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Review Article

Meta-analysis on the possible role of interluekin-10 rs1800896 polymorphism in association with prostate cancer susceptibility

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Abstract: Objective: Several studies have indicated that the interleukin-10 (*IL-10*) rs1800896 (-1082 A/G) polymorphism is associated with prostate cancer susceptibility. However, the current evidence was inconsistent. Therefore, we performed a meta-analysis to examine the association between *IL-10* rs1800896 polymorphism and prostate cancer risk. Methods: We searched PubMed, Embase, CBM, CNKI, and Wanfang Data to identify potential studies up to March, 2016. Odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the association between *IL-10* rs1800896 polymorphism and prostate cancer risk. Statistic analyses were performed through Stata 12.0 software. Results: A total of 13 article with 14 case-control studies, including 5,068 prostate cancer patients and 5,459 controls. Overall, no significant association was found between *IL-10* rs1800896 polymorphism and prostate cancer susceptibility. However, subgroup analysis showed that *IL-10* rs1800896 polymorphism increased the risk of prostate cacner in Asian populations (G vs A: OR = 1.44, 95% CI = 1.07-1.94; GA vs AA OR = 2.14, 95% CI: 1.01-4.53; GG+GA vs AA: OR = 1.91, 95% CI = 1.18-3.11). Conclusion: Our meta-analysis showed that *IL-10* rs1800896 polymorphism may not be associated with prostate cancer susceptibility in overall populaitons, however, it might increase the risk in Asians.

Keywords: Interleukin-10, meta-analysis, polymorphism, genetic, prostate cancer

Introduction

Prostate cancer is one of the most common cancers of males in the world [1]. The incidence of the disease varies according to different geographical location [2]. The factors driving the increment in prostate cancer are not totally understood. They may include the increment in prostate-specific antigen (PSA) screening and a decrease in the threshold of indicators for prostate biopsy or impact of an increasingly westernized lifestyle (especially in Chinese) [2-5]. Therefore, the prostate cancer still presents a major public health burden in the world. However, the etiology of the disease is still not entirely recognized. Studies suggested that the elevated risk of prostate cancer was associated with age, family history and race [6-8]. In addition, many researchers have identified other risk factors, especially genetic factors. With the development of molecular epidemiology, more evidence support a vital role of genetics in developing prostate cancer [9, 10].

Certain evidence derived from epidemiological and pathological studies suggest that chronic inflammation in prostate tissues may contribute to the development of prostate cancer [11]. Therefore, many genes functioned in inflammatory pathways have been considered to associate with prostate cancer susceptibility [12]. Interleukin-10 (IL-10) is an important and multifunctional anti-inflammatory cytokine mainly produced by immune cells (T cells, B cells, monocytes, and thymocytes). It can down-regulate T helper 1 cytokine and macrophage costimula-

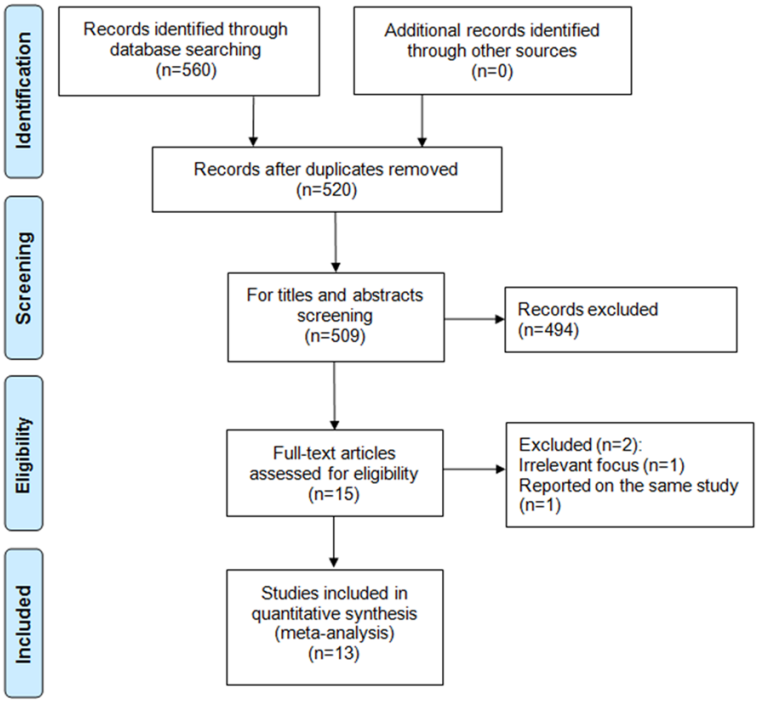

Figure 1. Flowchart of the study selection.

tory molecule expression [13]. Numerous studies suggested indicated that the *IL-10* gene polymorphism might increase the risk of developing prostate cancer. In 2011, two meta-analyses have addressed the relationship between the *IL-10* rs1800896 (-1082 A/G) polymorphism and risk of prostate cancer [14, 15]. However, they concluded that the *IL-10* rs1800896 polymorphism was not associated with prostate cancer. Furthermore, more case-control studies have been published during the five years since the previous meta-analyses published. Therefore, we performed the present meta-analysis to address a more precise result on the association between *IL-10* rs1800896 polymorphism and risk of developing prostate cancer.

Material and methods

Literature search

A comprehensive literature search was conducted in the electronic databases of PubMed, Embase, CBM, CNKI, and Wanfang Data (up to March, 2016). The following items and keywords were used to identify relevant studies: [(interleukin 10 OR interleukin-10 OR IL-10 OR IL10) AND (prostate OR prostatic) AND (cancer OR tumor OR neoplasm) AND (polymorphism OR variation)]. No language restriction was applied in the present meta-analysis. Reference lists of the included studies were manually searched.

Study selection criteria

The following inclusion criteria were applied to select eligible articles in the present meta-analysis: (1) using case-control or cohort design; (2) examining the association between *IL-10* rs1800896 polymorphism and prostate cancer risk; (3) including patients who were diagnosed with prostate cancer and controls who were cancer free; and (4) full-text articles providing sufficient data. Furthermore, the exclusion criteria were as following: (1) duplicate publications; (2) the study subject was not human; (3) letters, reviews or comments.

Data extraction and quality assessment

For each eligible study, the following information was extracted by two authors: the name of first author, publication year, publication language, study design, country, ethnicity of the study population, sample size, genotype distribution, and Hardy-Weinberg equilibrium (HWE) for controls. Any disagreements were resolved by discussion or a third author. The quality assessment of included studies was assessed using Newcastle-Ottawa scale (NOS) [16].

Statistical analysis

Whether genotype frequencies among controls were consistent with HWE was estimated by the χ^2 test and *P*-value more than 0.05 represented conformity. The summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to measure the strength of relationship between *IL-10* rs1800896 polymorphism and prostate cancer susceptibility in five genetic models: G vs. A, GG vs. AA, GA vs. AA, GG+GA vs. AA, and GG vs. GA+AA [17-19]. Between-study heterogeneity was mea-

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

Study	Country	Ethnicity	Publication language	Study design	Cases			HWE in controls	Controls			Quality score
					GG	AG	AA		GG	AG	AA	
McCarron et al [22]	United Kingdom	Caucasian	English	Case-control	56	113	78	Yes	57	120	46	8
Xu et al [23]	Sweden	Caucasian	English	Case-control	306	689	388	Yes	187	390	203	8
Michaud et al [24]	United States	Mixed	English	Case-control	290	599	356	Yes	383	857	523	8
Faupel-Badger et al [25]	United States	Caucasian	English	Case-control	85	251	173	Yes	73	194	115	8
Omrani et al [26]	Iran	Caucasian	English	Case-control	5	31	5	No	2	98	3	7
Zabaleta et al [27]	United States	Caucasian	English	Case-control	126	239	110	Yes	86	206	102	8
Zabaleta et al [27]	United States	African	English	Case-control	7	38	21	No	13	74	42	7
Kesarwani et al [28]	India	Caucasian	English	Case-control	12	78	69	No	45	103	111	8
Wang et al [29]	United States	Caucasian	English	Case-control	NA	NA	NA	Yes	52	128	78	8
Leon et al [30]	China	Asian	English	Case-control	4	6	2	Yes	6	12	6	7
Liu et al [31]	China	Asian	English	Case-control	4	36	222	Yes	3	27	240	8
VanCleave et al [32]	United States	African	English	Case-control	75	95	22	Yes	288	280	92	8
Niu et al [33]	China	Asian	Chinese	Case-control	18	56	24	No	20	26	42	7
Horvat et al [34]	Croatia	Caucasian	English	Case-control	24	59	37	Yes	24	54	42	8

HWE, Hardy-Weinberg equilibrium; NA, not available.

sured using the *Q*-test and I^2 metrics [20]. The random-effects model was used to pool the summary results [21]. Sensitivity analysis by excluding studies which controls not in consistent with HWE was conducted. Subgroup analyses based on ethnicity (Caucasian, Asian, African, and Mixed), publication language and sample size were performed. Publication bias was assessed by Begg's funnel plot and Egger's linear regression test. All the statistical analyses were performed using Stata 12.0 software. The significance level was 0.05 except for publication bias test (0.1).

Results

Study characteristics

A total of 560 potentially relevant articles involving the association between *IL-10* rs1800-896 polymorphism and the risk of prostate cancer were yielded after the initial search of the electronic databases. Finally, 13 publications [22-34] with 14 case-control studies were identified involving 5,068 prostate cancer patients and 5,459 controls (**Figure 1**). Of the 14 case-control stuides, seven were perofrmed in Caucasian populations, three in Aisan populations, two in African populations, and one in Mixed populations (Caucasian and Afircan). The included study characteristics and qulaity score were clearly presented in **Table 1**.

Meta-analysis

The summary results of the present meta-analysis are shown in **Table 2**. Overall, no significant relationship was found between *IL-10* rs180-0896 polymorphism and risk of prostate cancer in the total populations (G vs A: OR = 1.01, 95% CI = 0.92-1.11, **Figure 2**; GG vs AA: OR = 1.01, 95% CI = 0.83-1.23; GA vs SS: OR = 1.11, 95% CI = 0.92-1.35; GG+GA vs AA: OR = 1.03, 95% CI = 0.87-1.23; GG vs GA+AA: OR = 0.95, 95% CI = 0.81-1.11; **Table 2**). Sensitivity analysis by excluding studies not in HWE in controls showed similar results in total populations (**Table 2**). However, subgroup analysis according to ethnicity showed that the *IL-10* rs1800-896 polymorphism increased the risk of prostate cancer in Asian population (G vs A: OR = 1.44, 95% CI = 1.07-1.94; GA vs AA OR = 2.14, 95% CI: 1.01-4.53; GG+GA vs AA: OR = 1.91, 95% CI = 1.18-3.11; **Table 2**).

Publication bias

Begg's funnel plot seemed to be symmetric for all genetic models. **Figure 3** shows the shapes of the funnel plots of G vs A genetic model in overall analysis. The result was further favored by Egger's tests (P = 0.32 for G v. A; P = 80 for GG vs AA; P = 0.47 for GA vs AA; P = 0.72 for GG+GA vs AA; P = 0.98 for GG vs GA+AA; **Table 2**).

Discussion

The present meta-analysis summarized the available literatures to date regarding the association between *IL-10* rs1800896 polymorphism and the risk of prostate cancer. The results from the meta-analysis suggested that the

Table 2. Meta-analysis of the association between *IL-10* rs1800896 polymorphism and prostate cancer

Analysis	No of studies	Test of association			Heterogeneity		*P* for Egger's test
		OR	95% CI	*P*-value	I^2	*P*-value	
G vs. A							
Overall	14	1.01	0.92-1.11	0.84	47.2	0.03	0.32
HWE (yes)	10	1.01	0.91-1.12	0.86	52.4	0.03	
Ethnicity							
Caucasian	8	0.96	0.84-1.10	0.58	55.7	0.03	
Asian	3	1.44	1.07-1.94	0.02	0.0	0.99	
African	2	0.97	0.79-1.20	0.79	0.0	0.77	
Mixed	1	1.05	0.95-1.17	0.31	NA	NA	
Sample size							
≥500	7	1.03	0.92-1.16	0.58	55.9	0.03	
<500	7	0.98	0.80-1.18	0.80	39.9	0.13	
Language							
English	13	0.99	0.90-1.09	0.86	43.3	0.05	
Non-English	1	1.47	0.97-2.23	0.07	NA	NA	
GG vs. AA							
Overall	14	1.01	0.83-1.23	0.91	46.4	0.03	0.80
HWE (yes)	10	1.04	0.85-1.26	0.72	47.7	0.05	
Ethnicity							
Caucasian	8	0.93	0.68-1.25	0.62	65.7	<0.01	
Asian	3	1.59	0.81-3.12	0.18	0.0	0.97	
African	2	1.09	0.68-1.75	0.73	0.0	0.99	
Mixed	1	1.11	0.91-1.36	0.31	NA	NA	
Sample size							
≥500	7	1.09	0.89-1.33	0.43	49.4	0.07	
<500	7	0.86	0.56-1.31	0.47	36.7	0.15	
Language							
English	13	0.99	0.81-1.21	0.93	48.1	0.03	
Non-English	1	1.58	0.70-3.54	0.27	NA	NA	
GA vs. AA							
Overall	14	1.11	0.92-1.35	0.28	65.6	<0.01	0.47
HWE (yes)	10	1.04	0.88-1.23	0.61	51.1	0.03	
Ethnicity							
Caucasian	8	0.97	0.77-1.24	0.83	65.1	<0.01	
Asian	3	2.14	1.01-4.53	0.05	58.7	0.09	
African	2	1.25	0.83-1.88	0.28	0.0	0.45	
Mixed	1	1.03	0.87-1.22	0.76	NA	NA	
Sample size							
≥500	7	1.08	0.92-1.26	0.33	42.9	0.11	
<500	7	1.07	0.62-1.85	0.81	78.0	<0.01	
Language							
English	13	1.04	0.89-1.22	0.63	50.0	0.02	
Non-English	1	3.77	1.90-7.47	<0.01	NA	NA	
GG+GA vs AA							
Overall	13	1.03	0.87-1.23	0.71	59.0	<0.01	0.72
HWE (yes)	9	0.99	0.85-1.15	0.90	44.7	0.07	

Ethnicity							
Caucasian	7	0.89	0.72-1.09	0.25	51.8	0.05	
Asian	3	1.91	1.18-3.11	<0.01	25.6	0.26	
African	2	1.16	0.79-1.72	0.45	0.0	0.64	
Mixed	1	1.05	0.90-1.24	0.53	NA	NA	
Sample size							
≥500	6	1.02	0.90-1.15	0.79	23.6	0.26	
<500	7	1.01	0.63-1.62	0.96	73.5	<0.01	
Language							
English	12	0.98	0.85-1.13	0.76	40.6	0.07	
Non-English	1	2.82	1.51-5.24	<0.01	NA	NA	
GG vs. GA+AA							
Overall	13	0.95	0.81-1.11	0.52	42.4	0.05	0.98
HWE (yes)	9	0.99	0.90-1.10	0.92	0.0	0.47	
Ethnicity							
Caucasian	7	0.92	0.70-1.21	0.57	64.4	0.01	
Asian	3	0.93	0.51-1.68	0.81	0.0	0.63	
African	2	0.85	0.62-1.16	0.30	0.0	0.64	
Mixed	1	1.09	0.92-1.30	0.31	NA	NA	
Sample size							
≥500	6	1.00	0.87-1.14	0.94	27.4	0.23	
<500	7	0.89	0.58-1.37	0.61	51.4	0.06	
Language							
English	12	0.96	0.81-1.13	0.61	40.6	0.04	
Non-English	1	0.76	0.37-1.56	0.46	NA	NA	

CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; NA, not available.

IL-10 rs1800896 polymorphism was not associated with the risk of prostate cancer in overall population. However, subgroup analysis according to ethnicity showed that the *IL-10* rs1800896 polymorphism was associated with elevated risk of prostate cancer in Asian populations. No significant association between the disease and polymorphism was observed in other ethnicities.

The *IL-10* gene is located on chromosome 1q31-32 and contains five exons [35]. The rs1800896 polymorphism is the most studied loci of the *IL-10* gene related to prostate cancer risk. However, the results of the existing literatures were controversial. The original case-control studies were relatively small simple sizes. Hence, the statistical power was deficiency to detect the true gene effect. Two meta-analyses were published with the same topic [14, 15]. However, there were five years past since the two meta-analyses published and there were many other case-control studies were published. Therefore, it is urgent to perform a meta-analysis to update the evidence of the association between *IL-10* rs1800896 polymorphism and the risk of prostate cancer.

The results of meta-analysis suggested that, in Asian populations, the *IL-10* rs1800896 G allele carriers presented a roughly 1.44-fold higher risk of developing prostate cancer compared with A allele carriers. Additionally, GA and GG+GA genotype carriers separately presented 2.14- and 1.91-fold higher risk of developing prostate cancer compared with AA genotype carriers. Our meta-analysis differs from the previous meta-analysis analyzing the association between *IL-10* rs1800896 polymorphism and prostate cancer risk [14, 15]. Shao et al [14] performed a meta-analysis that addressed the effect of *IL-10* rs1800896 polymorphism and risk of prostate cancer with nine case-control studies in 2011. They concluded that *IL-10* rs1800896 polymorphism was not associated with the risk of prostate cancer. Zou et al [15] carried out a meta-analysis with 11 studies and suggested that *IL-10* rs1800896 polymorphism

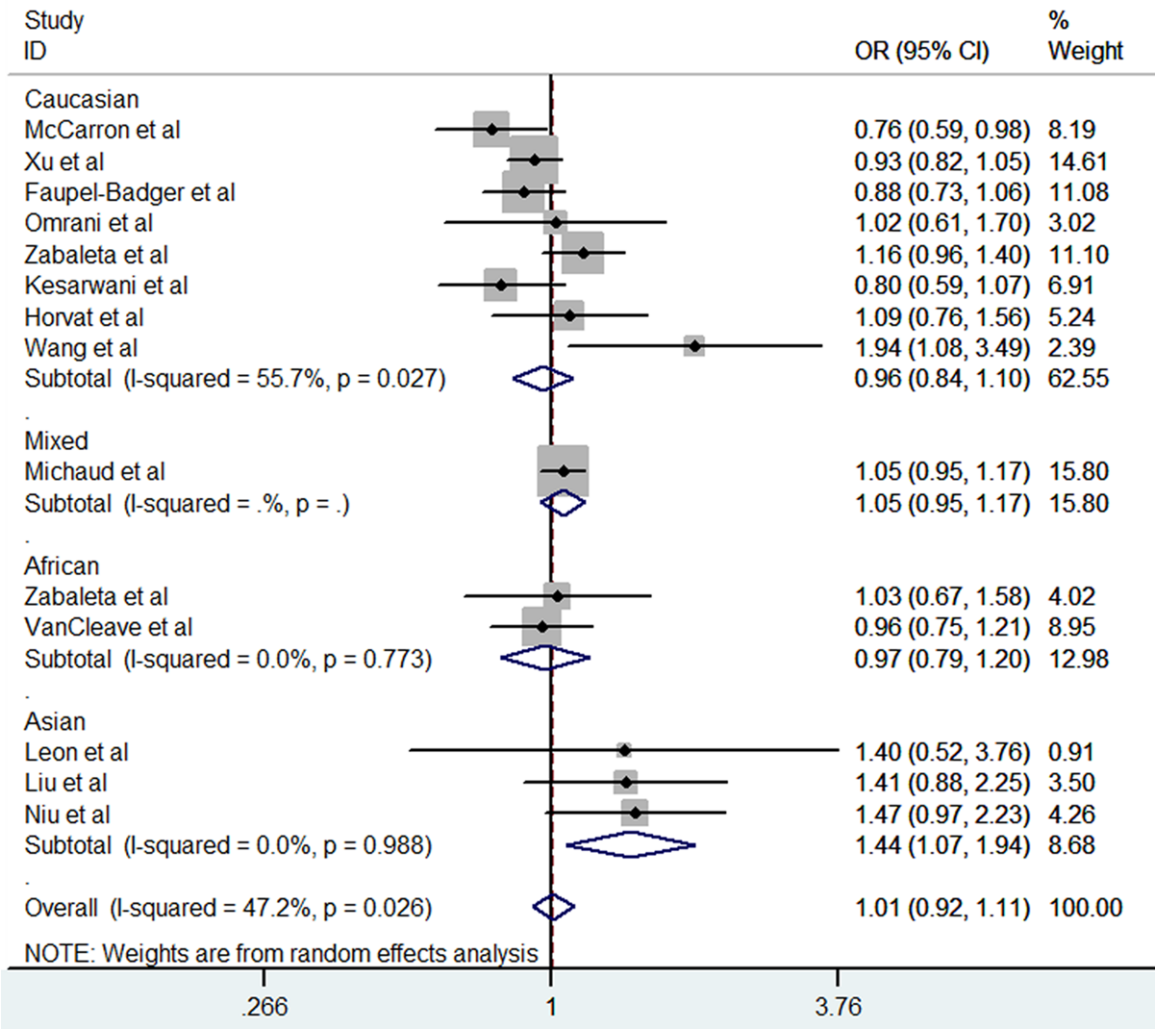

Figure 2. Forest plots of the meta-analysis for G vs A allele model. Note: Weights are from random-effects analysis. Abbreviations: CI, confidence interval; OR, odds ratio.

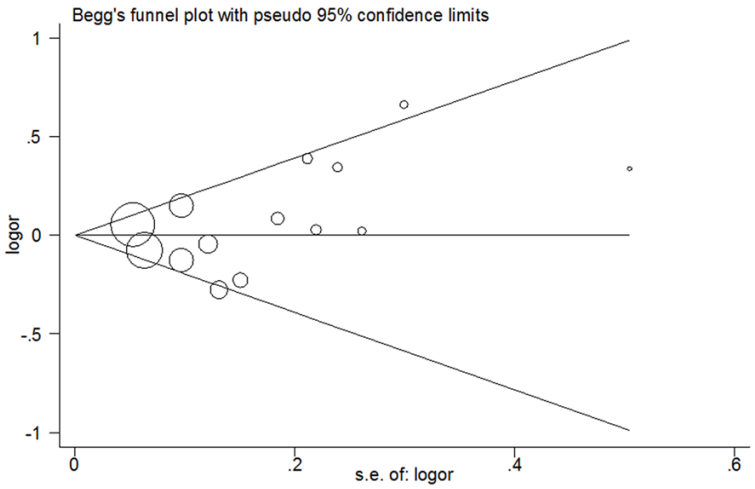

Figure 3. Begg's funnel plot of the G vs A genetic model. Abbreviations: SE, standard error; OR, odds ratio.

was not associated with the risk of prostate cancer. Both the two previous meta-analyses performed subgroup analysis according to ethnicity. However, they did not find the significant difference between *IL-10* rs1800896 polymorphism and prostate cancer susceptibility in Asian populations. In the present meta-analysis with 14 case-control studies from 13 articles, we found that *IL-10* rs1800896 polymorphism was associated with elevated risk of prostate cancer in Asian populations. Compared with previous

meta-analyses, our meta-analysis had a more comprehensive literature search. Furthermore, the statistical power was stronger than the previous meta-analyses to detect the true gene effect. Therefore, we believe that the present meta-analysis will help readers and researchers to between acknowledge the relationship between *IL-10* rs1800896 polymorphism and prostate cancer susceptibility. In addition, our meta-analysis also could indicate the further research fields of this topic.

Otherwise, like any other meta-analytic study, the present meta-analysis also has certain limitations that should be taken into consideration [18, 19, 36]. First, the meta-analysis is a retrospective study that is subject to biases of the included studies. Second, certain evidence of between-study heterogeneity of the included studies was detected. The heterogeneity might decrease the validity and reliability of the meta-analysis. The source of between-study heterogeneity might be derived from ethnicity or clinical issues (such as selection bias, measurement bias or grades of prostate cancer). Third, we could not eliminate the influence of publication bias even though we did not detect any evidence of publication bias using funnel plot and Egger's test. The publication bias is inevitable and can distort the result of the meta-analysis [19]. Fourth, although we found a significant association between *IL-10* rs1800896 polymorphism and the risk of prostate cancer in Asian populations, the sample size of the Asians were relatively small. Therefore, the aforementioned significant relationship was needed to be confirmed by further studies with well-designed and large sample sizes. Ultimately, due to limited data of the included studies, we could not perform haplotype analysis and gene-gene or gene-environment interaction analysis. The effect of single loci polymorphism might have limited influence on the prostate cancer susceptibility.

Briefly, the present meta-analysis concluded that the rs1800896 polymorphism in *IL-10* gene might be associated with increased risk of developing prostate cancer in Asian populations. However, further studies with well-design and large sample sizes are warranted to confirm the aforementioned conclusion.

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Disclosure of conflict of interest

None.

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