

Association of interleukin-6 (-174 G/C) polymorphism with the prostate cancer risk: A meta-analysis

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Abstract. The aim of the present study was to determine whether the interleukin-6 (IL-6) (-174 G/C) gene polymorphism correlates with prostate cancer. A meta-analysis based on former studies was conducted and the results suggest that there was no significant association between IL-6 (-174 G/C) polymorphism and the prostate cancer risk. However, a recent study published in January 2014 showed that the GG genotype may be associated with an increased risk of prostate cancer in Caucasian subjects, whereas the CC genotype was associated with an increased risk in the African-American subjects, which was inconsistent with former studies. Databases, including PubMed, Embase, Web of Science, the Cochrane Library, Chinese Biomedical Literature Database and Wanfang database, were searched between January 1994 and March 2014 to determine the eligible IL-6 (-174 G/C) polymorphism studies and the susceptibility of the prostate cancer risk. A total of 11 studies with 10,745 cases and 13,473 controls fulfilled the inclusion criteria subsequent to assessment by two investigators. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to examine the associations, and subgroup analyses were performed according to the ethnicity. Overall, no significant association was found between the IL-6 (-174 G/C) polymorphism and prostate cancer risk, whereas the subgroup analysis suggested that the association between the IL-6 (-174 G/C) polymorphism and prostate cancer was slightly significant under the homozygote (CC vs. GG: OR, 3.43; 95% CI, 1.01-11.71; $P=0.049$) and recessive models (CC vs. GG/GC: OR, 3.51; 95% CI, 1.04-11.82; $P=0.042$) in African-American patients. However, no significant association was found in the Caucasian, Asian or mixed populations under the five genetic models by stratifying studies for ethnicity. In conclusion, the present study suggested that there

was no significant association between the IL-6 (-174 G/C) polymorphism and prostate cancer risk in Caucasian and Asian patients, whereas the CC genotype may be associated with an increased risk in the African-American patients.

Introduction

Prostate cancer is the most common type of cancer diagnosis in males and the estimated new prostate cancer cases and mortalities in 2013 were 238,590 and 29,720, respectively (1). Several studies have been performed and their results suggested that the etiology of prostate cancer was extremely complicated, and may be associated with several factors, including smoking, environment, dietary habits, endocrine system, age and ethnicity (2-7). However, the accurate etiology and pathogenesis remain inconsistent. Recently, a number of studies suggested that inflammation and genetic factors may play an important role in the etiology of prostate cancer (8-14). The prostaglandin-endoperoxide synthase 2 gene that encodes the cyclooxygenase-2 enzyme has been verified to play an important role in the development of prostate cancer in numerous studies (15-18). The study by Woo *et al* (19) observed that tumor infiltrating B-cells were increased in prostate cancer tissue. The Lv *et al* (20) study suggested that hypoxia promoted the invasiveness of prostate cancer PC3 cells via hypoxia-inducible factor-1 α - and tumor necrosis factor- α -induced stabilization of Snail. McDonald *et al* (21) investigated the associations between systemic inflammatory markers and serum prostate-specific antigen (PSA) in 3,164 healthy males and found that elevated serum PSA (194 males, 6.1% of the total) was significantly associated with plasma fibrinogen, suggesting that the markers of systemic inflammation were associated with elevated PSA in males without a known prostate disease.

Among the cytokines involved in inflammation, interleukin-6 (IL-6) plays a key role in the inflammation process. IL-6 is one of the most potent proinflammatory cytokines during acute inflammation, inducing and regulating the production of acute phase proteins (22). Previously, several studies have shown that the IL-6 polymorphism is significantly associated with a number of diseases and plays an important role in the etiology of diseases (23-29). With regards to prostate cancer, the Mandić *et al* (30) study indicated that the IL-6 -174 single-nucleotide polymorphism (SNP) distribution may vary between ethnicities and that a single cytokine-gene

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polymorphism probably has only a minor influence on prostate cancer susceptibility. The study by Pierce *et al* (31) suggested that circulating IL-6 and its gene polymorphism did not influence the prostate cancer risk, whereas Mandal *et al* (32) had an opposing opinion. Due to these conflicting results, the present meta-analysis was conducted to provide a comprehensive assessment of the associations of the IL-6 (-174 G/C) gene polymorphism with the risk of prostate cancer.

Materials and methods

Search strategy. Databases, including PubMed, Embase, Web of Science, the Cochrane Library, Chinese Biomedical Literature Database and Wanfang database, were searched between January 1994 and March 2014 for all the possible studies using an analytical design (including case-control and cohort studies) that mainly studied the association between the IL-6 (-174 G/C) gene polymorphism and the susceptibility of prostate cancer. The search terms used included: 'Prostate cancer' or 'PCa;' 'interleukin 6' or 'IL-6;' and 'polymorphism,' 'single-nucleotide polymorphism,' 'SNP' or 'variation;' and there was no language restriction in the literature search. To find more eligible studies that may not have been included in the initial search, the references of the candidate studies were examined and searches of unpublished literature were conducted.

Inclusion and exclusion criteria. The studies in the meta-analysis were included according to the following criteria: i) Analytical design (including case-control and cohort studies); ii) evaluation of the prostate cancer risk and IL-6 (-174 G/C) gene polymorphism; iii) sufficient data, including the number or frequency of alleles and genotypes; and iv) genotype frequencies in control groups should be abided by the Hardy-Weinberg equilibrium (HWE). The exclusion criteria included: i) Case studies and reviews; ii) no sufficient data reported; and iii) duplicated studies.

Data extraction. The quantitative data of all the eligible studies were extracted according to the inclusion and exclusion criteria by two investigators independently and a consensus was attempted if the data for one investigator was inconsistent with the other. The following characteristics of each study were collected: Authors, year of publication, study design, ethnicity, group, sample size, alleles and IL-6 genotypes. Certain studies included more than one ethnicity, therefore the information data were extracted separately according to the ethnicity.

Data synthesis and statistical analysis. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to assess the associations between the IL-6 (-174 G/C) gene polymorphism and prostate cancer according to allele contrast (C vs. G), homozygote (CC vs. GG), heterozygote (GC vs. GG), dominant (GC/CC vs. GG) and recessive (CC vs. GC/GG) models, and $P < 0.05$ was considered to indicate a statistically significant difference. The subgroup analysis was also performed to determine whether there was a significant association between the IL-6 (-174 G/C) gene polymorphism and prostate cancer in different ethnicities. The heterogeneity assumption was checked by a χ^2 -based Q statistic test and

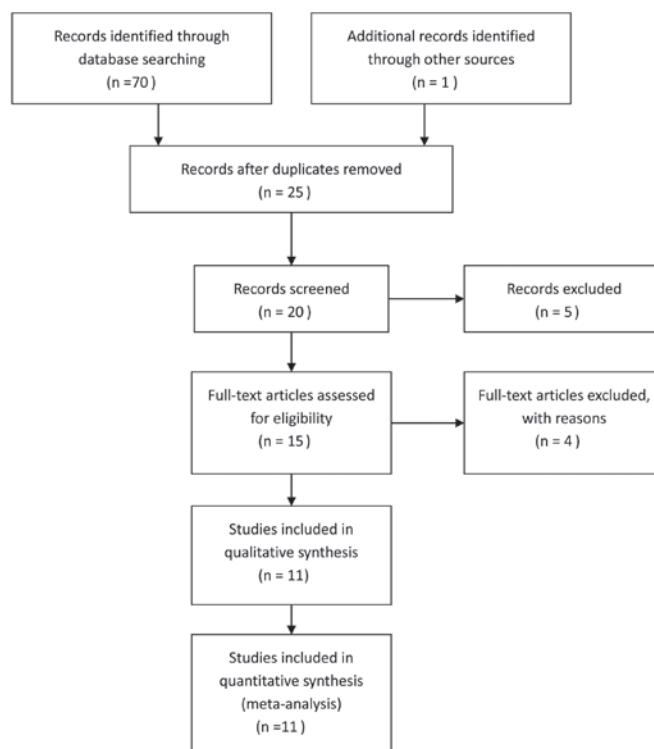


Figure 1. Study selection and inclusion process.

quantified by the I^2 metric value. When $I^2 > 50\%$ or $P < 0.10$, suggesting that a clear heterogeneity existed, the ORs were pooled by the random-effect model, but for other cases the fixed-effect model was used. In addition, the sensitivity analysis was performed by individually removing the included studies to assess the impact of each study on the combined effect of the present meta-analysis. Stata 12.0 software (StataCorp, College Station, TX, USA) was used to analyze the data in the study.

Results

Study characteristics. In the initial search, the total studies were identified and 11 studies (30-40) with 10,745 cases and 13,473 controls eventually satisfied the eligibility criteria (Fig. 1). Among these studies, 10 (30,32-40) were case-control studies and only one (31) was a cohort study. Three studies (31,32,40) were conducted in Caucasian and African-American patients; five (30,34-36,39) reported the results in Caucasian patients only, two studied Asian patients (37,38) and one (33) was conducted in a mixed population (Caucasian and African-American). Additionally, 10 studies (31-40) reported the alleles and genotypes of IL-6 (-174 G/C) and one (30) reported only the number of CC and GG+GC genotypes. The general demographical characteristics of the studies included in the meta-analysis are summarized in Table I. The genotype distributions in the controls of all the studies were consistent with HWE.

Meta-analysis results. In the meta-analysis, there were no associations found between the IL-6 (-174 G/C) polymorphism and prostate cancer susceptibility in the overall population in all the genetic models indicated in Table II (allele contrast:

Table I. General characteristics of the studies included in the meta-analysis.

Author	Year	Study design	Ethnicity	Group	Size	IL-6 alleles		IL-6 genotypes			(Refs.)
						G	C	GG	GC	CC	
Mandal <i>et al</i>	2014	Case-control	Caucasian	Case	84	128	40	50	28	6	(32)
				Control	78	82	74	26	30	22	
			African-American	Case	80	132	28	58	16	6	
				Control	62	110	14	48	14	0	
Mandic <i>et al</i>	2013	Case-control	Caucasian	Case	120	-	-	97 ^a	-	23	(30)
				Control	120	-	-	104 ^a	-	16	
Zhang <i>et al</i>	2010	Case-control	Mixed population	Case	193	246	140	80	86	27	(33)
				Control	197	275	119	100	75	22	
Dossus <i>et al</i>	2010	Case-control	Caucasian	Case	7939	10406	5468	3594	3218	1125	(34)
				Control	8508	11066	5950	3832	3402	1274	
Zabaleta <i>et al</i>	2009	Case-control	Caucasian	Case	74	72	76	19	34	21	(40)
				Control	401	415	387	126	163	112	
			African-American	Case	15	22	8	10	2	3	
				Control	57	92	22	41	10	6	
Wang <i>et al</i>	2009	Case-control	Caucasian	Case	250	298	202	91	116	43	(35)
				Control	252	296	208	84	128	40	
Moore <i>et al</i>	2009	Case-control	Caucasian	Case	957	867	1047	191	485	281	(36)
				Control	847	793	901	196	401	250	
Pierce <i>et al</i>	2009	Cohort study	Caucasian	Case	175	192	158	48	96	31	(31)
				Control	1758	2101	1415	648	805	305	
			African-American	Case	40	73	7	34	5	1	
				Control	260	475	45	216	43	1	
Bao <i>et al</i>	2008	Case-control	Asian	Case	136	272	0	136	0	0	(37)
				Control	120	240	0	120	0	0	
Kesarwani <i>et al</i>	2008	Case-control	Asian	Case	200	288	112	102	84	14	(38)
				Control	200	293	107	103	87	10	
Michaud <i>et al</i>	2006	Case-control	Caucasian	Case	484	563	405	170	223	91	(39)
				Control	613	753	473	230	293	90	

^aStudy only reported the number of CC and GG+GC genotypes. IL-6, interleukin-6.

C vs. G; heterozygote model: GC vs. GG; and homozygote model: CC vs. GG), Fig. 2 (dominant model: GC/CC vs. GG) and Fig. 3 (recessive model: CC vs. GG/GC). The subgroup analysis suggested that the IL-6 (-174 G/C) polymorphism was not significantly associated with prostate cancer in Asian, Caucasian and mixed population patients under the allele contrast, homozygote, heterozygote, dominant and recessive models. However, in African-American patients, the subgroup analysis suggested that there was a slightly significant association between the IL-6 (-174 G/C) polymorphism and prostate cancer risk in the homozygote and recessive models (CC vs. GG: OR, 3.43; 95% CI, 1.01-11.71; P=0.049; CC vs. GG/GC: OR, 3.51; 95% CI, 1.04-11.82; P=0.042, respectively) (Figs. 3 and 4) and no significant association was found in the allele contrast, heterozygote and dominant models (Table II and Fig. 2).

Sensitivity analysis. To evaluate the stability of the meta-analysis, a leave-one-out sensitivity analysis was performed. The sensitivity analysis suggested that the independent study by Mandal *et al* (32) influenced the interpretation of the results in

the homozygote and recessive models for African-American patients. When the Mandal *et al* (32) study was removed from the present meta-analysis, no significant association was found between the IL-6 (-174 G/C) polymorphism and the risk of prostate cancer in African-American patients under the homozygote (OR, 2.67; 95% CI, 0.69-10.36; P=0.17) and recessive models (OR, 2.64; 95% CI, 0.70-9.98; P=0.15). However, no single study influenced the results in the overall population by the sensitivity analysis.

Publication bias. The Begg's test was performed and the results did not reveal any evidence of clear asymmetry (C vs. G, P=0.95; CC vs. GG, P=0.73; GC vs. GG, P=0.54; GC/CC vs. GG, P=0.63; and CC vs. GC/GG, P=0.06), suggesting the absence of publication bias in the meta-analysis.

Discussion

Prostate cancer is a common cause of cancer mortality in males and it is widely considered that age, diet, ethnicity and environmental factors contribute to the prostate cancer

Table II. Results of the allele contrast, heterozygote and homozygote models for the IL-6 (-174 G/C) polymorphism and the risk of prostate cancer.

Comparison	Association test		Heterogeneity test		
	OR	95% CI	P-value	P	I ² (%)
Overall					
C vs. G	1.05	0.93-1.28	0.43	0.00	67.00
GC vs. GG	1.03	0.97-1.10	0.28	0.08	38.70
CC vs. GG	1.13	0.89-1.43	0.32	0.002	62.70
Ethnicity					
Caucasian					
C vs. G	1.00	0.87-1.15	0.98	0.00	77.80
GC vs. GG	1.03	0.97-1.09	0.34	0.02	60.10
CC vs. GG	1.03	0.79-1.33	0.83	0.001	72.60
African-American					
C vs. G	1.40	0.88-2.22	0.16	0.65	0.00
GC vs. GG	0.85	0.47-1.52	0.58	0.93	0.00
CC vs. GG	3.43	1.01-11.71	0.049 ^a	0.53	0.00
Asian					
C vs. G	1.06	0.78-1.45	0.69	1.00	0.00
GC vs. GG	0.97	0.65-1.46	0.90	1.00	0.00
CC vs. GG	1.41	0.60-3.33	0.43	1.00	0.00
Mixed population					
C vs. G	1.32	0.98-1.77	0.07	1.00	0.00
GC vs. GG	1.43	0.94-2.20	0.10	1.00	0.00
CC vs. GG	1.53	0.81-2.90	0.19	1.00	0.00

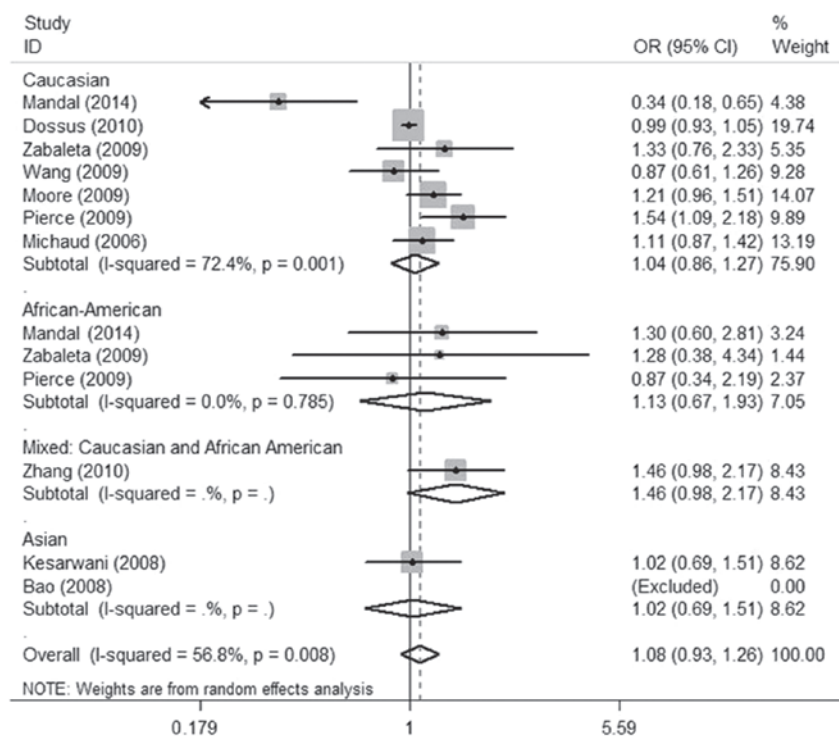
^aP≤0.05. IL-6, interleukin-6; OR, odds ratio; 95% CI, 95% confidence interval.

Figure 2. Forest plot describing the meta-analysis under the dominant model for the association between the interleukin-6 (-174 G/C) polymorphism and the risk of prostate cancer (GC/CC vs. GG). OR, odds ratio; 95% CI, 95% confidence interval.

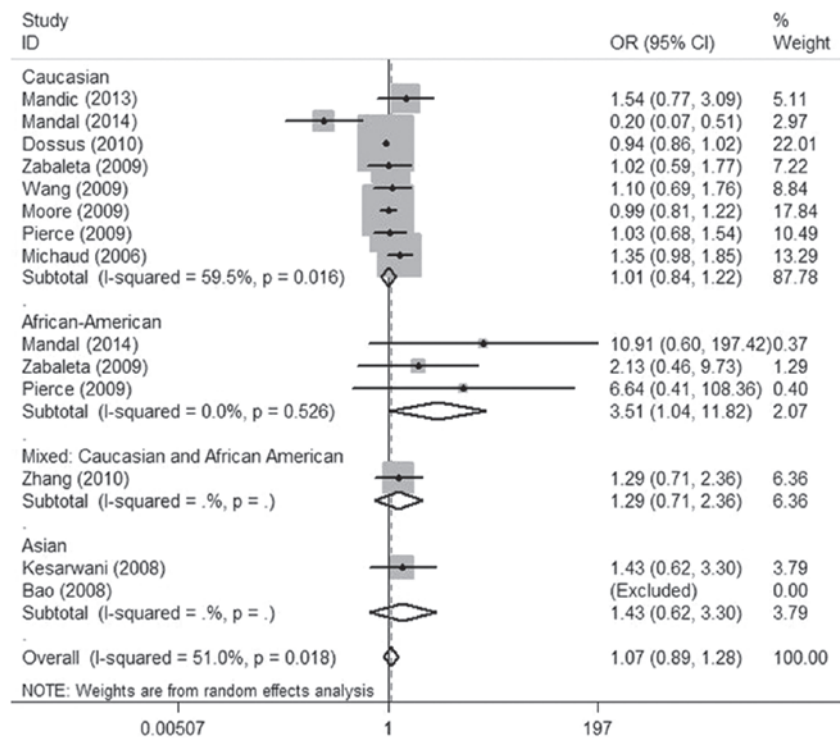


Figure 3. Forest plot describing the meta-analysis under the recessive model for the association between the interleukin-6 (-174 G/C) polymorphism and the risk of prostate cancer (CC vs. GG/GC). OR, odds ratio; 95% CI, 95% confidence interval.

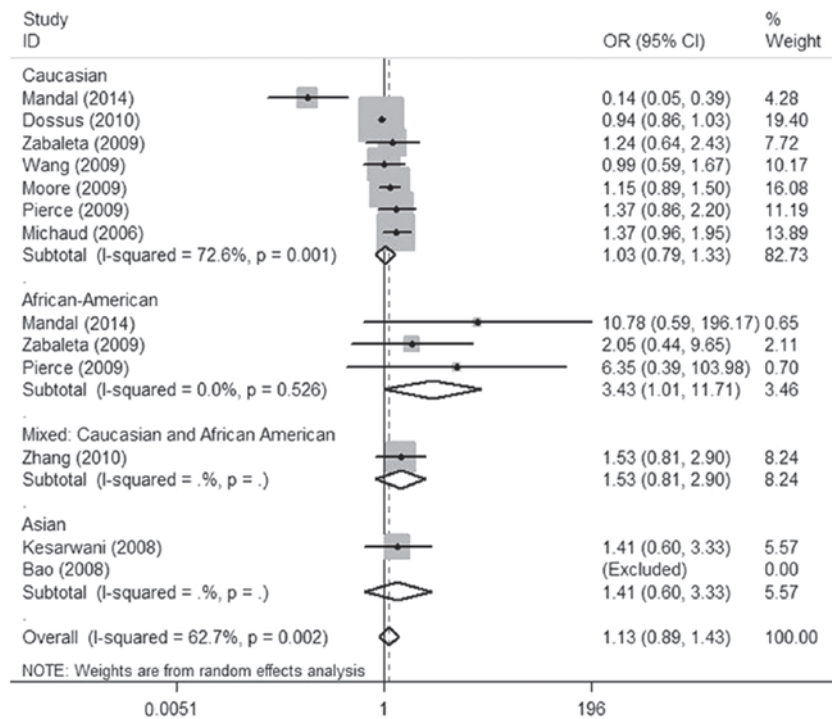


Figure 4. Forest plot describing the meta-analysis under the homozygote model for the association between the interleukin-6 (-174 G/C) polymorphism and the risk of prostate cancer (CC vs. GG). OR, odds ratio; 95% CI, 95% confidence interval.

etiology (2,5-7), but recently the genetic background and inflammation are considered as sensitive factors for the differences in prostate cancer susceptibility (37,40). Following the identification of the IL-6 (-174 G/C) polymorphism, attention to determine whether the IL-6 (-174 G/C) polymorphism

is associated with prostate cancer, not only in the overall population but also in different ethnicities, has increased. Bao *et al* (37) used TaqMan polymerase chain reaction to gene-type the IL-6 (-174 G/C) polymorphism for comparing the prostate cases and controls in terms of allele frequency,

genotype frequency and risk of prostate cancer. The results suggested that no significant association was found in the population of Han people in the Hubei region, which was also identified in Caucasian patients (36). Additionally, two meta-analyses (41,42) based on studies published 4-10 years ago also held the same conclusion. However, a recent study published in January 2014 by Mandal *et al* (32) suggested that the GG genotype may be associated with an increased risk of prostate cancer in Caucasian subjects, whereas the CC genotype was associated with an increased risk in the African-American subjects.

In order to determine whether the IL-6 (-174 G/C) polymorphism is associated with the prostate cancer risk in the overall population and different ethnic populations, the present meta-analysis of 11 independent studies was performed, which included 10,745 cases and 13,473 controls based on several recently published studies, whose results were inconsistent with former studies. In the meta-analysis, it was found that the IL-6 (-174 G/C) polymorphism is not a risk factor for prostate cancer in the overall population. However, the present study suggested that there was a slightly significant association between the IL-6 (-174 G/C) polymorphism and prostate risk in African-American patients under the homozygote and recessive models (CC vs. GG: OR, 3.43; 95% CI, 1.01-11.71; $P=0.049$; and CC vs. GG/GC: OR, 3.51; 95% CI, 1.04-11.82; $P=0.042$, respectively), which contradicts the results of the Magalhaes *et al* (41) meta-analysis. In addition, no significant associations were found in Asians and Caucasians, which is consistent with the Magalhaes *et al* (41) and Zhang *et al* (42) studies, suggesting that ancestral genetic factors in different populations may have an impact on prostate cancer susceptibility. Additionally, the removal of the Mandal *et al* (32) study from the present meta-analysis showed that no significant association was found between the IL-6 (-174 G/C) polymorphism and the risk of prostate cancer in African-American patients under the homozygote (OR, 2.67; 95% CI, 0.69-10.36; $P=0.17$) and recessive models (OR, 2.64; 95% CI, 0.70-9.98; $P=0.15$). The potential explanation for this may involve the different patients recruited in each independent study, as well as their different lifestyles, different experimental procedures and complex gene-gene and gene-environment interaction, which may also have contributed to these conflicting results.

Although the comprehensive analysis was conducted to show the association between the IL-6 (-174 G/C) gene polymorphism and prostate cancer risk, there are particular limitations that should be identified. Firstly, for the African-American patients, only three studies were conducted and the results of these studies were contradictory. Therefore, it may be difficult to explore the real association in African-American patients. Secondly, only two studies that were conducted in Asian patients fulfilled the inclusion criteria, which could not provide enough statistical power to detect the possible effects of the IL-6 (-174 G/C) gene polymorphism on prostate cancer in Asian patients. Thirdly, the studies included in the meta-analysis were conducted in Caucasian, Asian and African-American patients, which may not represent the negative associations in all the worldwide ethnicities. In addition, the possibility of gene-gene interactions or environmental factors or the possibility of linkage disequilibrium between the polymorphisms were also not considered in the study.

Therefore, larger-scale and well-designed studies are necessary to estimate the association between the IL-6 (-174 G/C) polymorphism and the risk of prostate cancer.

In conclusion, although there were certain limitations in the meta-analysis, the study was based on a substantial number of cases and controls and suggested that there was no significant association between IL-6 (-174 G/C) polymorphism and the prostate cancer risk in the overall population, as well as in Caucasian and Asian patients, whereas the CC genotype may be associated with an increased prostate cancer risk in the African-American patients. Due to these limitations, more studies that consider lifestyle, complex gene-gene and gene-environment interactions or family history should be conducted to further assess the associations of the IL-6 (-174 G/C) gene polymorphisms with the risk of prostate cancer.

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