Link between genetics and prostate cancer

Abstract

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 unclearly. The purpose of this study was to evaluate the relationship between rs2228001 in XPC, rs4073 in IL8, and rs2279744 in MDM2 with PCa susceptibility.

Materials and Methods: Electronic database of PubMed, Medline and Embase were searched for relevant studies between 2000 and 2014. The odd ratio (OR) with its 95% corresponding interval (CI) were employed to estimate the strength of association.

Results: Total 18 case-control studies, including 5725 PCa cases and 5900 healthy controls, were screened out. For XPC 939A/C polymorphism, 6 articles were included, and there was no evidence for a significant association between XPC gene 939A/C polymorphism and PCa in the overall population. We also did not find any associations in subgroup by ethnicity. For IL8 -251T/A variant, the A allele was not concerned with PCa risk when compared with those individuals without A allele in any genetic models. For MDM2 -309T/G mutation, the G allele was not associated with increased the risk of PCa in total population and subgroup analysis by ethnicity as well.

Conclusions: Our study found 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. However, further studies with large-scale populations and concerning the interactions of gene-gene and gene-environmental should be considered.

Keywords: prostate cancer; XPC; IL8; MDM2; polymorphism; meta-analysis

Introduction

Prostate cancer (PCa) is one of the most 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 [1, 2]. Every year, a total of 238, 590 new cases are emerging and 29, 720 death are occurring according to cancer statistics, 2013 [3]. Multi-risk factors such as hormones, family history and lifestyle are associated with PCa. Due to extreme heterogeneity in PCa incidence worldwide, major determining factors have not been described [4], and the pathogenesis is still unciearly. Furthermore, the prevention and treatment of PCa remain complicated for treatment options depending on disease stage and patient choice to a large extent [5]. Thus, there is an urgent need to explore the molecular mechanism under this disease and develop newer target therapies.

During the last two decades, genetic factors are considered to contribute substantially to the development of PCa. For example, high Bcl-2 expression was associated with lower biochemical-free survival in patients with advanced PCa [6]. Polymorphisms of CYPlAl [7] and prostate-specific antigen [8] genes were shown to be related with increase the risk of sporadic PCa, and might be predisposing factors for PCa. Several genes have been the most studied. The xeroderma pigmentosum complementation group C (XPC) gene 1s located on chromosome 3p25 and is a 940-residue DNA binding protein. It serves as the primary initiating factor in the global genome base excision repair (NER) in human. and plays an important role in the early

steps. especially in damage recognition. open complex formation and reparation [9]. Recent reports suggest XPC also stimulates repair of oxidative lesions by NER. In cells. XPC binds to hHR23B to form the XPC-hHR23B complex [10].

Which is involved in the DNA damage recognition and DNA repair initiation in the NER pathway. and necessary and sufficient to support NER activity in vitro [11].

Sequence variants of the XPC gene may alter NER capacity and modulate cancer risk.

One polymorphism. Lys939Gln (an A to C transversion) in exon 15 of XPC has been identified and is the most studied.

Interleukin-8 (IL8) gene. located on chromosome 4q12-21 in humans. 1s composed of four exons. three introns. and a proximal promoter region. It is an important member of CXC chemokine family [12]. and is produced by a wide range of normal cells to initiate and amplify acute inflammatory reactions [13]. IL8 is well known for its leukocyte chemotactic proper ties. 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 sit. aT/A single nucleotide polymorphism was 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. inhibiting and promoting 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 single nucleotide polymorphism 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 et al. showed that XPC Lys939Gln polymorphism might be a risk factor for PCa in Japanese population [20]; however, Liu et al. did not found a significant association between this polymorphism and PCa in Chinese population [21].

McCarron et al. firstly demonstrated that IL8 variant might have a significant effect on disease development of PCa [22]; whereas Michaud et al. identified that IL8 variant did not play a role in the risk of PCa [23]. Xu et al. suggested that MDM2 309G allele was significantly related with PCa risk [24]; while Jerry et al. found no association between MDM2 SNP309 polymorphism and recurrence risk, clinicopathologic variables, and overall survival outcome in PCa [25]. Therefore, the purpose of this meta-analysis is to summarize the existing evidence on the prevalence of the genetic polymorphisms in patients diagnosed with PCa, and comprehensive and reliable assess of these polymorphisms with PCa risk.

Materialsandmethods

Identificationandeligibilityofrelevantstudies

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 searched with English language restrictions, The search was focused on studies that had been conducted in human, Only full-text articles and the most recent studies were included in this meta-analysis,

Criteriaforinclusion

The inclusion criteria were as follows: 1) the paper should be case-control or cohort association studies: 2) PCa cases were diagnosed and histopathologically confirmed, controls were cancer free, unrelated, age- and sex-matched healthy individuals of similar ethnicity: 3) 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): 4) genotype distribution information and odds ratio (OR) with its 95% confidence interval (CI) were available: and 5) genotype distribution of control for a certain polymorphism must be m Hardy-Weinberg equilibrium (HWE),

Dataextraction

Two investigators independently assessed the quality of the included studies according to the data extracted from each study, Any disagreement was subsequently resolved by discussion 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 was measured by odds ratio (OR) and its 95% confidence interval (CI), which were calculated according to the method of Woolf. The Z test was employed to determine the significance of the pooled ORs, and a P value less than 0. 05 was 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. TT IL8 -251A/T;

GG+GT vs. TT MDM2 -309T/G; and recessive effect: CC vs. AC+AA XPC 939A/C; AA vs. AT+TT IL8 -251A! T; GG vs. GT+TT MDM2 -309T/G) were examined. The 12 test and the Q-statistic test were employed to assess the between-study heterogeneity. The fixed-effects model is used when the effects are assumed to be homogenous ce less than 50% for the 12 test and p-value more than 0. 01 for the Q-test), while the random effects model is used when they are heterogenous. The evidence of publication bias was assessed by visual funnel plot inspection. Statistical analyses were

conducted in Review Manager (version 5. 2, The Cochrane Collaboration), and followed the program described by Collaboration et al. [26]. All the tests were two-sided.

Results

Studyselection andcharacteristics

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 was 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. Among them, the research conducted by Agalliu I et al. consisted two study ethnicity. For IL8 -251T/A, 6 studies [33-38] included 1942 cases and 1964 controls, all of which were Caucasians ethnicity. For MDM2 -309T/G, 6 studies [39-44] contained 1538 cases and 1678 controls including Asian and Caucasians ethnicity. The detailed characteristics of the studies included were shown in Table 1. The distributions of genotypes in the individual studies were 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 were listed in Table 3. The heterogeneity between studies was

calculated, and the fixed effect model or random effect model was employed 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 in the overall population (C vs. A: 0R= l. 06, 95% Cl= 0. 97-1. 15, P= 0. 22; CC vs. AA: 0R= l. 19, 95%

Cl= 0. 85-1. 68, P= 0. 32; CC+AC vs. AA: 0R= l. 03, 95% Cl= 0. 92-1. 17, P= 0. 59; CC vs.

AC+AA: 0R= l. 20, 95% Cl= 0. 85-1. 70, P= 0. 30) as shown in Figure 2. We also evaluated the effect of the polymorphism by ethnicity. We also did not detect a significant association between XPC gene 939A/C polymorphism and PCa risk in Asians, Caucasians or African population (P> 0. 05).

AssociationofILS-251T/ApolymorphismandPCarisk

Table 4 displayed the summary of all genetic comparisons between IL8 -251 T/A polymorphism and PCa risk. As shown in Figure 3, the result suggested 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= l. Ol , 95% Cl= 0. 92-1. 10, P= 0. 88). No significant association was found in other genetic models (AA vs. TT: 0R= l. 03, 95% Cl= 0. 86-1. 23, P= 0. 75; AA+AT vs. TT: 0R= 0. 99, 95% Cl= 0. 79-1. 24, P= 0. 90; AA vs. AT+TT: 0R= l. 02, 95% Cl= 0. 88-1. 17, P= 0. 80).

AssociationbetweenMDM2-309T/GpolymorphismandPCarisk

The overall analysis of the studies concerning MDM2 polymorphism and PCa risk was listed in Table 5, and revealed no significant association of MDM2-309T/G polymorphism with PCa risk in any genetic models (G vs. T: 0R= 0. 89, 95% Cl= 0. 76-1. 05, P= 0. 17; GG vs. TT: 0R= 0. 81, 95% Cl= 0. 56-1. 17, P= 0. 25; GG+GT vs. TT: 0R= 0. 84, 95% Cl= 0. 67-1. 06, P= 0. 14; GG vs. GT+TT: 0R= 0. 96, 95% Cl= 0. 80-1. 16, P= 0. 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 risk in nether Asian (P> 0. 05) nor Caucasians (P> 0. 05) population no matter what kind of genetic model was used.

Sensitivityanalysesandpublicationbias

A single study included in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. The corresponding pooled Ors were not materially changed. which confirmed the stability of our overall result. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Figure 5).

Discussion

The present meta-analysis examined the association between three commonly studied gene polymorphisms XPC 939AIC. IL8 -251T/A. MDM2 -309T/G and PCa risk. 18 separate articles including 5725 PCa cases and 5900 health controls were retrieved in the final analysis. Overall. we did not detect a significant association of 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 form a XPC-RAD23B complex with RAD23B. which is specifically involved in global genome repair and works as the earliest dam age 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 [46]. 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 [47]. XPC polymorphisms have been associated with increased risk of many human cancers. such as bladder cancer [48] and digestive system cancers [49]. Our results was consistent with previous meta-analysis conducted by Zou YF et al. which screened out five studies including 1966 cases and 1970 controls, suggesting this variant was not associated with PCa risk [50].

IL8 is one of key members of the human a-chemokine subfamily, and acts as a potent chemoattractant and activator of neutrophils [51]. 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 clinic-pathological features for different cancers [52]. The corresponding gene polymorphisms may lead to the aberrant expression of IL8 and accordingly increase the risk of cancers. -251Aff polymorphism is aT-to-A change that occurs at

Nucleotide -251, and the less A allele can lead to the increased expression of IL8. Xue et al. found that IL8 -251 AA genotype is associated with the overall risk of developing gastric cancer and may seem to be more susceptible to overall gastric cancer in Asian populations [14]. Andia et al. demonstrated that IL8 gene promoter polymorphism (rs4073) may contribute to chronic reriodontitis [53]. Wang et al. have indicated that IL8 -251Aff polymorphism is associated with a significantly increased risk of cancers and may provide evidence-based medical certificate to study the cancer susceptibility [54]. However, no connection was found in 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 [55]. Studies have shown that MDM2 antagonists-activated wide-type p53 in combination with androgen depletion may provide an efficacious approach to PCa therapy [56]. The functional importance of this inter-action 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 [57]. MDM2 amplification and/or protein over-expression has been observed in many human cancers harbouring wild-type TP53, the gene coding for the p53 protein [58], and MDM2 over-xpression has been suggested to act as an alternative mechanism to p53 inactivation, promoting tumor growth [59]. The MDM2 gene plays a key role in the p53 pathway, and the SNP 309T/G single-

nucleotide polymorphism 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 overall analysis as well [60].

Several limitations of this meta-analysis should be addressed. Firstly, the subgroups may have a relatively lower power based on a small number of studies.

Secondly, a more precise analysis should be conducted if individual information including other covariates such as age, sex and smoking condition becomes available.

Thirdly, other genes which may interact with these genes should be considered.

In conclusion, the results from the present meta-analysis suggested that XPC, IL8 and MDM2 variants were not associated with increased risk of PCa. Further large and well-designed studies in various populations are needed to confirm our results.

Moreover, studies of gene-gene and gene-environment interactions between these polymorphisms and PCa risk should also be performed and considered.