation from HWE. The significance of pooled ORs was not influenced excessively after exclusion of this study (data not shown), indicating that our results were statistical robust.

**Publication bias**

The publication bias was evaluated in all comparison models by Begg’s funnel plot and Egger’s test. The funnel plot did not show obvious asymmetry in any of the five genetic models (CC vs GG: Begg’s p=0.631, Egger’s P=0.666; Figure 5).  

**Discussion**

The present study was designed to assess the association between IL-6 -174G>C polymorphism and risk of PCa. Our meta-analysis containing 12 studies from 10 articles with 27,298 subjects showed that this polymorphism predisposed no host susceptibility to PCa. The subgroup analysis stratified by ethnicity and source of controls demonstrated that IL-6 -174G>C polymorphism was associated with 1.2-fold higher risk of PCa in hospital-based controls, but did not reveal significant association with PCa by all the other genetic models. To our knowledge, our study was the available meta-analysis containing the most subjects comprehensively investigating the association between IL-6 -174G>C polymorphism and PCa susceptibility.

PCa is a multifactorial and complex disease, and chronic inflammation was considered as an important element during its formation. IL-6 was a mainstay in chronic inflammation and showed significantly increased risk in hospital-based populations (CC vs GG: OR=1.2, 95% CI=1.1-1.44, P=0.099; Table 2).

**Sensitivity analysis**

Sensitivity analysis was conducted to evaluate the influence of each individual study on the combined ORs by sequential omission of individual studies. The results showed that pooled effects remained stable when omitting every single study (Figure 4 showed the result under CC vs GC+GG model). Furthermore, sensitivity analysis was carried out by removal of the study of Pierce et al. [16] on African-Americans, in which the control populations showed deviation from HWE. The significance of pooled ORs was not influenced excessively after exclusion of this study (data not shown), indicating that our results were statistical robust.

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could promote prostate carcinogenesis by diverse mechanisms [10]. The most common single nucleotide polymorphism (SNP) of IL-6 gene, the IL-6 -174G>C polymorphism directly effects the expression levels of IL-6 in vivo [29]. Many studies reported the effects of IL-6 -174G>C polymorphism on the risk of PCa, but the results remained controversial. Michaud et al. found that this polymorphism was not associated with the risk of PCa in Caucasians [27]. However, Mandal et al. [13] reported that GG genotype was associated with increased risk of PCa in Caucasian population, whereas the CC genotype was correlated with elevated risk in the African-Americans. Moreover, a recently published genome-wide association studies (GWAS) identified 76 susceptibility loci associated with PCa risk and a meta-analysis containing subjects with diverse ethnic backgrounds identified 23 new susceptibility loci for PCa [30, 31]. Although IL-6 -174G>C polymorphism was not a susceptibility loci included in the aforementioned GWAS, it was also necessary to perform a comprehensive meta-analysis based on the previous released publications to provide compelling evidence of the potential role of IL-6 -174G>C polymorphism in PCa occurrence. Generally, our data showed that there was no significant association between this polymorphism and PCa risk, which was in line with the results of meta-analyses concerning the same issue [32-34]. Notably, the strength of our study was the inclusion of two original articles [18, 19] published more recently and the largest sample size among the studies, which guaranteed the statistical power of our meta-analysis.

There were several limitations need to be addressed in the current study. First of all, our results showed that IL-6 -174G>C polymorphism conferred increased PCa risk in hospital-based group under CC vs GG model. Because only four studies were included in this stratified analysis and the control selection might not be uniform in these studies, we could not rule out that the results were obtained by chance. Second, although no language restriction was applied on literature collection, only English-language studies were included in the final meta-analysis, thus, selection bias may occur.

In summary, the current meta-analysis provided evidence that there was no relevance of IL-6 -174G>C polymorphism and risk of PCa. Future prospective studies with sufficient samples and more ethnic groups are necessary to further test our findings.

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Disclosure conflict of interest

None.

Address correspondence to: Dr. Xian-Shu Gao, Department of Radiation Oncology, Peking University First Hospital, Beijing 100034, China. Tel: +86-10-83575239; Fax: +86-10-66551788; E-mail: doctorsgao@126.com

References

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