Original Article

Lack of association between XPC Lys939Gln polymorphism and prostate cancer risk: an updated meta-analysis based on 3039 cases and 3253 controls

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Abstract: Several studies have evaluated the relationship between xeroderma pigmentosum complementation group C (XPC) variants and prostate cancer (PCa) risk. However, the results remain inconclusive. The objective of this study was to identify the role of XPC Lys939Gln variant on PCa occurrence. Relevant case-control studies published between 2000 and 2014 were retrieved in electronic databases. The pooled odds ratio (ORs) and 95% confidence interval (CI) were employed to calculate the strength of association. Finally, a total of eight articles including 3039 PCa patients and 3203 healthy controls were screened out. Our results found that the frequency of C allele was a little higher in PCa cases than that in control, but it was not associated with the increased risk of PCa (C vs. A: OR=1.05, 95% CI=0.98-1.13, P=0.19). This insignificant association was also observed in other genetic models (P>0.05). In subgroup analysis by ethnicity, no significant relationship was found in any study-population (Asian, Caucasian and African) as well. In conclusions, our results indicated that XPC Lys939Gln polymorphism was not associated with PCa susceptibility. Further large well-designed epidemiologic studies with gene-gene and gene-environment interaction should be included and considered.

Keywords: Prostate cancer, XPC, polymorphism, meta-analysis

Introduction

Prostate cancer (PCa) is the second most common diagnosed non-skin cancer and the sixth leading cause of cancer death in males [1], accounting for 27% of total male cancers. According to cancer statistics, about 233000 new cases and 29480 death are estimated to have occurred in 2014 among men in the United States [2]. The well-established risk factors: smoking [3], alcohol [4] and family history [5] have been proven to be involved in PCa occurrence. However, the specific mechanisms of PCa progression remain largely unknown. Epidemiologic studies have shown that approximately 42% of all PCa risk factors can be attributed to genetic influences [6], and the genetic-environmental interaction may explain the ethnic difference and geographical variations in the incidence and mortality [7]. Early detection of PCa in asymptomatic average risk men will contribute to the reduced incidence and mortality [8]. Therefore, exploring more new gene indicators for PCa risk is valuable.

During the last decades, genomic rearrangements have drawn public attention. Many studies have shown that genetic variants, resulting from transcriptional or chromatin aberrancies, engage in prostate carcinogenesis mechanisms [9]. Nucleotide excision repair (NER), one major DNA-repair pathway in human cells, involved in DNA damage repair, is the primary defense mechanism against mutagenic exposure [10]. Xeroderma pigmentosum complementation group C (XPC), located on human chromosome 3p25, is the primary initiating factor in the global genome NER [11]. XPC is a 940-residue DNA binding protein, stimulating repair of oxidative lesions by base excision repair [12]. Mutation of this gene can result in human carcinogenesis. Several most common single nucleotide polymorphisms (SNPs) of XPC have been identified. Among which, rs2228001 in exon 15, an A to C substitution at position 939 leading to Lysine to Glutamine replacement, was the most studied site. It has been shown that XPC Lys939Gln polymorphism may be a risk factor for bladder carcinogenesis [13], urinary bladder cancer
susceptibility [14], lung cancer risk [15], and colorectal cancer susceptibility [16].

Although a number of case-control studies have investigated the association between XPC Lys939Gln polymorphism and PCa risk, the results of these studies were controversial. Hirata et al. suggested that XPC Lys939Gln might be risk factors for PCa in Japanese; while, Yang et al. demonstrated that XPC Lys939Gln was not associated with the increased risk of PCa [17]. Thus, we conducted this meta-analysis to systematically reevaluate the role of XPC Lys939Gln polymorphism in the risk of developing PCa.

Materials and methods

Search strategy

We conducted a systematical literature search on electronic databases of PubMed, Embases and Medline to retrieve the related articles published between January 2000 and December 2014. The following terms: “prostate cancer or prostatic carcinoma”, “xeroderma pigmentosum complementation group C or XPC” and “polymorphism or variant or mutation” as well as their combinations were employed as the search words. References of retrieved articles were screened manually. When the same authors or laboratories reported the similar issue on the same populations, only the most recent articles were included.

Inclusion and exclusion criteria

The eligible articles had to meet the following criteria: 1) case-control studies; 2) evaluating the relationship between XPC Lys939Gln polymorphisms and PCa risk; 3) the patients should be histopathologically confirmed, the controls should be unrelated, cancer free, age- and sex-matched healthy individuals of similar ethnicity; and 4) the results were presented in odd ratios (ORs) with its corresponding 95% confidence interval (CI), and the genotype information was available to extract.

The exclusion criteria were as follows: 1) duplicated reports from the same authors or laboratories; 2) reviews or conference papers; 3) non-English written articles; and 4) without control group or controls were not race-matched.

Date extraction

Two investigators independently assessed the related data provided by authors of each study. Each item should be final reached a consensus. The following details were extracted from each article: first author, publication year, coun-
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Table 1. Main characteristics of included studies in this meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Mean age (range)</th>
<th>Sample size</th>
<th>Genotype method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirata H</td>
<td>2007</td>
<td>Japan</td>
<td>Asian</td>
<td>68±5 67±15</td>
<td>165 135</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Agalliu I-a</td>
<td>2010</td>
<td>USA</td>
<td>Caucasian</td>
<td>70.2 (35-74) 69.3 (35-74)</td>
<td>1308 1266</td>
<td>GeneMapper</td>
</tr>
<tr>
<td>Agalliu I-b</td>
<td>2010</td>
<td>USA</td>
<td>African</td>
<td>65.6 (35-74) 64.1 (35-74)</td>
<td>149 85</td>
<td>GeneMapper</td>
</tr>
<tr>
<td>Liu Y</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>70.7±8.4 70.4±10.0</td>
<td>202 221</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Mandal RK</td>
<td>2012</td>
<td>India</td>
<td>Caucasian</td>
<td>62.6±8.9 59.1±10.4</td>
<td>192 224</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Mittal RD</td>
<td>2012</td>
<td>India</td>
<td>Caucasian</td>
<td>66.0±5.46 64.7±5.71</td>
<td>195 250</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Sorour AF</td>
<td>2013</td>
<td>Egypt</td>
<td>African</td>
<td>65.4±8.7 65.4±8.7</td>
<td>50 50</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Mirecka A</td>
<td>2014</td>
<td>Poland</td>
<td>Caucasian</td>
<td>68.3 (41.96) 64.6 (35-92)</td>
<td>720 1121</td>
<td>Sequencing</td>
</tr>
<tr>
<td>Zhang XJ</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>66.7±8.2 67.3±7.5</td>
<td>229 264</td>
<td>PCR-MALDI-TOF</td>
</tr>
</tbody>
</table>

Table 2. Distribution of alleles and genotypes information in XPC Lys939Gln polymorphism in included studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Cases</th>
<th>Controls</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AC</td>
<td>CC</td>
</tr>
<tr>
<td>Hirata H</td>
<td>77</td>
<td>78</td>
<td>10</td>
</tr>
<tr>
<td>Agalliu I-a</td>
<td>457</td>
<td>595</td>
<td>205</td>
</tr>
<tr>
<td>Agalliu I-b</td>
<td>70</td>
<td>61</td>
<td>16</td>
</tr>
<tr>
<td>Liu Y</td>
<td>86</td>
<td>85</td>
<td>31</td>
</tr>
<tr>
<td>Mandal RK</td>
<td>93</td>
<td>71</td>
<td>28</td>
</tr>
<tr>
<td>Mittal RD</td>
<td>94</td>
<td>73</td>
<td>28</td>
</tr>
<tr>
<td>Sorour AF</td>
<td>16</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Mirecka A</td>
<td>214</td>
<td>290</td>
<td>98</td>
</tr>
<tr>
<td>Zhang XJ</td>
<td>158</td>
<td>38</td>
<td>33</td>
</tr>
</tbody>
</table>

HWE, hardy-weinberg equilibrium. h.68item should be finalcles; raries.

Egger’s test were used to assess the publication bias (P< 0.10 was considered statistical significance). All statistical analyses were performed using Review Manage (v.5; Oxford, England), and the algorithms was as previous described by Deeks et al. [18].

Results

Characteristics of included studies

A total of eight case-control studies were eligible after filtering with the inclusion and exclusion criteria, including 3039 PCa patients and 3203 healthy controls. Figure 1 showed the searching process. Of the eight articles, one contained two study populations [19]. For ethnicities, three were Asian population [20-22], four were Caucasian population [19, 23-25], and two were African population [19, 26]. The total number of sample size of each study ranged from 100 to 2574. Genotypes of controls in all included studies were accord with HWE except the study conducted by Zhang et al. Table 1 showed the main characteristics of the included studies. Table 2 listed the alleles and genotypes information of each study in this meta-analysis.

Meta-analysis

Table 3 presented the results of the relationship between XPC Lys939Gln polymorphism and PCa risk. Between-studies heterogeneity
was assessed, and the fixed-effect model was used in the allele model and the dominant model; the random-effect model was used in the homozygous model, the heterozygous model and the recessive model. Overall, we found that the frequency of C allele of XPC Lys939Gln polymorphism was a little higher in PCa patients than that in healthy controls (36.7% versus 35.6%). However, the C allele was not associated with increased the risk of PCa (C vs. A: OR=1.05, 95% CI=0.98-1.13, P=0.30) as shown in Figure 2. This insignificant association between XPC Lys939Gln polymorphism and PCa susceptibility was also observed under any other genetic models (CC vs. AA: OR=1.22, 95% CI=0.93-1.60, P=0.19 (Figure 3A)), CC vs. AC: OR=1.25, 95% CI=0.94-1.65, P=0.07 (Figure 3B); CC+AC vs. AA: OR=1.02, 95% CI=0.92-1.13, P=0.70 (Figure 3C); CC vs. AC+AA: OR=1.24, 95% CI=0.95-1.62, P=0.11 (Figure 3D).

Subgroup analysis by ethnicity found no significant association among Asians (C vs. A: OR=1.04, 95% CI=0.79-1.37, P=0.78; CC vs. AA: OR=1.00, 95% CI=0.45-2.22, P=0.99; CC vs. AC: OR=0.95, 95% CI=0.40-2.25, P=0.90; CC+AC vs. AA: OR=1.06, 95% CI=0.84-1.34, P=0.62; CC vs. AC+AA: OR=0.99, 95% CI=0.44-2.21, P=0.97), Caucasians (C vs. A: OR=1.05, 95% CI=0.97-1.14, P=0.23; CC vs. AA: OR=1.29, 95% CI=0.94-1.77, P=0.11; CC vs. AC: OR=1.34, 95% CI=0.97-1.85, P=0.07; CC+AC vs. AA: OR=1.02, 95% CI=0.90-1.14, P=0.79; CC vs. AC+AA: OR=1.32, 95% CI=0.97-1.81, P=0.08) and Africans (C vs. A: OR=1.02, 95% CI=0.74-1.42, P=0.90; CC vs. AA: OR=1.20, 95% CI=0.57-2.52, P=0.63; CC vs. AC: OR=1.36, 95% CI=0.66-2.82, P=0.41; CC+AC vs. AA: OR=1.04, 95% CI=0.60-1.47, P=0.77; CC vs. AC+AA: OR=1.21, 95% CI=0.64-2.57, P=0.48) in any genetic models as well.

### Publication bias

The symmetry of funnel plot indicated that there was no obvious publication bias in this meta-analysis as shown in Figure 4. Egger’s test was employed to further assess publication bias, and the results showed the absence of the publication bias (P>0.01).

### Discussion

In this meta-analysis, we evaluated the role of XPC Lys939Gln polymorphism in PCa susceptibility. Overall, our results showed that XPC Lys939Gln polymorphism was not associated with PCa susceptibility. In the subgroup analysis by ethnicity, no significant association was found in three races (Asian, Caucasian and African) as well. Our results were consistent with previous meta-analysis (five separate case-control studies including 1966 cases and 1970 controls) which showed that this variant not likely contributed to susceptibility to PCa [27].

PCa is the most frequent cancer among males in economically developed countries. The pathogenesis of PCa is likely involved the genetic
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Factors. Genetic variants may contribute to PCa risk. Numerous genetic variants in the DNA repair pathway have been explored. XPC protein, a DNA damage recognition factor, involves in initiating GG-NER pathway by recognizing the DNA lesion and recruiting downstream factors. It not only functions as an early damage sensor in open complex formation and in repair of complex protein formations, but also in the removal of oxidative DNA damage and redox homeostasis and cell-cycle control [28]. XPC expression is regulated by p53 at the transcriptional level. It has been identified a functional p53 response element in vivo in the coding sequence of the XPC protein [29]. In cells, XPC forms a complex with the HR23B [30] and Centrin2 proteins [31]. XPC-HR23B has previously been shown to be necessary and sufficient to support NER activity in vitro [32]. Moreover, XPC expression could be enhanced by SIRT1 through reducing AKT-dependent nuclear localization of XPC transcription repressor [33].

XPC expression may be involved in the process of cancer development and associated with cancer risk. Hsiao et al. found that the expression of nuclear XPC was significantly lower in cutaneous squamous cell carcinoma compared with their adjacent normal epidermis, and proved that the decreased XPC expression was associated with recurrent rate and high-risk cutaneous squamous cell carcinoma [34]. Lai et al. observed that XPC protein expression correlated with tumor stage, cigarette smoking and poor survival; and XPC expression could predict drug resistance in patients with lung adenocarcinoma [35]. Bai et al. firstly investigated XPC expression in sporadic breast cancer tissues, and showed that XPC was involved in the initiation and progression of breast cancer [36]. In addition, genetic variants may influence the XPC expression, leading to the progression of disease. Qiao et al. identified two 3'UTR variants of XPC which might be associated with bladder cancer risk [37]. Berger et al. demonstrated that XPC coding variants could affect protein function, and/or 3'UTR variants result in an altered protein levels via allele-specific miR binding [38]. Cartault et al. found that a new G to C homozygous substitution at 3'-end of XPC in intron 12 (IVS 12-1G/C) in the patients leads to the abolition of an acceptor splicing site and the absence of the XPC protein; and the highest worldwide prevalence of xeroderma pigmentosum are in black Mahori patients [39]. These findings indicate that XPC may play a role in prevention of human carcinogenesis.

Several mutations have been identified in XPC gene. XPC Lys939Gln A/C polymorphism has been shown to play an important role in digestive system cancer susceptibility [40] and significantly increase the risk of lung cancer in Asian population [41]; and it is also deemed to be involved in modulating colorectal cancer susceptibility independently or jointly [42]. XPC PAT+- polymorphism has been proven to associate with urinary system cancer risk [43], and contribute to the risk for developing bladder cancer in a Chinese Han population [44]. XPC Ala499Val is shown to significantly associate with lung and breast cancer risk [45], and bladder cancer susceptibility [46]. However, no association was found between polymorphisms of XPC Lys939Gln or Ala499Val and helicobacter pylori infection-related gastric antrum.

**Figure 2.** Forest plots of XPC Lys939Gln polymorphism and prostate cancer susceptibility under the allele model.
Figure 3. Meta-analysis of the association between XPC Lys939Gln polymorphism and prostate cancer risk under genotype models: A. The homozygous model (CC vs. AA); B. The heterozygous model (CC vs. AC); C. The dominant model (CC+AC vs. AA); D. The recessive model (CC vs. AC+AA).
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Several limitations were presented in previous meta-analysis. Firstly, the clinical stages of patients with PCa could not be extracted from the included studies. In the future researches, we should consider the genetic polymorphisms in each stage of PCa. Secondly, significant heterogeneity between studies was presented, which may influence the results. Thirdly, the number of included studies was small. Fourthly, the mean ages of patients were a little older, while other age groups should also be included. Lastly, other XPC variants or risk factors should be taken into account, moreover, gene-gene and gene-environment interactions should be considered.

In conclusion, our results found no significant association between XPC Lys939Gln polymorphism and PCa development. Future well-designed studies involving different ethnic populations are still needed to further investigate the role of XPC Lys939Gln polymorphism in PCa risk.

References

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[34] Hsiao YP, Chao WR and Wey SJ. Decreased Expression of Xeroderma Pigmentosum Group C (XPC) Protein in Cutaneous Squamous Cell Carcinoma. Life Science Journal 2014; 11.


