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.[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] 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,[4] 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.[5] 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.[6] Polymorphisms of drug-metabolizing genes cytochrome P4501A1 (CYPlAl)[7] and prostate-specific antigen (PSA)[8] genes were shown to be related with increase the risk 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.[9] 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,[10] 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.[11] 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[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 properties. Many studies have

Department of Urology, Affiliated Hospital of Huzhou Teachers› College, The First People›s Hospital of Hu zhou, Hu zhou, 313000, China.

*Correspondence: Department of Urology, Affiliated Hospital of Huzhou Teachers› College, The First People›s Hospital of Huzhou, Huzhou, 313000, China.

Tel: +86 572 2575091. Fax: +86 572 2023728. E-mail: rongjiangwang_r@163.com.

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Table 1. Characteristics of the included studies in the meta-analysis.

First Author	Year	Country	Ethnicity	Cases No.	Control No.	Genotyping Method
XPC 939A/C						
Hirata[27]	2007	Japan	Asian	165	165	PCR-RFLP
Agalloi[32]	2010	USA	Caucasians	1308	1266	PCR-RFLP
Agalloi[32]	2010	USA	African-Americans	149	85	PCR
Liu[21]	2012	China	Asian	202	221	PCR-RFLP
Mittal[28]	2012	India	Caucasians	195	250	PCR
Sorour[29]	2013	Egypt	African	50	50	PCR-RFLP
Zhang[30]	2014	China	Asian	229	238	PCR, MALDI-TOF MS
IL8 -251T /A						
McCarron[22]	2002	UK	Caucasians	247	263	PCR
Michaud[23]	2006	USA	Caucasians	503	652	Taqman-PCR
Yang[38]	2006	Finland	Caucasians	520	418	Taqman
Wang[37]	2009	USA	Caucasians	254	252	Taqman
Zhang[35]	2010	USA	Caucasians	193	197	PCR
Dluzeniewski[36]	2012	USA	Caucasians	484	484	Taqman-PCR
MDM2 -309T/G						
Kibei[44]	2008	USA	Caucasians	186	222	Pyrosequencing
Stoehr[43]	2008	Germany	Caucasians	145	124	PCR-RFLP
Hirata[39]	2009	Japan	Asian	140	167	PCR-RFLP
XuB[42]	2010	China	Asian	209	268	PCR-RFLP
Knappskog[41]	2012	Norway	Caucasians	666	675	PCR
Manda[40]	2012	Indian	Caucasians	192	224	PCR-RFLP

Abbreviations: PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; MALDI-TOF MS, matrix-assisted laser desorption ionisation mass spectrometry – time of flight.

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, 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 found 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-

Table 2. Distribution of genotypes and alleles in the individual studies.

First Author	Cases					Controls				
XPC	**AA**	**AC**	**CC**	**A**	**C**	**AA**	**AC**	**CC**	**A**	**C**
Hirata[27]	77	78	10	232	98	72	70	23	214	116
Agalloi[32]	457	595	205	1509	1005	461	600	190	1522	980
Agalloi[32]	70	61	16	201	93	36	38	9	110	56
Liu[21]	86	85	31	257	147	102	100	19	304	138
Mittal[28]	94	73	28	261	129	127	104	19	358	142
Sorour[29]	16	25	9	57	43	18	27	5	63	37
Zhang[30]	58	38	33	354	104	170	37	31	377	99
IL8	**AA**	**AT**	**TT**	**A**	**T**	**AA**	**AT**	**TT**	**A**	**T**
McCarron[22]	59	122	57	240	236	54	105	76	213	257
Michaud[23]	112	225	147	449	519	151	310	152	612	614
Yang[38]	103	236	181	442	598	66	217	135	349	487
Wang[37]	69	127	58	265	243	62	138	52	262	242
Zhang[35]	60	102				80	93			
Dluzeniewski[36]	107	218	121	432	460	106	207	133	419	473
MDM2	**TT**	**GT**	**GG**	**T**	**G**	**TT**	**GT**	**GG**	**T**	**G**
Kibei[44]	85	88	13	258	114	90	98	32	278	162
Stoehr[43]	61	66	18	188	102	41	64	19	146	102
Hirata[39]	58	56	26	172	108	56	79	32	191	143
Xu B[42]	44	118	47	206	212	68	143	57	279	257
Knappskog[41]	297	277	92	871	461	305	295	75	905	445
Manda[40]	67	71	54	205	179	53	98	73	204	244

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 were 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;

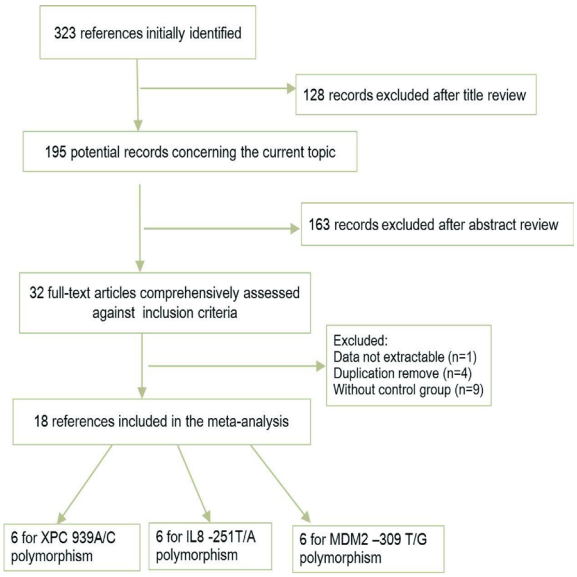

Figure 1. Flow chart diagram of literature review.

Table 3. Meta-analysis of xeroderma pigmentosum group C 939A/C polymorphism in prostate cancer.

Variables	Comparison	No.	OR (95% CI)	*P* Value*	Z	Ph**	I^2 (%)	Model
Overall	C vs. A	7	1.06 (0.97-1.15)	.22	1.22	0.29	18	F
	CC vs. AA	7	1.19 (0.85-1.68)	.32	1.00	0.04	54	R
	CC + AC vs. AA	7	1.03 (0.92-1.17)	.59	0.54	0.94	0	F
	CC vs. AC + AA	7	1.20 (0.85-1.70)	.30	1.04	0.03	58	R
Asian	C vs. A	3	1.04 (0.79-0.37)	.78	0.28	0.09	59	R
	CC vs. AA	3	1.00 (0.45-2.22)	.99	0.01	0.01	77	R
	CC + AC vs. AA	3	1.06 (0.84-1.34)	.62	0.49	0.62	0.0	F
	CC vs. AC + AA	3	0.99 (0.44-2.21)	.97	0.03	0.007	80	R
Caucasians	C vs. A	2	1.06 (0.95-1.18)	.27	1.09	0.24	29	F
	CC vs. AA	2	1.36 (0.77-2.42)	.29	1.06	0.08	67	R
	CC + AC vs. AA	2	1.03 (0.89-1.20)	.65	0.45	0.69	0.0	F
	CC vs. AC + AA	2	1.39 (0.76-2.53)	.28	1.08	0.06	72	R
African	C vs. A	2	1.02 (0.74-1.42)	.90	0.13	0.33	0.0	F
	CC vs. AA	2	1.20 (0.57-2.52)	.63	0.48	0.32	0.0	F
	CC+AC vs. AA	2	0.94 (0.60-1.47)	.77	0.29	0.49	0.0	F
	CC vs. AC + AA	2	1.28 (0.64-2.57)	.48	0.70	0.36	0.0	F

Abbreviations: OR, odds ratio; CI, confidence interval.
No, number of included studies.
* *P* value for overall effect.
** *P* value for heterogeneity among studies.

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 I2 test and the Q test were used to assess the between-study heterogeneity. 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.[26] All the tests were two-sided.

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

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

Comparison	No.	OR (95% Cl)	*P* Value*	Z	Ph**	I^2 (%)	Model
A vs. T	5	1.01 (0.92-1.10)	.88	0.15	0.23	29	F
AA vs. TT	5	1.03 (0.86-1.23)	.75	0.32	0.25	26	F
AA + AT vs. TT	5	0.99 (0.79-1.24)	.90	0.12	0.04	59	R
AA vs. AT + TT	6	1.02 (0.88-1.17)	.80	0.25	0.27	21	F

Abbreviations: OR, odds ratio; CI, confidence interval.
No, number of included studies.
* *P* value for overall effect.
** *P* value for heterogeneity among studies.

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

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

Abbreviations: OR, odds ratio; CI, confidence interval.
No, number of included studies.
* *P* value for overall effect.
** *P* value for heterogeneity among studies.

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, 0R = l.06, 95% CI: 97-1.15, *P* = .22; CC vs. AA, 0R = l.19, 95% CI: 0.85-1.68, *P* = .32; CC + AC vs. AA, OR = l.03, 95% CI: 0.92-1.17, *P* = .59; CC vs. AC + AA, OR = l.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 = l.0l, 95% CI: 0.92-1.10, *P* = .88). No significant association was found in other genetic models (AA vs. TT, OR = l.03, 95% CI: 0.86-1.23, *P* = .75;

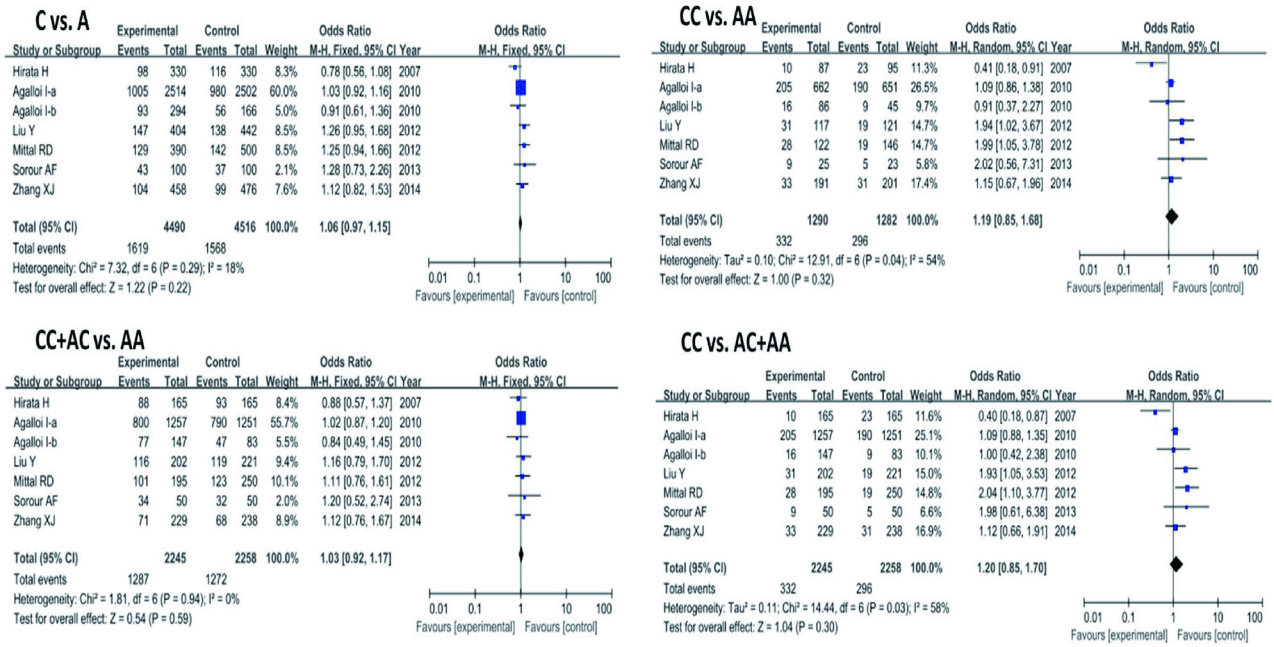

Figure 2. Forest plot on the association between C allele in xeroderma pigmentosum group C gene and risk of prostate cancer.

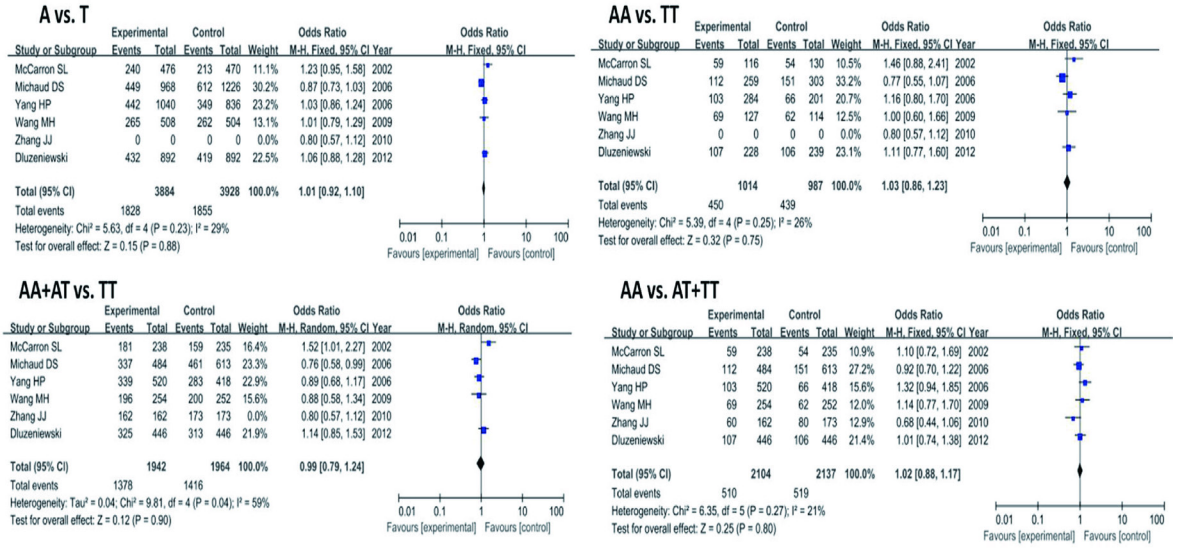

Figure 3. Meta-analysis of the association between interleukin 8 -251T/A polymorphism and risk of prostate cancer.

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 asymmetry, 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

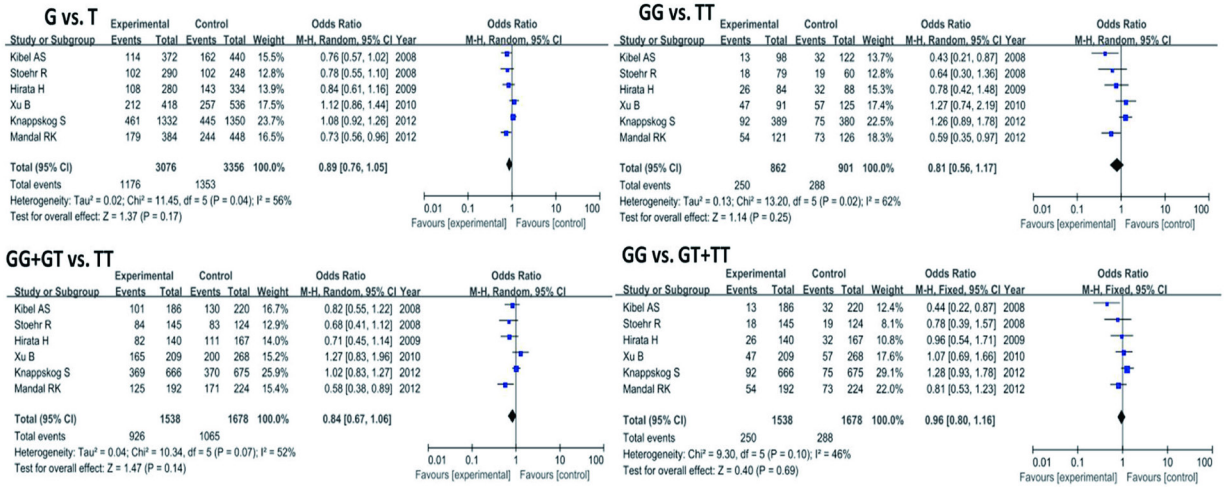

Figure 4. Forest plot of mouse double minute 2 (MDM2) homolog gene -309T/G polymorphism with risk of prostate cancer under each genetic models.

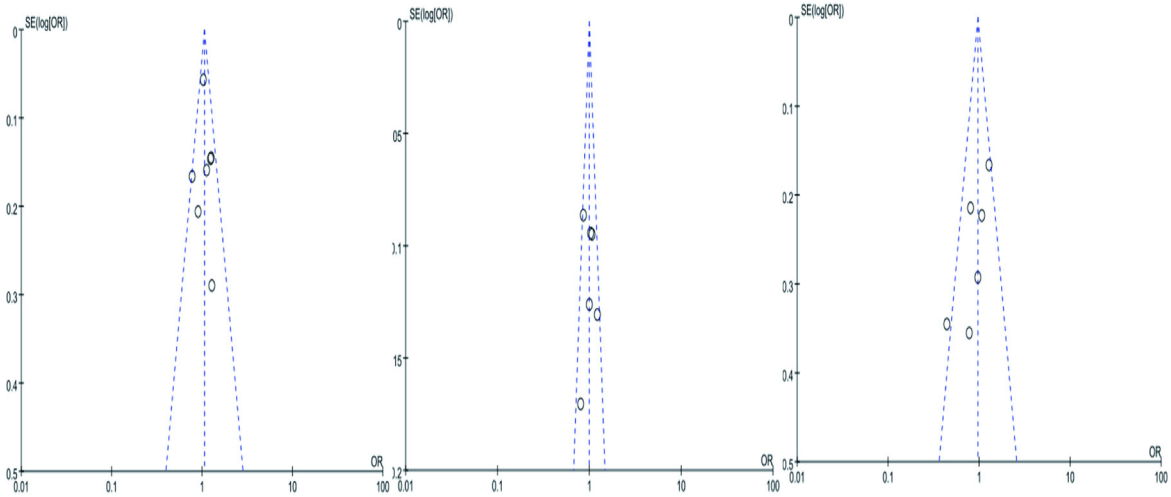

Figure 5. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association.

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 and colleagues in which screened out five studies including 1966 cases and 1970 controls, demonstrated that 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 clinicopathological features for different cancers.[52] 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.[14] Andia and colleagues demonstrated that IL8 gene promoter polymorphism (rs4073) may contribute to chronic periodontitis.[53] 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.[54] 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.[55] Studies have shown that MDM2 antagonists-activated wild-type p53 in combination with androgen depletion may provide an efficacious approach to PCa therapy.[56] 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.[57] 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,[58] and MDM2 over expression 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 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.[60] 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

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300.
2. Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A. Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer. 2010;46:3040-52.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11-30.
4. Nwosu V, Carpten J, Trent JM, Sheridan R. Heterogeneity of genetic alterations in prostate cancer: evidence of the complex nature of the disease. Hum Mol Genet. 2001;10:2313-8.
5. Halperin R, Maas B, Pickles T. Complications of prostate cancer treatment. Lancet Oncol. 2014;15:e151-2.
6. Anvari K, Seilanian Toussi M, Kalantari M, et al. Expression of Bcl-2 and Bax in advanced or metastatic prostate carcinoma. Urol J. 2012;9:381-8.
7. Shaik AP, Jamil K, Das P. CYP1A1 polymorphisms and risk of prostate cancer: a meta-analysis. Urol J. 2009;6:78-86.
8. Samzadeh M, Hasanzad M, Jamaldini SH, Haghdoost AA, Afshari M, Ziaee SA. Association of G/A polymorphism, rs266882, in AREI region of the prostate-specific antigen gene with prostate cancer risk and clinicopathological features. Urol J. 2012;9:691-9.
9. Shell SM, Hawkins EK, Tsai MS, Hlaing AS, Rizzo CJ, Chazin WJ. Xeroderma pigmentosum complementation group C protein (XPC) serves as a general sensor of damaged DNA. DNA Repair (Amst). 2013;12:947-53.
10. Masutani C, Araki M, Sugasawa K, et al. Identification and characterization of XPC-binding domain of hHR23B. Mol Cell Biol. 1997;17:6915-23.
11. Araújo SJ, Tirode F, Coin F, et al. Nucleotide excision repair of DNA with recombinant human proteins: definition of the minimal set of factors, active forms of TFIIH, and modulation by CAK. Genes Dev. 2000;14:349-59.
12. Strieter RM. Interleukin-8: a very important chemokine of the human airway epithelium. Am J Physiol Lung Cell Mol Physiol. 2002;283:L688-9.
13. Choi SE, Kim TH, Yi SA, et al. Capsaicin attenuates palmitate-induced expression of macrophage inflammatory protein 1 and interleukin 8 by increasing palmitate oxidation and reducing c-Jun activation in THP-1 (human acute monocytic leukemia cell) cells. Nutr Res. 2011;31:468-78.
14. Xue H, Liu J, Lin B, Wang Z, Sun J, Huang G. A meta-analysis of interleukin-8 -251 promoter polymorphism associated with gastric cancer risk. PLoS One. 2012;7:e28083.
15. Wang N, Zhou R, Wang C, et al. -251 T/A polymorphism of the interleukin-8 gene and cancer risk: a HuGE review and meta-analysis based on 42 case-control studies. Mol Biol Rep. 2012;39:2831-41.
16. Di J, Zhang Y, Zheng J. Reactivation of p53 by inhibiting Mdm2 E3 ligase: a novel antitumor approach. Curr Cancer Drug Targets. 2011;11:987-94.
17. Wade M1, Li YC, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. Nat Rev Cancer. 2013;13:83-96.
18. Tang YA, Lin RK, Tsai YT, et al. MDM2 overexpression deregulates the transcriptional control of RB/E2F leading to DNA methyltransferase 3A overexpression in lung cancer. Clin Cancer Res. 2012;18:4325-33.
19. Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell. 2004;119:591-602.
20. Hirata H, Hinoda Y, Tanaka Y, et al. Polymorphisms of DNA repair genes are risk factors for prostate cancer. Eur J Cancer. 2007;43:231-7.
21. Liu Y, Chen Z, Wei Q, et al. Poly (AT) polymorphism in the XPC gene and smoking enhance the risk of prostate cancer in a low-risk Chinese population. Cancer Genet. 2012;205:205-11.
22. McCarron SL, Edwards S, Evans PR, et al. Influence of cytokine gene polymorphisms on the development of prostate cancer. Cancer Res. 2002;62:3369-72.
23. Michaud DS, Daugherty SE, Berndt SI, et al. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. Cancer Res. 2006;66:4525-30.
24. Xu Z, Wei B. Editorial comment from Dr Xu and Dr Wei to Murine double minute 2 promoter SNP309 polymorphism and prostate cancer risk: a meta-analysis. Int J Urol. 2012;19:922.
25. Jaboin JJ, Hwang M, Perez CA, et al. No evidence for association of the MDM2-309 T/G promoter polymorphism with prostate cancer outcomes. Urol Oncol. 2011;29:319-23.
26. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
27. Hirata H, Hinoda Y, Tanaka Y, et al. Polymorphisms of DNA repair genes are risk factors for prostate cancer. Eur J Cancer. 2007;43:231-7.
28. Mittal RD, Mandal RK. Genetic variation in nucleotide excision repair pathway genes influence prostate and bladder cancer susceptibility in North Indian population Indian J Hum Genet. 2012;18:47-55.

29. Sorour AF, Talaat IM, Youssif TMA, Atta MA. Detection of Polymorphisms of DNA Repair Genes (XRCC1 and XPC) in Prostate Cancer. JCT. 2013;10:1499-1505 .
30. Zhang XJ, Liu P, Zhu F. Polymorphisms of DNA repair-related genes with susceptibility and prognosis of prostate cancer. Genet Mol Res. 2014;13:4419-24.
31. Liu Y, Chen Z, Wei Q, et al. Poly (AT) polymorphism in the XPC gene and smoking enhance the risk of prostate cancer in a low-risk Chinese population. Cancer Genet. 2012;205:205-11.
32. Agalliu I, Kwon EM, Salinas CA, Koopmeiners JS, Ostrander EA, Stanford JL. Genetic variation in DNA repair genes and prostate cancer risk: results from a population-based study. Cancer Causes Control. 2010;21:289-300.
33. Michaud DS1, Daugherty SE, Berndt SI, et al. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. Cancer Res. 2006;66:4525-30.
34. McCarron SL1, Edwards S, Evans PR, et al. Influence of cytokine gene polymorphisms on the development of prostate cancer. Cancer Res. 2002;62:3369-72.
35. Zhang J, Dhakal IB, Lang NP, Kadlubar FF. Polymorphisms in inflammatory genes, plasma antioxidants, and prostate cancer risk. Cancer Causes Control. 2010;21:1437-44.
36. Dluzeniewski PJ, Wang MH, Zheng SL, et al. Variation in IL10 and other genes involved in the immune response and in oxidation and prostate cancer recurrence. Cancer Epidemiol Biomarkers Prev. 2012;21:1774-82.
37. Wang MH, Helzlsouer KJ, Smith MW, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. Prostate. 2009;69:874-85.
38. Yang HP, Woodson K, Taylor PR, et al. Genetic variation in interleukin 8 and its receptor genes and its influence on the risk and prognosis of prostate cancer among Finnish men in a large cancer prevention trial. Eur J Cancer Prev. 2006;15:249-53.
39. Hirata H1, Hinoda Y, Kikuno N, et al. Bcl2 -938C/A polymorphism carries increased risk of biochemical recurrence after radical prostatectomy. J Urol. 2009;181:1907-12.
40. Mandal RK, Mittal RD. Are cell cycle and apoptosis genes associated with prostate cancer risk in North Indian population? Urol Oncol. 2012;30:555-61.
41. Knappskog S, Trovik J, Marcickiewicz J, et al. SNP285C modulates oestrogen receptor/Sp1 binding to the MDM2 promoter and reduces the risk of endometrial but not prostatic cancer. Eur J Cancer. 2012;48:1988-96.
42. Xu B, Xu Z, Cheng G, et al. Association between polymorphisms of TP53 and MDM2 and prostate cancer risk in southern Chinese. Cancer Genet Cytogenet. 2010;202:76-81.
43. Stoehr R, Hitzenbichler F, Kneitz B, et al. Mdm2-SNP309 polymorphism in prostate cancer: no evidence for association with increased risk or histopathological tumour characteristics. Br J Cancer. 2008;99:78-82.
44. Kibei AS, Jin CH, Klim A, et al. Association between polymorphisms in cell cycle genes and advanced prostate carcinoma. Prostate. 2008;68:1179-86.
45. Bergink S, Toussaint W, Luijsterburg MS, et al. Recognition of DNA damage by XPC coincides with disruption of the XPC-RAD23 complex. J Cell Biol. 2012;196:681-8.
46. Fleming ND, Agadjanian H, Nassanian H, et al. Xeroderma pigmentosum complementation group C single-nucleotide polymorphisms in the nucleotide excision repair pathway correlate with prolonged progression-free survival in advanced ovarian cancer. Cancer. 2012;118:689-97.
47. Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. Arch Dermatol. 1994;130:1018-21.
48. Li WQ, Pfeiffer RM, Hyland PL, et al. Genetic polymorphisms in the 9p21 region associated with risk of multiple cancers. Carcinogenesis. 2014;35:2698-705.
49. Jiang X, Zhou LT, Zhang SC, Chen K. XPC Polymorphism Increases Risk of Digestive System Cancers: Current Evidence from A Meta-Analysis. Chin J Cancer Res. 2012;24:181-9.
50. Zou YF, Tao JH, Ye QL, et al. Association of XPC gene polymorphisms with susceptibility to prostate cancer: evidence from 3,936 subjects. Genet Test Mol Biomarkers. 2013;17:926-31.
51. Matsushima K, Baldwin ET, Mukaida N. Interleukin-8 and MCAF: novel leukocyte recruitment and activating cytokines. Chem Immunol. 1992;51:236-65.
52. Cacev T, Radosević S, Krizanac S, Kapitanović S. Influence of interleukin-8 and interleukin-10 on sporadic colon cancer development and progression. Carcinogenesis. 2008;29:1572-80.
53. Andia DC, de Oliveira NF, Letra AM, Nociti FH Jr, Line SR, de Souza AP. Interleukin-8 gene promoter polymorphism (rs4073) may contribute to chronic periodontitis. J Periodontol. 2011;82:893-9.
54. Wang Z, Liu Y, Yang L, Yin S, Zang R, Yang G. The polymorphism interleukin-8 -251A/T is associated with a significantly increased risk of cancers from a meta-analysis. Tumour Biol. 2014;35:7115-23.
55. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature.

1997;387:299-303.

56. Tovar C, Higgins B, Kolinsky K, et al. MDM2 antagonists boost antitumor effect of androgen withdrawal: implications for therapy of prostate cancer. Mol Cancer. 2011;10:49.

57. Toledo F, Wahl GM. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. Nat Rev Cancer. 2006;6:909-23.

58. Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. Nucleic Acids Res. 1998;26:3453-9.

59. Bartel F1, Meye A, Würl P, et al. Amplification of the MDM2 gene, but not expression of splice variants of MDM2 MRNA, is associated with prognosis in soft tissue sarcoma. Int J Cancer. 2001;95:168-75.

60. Chen T, Yi SH, Liu XY, Liu ZG. Meta-analysis of associations between the MDM2-T309G polymorphism and prostate cancer risk. Asian Pac J Cancer Prev. 2012;13:4327-30.