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

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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 (CYP1AI)⁽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

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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

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

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-

				8						
First Author	Cases					Controls				
XPC	AA	AC	CC	Α	С	AA	AC	CC	Α	С
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	Α	Т	AA	AT	TT	Α	Т
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	Т	G	TT	GT	GG	Т	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
$\mathrm{Xu}~\mathrm{B}^{42}$	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

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

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;



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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

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

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 939Å/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.

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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

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

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, OR =1.06, 95% CI: 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 be-

tween 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;

C vs. A	Experim	ental	Cont	ol		Odds Ratio			Odd	Is Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	Q	M-H, Fit	xed, 95% (
Hirata H	98	330	116	330	8.3%	0.78 [0.56, 1.08]	2007			-		
Agalloi I-a	1005	2514	980	2502	60.0%	1.03 [0.92, 1.16]	2010					
Agalloi I-b	93	294	56	166	5.0%	0.91 [0.61, 1.36]	2010			+		
Liu Y	147	404	138	442	8.5%	1.26 [0.95, 1.68]	2012			-		
Mittal RD	129	390	142	500	8.5%	1.25 [0.94, 1.66]	2012					
Sorour AF	43	100	37	100	2.1%	1.28 [0.73, 2.26]	2013			+-		
Zhang XJ	104	458	99	476	7.6%	1.12 [0.82, 1.53]	2014			t		
Total (95% CI)		4490		4516	100.0%	1.06 [0.97, 1.15]				•		
Total events	1619		1568									
Heterogeneity: Chi2 =	7.32, df = 6	(P=0.)	29); l ² = 1	8%						+	+	400
Test for overall effect:	Z = 1.22 (F	9 = 0.22)				F	0.01 avours	0.1 fexperimental	1 Favours	10 (cont	roll

CC+AC vs. AA

	Experim	ental	Contr	ol		Odds Ratio			0	dds Ratio)	
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H.	Fixed, 95	% CI	
firata H	88	165	93	165	8.4%	0.88 [0.57, 1.37]	2007			+		
galloi I-a	800	1257	790	1251	55.7%	1.02 [0.87, 1.20]	2010					
galloi I-b	77	147	47	83	5.5%	0.84 [0.49, 1.45]	2010			+		
iu Y	116	202	119	221	9.4%	1.16 [0.79, 1.70]	2012			+		
littal RD	101	195	123	250	10.1%	1.11 [0.76, 1.61]	2012			+		
orour AF	34	50	32	50	2.0%	1.20 [0.52, 2.74]	2013			+		
hang XJ	71	229	68	238	8.9%	1.12 [0.76, 1.67]	2014			+		
otal (95% CI)		2245		2258	100.0%	1.03 [0.92, 1.17]				•		
otal events	1287		1272									
leterogeneity: Chi2 =	1.81, df = 6	6 (P = 0.	94); l² = 0	1%				-	1	+	+	100
est for overall effect:	Z = 0.54 (F	P = 0.59					F	10.0	U.I	tall Eave	10	TOU

CC vs. AA	Experim	ental	Contr	ol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% CI
Hirata H	10	87	23	95	11.3%	0.41 [0.18, 0.91]	2007	
Agalloi I-a	205	662	190	651	26.5%	1.09 [0.86, 1.38]	2010	•
Agalloi I-b	16	86	9	45	9.7%	0.91 [0.37, 2.27]	2010	
Liu Y	31	117	19	121	14.7%	1.94 [1.02, 3.67]	2012	
Mittal RD	28	122	19	146	14.7%	1.99 [1.05, 3.78]	2012	
Sorour AF	9	25	5	23	5.8%	2.02 [0.56, 7.31]	2013	
Zhang XJ	33	191	31	201	17.4%	1.15 [0.67, 1.96]	2014	-
Total (95% CI)		1290		1282	100.0%	1.19 [0.85, 1.68]		•
Total events	332		296					
Heterogeneity: Tau ² =	0.10; Chi2	= 12.91,	df = 6 (P	= 0.04); l ² = 54%			
Test for overall effect:	Z = 1.00 (F	P = 0.32)					Fa	avours (experimental) Favours (control)

CC vs. AC+AA

	Experim	ental	Contr	ol		Odds Ratio		Odd	s Ratio	
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Ran	dom, 95% CI	
lirata H	10	165	23	165	11.6%	0.40 [0.18, 0.87]	2007			
galloi I-a	205	1257	190	1251	25.1%	1.09 [0.88, 1.35]	2010		•	
galloi I-b	16	147	9	83	10.1%	1.00 [0.42, 2.38]	2010	-	•	
iu Y	31	202	19	221	15.0%	1.93 [1.05, 3.53]	2012		-	
Aittal RD	28	195	19	250	14.8%	2.04 [1.10, 3.77]	2012		-	
forour AF	9	50	5	50	6.6%	1.98 [0.61, 6.38]	2013	-	· · ·	
hang XJ	33	229	31	238	16.9%	1.12 [0.66, 1.91]	2014	-	+	
otal (95% CI)		2245		2258	100.0%	1.20 [0.85, 1.70]			•	
otal events	332		296							
leterogeneity: Tau ² =	0.11; Chi2	= 14.44,	df = 6 (P	= 0.03); 2 = 58%	6			+ +	
est for overall effect:	Z = 1.04 (F	9 = 0.30)					Fa	0.01 0.1 avours [experimental]	1 10 Favours (con	100 trol]

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

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A vs. T									AA vs. TT						011-0-1		011-0-1
	Experim	ental	Contr	ol		Odds Ratio		Odds Ratio		Experime	ntal	Contro	DI		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
McCarron SL	240	476	213	470	11.1%	1.23 (0.95, 1.58)	2002		McCarron SL	59	116	54	130	10.5%	1.46 [0.88, 2.41]	2002	
Michaud DS	449	968	612	1226	30.2%	0.87 (0.73, 1.03)	2006		Michaud DS	112	259	151	303	33.2%	0.77 [0.55, 1.07]	2006	-
Yang HP	442	1040	349	836	23.2%	1.03 [0.86, 1.24]	2006	•	Yang HP	103	284	66	201	20.7%	1.16 [0.80, 1.70]	2006	-
Wang MH	265	508	262	504	13.1%	1 01 [0 79, 1 29]	2009	+	Wang MH	69	127	62	114	12.5%	1.00 [0.60, 1.66]	2009	-
Zhang JJ	0	0	0	0	0.0%	0.80 [0.57, 1.12]	2010		Zhang JJ	0	0	0	0	0.0%	0.80 [0.57, 1.12]	2010	
Dluzeniewski	432	892	419	892	22.5%	1 06 [0.88, 1 28]	2012	•	Dluzeniewski	107	228	106	239	23.1%	1.11 [0.77, 1.60]	2012	*
DIGEONORION	101	OOL	110	001		1100 [0100] 1120]	LUIL	2									
Total (95% CI)		3884		3928	100.0%	1.01 [0.92, 1.10]		•	Total (95% CI)		1014		987	100.0%	1.03 [0.86, 1.23]		•
Total events	1828		1855						Total events	450		439				10	
Heterogeneity: Chi2 = 5	5.63 df = 4	(P = 0.2)	3): 12 = 2	9%			1		Heterogeneity: Chi2 = 5	5.39, df = 4	(P = 0.2	5); l² = 28	5%			H	1 01 1 10 100
Test for overall effect:	7 = 0 15 /F	2 = 0.88)		010				0.01 0.1 1 10 100	Test for overall effect:	Z = 0.32 (P	= 0.75)					Eauto	re lovnerimentall Eavoure (control)
rest for oreful encou.	- 0.10 li	- 0.00)					Fav	ours [experimental] Favours [control]								ravu	ais [experimental] Payou's [control]
AA+AT vs. T	т								AA vs. AT	+TT							
AA+AT vs. T	Experimen	ntal	Control			Odds Ratio		Odde Ratio	AA vs. AT	+TT					011 0.1		011.01
AA+AT vs. T	Experimer Experimer	ntal Total E	Control	ntal V	Veight	Odds Ratio	Vear	Odds Ratio	AA vs. AT	+TT Experi	imental	Co	ntrol		Odds Ratio		Odds Ratio
AA+AT vs. T	Experimer Events	ntal Total E	Control vents T	otal V	Veight	Odds Ratio M-H. Random, 95% CI	Year 2002	Odds Ratio M-H, Random, 95% Cl	AA vs. AT	Experi	imental s Tota	Co I Even	ntrol ts Tot	tal Weigl	Odds Ratio	CI Year	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL	Experimer Events 181	ntal Total E 238	Control vents T 159	otal V 235	Veight 16.4%	Odds Ratio M-H. Random, 95% CI 1.52 [1.01, 2.27]	2002	Odds Ratio M-H. Random, 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL	Experi Experi <u>p Events</u> 59	imental <u>s Tota</u> 9 23	Co I <u>l Even</u> 8 {	ntrol ts Tot 54 23	tal Weig 35 10.9'	Odds Ratio <u>M-H, Fixed, 95%</u> % 1.10 [0.72, 1.6	Cl Year 9] 2002	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Vace MB	Experimer Events 181 337 230	ntal <u>Total E</u> 238 484 520	Control vents T 159 461 292	otal V 235 613	Veight 16.4%	Odds Ratio M-H. Random, 95% CI 1.52 (1.01, 2.27) 0.76 (0.58, 0.99) 0.88 (0.68, 1.17)	2002 2006	Odds Ratio M-H. Random, 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS	Experi Experi <u>p Events</u> 59 112	imental <u>s Tota</u> 9 23 2 48	Co I <u>I Even</u> 8	ntrol t <u>s Tot</u> 54 2: 51 6'	tal Weigl 35 10.9' 13 27.2'	Odds Ratio nt <u>M-H, Fixed, 95%</u> % 1.10 [0.72, 1.6 % 0.92 [0.70, 1.2	Cl Year 9] 2002 2] 2006	Odds Ratio M-H. Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Yang HP Wicca MH	Experimer Events 181 337 339	ntal <u>Total E</u> 238 484 520 254	Control vents T 159 461 283 200	otal V 235 613 418	Veight 16.4% 23.3% 22.9%	Odds Ratio M-H. Random, 95% CI 1.52 (1.01, 2.27) 0.76 (0.58, 0.99) 0.89 (0.68, 1.17)	2002 2006 2006	Odds Ratio M-H, Random, 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP	Experi Experi <u>p Events</u> 59 112 103	imental <u>s Tota</u> 2 48 3 52	Co I <u>I Even</u> 8 6 4 15 0 6	ntrol t <u>s Tot</u> 54 2: 51 6 [:] 56 4 [:]	tal Weigl 35 10.9 13 27.2 18 15.6	Odds Ratio nt M-H, Fixed, 95% % 1.10 [0.72, 1.6 % 0.92 [0.70, 1.2 % 1.32 [0.94, 1.8	Cl Year 9] 2002 2] 2006 5] 2006	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Yang HP Wang MH Zhene LL	Experimer Events 181 337 339 196	ntal <u>Total E</u> 238 484 520 254 162	Control vents T 159 461 283 200 172	<u>otal V</u> 235 613 418 252	Veight 16.4% 23.3% 22.9% 15.6%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.52 [1.01, 2.27] 0.76 [0.58, 0.99] 0.88 [0.68, 1.17] 0.88 [0.58, 1.34]	2002 2006 2006 2009	Odds Ratio M-H. Random, 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH	Experi Experi <u>p Events</u> 59 112 103 69	imental s Tota 2 48 3 52 9 25	Co <u>I Even</u> 8 5 4 15 0 6 4 6	ntrol ts Tot 54 2: 51 6: 56 4: 52 2:	tal Weigl 35 10.9 13 27.2 18 15.6 52 12.0	Odds Ratio <u>M-H, Fixed, 95%</u> % 1.10 [0.72, 1.6 % 0.92 [0.70, 1.2 % 1.32 [0.94, 1.8 % 1.14 [0.77, 1.7	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dhenenimuti	Experimer Events 181 337 339 196 162	ntal <u>Total E</u> 238 484 520 254 162 446	Control vents T 159 461 283 200 173 212	otal V 235 613 418 252 173	Veight 16.4% 23.3% 22.9% 15.6% 0.0%	Odds Ratio <u>M-H. Random, 95% Cl</u> 1.52 [1.01, 2.27] 0.76 [0.58, 0.99] 0.89 [0.68, 1.17] 0.88 [0.58, 1.34] 0.80 [0.57, 1.12] 1.14 [0.5 1.52]	2002 2006 2006 2009 2010	Odds Ratio M-H. Random. 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH Zhang JJ	Experi Experi <u>p Events</u> 59 112 103 69 60	imental <u>s Tota</u> 2 48 3 52 9 25 0 16	Co <u>I Even</u> 8 5 4 15 0 6 4 6 2 8	ntrol ts Tol 54 23 51 6 56 4 56 4 52 25 50 17	tal Weigl 35 10.9 13 27.2 18 15.6 52 12.0 73 12.9	Odds Ratio ht M-H, Fixed, 95% % 1.10 [0.72, 1.6 % 0.92 [0.70, 1.2 % 1.32 [0.94, 1.8 % 1.14 [0.77, 1.7 % 0.68 [0.44, 1.0	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010	Odds Ratio M-H. Fixed. 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski	Experimer Events 181 337 339 196 162 325	ntal 238 484 520 254 162 446	Control vents T 159 461 283 200 173 313	otal V 235 613 418 252 173 446	Veight 16.4% 23.3% 22.9% 15.6% 0.0% 21.9%	Odds Ratio M-H, Random, <u>95% C1</u> 1.52 (1.01, 2.27) 0.76 (0.58, 0.99) 0.89 (0.68, 1.17) 0.88 (0.58, 1.34) 0.80 (0.57, 1.12) 1.14 (0.85, 1.53)	2002 2006 2006 2009 2010 2012	Odds Ratio M-H. Random. 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski	Experi Experi <u>p Events</u> 112 103 69 60 107	imental <u>s Tota</u> 2 48 3 52 9 25 0 16 7 44	Co Even 8 5 4 15 0 6 4 6 2 8 6 10	ntrol ts Tot 54 2: 51 6 56 4 52 2: 50 1 50 1 50 4	tal Weigl 35 10.9' 13 27.2' 18 15.6' 52 12.0' 73 12.9' 46 21.4'	Odds Ratio ht M-H, Fixed, 95% 6 0.92 [0.70, 1.2 6 1.32 [0.94, 1.8 7 1.14 [0.77, 1.7 8 0.68 [0.44, 1.0 9 1.01 [0.74, 1.3	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010 8] 2012	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% Cl)	Experiment 181 337 339 196 162 325	ntal <u>Total E</u> 238 484 520 254 162 446 1942	Control vents T 159 461 283 200 173 313	otal V 235 613 418 252 173 446 964 1	Veight 16.4% 23.3% 22.9% 15.6% 0.0% 21.9% 00.0%	Odds Ratio M-H. Random, 95% CI 1.52 [1.01, 2.27] 0.76 [0.58, 0.99] 0.89 [0.68, 1.17] 0.88 [0.58, 1.34] 0.80 [0.57, 1.12] 1.14 [0.85, 1.53] 0.99 [0.79, 1.24]	2002 2006 2006 2009 2010 2012	Odds Ratio M-H. Random. 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski	Experi <u>Experi</u> <u>55</u> 112 103 65 60 107	imental <u>s Tota</u> 2 23 2 48 3 52 9 25 0 16 7 44	Co <u>I Even</u> 8 8 4 15 0 6 4 6 2 8 6 10	ntrol ts Tol 54 2: 51 6 56 4 56 4 52 2: 50 17 50 4	tal Weigl 35 10.9' 13 27.2' 18 15.6' 52 12.0' 73 12.9' 46 21.4'	Odds Ratio t. <u>M-H, Fixed, 95%</u> % 1.10 [0.72, 1.6 % 0.92 [0.70, 1.2 % 1.32 [0.94, 1.8 % 1.14 [0.77, 1.7 % 0.68 [0.44, 1.0 % 1.01 [0.74, 1.3	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010 8] 2012	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCaron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% Cl) Total events	Experiment Events 181 337 339 196 162 325 1378	ntal <u>Total E</u> 238 484 520 254 162 446 1942	Control vents T 159 461 283 200 173 313 11 1416	otal V 235 613 418 252 173 446 964 1	Veight 16.4% 23.3% 22.9% 15.6% 0.0% 21.9% 00.0%	Odds Ratio <u>M-H. Random, 95% CI</u> 1.52 [1.01, 2.27] 0.76 [0.58, 0.99] 0.88 [0.68, 1.37] 0.88 [0.58, 1.34] 0.80 [0.57, 1.12] 1.14 [0.85, 1.53] 0.99 [0.79, 1.24]	2002 2006 2006 2009 2010 2012	Odds Ratio M-H. Random, 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% CI)	Experi <u>Experi</u> <u>59</u> 112 103 69 60 107	imental <u>s Tota</u> 2 48 3 52 9 25 9 25 9 16 7 44 210	Co <u>I Even</u> B 5 4 15 0 6 4 6 2 8 6 10 4	ntrol ts Tol 54 2: 51 6' 56 4' 52 2: 50 17 50 4 213	tal Weigl 35 10.9 13 27.2 18 15.6 52 12.0 73 12.9 46 21.4 37 100.0	Odds Ratio 11 M-H, Fixed, 95% 1.10 (0.72, 16 0.92 (0.70, 1.2 1.32 (0.94, 1.8 1.14 (0.77, 1.7 0.68 (0.44, 1.0 1.01 (0.74, 1.3 1.02 (0.88, 1.1	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010 8] 2012 7]	Odds Ratio M-H. Fixed. 95% Cl
AA+AT vs. T Study or Subgroup McCaron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% CI) Total events Heteropenetic Tar2 = 0	Experimer Events 181 337 339 196 162 325 1378 04 Ch ² =	ntal <u>Total E</u> 238 484 520 254 162 446 1942 9.81. df =	Control vents T 159 461 283 200 173 313 111 1416 4 (P = 0	otal V 235 613 418 252 173 446 446 964 1	Veight 16.4% 23.3% 22.9% 15.6% 0.0% 21.9% 00.0% = 59%	Odds Ratio M-H. Random. 95% CI 1.52 (10.1, 2.27) 0.76 (0.58, 0.99) 0.88 (0.68, 1.17) 0.88 (0.58, 1.34) 0.80 (0.57, 1.12) 1.14 (0.85, 1.53) 0.99 (0.79, 1.24)	2002 2006 2006 2009 2010 2012	Odds Ratio M-H. Random .95% Cl	AA vs. AT <u>Study or Subgrou</u> McCaron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% CI) Total events	+TT Experi p Events 59 112 103 69 60 107 510	imental <u>s Tota</u> 2 48 3 52 3 52 3 52 3 52 3 52 3 52 3 52 3 25 3 16 7 44 210	Co <u>I Even</u> 8 5 4 15 0 6 4 6 2 8 6 10 4 51	ntrol ts Tol 54 2: 51 6: 56 4: 52 2: 50 1: 50 4: 50 1: 50 4: 50 1: 50 4: 51 5: 51 6: 52 2: 50 1: 50 1: 50 1: 51 5: 52 2: 50 1: 50 1: 5	tal Weigl 35 10.9' 13 27.2' 18 15.6' 52 12.0' 73 12.9' 46 21.4' 37 100.0'	Odds Ratio 11 M-H, Fixed, 95% 1.10 (0.72, 1.6 0.92 (0.70, 1.2 1.32 (0.94, 1.8 1.14 (0.77, 1.7 0.68 (0.44, 1.0 1.01 (0.74, 1.3 1.02 (0.88, 1.1	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010 8] 2012 7]	Odds Ratio M-H, Fixed, 95% Cl
AA+AT vs. T Study or Subgroup McCaron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% C!) Total events Heterogeneity: Tau ^a = 0.	Experimer Events 181 337 339 196 162 325 1378 .04; Chi ² = 1 .04; Chi ² = 0	ntal <u>Total E</u> 238 484 520 254 162 446 1942 9.81, df = 0.90)	Control vents T 159 461 283 200 173 313 1416 4 (P = 0	otal V 235 613 418 252 173 446 964 1 .04); P	Veight 16.4% 23.3% 22.9% 15.6% 0.0% 21.9% 00.0% = 59%	Odds Ratio M-H. Random. 95% CI 1.52 [1.01, 2.27] 0.76 [0.58, 0.99] 0.89 [0.68, 1.71] 0.88 [0.58, 1.34] 0.80 [0.57, 1.12] 1.14 [0.85, 1.53] 0.99 [0.79, 1.24]	2002 2006 2006 2009 2010 2012	Odds Ratio M-H. Random. 95% Cl	AA vs. AT <u>Study or Subgrou</u> McCarron SL Michaud DS Yang HP Wang MH Zhang JJ Dluzeniewski Total (95% CI) Total events Heterogeneity: Ch ²	+TT Experi p Events 59 112 103 69 60 107 107 510 510	imental <u>s Tota</u> <u>9</u> 23 <u>2</u> 48 <u>3</u> 52 <u>9</u> 25 <u>9</u> 25 <u>9</u> 16 <u>7</u> 44 <u>210</u> <u>9</u> <u>5</u> (P = 1)	Co <u>I Even</u> B 5 4 15 0 6 4 6 2 8 6 10 4 51 0.27); I ²	ntrol ts Tol 54 23 51 6 ⁻ 56 4 ⁻ 213 30 17 306 4 ⁻ 213 99 9	tal Weigl 35 10.9' 13 27.2' 18 15.6' 52 12.0' 73 12.9' 46 21.4' 37 100.0'	Odds Ratio nt. M-H, Fixed, 95% 1.10 [0.72, 1.6 0.92 [0.70, 1.2 1.32 [0.94, 1.8 1.14 [0.77, 1.7 0.68 [0.44, 1.0 1.01 [0.74, 1.3 1.02 [0.88, 1.1	Cl Year 9] 2002 2] 2006 5] 2006 0] 2009 6] 2010 8] 2012 7]	Odds Ratio M-H, Fixed, 95% Cl

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

G ve T								GG vs TT							
G VS. 1	Experime	ntal	Contro	d l		Odds Ratio	Odds Ratio	00 05.11	Experime	ntal	Contro	ol .		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total I	Events	Total	Weight	M-H, Random, 95% CI Ye	r M-H, Random, 95% Cl	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yes	ar M-H, Random, 95% Cl
Kibel AS	114	372	162	440	15.5%	0.76 [0.57, 1.02] 200	8 -	Kibel AS	13	98	32	122	13.7%	0.43 [0.21, 0.87] 200	
Stoehr R	102	290	102	248	12.8%	0.78 [0.55, 1.10] 200	8 -	Stoehr R	18	79	19	60	12.8%	0.64 [0.30, 1.36] 200	
Hirata H	108	280	143	334	13.9%	0.84 [0.61, 1.16] 200	9 -	Hirata H	26	84	32	88	15.3%	0.78 [0.42, 1.48] 200	9
Xu B	212	418	257	536	17.5%	1.12 [0.86, 1.44] 201	o 🏲	Xu B	47	91	57	125	17.4%	1.27 [0.74, 2.19] 201	10
Knappskog S	461	1332	445	1350	23.7%	1.08 [0.92, 1.26] 201	2	Knappskog S	92	389	75	380	22.5%	1.26 [0.89, 1.78] 201	2
Mandal RK	179	384	244	448	16.5%	0.73 [0.56, 0.96] 201	2 -	Mandal RK	54	121	73	126	18.3%	0.59 [0.35, 0.97] 201	2
Total (95% CI)		3076		3356	100.0%	0.89 [0.76, 1.05]	•	Total (95% CI)		862		901	100.0%	0.81 [0.56, 1.17]	•
Total events	1176		1353					Total events	250		288				
Heterogeneity: Tau ² = 0	0.02; Chi ² =	11.45, d	f = 5 (P	= 0.04);	1 ² = 56%		0.01 0.1 1 10 100	Heterogeneity: Tau ² =	0.13; Chi ² =	13.20,	df = 5 (P :	= 0.02);	$ ^2 = 62\%$		
Test for overall effect: 2	2 = 1.37 (P	0.17)					Eavours [experimental] Eavours [control]	Test for overall effect:	Z = 1.14 (P :	= 0.25)					Eavours [experimental] Eavours [control]
							avoura (experimental) in avoura (control)								ravours (experimental) ravours (control)
GG+GT vs. T	г							GG vs. GT+	TT						
	Experim	Intal	Contr	ol		Odds Ratio	Odds Ratio		Exporim	ental	Cont	rol		Odds Ratio	Odds Ratio
	LAPOINI		00111						Lybernin						
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Ye	ar M-H, Random, 95% Cl	Study or Subgroup	Events	Tota	Events	Total	Weight	M-H, Fixed, 95% CI Yea	ar M-H, Fixed, 95% Cl
Study or Subgroup Kibel AS	Events 101	Total 186	Events 130	Total 220	Weight 16.7%	M-H, Random, 95% CI Ye 0.82 [0.55, 1.22] 20	ar M-H, Random, 95% Cl 08	Study or Subgroup Kibel AS	Events 13	Tota 186	Events	Total 220	Weight 12.4%	M-H. Fixed, 95% CI Yes 0.44 [0.22, 0.87] 200	ar M-H. Fixed, 95% Cl
Study or Subgroup Kibel AS Stoehr R	Events 101 84	Total 186 145	Events 130 83	Total 220 124	Weight 16.7% 12.9%	M-H, Random, 95% Cl Ye 0.82 [0.55, 1.22] 20 0.68 [0.41, 1.12] 20	ar M-H, Random, 95% Cl 08	Study or Subgroup Kibel AS Stoehr R	Events 13 18	Tota 186 145	Events 32 5 19	Tota 220 124	Weight 12.4% 8.1%	M-H, Fixed, 95% Cl Yes 0.44 [0.22, 0.87] 200 0.78 [0.39, 1.57] 200	ar M-H, Fixed, 95% Cl 18 18
Study or Subgroup Kibel AS Stoehr R Hirata H	Events 101 84 82	Total 186 145 140	Events 130 83 111	Total 220 124 167	Weight 16.7% 12.9% 14.0%	M-H, Random, 95% Cl Yr 0.82 [0.55, 1.22] 20 0.68 [0.41, 1.12] 20 0.71 [0.45, 1.14] 20	ar M-H, Random, 95% Cl 08	<u>Study or Subgroup</u> Kibel AS Stoehr R Hirata H	Events 13 18 26	Tota 186 145 140	Events 32 5 19 0 32	Total 220 124 167	Weight 12.4% 8.1% 10.8%	M-H, Fixed, 95% CI Yea 0.44 [0.22, 0.87] 200 0.78 [0.39, 1.57] 200 0.96 [0.54, 1.71] 200	ar <u>M-H, Fixed, 95% Cl</u> 18
Study or Subgroup Kibel AS Stoehr R Hirata H Xu B	Events 101 84 82 165	Total 186 145 140 209	Events 130 83 111 200	Total 220 124 167 268	Weight 16.7% 12.9% 14.0% 15.2%	M-H, Random, 95% Cl Yı 0.82 [0.55, 1.22] 20 0.68 [0.41, 1.12] 20 0.71 [0.45, 1.14] 20 1.27 [0.83, 1.96] 20	ar M-H, Random, 95% Cl 08	Study or Subgroup Kibel AS Stoehr R Hirata H Xu B	Events 13 18 26 47	Tota 186 145 140 209	Events 32 5 19 0 32 9 57	Total 220 124 167 268	Weight 12.4% 8.1% 10.8% 17.6%	M-H, Fixed, 95% Cl Yea 0.44 [0.22, 0.87] 200 0.78 [0.39, 1.57] 200 0.96 [0.54, 1.71] 200 1.07 [0.69, 1.66] 201	ar M-H, Fixed, 95% Cl 18
Study or Subgroup Kibel AS Stoehr R Hirata H Xu B Knappskog S	Events 101 84 82 165 369	Total 186 145 140 209 666	Events 130 83 111 200 370	Total 220 124 167 268 675	Weight 16.7% 12.9% 14.0% 15.2% 25.9%	M-H, Random, 95% CI Y 0.82 [0.55, 1.22] 20 0.68 [0.41, 1.12] 20 0.71 [0.45, 1.14] 20 1.27 [0.83, 1.96] 20 1.02 [0.83, 1.27] 20	ar M-H, Random, 95% Cl 08 • • 09 • • 10 • • 12 • •	<u>Study or Subgroup</u> Kibel AS Stoehr R Hirata H Xu B Knappskog S	Events 13 18 26 47 92	Tota 186 145 140 209 666	Events 3 32 5 19 0 32 9 57 5 75	Total 220 124 167 268 675	Weight 12.4% 8.1% 10.8% 17.6% 29.1%	M-H, Fixed, 95% CI Ye; 0.44 [0.22, 0.87] 200 0.78 [0.39, 1.57] 200 0.96 [0.54, 1.71] 200 1.07 [0.69, 1.66] 201 1.28 [0.93, 1.78] 201	ar M-H, Fixed, 95% Cl 18 19 2 1 1 1 1 1 1 1 1 1 1 1 1 1
<u>Study or Subgroup</u> Kibel AS Stoehr R Hirata H Xu B Knappskog S Mandal RK	Events 101 84 82 165 369 125	Total 186 145 140 209 666 192	Events 130 83 111 200 370 171	Total 220 124 167 268 675 224	Weight 16.7% 12.9% 14.0% 15.2% 25.9% 15.4%	<u>M-H. Random, 95% CI Yi</u> 0.82 [0.55, 1.22] 20 0.68 [0.41, 1.12] 20 0.71 [0.45, 1.14] 20 1.27 [0.83, 1.96] 20 1.02 [0.83, 1.27] 22 0.58 [0.38, 0.89] 20	ar M-H, Random, 95% Cl 08 • • • • • • • • • • • • • • • • • • •	<u>Study or Subgroup</u> Kibel AS Stoehr R Hirata H Xu B Knappskog S Mandal RK	Events 13 18 26 47 92 54	Tota 186 145 140 209 666 192	Events 3 32 5 19 0 32 9 57 5 75 2 73	Total 220 124 167 268 675 224	Weight 12.4% 8.1% 10.8% 17.6% 29.1% 22.0%	M-H. Fixed, 95% CI Ye: 0.44 (0.22, 0.87) 200 0.78 (0.39, 1.57) 200 0.96 (0.54, 1.71) 200 1.07 (0.69, 1.66) 201 1.28 (0.93, 1.78) 201 0.81 (0.53, 1.23) 201	ar M-H, Fixed, 95% Cl 18 18 19 19 2 2 1 1 1 1 1 1 1 1 1 1 1 1 1
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<u>Study or Subgroup</u> Kibel AS Stoehr R Hirata H Xu B Knappskog S Mandal RK Total (95% CI) Total events Heterogeneity: Tau ² =	Events 101 84 82 165 369 125 926 0.04; Chi ² :	Total 186 145 140 209 666 192 1538 10.34,	Events 130 83 111 200 370 171 1065 df = 5 (P	Total 220 124 167 268 675 224 1678 = 0.07	Weight 16.7% 12.9% 14.0% 15.2% 25.9% 15.4% 100.0%); I ² = 52 ⁱ	M-H. Random, 95%, CI Y, 0.82 (0.55, 1.22) 2 0.68 (0.41, 1.12) 2 0.71 (0.45, 1.14) 2 1.27 (0.83, 1.96) 2 0.58 (0.38, 0.89) 2 0.84 (0.67, 1.06)	ar M-H, Random, 95% Cl 08 09 10 12 12 12 10 10 10 10 10 10 10 10 10 10	Study or Subgroup. Kibel AS Stoehr R Hirata H Xu B Knappskog S Mandal RK Total (95% CI) Total events Heterogeneity: Chi ^p =	Events 13 18 26 47 92 54 250 9.30, df = 5	Tota 186 145 140 209 666 192 1538	I Events 5 32 5 19 0 32 9 57 5 75 2 73 2 288 0.10); 2 = 4 288	Total 220 124 167 268 675 224 1678	Weight 12.4% 8.1% 10.8% 17.6% 29.1% 22.0%	M-H, Fixed, 95% CI Yez 0.44 (0.22, 0.87) 200 0.78 (0.39, 1.57) 200 0.96 (0.54, 1.71) 200 1.07 (0.69, 1.66) 201 1.28 (0.33, 1.78) 201 0.81 (0.53, 1.23) 201 0.96 [0.80, 1.16]	nr M.H. Fixed, 95% Cl 8 9 9 2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
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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. $^{\scriptscriptstyle (50)}$ 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.

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