RESEARCH ARTICLE

Genetic Polymorphism of Interleukin-1A (IL-1A), IL-1B, and IL-1 Receptor Antagonist (IL-1RN) and Prostate Cancer Risk

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Abstract

Purpose: We aimed to investigate the associations between polymorphisms of interleukin-1A (IL-1A), IL-1B, and IL-1 receptor antagonist (IL-1RN) and prostate cancer (PCa) risk. Materials and Methods: A comprehensive search for articles of MEDLINE and EMBASE databases and bibliographies of retrieved articles published up to August 3, 2014 was performed. Methodological quality assessment of the trials was based on a standard quality scoring system. The meta-analysis was performed using STATA 12.0. Results: We included 9 studies (1 study for IL-1A, 5 studies for IL-1B, and 3 studies for IL-1RN), and significant association was found between polymorphisms of IL-1B-511 (rs16944) as well as IL-1B-31 (rs1143627) and PCa risk. IL-1B-511 (rs16944) polymorphism was significantly associated with PCa risk in homozygote and recessive models, as well as allele contrast (TT *vs* CC: OR, 0.74; 95% CI, 0.58-0.94; *P*=0.012; TT *vs* TC+CC; OR, 0.79; 95% CI, 0.63-0.98; *P*=0.033; T *vs* C: OR, 0.86; 95% CI, 0.77-0.96; *P*=0.008). The association between IL-1B-31 (rs1143627) polymorphism and PCa risk was weakly significant under a heterozygote model (OR, 1.35; 95% CI, 1.00-1.80; *P*=0.047). Conclusions: Sequence variants in IL-1B-511 (rs16944) and IL-1B-31 (rs1143627) are significantly associated with PCa risk, which provides additional novel evidence that proinflammatory cytokines and inflammation play an important role in the etiology of PCa.

Keywords: Prostate cancer - polymorphism - meta-analysis - interleukin-1 - interleukin-1 receptor antagonist

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Introduction

Prostate cancer (PCa) has become the most common diagnosed malignant tumors and the second leading cause of death due to the cancer among men in the United States (Siegel et al., 2013). Twin study suggests that 16% to 45% of the risk of PCa may be explained by genetic factors (Baker et al., 2005), little of which are due to high penetrance genes. However, common genetic polymorphisms are likely to play an important role among sporadic cases of PCa (Eeles et al., 2014).

Chronic inflammation is one of several factors associated with the development of PCa. Epidemiological studies demonstrate that sexually transmitted infections and prostatitis are associated with PCa risk (Dennis et al., 2002; Patel et al., 2005). Interleukins (ILs) are a group of cytokines which are critical in the regulation of inflammation. Not only PCa risk, but also PCa prognosis was associated with various ILs levels (Domingo-Domenech et al., 2006; Dwivedi et al., 2011). Variants in cytokine genes are associated with increased inflammation and cytokine production. Common polymorphisms of proinflammatory and anti-inflammatory cytokine genes can influence cytokine production, which may play a role in development of PCa.

Several studies have been conducted on ILs variants and PCa risk. IL-6 variants were found to have little association with PCa risk (Yang et al., 2014). Though several studies reported no association between IL-8-251 polymorphism and PCa risk (Yang et al., 2006), a reduction in risk was observed among carriers of -251A (Wang et al., 2012). IL-10 is the most studied IL in the context of IL variants and PCa risk. Most studies have inconsistent results, and the most recent meta-analysis showed that IL-10 (rs1800871) polymorphism was not significantly associated with PCa (Yu et al., 2013). However, another meta-analysis suggested that IL-10 (rs1800871) and IL-10 (rs1800872) polymorphisms might be modestly associated with advanced PCa and might therefore impact disease progression (Shao et al., 2011).

The IL-1 system plays an important role in protection against many different injuries, ranging from microbial invasion to malignant transformation. IL-1 family includes two bioactive ligands (IL-1A and IL-1B). The interleukin-1 receptor antagonist (IL-1RN) also belongs to the IL-1 family. All the three molecules bind to the same IL-1 receptors. IL-1A and IL-1B are proinflammatory cytokines. By binding to the receptors, a cascade of events are initiated leading to recruitment and activation of macrophages and neutrophils, vascular dilation and fever, and a potent proinflammatory immune response (Dinarello, 1988). When IL-1RN, the anti-inflammatory

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cytokine, binds to the same receptors, no signal transduction will be elicited on and thereby the activity of IL-1 is blocked (McIntyre et al., 1991). IL-1 and IL-1RN polymorphisms have also been linked to several malignant tumors, including gastric cancer (El-Omar et al., 2000; Yamamoto-Furusho et al., 2011), hepatocellular cancer (Wang et al., 2003), lung cancer (Zienolddiny et al., 2004), and so on. But the association between polymorphisms of IL-1 family, including IL-1A, IL-1B, and IL-1RN and PCa risk was little studied. Several studies reported there was no significant association between PCa risk and IL-1B polymorphism as well as IL-1RN polymorphism. Due to the relatively small sample size, the present meta-analysis was conducted to provide a better assessment of the associations of the IL-1 family polymorphisms with the PCa risk.

Materials and Methods

Search strategy

We conducted a comprehensive literature search in the Cochrane Library, PubMed, and EMBASE, using the search terms "prostatic neoplasms OR prostatic cancer OR prostate cancer OR prostate neoplasms OR PCa", "polymorphism OR single nucleotide polymorphism OR SNP OR variation OR genotype", and "interleukin-1 OR IL-1 OR IL-1A OR IL-1B OR interleukin-1 receptor antagonist OR IL-1RN" and various combinations of these terms. All the articles were updated on August 3, 2014. The search was performed without any limitations of language. Review articles, original articles, and other studies of interest were examined to identify additional eligible studies.

Selection criteria

The studies in this meta-analysis were included according to the following criteria: (1) studies investigating the association between PCa risk and polymorphisms of IL-1 family, including IL-1A, IL-1B, and IL-1RN; (2) case-control or cohort studies; (3) sufficient data, including the number or frequency of alleles and genotypes; and (4) genotype frequencies in control groups should be abided by the Hardy-Weinberg equilibrium (HWE). If serial studies of the same population from the same group were reported, the most recent or largest population was chosen. The exclusion criteria included: (1) animal studies, case studies and reviews; (2) no sufficient data reported; and (3) duplicated studies.

Data extraction and quality score assessment

Xu and Jiang independently evaluated the eligibility of all retrieved studies from the databases and extracted the relevant data from each included study by using a unified data form. The collected parameters included: first author's surname, year of publication, ethnicity, sample size, polymorphism investigated, genotyping methods, and matching variables. The two investigators verified data accuracy by comparing collection forms between investigators. If different results were generated, they would carry out discussions until a consensus was reached.

The quality of the selected studies was independently evaluated by Xu and Jiang. The criteria for quality appraisal are listed in Table 1. The quality scoring system was first reported by Thakkinstian et al. (Thakkinstian et al., 2005). Scores ranged from 0 to 14, with higher scores indicating better quality. Disagreements were resolved by consensus.

Statistical analysis

The pooled odds ratio (OR) with 95% confidence interval (95%CI) was calculated to assess the associations between PCa risk and polymorphisms of IL-1 family, including IL-1A, IL-1B, and IL-1RN according to allele contrast, homozygote, heterozygote, dominant and recessive models. $p<0.05$ was considered to indicate a statistically significant difference. The heterogeneity assumption was checked by a χ^2-based Q statistic test and quantified by the I^2 metric value. When no statistical heterogeneity was found (I^2 <50% or $p>0.10$), the ORs and 95%CI would be estimated for each study in the fixed-effect model (Mantel-Haenszel method) (Mantel and Haenszel, 1959). Otherwise, the random-effect model (DerSimonian and Laird method) was applied (DerSimonian and Laird, 1986). Stata 12.0 software (StataCorp, College Station, TX, USA) was used to analyze the data in the study.

Results

Study characteristics

As shown in Figure 1, a total of 153 published records found on Cochrane Library, PubMed, and EMBASE were identified. After the titles and abstracts were reviewed, 141 of these articles were excluded: 87 were not related to gene polymorphisms, 43 discussed polymorphisms other than IL-1 family (IL-1A, IL-1B, and IL-1RN), and 11 were reviews or meta-analysis. Manual search of references cited in the published studies did not reveal any more relevant articles. These 12 full-text articles were then subjected to further examination, and 3 studies excluded. 1 article was exclude since it mainly discussed IL-1B and PCa aggressiveness (Zabaleta et al., 2009). 1 article was exclude since it mainly discussed IL-1B and PCa recurrence (Dluzniewski et al., 2012). The other article was exclude since it mainly discussed IL-1B and fatigue in PCa patients treated with androgen deprivation therapy (Jim et al., 2012). Thus, a total of 9 records with

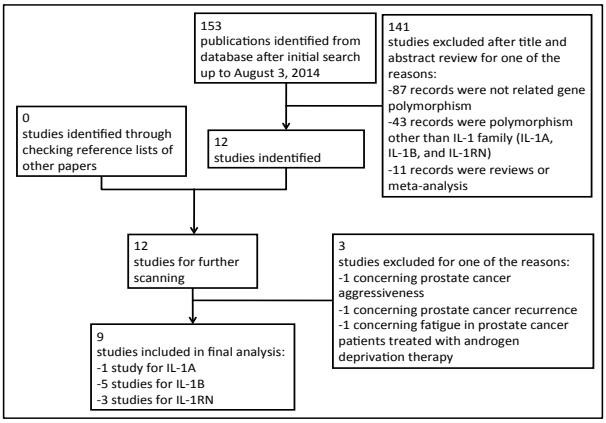

Figure 1. Study Selection and Inclusion Process

therapy (Jim et al., 2012). Thus, a total of 9 records with a case-control design met the inclusion criteria for the meta-analysis, including 1 study for IL-1A (Saenz-Lopez et al., 2008), 5 studies for IL-1B (McCarron et al., 2002; Michaud et al., 2006; Zabaleta et al., 2008; Wang et al., 2009; Zhang et al., 2010), and 3 studies for IL-1RN (Lindmark et al., 2005; Xu et al., 2005; Cheng et al., 2007).

The corresponding characteristics of 9 studies are presented in Table 2. Among them, 5 were performed in Caucasians populations, and the other 4 were performed in mixed populations. Only 1 study (Saenz-Lopez et al., 2008) discussed IL-1A-889 (rs1800587) polymorphism and PCa risk. 5 studies investigated IL-1B polymorphism and PCa risk, of which 4 studies (McCarron et al., 2002; Michaud et al., 2006; Zabaleta et al., 2008; Zhang et al., 2010) examined IL-1B-511 (rs16944) polymorphism, 2 studies (Michaud et al., 2006; Zabaleta et al., 2008)

Table 1. Scale for Quality Assessment

Criteria	Score
1. Representativeness of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without clearly defined sampling frame or with extensive inclusion/exclusion criteria	1
Not described	0
2. Source of controls	
Population- based	3
Blood donors or volunteers	2
Hospital-based (cancer -free patients)	1
Not described	0
3. Pecimens of cases determining genotypes	
White blood cells or normal tissues	1
Tumor tissues or exfoliated cells of tissue	0
4. Ascertainment of prostate cancer	
Histopathologic confirmation	2
Diagnosis of prostate cancer by patient medical record	1
Not described	0
5. Total sample size	
≥1000	3
≥400 but <1000	2
≥200 but <400	1
<200	0
6. Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	1
Hardy-Weinberg disequilibrium	0
7. Quality control of genotyping methods	
Repetition of partial/total tested samples	1
Not described	0

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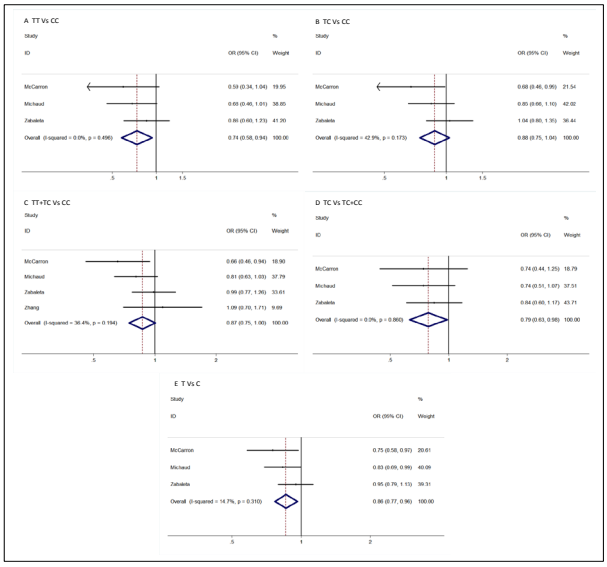

Figure 2. Forest Plot Describing the Meta-Analysis for the Association between the IL-1B-511 (rs16944) Polymorphism and Prostate Cancer Risk. A: homozygote model (TT *vs* CC); B: heterozygote model (TC *vs* CC); C: dominant model (TT+TC *vs* CC); D: recessive model (TT *vs* TC+CC); E: allele contrast (T *vs* C)

Table 2. Characteristics of Included Studies in this Meta-Analysis

Study	Year	Study design	Ethnicity	Size (case/control)	Polymorphism investigated	Genotyping methods	Matching variables	Quality scores
McCarron	2002	Case-control	Caucasian	243/261	IL-1B-511 (rs16944)	ARMS-PCR	Age	8
Lindmark	2005	Case-control	Caucasian	1372/775	IL-1RN (rs3087263) IL-1RN (rs315951)	TaqMan	Age, sex, region	13
Xu	2005	Case-control	Caucasian	1444/866	IL-1RN (rs3087263) IL-1RN (rs315951)	MassARRAY	Age, geographic origin	13
Michaud	2006	Case-control	Mixed population	473/607	IL-1B-511 (rs16944) IL-1B+3953 (rs1143634)	TaqMan	Age, ethnicity	13
Cheng	2007	Case-control	Caucasian	506/506	IL-1RN (rs3087263) IL-1RN (rs315951)	TaqMan	Age, ethnicity, medical institution	10
Zabaleta	2008	Case-control	Mixed population	544/523	IL-1B-511 (rs16944) IL-1B+3953 (rs1143634) IL-1B-31 (rs1143627)	TaqMan	NR	8
Saenz-Lopez	2008	Case-control	Caucasian	297/303	IL-1A-889 (1800587)	TaqMan	NR	10
Wang	2009	Case-control	Mixed population	243/248	IL-1B-31 (rs1143627)	TaqMan	Age, ethnicity	11
Zhang	2010	Case-control	Mixed population	165/172	IL-1B-511 (rs16944)	MassARRAY	Age, ethnicity, contry	8

NR: not reported, ARMS-PCR: amplification refractory mutation system-polymerase chain reaction

2007) investigated IL-1RN (rs315951 and rs3087263) polymorphism and PCa risk. Genotyping was performed using amplification refractory mutation system-PCR (ARMS-PCR), TaqMan assay, and MassARRAY platform on genomic DNA. The quality scores range from 8 to 13.

Meta-analysis results

Since there was only one article examined the association between IL-1A polymorphism and PCa risk, we carried out meta-analysis for IL-1B and IL-1RN. In this meta-analysis, significant association was demonstrated between IL-1B-511 (rs16944) polymorphism and PCa risk in homozygote and recessive models, as well as allele contrast (TT *vs* CC: OR, 0.74; 95%CI, 0.58-0.94; *p*=0.012; TT *vs* TC+CC; OR, 0.79; 95%CI, 0.63-0.98; *p*=0.033; T *vs* C: OR, 0.86; 95%CI, 0.77-0.96; *p*=0.008) (Table 3, Figure 2), but no significant association was found in the heterozygote and dominant models (Table 3, Figure 2). There was also a slightly significant association between the IL-1B-31 (rs1143627) polymorphism and PCa risk in the heterozygote model (OR, 1.35; 95%CI, 1.00-1.80; *p*=0.047) (Table 3, Figure 4). No significant association was observed between the IL-1B+3953 (rs1143634) polymorphism and PCa risk in all genetic models (additive genetic models: TT *vs* CC and TC *vs* CC, recessive genetic model: TT *vs* TC+CC, dominant genetic model: TT+TC

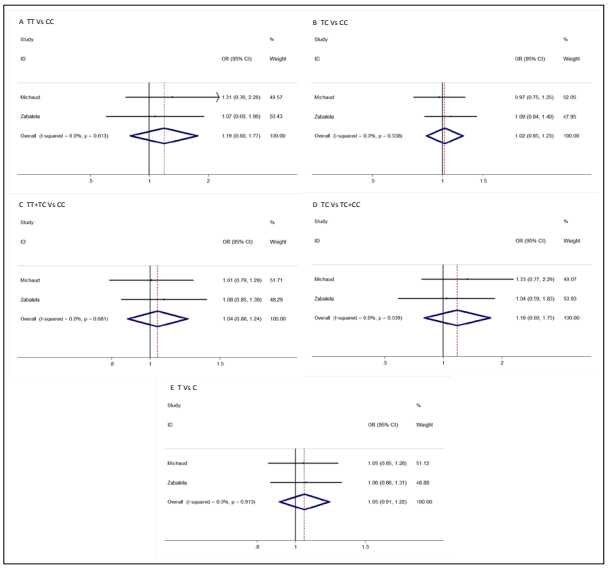

Figure 3. Forest Plot Describing the Meta-Analysis for the Association between the IL-1B+3953 (rs1143634) Polymorphism and Prostate Cancer Risk. A: homozygote model (TT *vs* CC); B: heterozygote model (TC *vs* CC); C: dominant model (TT+TC *vs* CC); D: recessive model (TT *vs* TC+CC); E: allele contrast (T *vs* C)

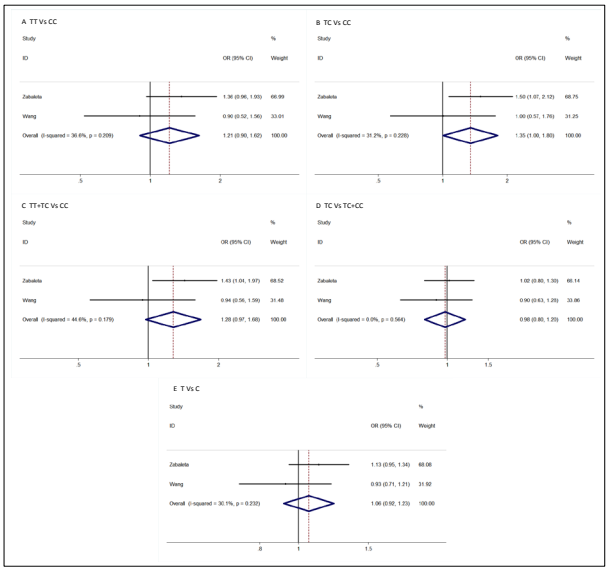

Figure 4. Forest Plot Describing the Meta-Analysis for the Association between the IL-1B-31 (rs1143627) Polymorphism And Prostate Cancer Risk. A: homozygote model (TT *vs* CC); B: heterozygote model (TC *vs* CC); C: dominant model (TT+TC *vs* CC); D: recessive model (TT *vs* TC+CC); E: allele contrast (T *vs* C)

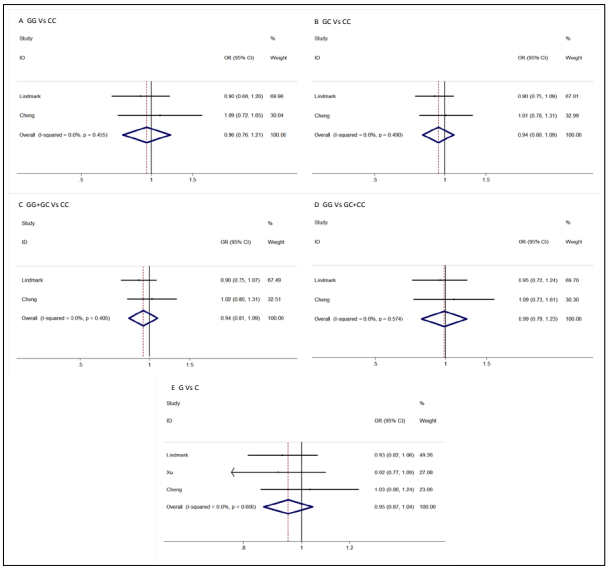

Figure 5. Forest Plot Describing the Meta-Analysis for the Association between the IL-1RN (rs315951) Polymorphism and Prostate Cancer Risk. A: homozygote model (GG *vs* CC); B: heterozygote model (GC *vs* CC); C: dominant model (GG+GC *vs* CC); D: recessive model (GGVs GC+CC); E: allele contrast (G *vs* C)

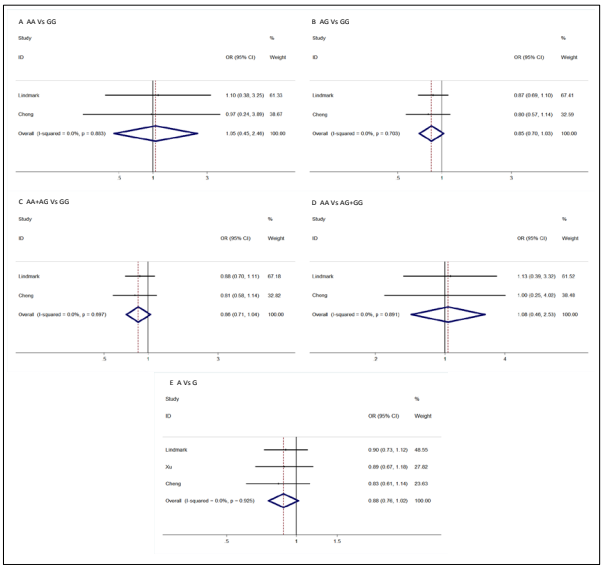

Figure 6. Forest Plot Describing the Meta-Analysis for the Association between the IL-1RN (rs3087263) Polymorphism and Prostate Cancer Risk. A: homozygote model (AA *vs* GG); B: heterozygote model (AG *vs* GG); C: dominant model (AA+AG *vs* GG); D: recessive model (AAVs AG+GG); E: allele contrast (A *vs* G)

Table 3. Meta-Analysis of the IL-1 Polymorphisms on Prostate Cancer Risk

Polymorphism investigated	No. of studies	Test of association			Test of heterogeneity			Begg's test
		OR	95% CI	*P*	Q	I^2	*P*	*P*
IL-1A								
IL-1A-889 (rs1800587)								
TT+CT *vs* CC	1	1.23	0.89-1.82	0.2	-	-	-	
C *vs* T	1	1.14	0.89-1.46	0.297	-	-	-	
IL-1B								
IL-1B-511 (rs16944)								
TT *vs* CC	3	0.74	0.58-0.94	0.012	1.4	0.00%	0.496	0.117
TC *vs* CC	3	0.88	0.75-1.04	0.129	3.5	42.90%	0.173	0.117
TT+TC *vs* CC	4	0.87	0.75-1.01	0.058	4.72	36.40%	0.194	0.174
TT *vs* TC+CC	3	0.79	0.63-0.98	0.033	0.3	0.00%	0.86	0.602
T *vs* C	3	0.86	0.77-0.96	0.008	2.34	14.70%	0.31	0.602
IL-1B+3953 (rs1143634)								
TT *vs* CC	2	1.19	0.80-1.77	0.39	0.26	0.00%	0.613	
TC *vs* CC	2	1.02	0.85-1.23	0.796	0.38	0.00%	0.538	
TT+TC *vs* CC	2	1.04	0.88-1.24	0.628	0.17	0.00%	0.681	
TT *vs* TC+CC	2	1.18	0.80-1.75	0.406	0.38	0.00%	0.539	
T *vs* C	2	1.05	0.91-1.22	0.477	0.01	0.00%	0.913	
IL-1B-31 (rs1143627)								
TT *vs* CC	2	1.21	0.90-1.62	0.203	1.58	36.60%	0.209	
TC *vs* CC	2	1.35	1.00-1.80	0.047	1.45	31.20%	0.228	
TT+TC *vs* CC	2	1.28	0.98-1.68	0.076	1.8	44.60%	0.179	
TT *vs* TC+CC	2	0.98	0.80-1.20	0.832	0.33	0.00%	0.564	
T *vs* C	2	1.06	0.92-1.23	0.421	1.43	30.10%	0.232	
IL-1RN								
IL-1RN (rs315951)								
GG *vs* CC	2	0.96	0.76-1.21	0.709	0.56	0.00%	0.455	
GC *vs* CC	2	0.94	0.80-1.09	0.395	0.48	0.00%	0.49	
GG+GC *vs* CC	2	0.94	0.81-1.09	0.403	0.69	0.00%	0.405	
GG *vs* GC+CC	2	0.99	0.79-1.24	0.916	0.32	0.00%	0.574	
G *vs* C	3	0.95	0.87-1.04	0.28	1.02	0.00%	0.6	0.117
IL-1RN (rs3087263)								
AA *vs* GG	2	1.05	0.45-2.46	0.907	0.02	0.00%	0.883	
AG *vs* GG	2	0.85	0.70-1.03	0.102	0.15	0.00%	0.703	
AA+AG *vs* GG	2	0.86	0.71-1.04	0.116	0.15	0.00%	0.697	
AA *vs* AG+GG	2	1.08	0.46-2.53	0.858	0.02	0.00%	0.891	
A *vs* G	3	0.88	0.76-1.02	0.098	0.16	0.00%	0.925	0.117

vs CC, and allele contrast: T *vs* C; Table 3, Figure 3). No significant association was observed between the IL-1RN (rs315951) polymorphism and PCa risk in all genetic models (additive genetic models: GG *vs* CC and GC *vs* CC, recessive genetic model: GG *vs* GC+CC, dominant genetic model: GG+GC *vs* CC, and allele contrast: G *vs* C; Table 3, Figure 5). As for IL-1RN (rs3087263) and PCa risk, no significant association was also observed in all genetic models (additive genetic models: AA *vs* GG and AG *vs* GG, recessive genetic model: AA *vs* AG+GG, dominant genetic model: AA+AG *vs* GG, and allele contrast: A *vs* G; Table 3, Figure 6).

Publication bias

If the meta-analysis included 3 or more than 3 studies, the Begg's test was performed. As listed in Table 3, no evidence of clear asymmetry was revealed.

Discussion

Epidemiological as well as pathological studies indicate that inflammation is one of several factors associated with the development of PCa (Dal Moro and Zattoni, 2013; Guo et al., 2013; Vignozzi and Maggi, 2014). Therefore, it is reasonable to assume that sequence variants in genes coding proinflammatory and anti-inflammatory cytokines influence PCa risk, since cytokine gene polymorphisms may lead to an altered production of cytokines (Hollegaard and Bidwell, 2006). Meta-analyses have been performed about the association between polymorphisms of proinflammatory [IL-6, IL-8, and tumor necrosis factor-α (TNF-α)] (Wang et al., 2012; Ma et al., 2014; Yang et al., 2014) and anti-inflammatory (IL-10) (Yu et al., 2013) cytokines and PCa risk. Another proinflammatory cytokine, IL-1, though important in inflammation, was not fully examined about its role in the development of PCa. IL-1 family ligands, namely IL-1A, IL-1B, and IL-1RN, might play important roles in PCa development. We are the first to conduct meta-analysis about IL-1 in order to seek the unrevealed association between IL-1 polymorphism and PCa.

In our meta-analysis, IL-1A, IL-1RN (rs315951 and rs3087263), as well as IL-1B+3953 (rs1143634) polymorphisms were not significantly associated with PCa risk in in all genetic models (additive genetic models, recessive genetic model, dominant genetic model, and

allele contrast). However, our meta-analysis revealed IL-1B-511 (rs16944) polymorphism was significantly associated with PCa risk in homozygote and recessive models, as well as allele contrast (TT *vs* CC: OR, 0.74; 95%CI, 0.58-0.94; *p*=0.012; TT *vs* TC+CC; OR, 0.79; 95%CI, 0.63-0.98; *p*=0.033; T *vs* C: OR, 0.86; 95%CI, 0.77-0.96; *p*=0.008) (Table 3, Figure 2), and IL-1B-31 (rs1143627) polymorphism was also slightly significantly associated with PCa risk in the heterozygote model (OR, 1.35; 95%CI, 1.00-1.80; *p*=0.047) (Table 3, Figure 4).

IL-1 is involved in cancer initiation and progression. After IL-1A and IL-1B are bound to IL-1 receptor of type I (IL-1RI), IL-1 receptor-associated kinase (IRAK)-1 and TNF receptor-associated factor (TRAF) 6 are recruited to the cytoplasmic domain of the receptor and transmit a signal leading to nuclear factor-κB (NF-κB) activation. IL-1A and IL-1B have different functions which rely on the form in which are presented by the cells (Bradley and Pober, 2001). Most IL-1B remains intracellular and is secreted in limited amounts. However, L-1A is usually bound to the plasma membrane and its secretion is much lesser than IL-1B (Apte and Voronov, 2008). Moreover, IL-1RN can attenuate the signals elicited by IL-1A and IL-1B. On activation by IL-1A and IL-1B, NF-κB is capable of promoting tumor cell survival through anti-apoptotic signaling in PCa (Nguyen et al., 2014). Furthermore, NF-κB can promote cell proliferation by the induction of cyclin D1 and cyclin D2 (Guttridge et al., 1999; Iwanaga et al., 2008). Besides, loss of immunoexpression of IL-1RN was a characteristic feature of PCa compared with normal prostate samples (Ricote et al., 2004).

Several limitations of this meta-analysis need to be considered. First, the sample sizes in this analysis were not adequate. Most analyses just included 2 or 3 studies. Though we revealed some significant association between IL-1B polymorphisms (rs16944 and rs1143627) and PCa risk, more well-designed population-based studies should be carried out to further investigate the association. Second, the overall outcomes were based on individual unadjusted ORs. A more precise estimation will be reached if confounding factors, such as smoking status, age, and environmental factors, were adjusted. Third, most controls in the included studies were not population-based and were not consistently screened across the included studies. Therefore, controls from different studies may have different risks of developing PCa.

In summary, our meta-analysis suggested that sequence variants in IL-1B-511 (rs16944) and IL-1B-31 (rs1143627) significantly associated with PCa risk. This observation provides additional novel evidence that proinflammatory cytokines and inflammation play an important role in the etiology of PCa.

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