A Systematic Review and Meta-Analysis of Three Gene Variants Association with Risk of Prostate Cancer: An Update

Yu Chen, Huan Zhong, Jian-Guo Gao, Jian-Er Tang, Rongjiang Wang*

Purpose: Prostate cancer (PCa) is one of the most commonly diagnosed male malignancies. Numerous studies have investigated the role of genetic variants in PCa risk. However, the results remain unclear. The purpose of this study was to evaluate the relationship between single-nucleotide polymorphism (SNP) rs2228001 in xeroderma pigmentosum group C (XPC), SNP rs4073 in interleukin 8 (IL8), and SNP rs2279744 in mouse double minute 2 (MDM2) homolog gene with PCa susceptibility.

Materials and Methods: Electronic database of PubMed, Medline, and Embase were searched for eligible articles published between January 2000 and April 2014. The odd ratio (OR) with its 95% confidence interval (CI) were calculated to estimate the strength of association.

Results: A total 18 case-control studies, including 5725 PCa cases and 5900 healthy controls, were screened out. Six studies were eligible for each SNP. For XPC 939A/C polymorphism, no significant association was found with PCa risk in the whole population (P > .05). No relationship in subgroup analysis was found by ethnicity. For IL8 -251T/A variant, the A allele was not related with PCa risk in any genetic models when compared with those individuals without A allele. For MDM2 -309T/G mutation, the G allele was not associated with the increased risk of PCa in total population and subgroup analysis by ethnicity as well.

Conclusion: Our study demonstrated that all these three genetic polymorphisms were not associated with an increased risk of developing PCa, which might also provide an insight into the future research. Further large-scale studies with concerning the gene-gene and gene-environment interactions are needed to elucidate final conclusion.

Keywords: prostatic neoplasms; genetics; risk factors; gene expression regulation; humans; tumor marker; biological.

INTRODUCTION

Prostate cancer (PCa) is the common malignancies among men in the world. It is also the second and third cause of cancer-related death in the USA and Europe, respectively. Every year, a total of 238,590 new cases are emerging and 29,720 death are occurring according to cancer statistics, 2013. Multiple risk factors such as hormones, family history and lifestyle are associated with PCa. Due to extreme heterogeneity in PCa incidences worldwide, major determining factors have not been detected yet, and the pathogenesis mechanism is still unclear. Furthermore, the prevention and treatment of PCa remain complicated for treatment options depending on disease stage and patient choice. Thus, there is an urgent need to explore the molecular mechanism underlying this disease and develop novel target therapies. During the last two decades, genetic factors are considered to contribute substantially in the development of PCa. For example, increased B-cell lymphoma 2 (Bcl-2) expression was associated with lower biochemical-free survival in patients with advanced PCa.

Polymorphisms of drug-metabolizing genes cytochrome P4501A1 (CYP1A1) and prostate-specific antigen (PSA) genes were shown to be related with the increase of sporadic PCa, and they might be predisposing factors for PCa. Several genes were shown to be involved in the pathogenicity of PCa. The xeroderma pigmentosum group C (XPC) gene is located on chromosome 3p25 and is a 940-residue DNA binding protein. It serves as the primary initiating factor in the global genome nucleotide excision repair (GG-NER) in human, and plays a vital role in the early steps, especially in damage recognition, open complex formation and reparation. Recent reports suggest that XPC also stimulates repair of oxidative lesions by NER. In cells, XPC binds to human homolog of reticulum-associated degradation B (Rad) 23 (hHR23B) to form the XPC-hHR23B complex, which is involved in the DNA damage recognition and DNA repair initiation in the NER pathway, and is necessary to support NER activity in vitro. Sequence variants of the XPC gene may alter NER capacity and modulate cancer risk. One single-nucleotide polymorphism (SNP) Lys939Gln (an A to C substitution) in exon 15 of XPC has been identified and is the most studied. Interleukin-8 (IL8) gene, located on chromosome 4q12-21 in humans, is composed of four exons, three introns, and a proximal promoter region. It is an important member of CXC chemokine family and is produced by a wide range of normal cells to initiate and amplify acute inflammatory reactions. IL8 is well known for its leukocyte chemotactic properties. Many studies have
demonstrated that IL8 may play a vital role in tumorigenesis, including angiogenesis, adhesion, invasion and metastasis.\(^{14}\) In the promoter region of the IL8 gene 251 base pairs upstream of the transcriptional start site, a T/A SNP has been identified, and studies have shown that it influences the production of IL8 and affects the transcriptional activity of the IL8 promoter.\(^{15}\)

Mouse double-minute 2 (MDM2) is an E3-ubiquitin ligase which could bind to p53 with high affinity. It inhibits and promotes the degradation of the tumor suppressor protein, p53.\(^{16,17}\) Overexpression of MDM2 is associated with tumor proliferation, and an early onset of tumorigenesis.\(^{18}\) Studies have demonstrated that a mutation in the promoter region of the MDM2 gene (-309 T/G; SNP309) could result in increasing the expression of MDM2, leading to the attenuation of p53.\(^{19}\) Although independent study has identified the association between these polymorphisms and PCa risk, the results remained inconsistent rather than conclusive. Hirata and colleagues showed that XPC Lys939Gln polymorphism might be a risk factor for PCa in Japanese population;\(^{20}\) however, Liu and colleagues did not find a significant association between this polymorphism and PCa in Chinese population.\(^{21}\) McCarron and colleagues firstly demonstrated that IL8 variant might have a significant effect on development of PCa;\(^{22}\) whereas Michaud and colleagues identified that IL8 variant did not play a role in the risk of PCa.\(^{23}\) Xu and colleagues suggested that MDM2 309G allele is significantly related with PCa risk;\(^{24}\) while Jerry and colleagues found no association between MDM2 SNP 309 and disease recurrence risk, clinicopathologic variables and overall survival outcome in PCa.\(^{25}\) Therefore, the objective of this study was to systematically evaluate the prevalence of the above mentioned genetic polymorphisms in patients diagnosed with PCa, and comprehensive and reliable assessment of correlations of these polymorphisms with PCa risk.

**MATERIALS AND METHODS**

**Identification and Eligibility of Relevant Studies**

We conducted a comprehensive literature search using the electronic database of PubMed, Medline, and Embase for relevant articles published between January 2000 and April 2014. The following terms «prostate cancer or prostatic cancer», «xeroderma pigmentosum complementation group C or XPC», «interleukin-8 or IL8», «murine double minute 2 or MDM2», and «polymorphisms or variants or mutations» as well as their combinations were used to retrieve the related articles. References of retrieved articles were restricted with English language. Our research fo-
cused on studies that had been conducted in human.

Criteria for Inclusion
The included studies must meet the following criteria: 1) the paper should be case-control or cohort association studies; 2) PCa cases were diagnosed and histopathologically confirmed; 3) controls were cancer free, unrelated, age- and sex-matched healthy individuals of similar ethnicity; 4) each study included at least one of the three polymorphisms, rs2228001 in XPC (939A/C), rs4073 in IL8 (-251T/A), and rs2279744 in MDM2 (-309T/G); 5) genotype distribution information in cases and controls was available to extract; and 5) genotype distribution of control for a certain polymorphism must be in Hardy-Weinberg equilibrium (HWE).

Data Extraction
Two investigators independently assessed the quality of the included studies according to the data extracted from each study. Any disagreement was solved by consulting with a third author. The following information was extracted from each article: first author, year of publication, country, ethnicity, total numbers, and genotype distributions in PCa cases and controls.

Statistical Analysis
The overall association between genetic polymorphisms and PCa risk was measured by odds ratio (OR) and its 95% confidence interval (CI). The Z test was employed to determine the significance of the pooled ORs with a P value less than .05 considered statistically significant. The allelic model (C vs. A for XPC 939A/C; A vs. T for IL8-251A/T; G vs. T for MDM2-309T/G) and genotype genetic models (co-dominant effects: CC vs. AA XPC 939A/C; AA vs. TT IL8-251A/T; GG vs. TT MDM2-309T/G; dominant effect: CC+AC vs. AAXPC 939A/C; AA+AT vs. AAT, IL8; GG+GT vs. GGT, MDM2) were used. The I² test was employed to assess the heterogeneity among studies, with an I² value greater than 50% indicating significant heterogeneity.
Table 3. Meta-analysis of xeroderma pigmentosum group C 939A/C polymorphism in prostate cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Comparison</th>
<th>No</th>
<th>OR (95% CI)</th>
<th>P Value*</th>
<th>Z</th>
<th>Ph**</th>
<th>I² (%)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>C vs. A</td>
<td>7</td>
<td>1.06 (0.97-1.15)</td>
<td>.22</td>
<td>1.22</td>
<td>0.29</td>
<td>18</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AA</td>
<td>7</td>
<td>1.19 (0.85-1.68)</td>
<td>.32</td>
<td>1.00</td>
<td>0.04</td>
<td>54</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>CC + AC vs. AA</td>
<td>7</td>
<td>1.03 (0.92-1.17)</td>
<td>.59</td>
<td>0.54</td>
<td>0.94</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AC + AA</td>
<td>7</td>
<td>1.20 (0.85-1.70)</td>
<td>.30</td>
<td>1.04</td>
<td>0.03</td>
<td>58</td>
<td>R</td>
</tr>
<tr>
<td>Asian</td>
<td>C vs. A</td>
<td>3</td>
<td>1.04 (0.79-0.37)</td>
<td>.78</td>
<td>0.28</td>
<td>0.09</td>
<td>59</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>CC vs. AA</td>
<td>3</td>
<td>1.00 (0.45-2.22)</td>
<td>.99</td>
<td>0.01</td>
<td>0.01</td>
<td>77</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>CC + AC vs. AA</td>
<td>3</td>
<td>1.06 (0.84-1.34)</td>
<td>.62</td>
<td>0.49</td>
<td>0.62</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AC + AA</td>
<td>3</td>
<td>0.99 (0.44-2.21)</td>
<td>.97</td>
<td>0.03</td>
<td>0.007</td>
<td>80</td>
<td>R</td>
</tr>
<tr>
<td>Caucasians</td>
<td>C vs. A</td>
<td>2</td>
<td>1.06 (0.95-1.18)</td>
<td>.27</td>
<td>1.09</td>
<td>0.24</td>
<td>29</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AA</td>
<td>2</td>
<td>1.36 (0.77-2.42)</td>
<td>.29</td>
<td>1.06</td>
<td>0.08</td>
<td>67</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>CC + AC vs. AA</td>
<td>2</td>
<td>1.03 (0.89-1.20)</td>
<td>.65</td>
<td>0.45</td>
<td>0.69</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AC + AA</td>
<td>2</td>
<td>1.39 (0.76-2.53)</td>
<td>.28</td>
<td>1.08</td>
<td>0.06</td>
<td>72</td>
<td>R</td>
</tr>
<tr>
<td>African</td>
<td>C vs. A</td>
<td>2</td>
<td>1.02 (0.74-1.42)</td>
<td>.90</td>
<td>0.13</td>
<td>0.33</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AA</td>
<td>2</td>
<td>1.20 (0.57-2.52)</td>
<td>.63</td>
<td>0.48</td>
<td>0.32</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC+AC vs. AA</td>
<td>2</td>
<td>0.94 (0.60-1.47)</td>
<td>.77</td>
<td>0.29</td>
<td>0.49</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>CC vs. AC + AA</td>
<td>2</td>
<td>1.28 (0.64-2.57)</td>
<td>.48</td>
<td>0.70</td>
<td>0.36</td>
<td>0</td>
<td>F</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval.
* P value for overall effect.
** P value for heterogeneity among studies.

Table 4. Meta-analysis of interleukin 8 -251T/A polymorphism in prostate cancer.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No</th>
<th>OR (95% CI)</th>
<th>P Value*</th>
<th>Z</th>
<th>Ph**</th>
<th>I² (%)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs. T</td>
<td>5</td>
<td>1.01 (0.92-1.10)</td>
<td>.88</td>
<td>0.15</td>
<td>0.23</td>
<td>29</td>
<td>F</td>
</tr>
<tr>
<td>AA vs. TT</td>
<td>5</td>
<td>1.03 (0.86-1.23)</td>
<td>.75</td>
<td>0.32</td>
<td>0.25</td>
<td>26</td>
<td>F</td>
</tr>
<tr>
<td>AA + AT vs. TT</td>
<td>5</td>
<td>0.99 (0.79-1.24)</td>
<td>.90</td>
<td>0.12</td>
<td>0.04</td>
<td>59</td>
<td>R</td>
</tr>
<tr>
<td>AA vs. AT + TT</td>
<td>6</td>
<td>1.02 (0.88-1.17)</td>
<td>.80</td>
<td>0.25</td>
<td>0.27</td>
<td>21</td>
<td>F</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval.
* P value for overall effect.
** P value for heterogeneity among studies.

RESULTS
Study Selection and Characteristics
The electronic database search identified 323 references. After applying the inclusion criteria, 32 full-text articles comprehensively assessed against inclusion criteria. Removing duplicate documents, 18 articles were ultimately included in the systematic review and meta-analysis. The study selection process is shown in Figure 1. For XPC 939A/C, 6 studies(27-32) consisted three ethnicity (Asian, Caucasians and African) reporting 2245 cases and 2258 controls were selected. Among them, the research conducted by Agalliu and colleagues(32) consisted two ethnicities. For IL8 -251T/A, 6 studies(33-38) included 1942 cases and 1964 controls were enrolled, all of which had Caucasians ethnicity. For MDM2 -309T/G, 6 studies(39-44) contained 1538 cases and 1678 controls including Asian and Caucasians ethnicities were selected. The main characteristics of the included studies are listed in Table 1. The distributions of genotypes in the individual studies are presented in Table 2.

Association between XPC 939A/C Variant and PCa Risk
The results of allele and genotypes of XPC polymorphism in this meta-analysis are shown in Table 3. The heterogeneity between studies was calculated, and the fixed-effects model is used when the effects are assumed to be homogenous (less than 50% for the I² test and P value more than .01 for the Q test), while the random effects model is used when they are heterogeneous. The evidence of publication bias was assessed by visual funnel plot inspection. Statistical analyses were conducted using Review Manager (RevMan) software (version 5.2, The Cochrane Collaboration, Oxford, UK), and followed the program described by Collaboration and colleagues.(25) All the tests were two-sided.
fixed effect model or random effect model was performed for assessing the pooled OR. Overall, the frequency of C allele is a little bit higher in PCa cases than that in the healthy controls (36.1% vs. 34.7%). However, there was no evidence for a significant association between XPC gene 939A/C polymorphism and PCa risk in the whole population (C vs. A, OR = 1.06, 95% CI: 0.97-1.15, \( P = .22 \); CC vs. AA, OR = 1.19, 95% CI: 0.85-1.68, \( P = .32 \); CC + AC vs. AA, OR = 1.03, 95% CI: 0.92-1.17, \( P = .59 \); CC vs. AC + AA, OR = 1.20, 95% CI: 0.85-1.70, \( P = .30 \)) (Figure 2). We also evaluated the effect of the polymorphism by ethnicity. We did not detect a significant association between XPC gene 939A/C polymorphism and PCa risk in Asians, Caucasians, or African population (\( P > .05 \)).

### Association between IL8 -251 T/A Polymorphism and PCa Risk

Table 4 demonstrates the summary of all genetic comparisons between IL8 -251 T/A polymorphism and PCa risk. As shown in Figure 3, the result demonstrated that the variant A allele did not have a significant increased risk of PCa compared with those individuals without A allele (A vs. C, OR = 1.01, 95% CI: 0.92-1.10, \( P = .88 \)). No significant association was found in other genetic models (AA vs. TT, OR = 1.03, 95% CI: 0.86-1.23, \( P = .75 \)).

### Table 5. Meta-analysis of mouse double minute 2 (MDM2) homolog gene -309T/G polymorphism in prostate cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Comparison</th>
<th>No.</th>
<th>OR (95% CI)</th>
<th>( P ) Value*</th>
<th>Z</th>
<th>( I^2 ) (%)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>G vs. T</td>
<td>6</td>
<td>0.89 (0.76-1.05)</td>
<td>.17</td>
<td>1.37</td>
<td>0.04</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>GG vs. TT</td>
<td>6</td>
<td>0.81 (0.56-1.17)</td>
<td>.25</td>
<td>1.14</td>
<td>0.02</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>GG + GT vs. TT</td>
<td>6</td>
<td>0.84 (0.67-1.06)</td>
<td>.14</td>
<td>1.47</td>
<td>0.07</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>GG vs. GT + TT</td>
<td>6</td>
<td>0.96 (0.80-1.16)</td>
<td>.69</td>
<td>0.40</td>
<td>0.10</td>
<td>46</td>
</tr>
<tr>
<td>Asian</td>
<td>G vs. T</td>
<td>2</td>
<td>1.00 (0.82-1.22)</td>
<td>.00</td>
<td>0.00</td>
<td>0.17</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>GG vs. TT</td>
<td>2</td>
<td>1.04 (0.69-1.56)</td>
<td>.86</td>
<td>0.18</td>
<td>0.25</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>GG + GT vs. TT</td>
<td>2</td>
<td>0.96 (0.54-1.70)</td>
<td>.89</td>
<td>0.14</td>
<td>0.07</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>GG vs. GT + TT</td>
<td>2</td>
<td>1.03 (0.73-1.46)</td>
<td>.86</td>
<td>0.17</td>
<td>0.77</td>
<td>0.0</td>
</tr>
<tr>
<td>Caucasians</td>
<td>G vs. T</td>
<td>4</td>
<td>0.85 (0.68-1.06)</td>
<td>.14</td>
<td>1.47</td>
<td>0.03</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>GG vs. TT</td>
<td>4</td>
<td>0.71 (0.41-1.20)</td>
<td>.20</td>
<td>1.29</td>
<td>0.01</td>
<td>73</td>
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<tr>
<td></td>
<td>GG + GT vs. TT</td>
<td>4</td>
<td>0.80 (0.60-1.05)</td>
<td>.10</td>
<td>1.62</td>
<td>0.08</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>GG vs. GT + TT</td>
<td>4</td>
<td>0.83 (0.54-1.27)</td>
<td>.39</td>
<td>0.87</td>
<td>0.03</td>
<td>67</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, odds ratio; CI, confidence interval.

* \( P \) value for overall effect.

** \( P \) value for heterogeneity among studies.

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Figure 2. Forest plot on the association between C allele in xeroderma pigmentosum group C gene and risk of prostate cancer.
AA + AT vs. TT, OR = 0.99, 95% CI: 0.79-1.24, \( P = .90 \); AA vs. AT + TT, OR = 1.02, 95% CI: 0.88-1.17, \( P = .80 \).

**Association Between MDM2 -309T/G Polymorphism and PCa Risk**

The overall analysis of the studies concerning MDM2 polymorphism and PCa risk is shown in Table 5, which revealed no significant association between MDM2 -309T/G polymorphism with PCa risk in any genetic models (G vs. T, OR = 0.89, 95% CI: 0.76-1.05, \( P = .17 \); GG vs. TT, OR = 0.81, 95% CI: 0.56-1.17, \( P = .25 \); GG + GT vs. TT, OR = 0.84, 95% CI: 0.67-1.06, \( P = .14 \); GG vs. GT + TT, OR = 0.96, 95% CI: 0.80-1.16, \( P = .69 \)) as shown in Figure 4. In subgroup analysis based on ethnicity, we found that MDM2 -309T/G variant did not significantly increase the risk of PCa neither in Asian (\( P > .05 \)) nor in Caucasians (\( P > .05 \)) population, no matter what kind of genetic model was used.

**Sensitivity Analyses and Publication Bias**

Each included study was deleted every time to verify whether the individual data influenced the ORs. Our results showed that the pooled ORs were not significantly changed, confirming the stability of our overall result. The funnel plots did not show any obvious bias, further indicating that there was no publication bias in our meta-analysis (Figure 5).

**DISCUSSION**

The present meta-analysis examined the association between three commonly studied gene polymorphisms XPC 939AIC, IL8 -251T/A, and MDM2 -309T/G with PCa risk. Eighteen separate articles including 5725 PCa cases and 5900 healthy controls were retrieved in the final analysis. Overall we did not detect a significant association between these three gene polymorphisms with PCa in any genetic models. Similar results were found in stratification analyses by ethnicity. The XPC gene contains 16 exons and 15 introns. It can interact with RAD23B to form a XPC-RAD23B complex, specifically involving in global genome repair and works as the earliest damage detector to initiate the NER pathway. (45) Studies have proved that XPC is...
a key component of the NER pathway that participates in DNA damage repair.\(^4\) Mutations in this gene, result in xeroderma pigmentosum, a rare autosomal recessive disorder characterized by increased sensitivity to sunlight and the development of skin cancer at an early age.\(^5\) XPC polymorphisms have been associated with increased risk of many human cancers such as bladder cancer,\(^6\) and digestive system cancers.\(^7\) Our results were consistent with previous meta-analysis conducted by Zou and colleagues in which screened out five studies including 1906 cases and 1970 controls, demonstrated that this variant was not associated with PCa risk.\(^8\) IL8 is one of key members of the human a-chemokine subfamily, and acts as a potent chemoattractant and activator of neutrophils.\(^9\) It is produced by normal cells including monocytes, neutrophils, fibroblasts, and endothelial cells. IL8 is involved in thrombophilia and angiogenesis, and highly expressed in various human cancers. It also plays an important role in chronic infection, inflammation, and cancer development, and its overexpression may implicate the increased susceptibility or the modulated clinicopathological features for different cancers.\(^10\) The corresponding gene polymorphisms may lead to the aberrant expression of IL8 and accordingly increase the risk of cancers. The -251T/A polymorphism is a T-to-A substitution that occurs at nucleotide -251, and the less A allele can lead to the increased expression of IL8. Xue and colleagues found that IL8 -251 AA genotype is associated with the overall risk of developing gastric cancer and may seem to cause more susceptibility to gastric cancer in Asian populations.\(^11\) Andia and colleagues demonstrated that IL8 gene promoter polymorphism (rs4073) may contribute to chronic periodontitis.\(^12\) Wang and colleagues reported that IL8 -251T/A polymorphism is associated with a significantly increased risk of cancers and may provide evidence-based medical certificate to study the cancer susceptibility.\(^13\) However, no connection was found with PCa risk in our meta-analysis. MDM2 is a major regulator of p53 function. It is well known that the functional role of MDM2 is related to the negative regulation of tumor suppressor p53. It acts with p53 in a feedback loop where p53 activates MDM2 at the transcriptional levels while MDM2 binds, inhibits and degrades the p53 protein through E3 ligase activity.\(^14\) Studies have shown that MDM2 antagonists-activated wild-type p53 in combination with androgen depletion may provide an efficacious approach to PCa therapy.\(^15\) The functional importance of this interaction is illustrated by the findings that reduction of the MDM2 expression level inhibits tumor formation in mice while depletion of the MDM2 gene leads to embryonic lethality, an effect rescued by concomitant p53 deletion.\(^16\) MDM2 amplification and/or protein over expression has been observed in many human cancers harboring wild-type TP53, the gene coding for the p53 protein,\(^17\) and MDM2 over expression has been suggested to act as an alternative mechanism to p53 inactivation, promoting tumor growth.\(^18\) The MDM2 gene plays a key role in the p53 pathway, and the SNP 309T/G in the promoter region of MDM2 has been shown to be associated with increased risk of cancer. However, we did not find a relationship between this polymorphism and PCa risk. Previous meta-analysis covering 4 independent studies showed no significant association between MDM2 309T/G polymorphism and PCa risk in whole analysis as well.\(^19\) Several limitations in this meta-analysis should be acknowledged. Firstly, the subgroups may have a relatively lower power based on a small number of studies. Secondly, other covariates such as age, sex and smoking status should be included to get a more precise result. Thirdly, other genes which may interact with these genes should be considered.

**CONCLUSION**

In conclusion, our results demonstrated that XPC, IL8, and MDM2 variants were not associated with increased risk of PCa. Further large scale studies with different populations and ethnicities are needed to confirm our results. Moreover studies addressing gene–gene and gene-environment interactions and polymorphisms in these 3 genes and the risk of PCa should also be performed and considered.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**

Figure 5. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association.


