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Association between *interleukin-6* polymorphisms and urinary system cancer risk: evidence from a meta-analysis

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Background: *Interleukin-6* (*IL-6*) is a multifunctional proinflammatory cytokine involved in cancer initiation and progression. Numerous studies have investigated the associations between *IL-6* polymorphisms (*IL-6* −174G>C, −592G>C, −597G>A) and risk of urinary system cancers, including prostate cancer, bladder cancer, and renal cell cancer. However, conclusions from these studies were controversial. Thus, we conducted the current meta-analysis to obtain the comprehensive profile regarding the association between *IL-6* polymorphisms and urinary system cancer risk.

Methods: According to inclusion and exclusion criteria, the associations of *IL-6* polymorphisms with urinary system cancer were searched from database and analyzed using STATA 12.0 statistical software. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the associations.

Results: A total of 20 previous publications consisting of 15,033 cases and 17,655 controls were involved in this meta-analysis. Significant association was observed in overall population regarding *IL-6* −592G>C polymorphisms (G vs C: OR =0.1.30, 95% CI =1.13−2.52; GG vs CC: OR =1.81, 95% CI =1.31−2.52; GG vs GC + CC: OR =1.33, 95% CI =1.02−1.75; GG + GC vs CC: OR =1.41, 95% CI =1.09−1.83). In the stratified analyses by ethnicity, the significant associations were found among Asian (GG vs CC: OR =1.89, 95% CI =1.34−2.66; GG + GC vs CC: OR =1.43, 95% CI =1.09−1.87) and Black population (GC vs CC: OR =0.20, 95% CI =0.05−0.82) rather than Caucasian men. Likewise, there were noticeable associations in almost all the other subanalyses such as cancer types, control sources, genotyped methods, and sample sizes. However, no significant associations were identified between any of *IL-6* −174G>C polymorphisms with urinary system cancer, except for Asian population (G vs C: OR =0.81, 95% CI =0.70−0.95; GG vs CC: OR =0.51, 95% CI =0.35−0.74; GC vs CC: OR =0.49, 95% CI =0.33−0.72; GG + GC vs CC: OR =0.50, 95% CI =0.35−0.72; respectively). In addition, no significant associations were detected between *IL-6* −597G>A polymorphism and urinary system cancer, regardless of whole or subgroups.

Conclusion: This meta-analysis presents a relatively comprehensive view of the associations between *IL-6* polymorphism and urinary system cancer risk to explore the carcinogenic mechanisms, which will help shed light on the clinical diagnosis and therapy for urinary system cancer. However, further detailed studies are needed to verify our conclusion.

Keywords: *IL-6*, polymorphism, urinary system cancer, risk, inflammation, meta-analysis

Introduction

Cancer has become a challenging problem which severely threatens public health. There has been a progressive increase in the incidence and mortality of urinary system cancer, which has drawn extensive attention in clinic. Most recent cancer statistics in

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2015 by the American Cancer Society have estimated that the incidence of prostate cancer (PCa) is still top-ranked (26%) in men, which is significantly more than that of any other cancer types, including lung cancer or colorectal cancer. Meanwhile, bladder cancer (BCa, 7%) and renal cell cancer (RCC, 5%) are in fourth and seventh place, respectively. Correspondingly, PCa is the second leading cause of male cancer-related deaths, with approximately 220,800 deaths calculated in the USA. BCa (4%) and RCC (3%) are in eighth and tenth place, respectively.[1] The mechanism of carcinogenesis is still largely unexplored. During the past decades, apart from genetic mutations that have raised major concerns about cancer in clinical practice, the role of inflammation has also been recognized as an arresting risk factor in the etiology of cancer. So far, definite causal relationships have been established between gastric cancer and *Helicobacter pylori*, colon cancer and inflammatory bowel disease.[2] More importantly, substantial evidences suggest a possible risk factor for chronic inflammation in urinary system cancer such as PCa and prostatitis,[3] BCa and schistosomiasis,[4] RCC and nephritis.[5]

Molecular mechanisms underlying inflammation-associated cancer include DNA damage,[6] disruption of the immune response, and alternation of the tumor microenvironment,[7] which are all closely related to disequilibrium of inflammatory cytokines. IL-6 is a cancer-associated multifunctional proinflammatory cytokine produced by activated T-cells, B-cells, monocytes, as well as cancerous cells. The *IL-6* gene, located at chromosome 7p21–24, is composed of four introns and five exons. Since single nucleotide polymorphisms (SNPs) of *IL-6* gene promoter may affect the expression and secretion of IL-6, and subsequently the altered circulating levels might result in relevant biological responses, the *IL-6* polymorphism has been regarded as a crucial modulator in pathogenesis of various cancer types, including breast cancer,[8] colorectal cancer,[9] hepatocellular carcinoma,[10] and so on. Notably, although several studies have shown that *IL-6* polymorphisms could be involved in the development of urinary system cancer, the conclusions were not consistent.[11–13] The probable reasons may be the relatively small cohort size in each published study. Meta-analysis primarily focuses on comparing and integrating results from individual investigations to provide a relatively precise and accurate estimation, which can explore the authentic and comprehensive effects via statistical analyses.[14] Herein, we conducted the updated meta-analysis to evaluate the associations between *IL-6* polymorphisms and urinary system cancer risk.

Materials and methods

Identification and eligibility of relevant studies

For the study, we searched the following widely used electronic literature databases: PubMed, Embase, China Biology Medicine disc, and China National Knowledge Infrastructure, for the following terms: "*interleukin6* or *interleukin-6* or *IL-6* or *IL6*", "prostate cancer", "bladder cancer", "renal cell cancer", "urinary system cancer", and "polymorphism or polymorphisms". The last search was updated on June 5, 2015. No language restrictions were performed in this meta-analysis. All retrieved articles and reviews were searched to identify other relevant publications. When the different ethnicities appeared in a reported article, we treated them independently.

Inclusion criteria

The relevant studies in meta-analysis were included using the following criteria: 1) studies that were case–control or cohort studies; 2) studies that performed the associations between *IL-6* polymorphisms and urinary system cancer risk and acquired sufficient information for odds ratios (ORs) and their 95% confidence intervals (CIs); and 3) urinary system cancers were histologically confirmed in case group. Studies were considered unqualified if they met the following criteria: 1) no data regarding associations between *IL-6* polymorphisms and urinary system cancer risk; 2) duplicate of previous publication (when the same cohort was used in several publications, only the most complete information was included after careful examination); and 3) reviews or abstracts.

Data extraction

The information was independently extracted from each eligible publication with inclusion and exclusion criteria by two authors. If there were disagreements, we resolved it through a discussion (K Zhang and L Zhang), or got it reviewed by a third author (J Zhou).

The following information was collected from each study: first author, year of publication, study country, race, genotyped method, study design, polymorphisms, the number of case and control, the type of cancer, and *P*-value of Hardy–Weinberg equilibrium (HWE) in control. The quality of each included study was evaluated by the Newcastle–Ottawa Scale, including selection of groups, comparability of the group, and ascertainment of exposure. The Newcastle–Ottawa Scale scores ranged from 0 to 10 stars. A study awarded seven or more stars was regarded as a high-quality study.[15] We did not contact the corresponding author even

if primary genotype frequency information was unavailable. Subsequently, we classified the urinary system cancer as PCa, BCa, and RCC. Ethnicity was stratified into three groups: Caucasian, Black, and Asian population. If the studies did not explain or separate the source of ethnicity, we named it as "mixed". Study designs were defined as hospital-based and population-based studies. Genetyped methods were divided into TaqMan, polymerase chain reaction (PCR), or others, including PCR-restriction fragment length polymorphism, PCR-sequence-specific primer, Massarray, GoldenGate, and sequencing.

Statistical analysis

We explored the relationship of *IL-6* polymorphisms and risk to urinary system cancer using STATA version 12.0 (StataCorp LP, College Station, TX, USA). OR and 95% CI were used to estimate the strength of relationship between *IL-6* polymorphisms and the susceptibility to cancer. We determined the associations with cancer risk underlying genotyping models, including allele comparison, recessive model, dominant model, homozygote model, and heterozygote model. Meanwhile, test of heterogeneity was measured by the chi-square-based Q test and the I^2 test ($I^2<25\%$ no heterogeneity, $25\%\leq I^2\leq 50\%$ moderate heterogeneity, $I^2>50\%$ extreme heterogeneity).[16] If $I^2>50\%$ or $P<0.10$ for the Q test, the heterogeneity of studies was considered statistically significant. As a result, the pooled OR estimation of study was calculated by the random-effects (DerSimonian and Laird method) model;[17] otherwise, the fixed-effects (Mantel and Haenszel method) model was introduced.[18]

The stability of the results was assessed by applying one-way sensitivity analyses, which individually removed studies in meta-analysis to explore the impact of each study on the pooled OR.

Potential publication biases were assessed by the Begg's funnel plots in which the log OR was plotted against its standard error. $P<0.05$ by Begg's funnel plots was considered as a statistically significant publication bias.[19] Additionally, we subclassified studies into different subgroups, including cancer type, ethnicity, source of control, genotyped method, and sample size.

Results

Characteristics of eligible studies

According to inclusion and exclusion criteria, a total of 17 studies with 15,033 cases and 17,655 controls satisfied the eligible studies.[11–13,20–33] Three eligible publications investigated two different ethnicities and we independently separated them into meta-analysis. Therefore, this updated meta-analysis was established based on 20 studies (Figure 1). Of the 20 studies, three *IL-6* polymorphisms were reported (−174G>C; −592G>C; and −597G>A) and eleven Caucasian, three Black, and six Asian population were estimated. Among the cancer types, 15, three, and two studies were related to PCa, BCa, and RCC, respectively.

Of the 20 studies, 19 were written in English and one was published in Chinese. The sample sizes ranged from 72 to 16,445. Meanwhile, nine TaqMan, five PCR, and six others in genotyped methods were applied. According to the source of control, seven were hospital-based and 13 were population-based as controls. The results of HWE test in control were calculated in eligible studies. All cancerous specimens were histologically confirmed. The characteristics of studies investigating the associations of *IL-6* polymorphisms with urinary system cancer are shown in Table 1.

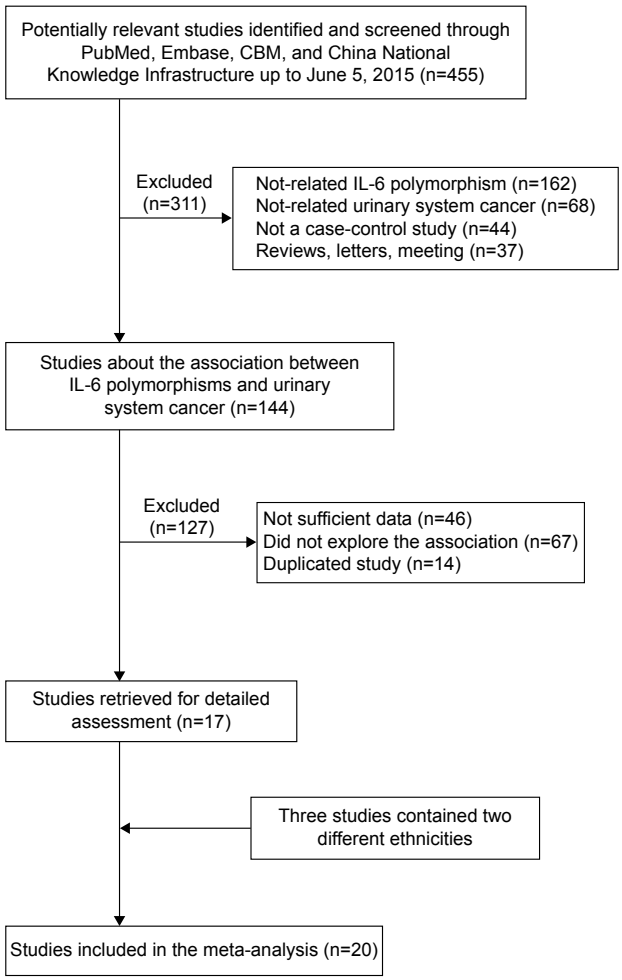

Figure 1 Flow diagram of the inclusion and exclusion of studies.
Abbreviations: CBM, China Biology Medicine disc; IL, interleukin.

Table 1 Characteristics of the eligible studies in this meta-analysis

First author	Year	Country	Ethnicity	Cancer type	Genotyped method	Design	Polymorphisms	Case/control	HWE	NOS
Mandal et al[26]	2014	USA	Caucasian	Prostate	PCR	PB	−174G>C	84/78	0.043	9
			Black	Prostate	PCR	PB	−174G>C	80/62	0.316	
Moore et al[28]	2009	Finland	Caucasian	Prostate	TaqMan	PB	−174G>C	1,041/1,048	0.152	8
Kesarwani et al[23]	2008	India	Asian	Prostate	PCR	HB	−174G>C	200/200	0.120	8
Lu et al[25]	2011	People's Republic of China	Asian	Prostate	PCR-RFLP	HB	−592G>C	200/279	0.051	7
Wang et al[31]	2009	USA	Caucasian	Prostate	TaqMan	PB	−174G>C to −592G>C	258/258	0.449/0.405	8
							−597G>A		0.866	
Pierce et al[29]	2009	USA	Caucasian	Prostate	TaqMan	PB	−174G>C to −592G>C	175/1,934	0.132/0.161	8
			Black	Prostate	TaqMan	PB	−174G>C to −592G>C	40/300	0.853/0.470	
Zabaleta et al[32]	2009	USA	Caucasian	Prostate	TaqMan	HB	−174G>C to −597G>A	74/401	0.000/0.199	7
			Black	Prostate	TaqMan	HB	−174G>C to −597G>A	15/57	0.000/0.646	
Kwon et al[24]	2011	USA	Caucasian	Prostate	Sequencing	PB	−174G>C	1,309/1,265	0.995	9
Michaud et al[27]	2006	USA	Caucasian	Prostate	TaqMan	PB	−174G>C	484/613	0.832	8
Sun et al[30]	2004	Sweden	Caucasian	Prostate	Massarray	PB	−174G>C to −592G>C	1,345/761	0.492/0.211	8
							−597G>A		0.632	
Dossus et al[11]	2010	Germany	Caucasian	Prostate	GoldenGate	PB	−174G>C	7,937/8,508	0.000	8
Bao et al[20]	2008	People's Republic of China	Asian	Prostate	TaqMan	PB	−592G>C	136/120	0.000	7
Liu et al[13]	2015	People's Republic of China	Asian	Renal	PCR-RFLP	HB	−174G>C to −592G>C	216/216	0.098/0.001	8
Basturk et al[21]	2004	Turkey	Caucasian	Renal	PCR-SSP	PB	−174G>C	25/49	0.007	9
Ahirwar et al[33]	2008	India	Asian	Bladder	PCR	PB	−174G>C	136/200	0.027	8
Guey et al[22]	2010	Spain	Caucasian	Bladder	TaqMan	HB	−174G>C	1,017/1,065	0.356	8
Ebadi et al[12]	2014	Iran	Asian	Bladder	PCR	HB	−174G>C	261/251	0.579	8

Abbreviations: HB, hospital-based; HWE, Hardy–Weinberg equilibrium (in control); NOS, the Newcastle–Ottawa Scale; PB, population-based; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; PCR-SSP, polymerase chain reaction and sequence-specific primer.

Quantitative synthesis

Meta-analysis for *IL-6* −174G>C polymorphism with urinary system cancer

According to the inclusion criteria, 15 studies with 14,697 cases and 17,266 controls were analyzed. We conducted analyses using random-effects or fixed-effects model in overall population. As a result, we did not find any association between *IL-6* −174G>C polymorphism and urinary system cancer risk in overall population (G vs C: OR =0.97, 95% CI =0.89–1.05; GG vs CC: OR =0.89, 95% CI =0.75–1.06; GC vs CC: OR =0.92, 95% CI =0.79–1.07; GG vs GC + CC: OR =1.00, 95% CI =0.96–1.05; GG + GC vs CC: OR =0.91, 95% CI =0.79–1.06, respectively). However, a certain association was found in Asian population (G vs C: OR =0.81, 95% CI =0.70–0.95; GG vs CC: OR =0.51, 95% CI =0.35–0.74; GC vs CC: OR =0.49, 95% CI =0.33–0.72; GG + GC vs CC: OR =0.50, 95% CI =0.35–0.72, respectively). The same result was revealed by codominant model in subgroup of HWE (GG vs CC: OR =0.83, 95% CI =0.69–0.99). Meanwhile, we performed comprehensive analyses subclassified by

Table 2 Stratified analysis of the IL-6 −174G>C polymorphisms and urinary system cancer

Variables	Group	Case/control	Allele G vs C OR (95% CI)	I^2 (%)	P^h	Homozygous GG vs CC OR (95% CI)	I^2 (%)	P^h	Heterozygous GC vs CC OR (95% CI)	I^2 (%)	P^h	Recessive GG vs GC + CC OR (95% CI)	I^2 (%)	P^h	Dominant GG + GC vs CC OR (95% CI)	I^2 (%)	P^h
	Overall	14,697/17,266	0.97 (0.89–1.05)	62.40	0.000	0.89 (0.75–1.06)	63.80	0.000	0.92 (0.79–1.07)	57.20	0.001	1.00 (0.96–1.05)	39.20	0.045	0.91 (0.79–1.06)	61.40	0.000
Cancer type	Prostate (13)	13,042/15,485	0.98 (0.90–1.07)	62.80	0.001	0.94 (0.79–1.13)	59.20	0.003	1.03 (0.96–1.11)	34.20	0.108	1.00 (0.95–1.05)	47.20	0.030	0.98 (0.85–1.12)	50.5	0.019
	Bladder (3)	1,414/1,516	0.88 (0.65–1.19)	76.10	0.015	0.68 (0.32–1.43)	80.2	0.006	0.58 (0.25–1.35)	81.60	0.004	1.08 (0.93–1.25)	45.30	0.161	0.64 (0.30–1.35)	80.90	0.005
	Renal (2)	241/265	1.11 (0.50–2.48)	72.40	0.057	1.67 (0.07–37.23)	77.80	0.034	1.99 (0.06–62.01)	81.10	0.021	0.92 (0.64–1.31)	0.00	0.535	1.79 (0.07–46.45)	80.00	0.025
Ethnicity	Asian (4)	813/867	**0.81 (0.70–0.95)**	0.00	0.635	**0.51 (0.35–0.74)**	0.00	0.586	**0.49 (0.33–0.72)**	40.80	0.167	0.89 (0.73–1.08)	0.00	0.932	**0.50 (0.35–0.72)**	0.00	0.408
	Caucasian (11)	13,749/15,980	1.02 (0.93–1.11)	69.80	0.000	1.00 (0.85–1.18)	63.30	0.002	1.04 (0.97–1.11)	36.30	0.108	1.00 (0.90–1.12)	60.50	0.005	1.01 (0.89–1.15)	53.10	0.019
	Black (3)	135/419	0.72 (0.45–1.14)	0.00	0.646	0.32 (0.10–1.05)	0.00	0.574	**0.20 (0.05–0.82)**	0.00	0.695	0.88 (0.52–1.49)	0.00	0.800	0.31 (0.10–1.01)	0.00	0.577
Study design	HB (6)	1,783/2,190	0.99 (0.90–1.09)	35.80	0.168	0.91 (0.72–1.13)	35.30	0.172	0.87 (0.70–1.08)	1.50	0.406	1.03 (0.90–1.17)	15.70	0.313	0.89 (0.72–1.10)	23.30	0.259
	PB (12)	12,914/15,076	0.98 (0.89–1.09)	70.50	0.000	0.93 (0.75–1.15)	71.40	0.000	0.95 (0.79–1.14)	66.50	0.001	1.00 (0.95–1.05)	49.70	0.025	0.95 (0.79–1.14)	69.50	0.000
Genotype method	TaqMan (8)	3,104/5,676	0.97 (0.90–1.04)	18.70	0.282	0.90 (0.77–1.04)	0.00	0.479	0.98 (0.85–1.12)	0.00	0.509	0.96 (0.87–1.07)	44.90	0.080	0.95 (0.84–1.08)	0.00	0.636
	PCR (5)	761/791	0.99 (0.63–1.55)	85.20	0.000	0.80 (0.27–2.38)	84.00	0.000	0.65 (0.24–1.73)	77.80	0.001	1.08 (0.73–1.59)	68.40	0.013	0.74 (0.27–2.08)	82.70	0.000
	Others (5)	10,832/10,799	1.02 (0.98–1.06)	47.50	0.107	0.99 (0.80–1.21)	61.40	0.035	0.97 (0.79–1.19)	62.90	0.029	1.01 (0.96–1.07)	0.00	0.731	0.97 (0.80–1.19)	65.20	0.022
Sample size	≥500 (8)	13,827/15,703	1.01 (0.97–1.04)	41.00	0.094	1.02 (0.95–1.09)	32.80	0.155	1.03 (0.96–1.10)	0.20	0.432	1.00 (0.95–1.05)	45.60	0.065	1.02 (0.96–1.09)	11.80	0.336
	<500 (10)	870/1,563	0.99 (0.73–1.35)	73.90	0.000	0.78 (0.38–1.62)	74.00	0.000	0.70 (0.34–1.41)	70.30	0.001	1.01 (0.84–1.21)	39.60	0.103	0.76 (0.38–1.51)	73.80	0.000
HWE	Yes (12)	8,271/9,293	0.97 (0.92–1.02)	39.90	0.068	0.83 (0.69–0.99)	50.00	0.020	0.85 (0.71–1.01)	54.00	0.01	0.98 (0.91–1.06)	22.80	0.213	0.85 (0.73–1.00)	51.00	0.017

Note: The values shown in bold indicate that statistically significant associations were observed between the paired groups.

Abbreviations: CI, confidence interval; OR, odds ratio; P^h, *P*-value of heterogeneity test; PCR, polymerase chain reaction; HB, hospital-based; PB, population-based; HWE, Hardy–Weinberg equilibrium (in control).

cancer types, control sources, genotyped methods, and the sample sizes, and eventually found no associations among each subgroup (Table 2).

Meta-analysis for *IL-6* −592G>C polymorphism with urinary system cancer

The association between *IL-6* −592G>C polymorphism and urinary system cancer risk was assessed in seven studies with a total of 2,370 cases and 3,868 controls. Among which, six studies regarding PCa and one study regarding RCC were involved in the meta-analysis. As shown in Table 2, associations were observed in overall population (G vs C: OR =0.1.30, 95% CI =1.13–2.52; GG vs CC: OR =1.81, 95% CI =1.31–2.52; GG vs GC + CC: OR =1.33, 95% CI=1.02–1.75; GG+GC vs CC: OR=1.41, 95% CI=1.09–1.83). Besides, it seemed that there were some associations via subanalyses regarding cancer types, ethnicities, sources of control, genotyped methods, as well as sample sizes (Table 3).

Meta-analysis for *IL-6* −597G>A polymorphism with urinary system cancer

Only four independent studies with 1,692 cases and 1,477 controls were included in such meta-analysis, including four studies upon PCa. The findings suggested no associations could be identified (G vs A: OR =0.96, 95% CI =0.87–1.07; GG vs AA: OR =0.92, 95% CI =0.74–1.15; GA vs AA: OR =0.93, 95% CI =0.77–1.14; GG vs GA + AA: OR =0.97, 95% CI =0.82–1.15; GG + GA vs AA: OR =0.93, 95% CI =0.77–1.12). Similarly, we did not find any association after comprehensive analyses conducted in aforementioned subgroups (Table 4).

Sensitivity analysis

One-way sensitivity analyses were individually performed by removing studies to assess the stability of the pooled results. Specifically, each single study included in the meta-analysis was deleted each time to observe the influence of the individual data to the pooled ORs, and none of which affected the pooled OR value, suggesting that the results of this meta-analysis were stable (Figure 2A–C).

Evaluation of publication bias

Begger's funnel plot revealed that no evidences of publication bias were found in different alleles of *IL-6* polymorphisms (*IL-6* −174G>C: *P*=0.820; *IL-6* −592G>C: *P*=0.881; *IL-6* −597G>A: *P*=1.000, Figure 3). Meanwhile, there was also no significant funnel asymmetry that could reveal publication bias in each subgroup meta-analysis (data not shown).

Table 3 Stratified analysis of the IL-6 –592G>C polymorphisms and urinary system cancer

Variables	Group	Case/control	Allele G vs C OR (95% CI)	I^2 (%)	P^h	Homozygous GG vs CC OR (95% CI)	I^2 (%)	P^h	Heterozygous GC vs CC OR (95% CI)	I^2 (%)	P^h	Recessive GG vs GC + CC OR (95% CI)	I^2 (%)	P^h	Dominant GG + GC vs CC OR (95% CI)	I^2 (%)	P^h
	Overall	2,370/3,868	**1.30 (1.13–1.49)**	34.00	0.169	**1.81 (1.31–2.52)**	27.90	0.216	1.18 (0.88–1.58)	41.70	0.113	**1.33 (1.02–1.75)**	51.40	0.055	**1.41 (1.09–1.83)**	24.40	0.243
Cancer type	Prostate (6)	2,154/3,652	**1.39 (1.19–1.63)**	6.40	0.376	**2.08 (1.43–3.03)**	19.60	0.286	1.14 (0.82–1.57)	49.90	0.076	**1.42 (1.16–1.73)**	40.70	0.134	**1.44 (1.09–1.92)**	35.80	0.168
	Renal (1)	216/216	0.99 (0.73–1.34)	–	–	1.18 (0.60–2.30)	–	–	1.40 (0.69–2.84)	–	–	0.91 (0.62–1.33)	–	–	1.25 (0.65–2.40)	–	–
Ethnicity	Asian (3)	552/615	1.37 (0.98–1.90)	70.70	0.033	**1.89 (1.34–2.66)**	24.70	0.265	1.20 (0.88–1.62)	46.50	0.154	1.52 (0.83–2.77)	78.80	0.009	**1.43 (1.09–1.87)**	25.70	0.260
	Caucasian (3)	1,778/2,953	1.20 (0.95–1.51)	0.00	0.500	1.60 (0.45–5.71)	18.10	0.295	1.34 (0.37–4.84)	8.60	0.335	1.19 (0.93–1.51)	0.00	0.513	1.57 (0.44–5.61)	17.40	0.298
	Black (1)	40/300	1.65 (0.58–4.71)	–	–	0.15 (0.01–2.39)	–	–	**0.04 (0.00–0.98)**	–	–	2.29 (0.68–7.74)	–	–	0.13 (0.01–2.13)	–	–
Study design	HB (2)	416/495	1.21 (0.83–1.76)	70.40	0.066	1.69 (0.88–3.25)	57.10	0.127	1.03 (0.72–1.46)	0.00	0.327	1.44 (0.57–3.68)	88.30	0.003	1.24 (0.90–1.70)	0.00	0.979
	PB (5)	1,954/3,373	**1.36 (1.13–1.65)**	22.80	0.269	**1.90 (1.12–3.22)**	32.80	0.203	1.61 (0.94–2.77)	47.80	0.105	**1.29 (1.04–1.61)**	0.00	0.435	**1.84 (1.17–2.92)**	34.20	0.193
Genotype	TaqMan (4)	609/2.612	1.41 (1.09–1.82)	40.60	0.168	**1.77 (1.01–3.09)**	43.50	0.150	0.49 (0.08–2.97)	57.80	0.069	1.31 (0.96–1.79)	20.90	0.285	**1.75 (1.08–2.82)**	44.90	0.142
method	Others (3)	1,761/1,256	**1.25 (1.06–1.48)**	42.90	0.174	**1.84 (1.23–2.75)**	33.00	0.225	1.08 (0.76–1.52)	14.40	0.311	1.36 (0.85–2.17)	76.60	0.014	1.29 (0.94–1.76)	0.00	0.487
Sample size	≥500 (3)	1,778/2,953	1.20 (0.95–1.51)	0.00	0.500	1.60 (0.45–5.71)	18.10	0.295	1.34 (0.37–4.84)	8.60	0.335	1.19 (0.93–1.51)	0.00	0.513	1.57 (0.44–5.61)	17.40	0.298
	<500 (4)	592/915	**1.38 (1.03–1.86)**	56.90	0.073	**1.83 (1.31–2.57)**	48.60	0.120	1.16 (0.64–2.12)	62.70	0.045	1.60 (0.94–2.71)	70.30	0.018	**1.40 (1.07–1.83)**	45.30	0.139
HWE	Yes (5)	2,018/3,532	**1.31 (1.10–1.55)**	0.00	0.603	**2.02 (1.24–3.28)**	35.20	0.187	0.93 (0.63–1.37)	35.50	0.185	**1.37 (1.11–1.70)**	48.60	0.100	1.22 (0.86–1.73)	20.40	0.285

Note: The values shown in bold indicate that statistically significant associations were observed between the paired groups.
Abbreviations: CI, confidence interval; HB, hospital-based; PB, population-based; OR, odds ratio; P^h, *P*-value of heterogeneity test; HWE, Hardy–Weinberg equilibrium (in control).

Table 4 Stratified analysis of the IL-6 –597G>A polymorphisms and urinary system cancer

Variables	Group	Case/control	Allele G vs A OR (95% CI)	I^2 (%)	P^h	Homozygous GG vs AA OR (95% CI)	I^2 (%)	P^h	Heterozygous GA vs AA OR (95% CI)	I^2 (%)	P^h	Recessive GG vs GA + AA OR (95% CI)	I^2 (%)	P^h	Dominant GG + GA vs AA OR (95% CI)	I^2 (%)	P^h
Cancer type	Prostate (4)	1,692/1,477	0.96 (0.87–1.07)	0.00	0.400	0.92 (0.74–1.15)	8.60	0.350	0.93 (0.77–1.14)	21.60	0.281	0.97 (0.82–1.15)	0.00	0.694	0.93 (0.77–1.12)	24.40	0.265
Ethnicity	Caucasian (3)	1,677/1,420	0.96 (0.86–1.07)	29.60	0.242	0.92 (0.74–1.15)	38.30	0.198	0.93 (0.77–1.14)	47.50	0.149	0.97 (0.82–1.15)	0.00	0.494	0.93 (0.77–1.12)	49.00	0.141
	Black (1)	15/57	1.25 (0.26–6.02)	–	–	0.66 (0.02–17.35)	–	–	0.71 (0.02–23.31)	–	–	1.15 (0.22–6.11)	–	–	0.64 (0.02–16.86)	–	–
Study design	HB (2)	89/458	1.16 (0.81–1.66)	0.00	0.927	1.51 (0.68–3.34)	0.00	0.610	1.82 (0.86–3.87)	0.00	0.592	0.99 (0.59–1.66)	0.00	0.853	1.69 (0.82–3.49)	0.00	0.556
	PB (2)	1,603/1,019	0.95 (0.85–1.06)	43.10	0.185	0.88 (0.70–1.11)	31.20	0.228	0.88 (0.72–1.08)	0.00	0.593	0.97 (0.81–1.16)	29.00	0.235	0.88 (0.72–1.07)	0.00	0.374
Genotype	TaqMan (3)	347/716	1.12 (0.91–1.38)	0.00	0.965	1.27 (0.82–1.95)	0.00	0.774	1.21 (0.81–1.82)	0.00	0.372	1.11 (0.83–1.50)	0.00	0.851	1.24 (0.84–1.82)	0.00	0.495
method	Others (1)	1,345/761	0.91 (0.80–1.03)	–	–	0.82 (0.64–1.06)	–	–	0.86 (0.68–1.08)	–	–	0.92 (0.75–1.12)	–	–	0.85 (0.68–1.05)	–	–
Sample size	≥500 (2)	1,603/1,019	0.95 (0.85–1.06)	43.10	0.185	0.88 (0.70–1.11)	31.20	0.228	0.88 (0.72–1.08)	0.00	0.593	0.97 (0.81–1.16)	29.00	0.235	0.88 (0.72–1.07)	0.00	0.374
	<500 (2)	89/458	1.16 (0.81–1.66)	0.00	0.927	1.51 (0.68–3.34)	0.00	0.610	1.82 (0.86–3.87)	0.00	0.592	0.99 (0.59–1.66)	0.00	0.853	1.69 (0.82–3.49)	0.00	0.556
HWE	Yes (4)	1,692/1,477	0.96 (0.87–1.07)	0.00	0.400	0.92 (0.74–1.15)	8.60	0.350	0.93 (0.77–1.14)	21.60	0.281	0.97 (0.82–1.15)	0.00	0.694	0.93 (0.77–1.12)	24.40	0.265

Abbreviations: CI, confidence interval; HB, hospital-based; PB, population-based; OR, odds ratio; P^h, *P*-value of heterogeneity test; HWE, Hardy–Weinberg equilibrium (in control).

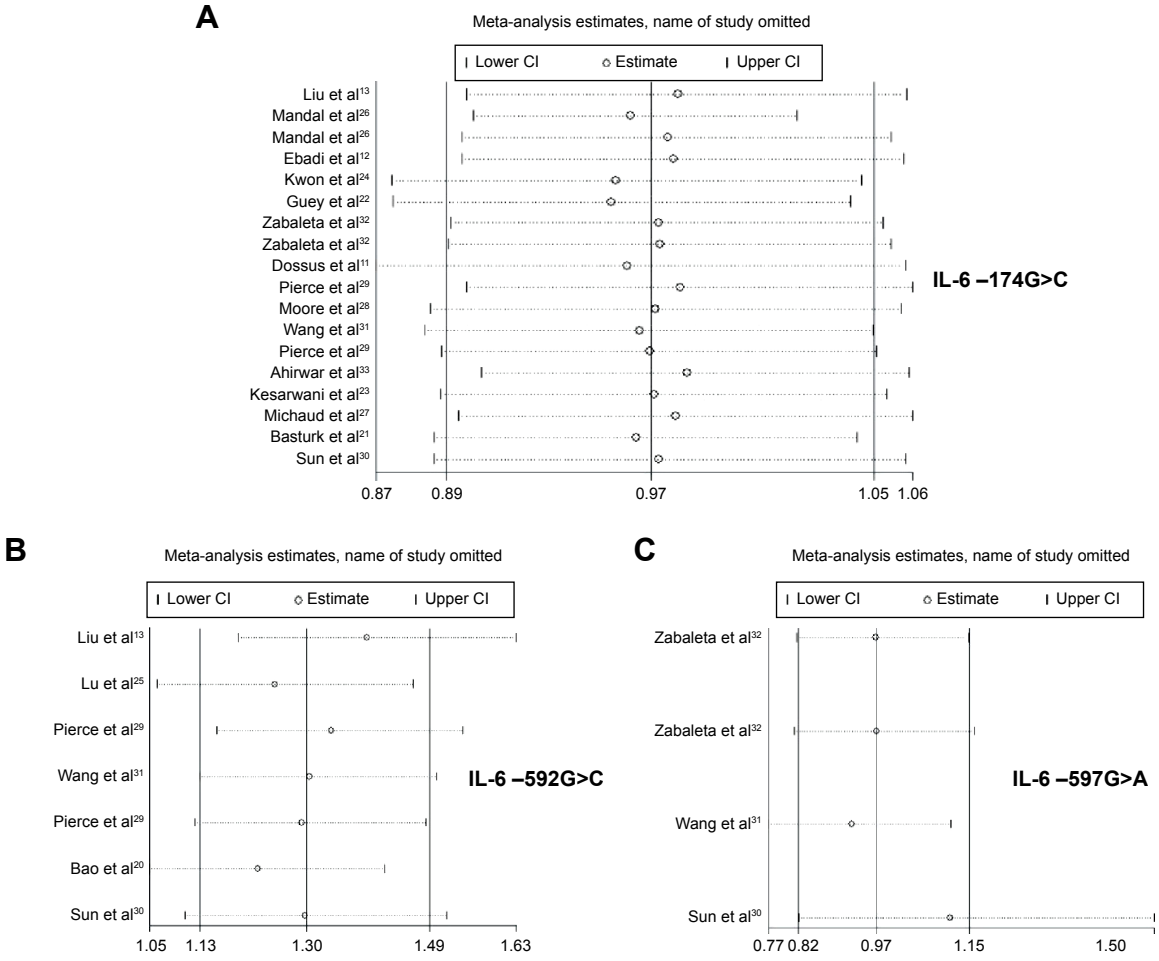

Figure 2 One-way sensitivity analysis of the IL-6 –174G>C (**A**), IL-6 –592G>C (**B**), and IL-6 –597G>A (**C**) polymorphisms with overall cancer risk.
Abbreviations: CI, confidence interval; IL, interleukin.

Discussion

Until now, investigations focused on the associations between *IL-6* polymorphisms and urinary system cancer risk were relatively rare and inconclusive. To the best of our knowledge, the current meta-analysis is a relatively detailed comprehensive summary to explore the associations between three *IL-6* polymorphisms (–174G>C, –592G>C, and –597G>A) and urinary system cancers, including PCa, BCa, and RCC. Meanwhile, further analyses were conducted in different subgroups to explore the potential associations. As a result, the current meta-analysis showed distinct associations between *IL-6* –592G>C polymorphisms and urinary system cancers in overall group and most of the subgroups. Intriguingly, no associations in overall population between *IL-6* –174G>C polymorphism and urinary system cancers were found. However, in the subgroup analysis of ethnicity, a linkage was solely confirmed in Asian population rather than any other. Meanwhile, no associations between –592G>C and urinary system cancers were detected in overall population and different subgroups, which results indicated that for certain population, cancer susceptibility may be associated with different genes, different loci within the same gene, or even different polymorphisms at the same locus.[34]

Recently, several published meta-analyses have paid much attention to explore the associations of *IL-6* polymorphisms with various cancer types. On one hand, the associations seemed to be invalid. Concretely, Yu et al[35] addressed that there was no association between a functional polymorphism *IL-6* –174G>C and breast cancer risk, regardless of the distinct ethnicities. Likewise, Wang et al[36] showed that *IL-6* –174G>C, –592G>C, and –597G>A polymorphisms were not associated with gastric cancer risk; subsequent subgroup analysis also did not explore any significant association in Asian or Caucasian population. Besides, no associations were found between *IL-6* –174G>C and lung cancer.[37] On the other hand, some definite associations could be found between specific *IL-6* polymorphisms and various cancer types. Based on the meta-analysis by Liu et al,[38] *IL-6* –174G>C, but not *IL-6* –592G>C, polymorphism could be linked with hepatocellular carcinoma risk. In the

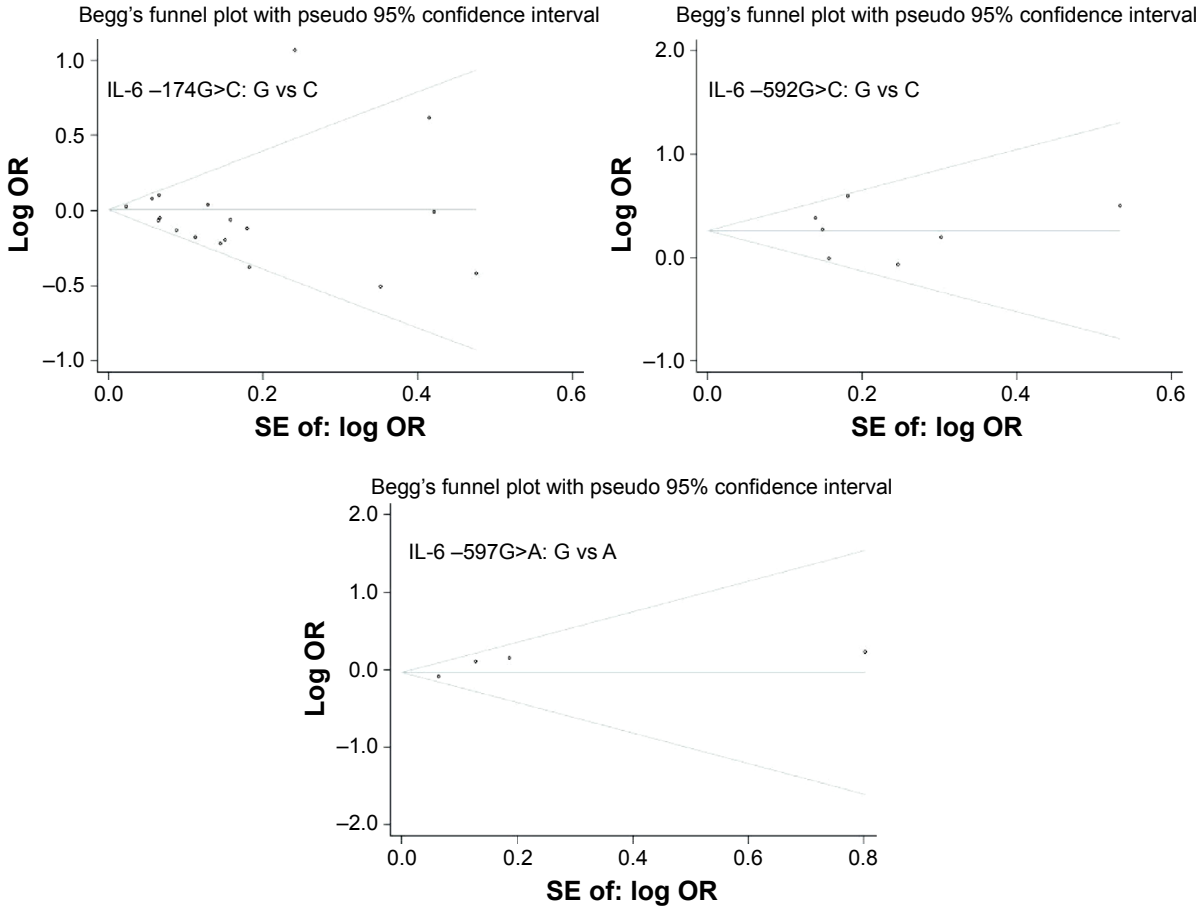

Figure 3 Begg's funnel plots to examine publication bias in different alleles of IL-6 polymorphisms.
Abbreviations: IL, interleukin; log OR, natural logarithm of OR; SE of: log OR, standard error of the log OR.

subgroup analysis of healthy population-based control and hepatocirrhosis population-based control, a significant association was detected between −174G>C polymorphism and hepatocellular carcinoma risk. For PCa, similar association with polymorphism was also confirmed.[39] Besides, Joshi et al[40] revealed associations between *IL-6* −174G>C polymorphism and genitourinary cancers risk in Ancestral North Indians. Notably, different *IL-6* polymorphisms were probably associated with different cancer types, thus, we performed a relatively comprehensive meta-analysis simultaneously, including three *IL-6* polymorphisms, three urinary system cancers, and corresponding subgroups in the current meta-analysis.

IL-6 gene is located on chromosome 7p21–24, whose promoter region contains several SNPs. It has been widely reported that −174G>C, −592G>C, and −597G>A might show considerable impact on initiation and progression of cancer. Previous studies found that IL-6 could go through a functional alternation from paracrine to autocrine growth factor in the development of cancer, especially for PCa[41] and multiple myeloma.[42] Concretely, IL-6 acted as a paracrine growth factor on the hormone-sensitive lymph node carcinoma of prostate cells, while as an autocrine growth factor on the castration-resistant PC-3 PCa cells.[43,44] Compared with healthy people or patients with localized cancer, IL-6 serum levels were increased in patients with distant bone metastasis or castration-resistant PCa.[45] *IL-6* promoter haplotypes (−174G>C, −592G>C, and −597G>A) have shown significant effects on transcriptional regulation and disease association.[46] Specifically, previous studies regarding the effect of −174G>C on transcription factor binding have shown that −174G>C transversion gates the GATA1 access to *IL-6* promoter, thereby linking the SNPs to differential risk of inflammation-related diseases such as PCa.[47] Accordingly, homozygotes for the G allele have been shown to have higher plasma levels of IL-6, higher *IL-6* gene transcription activity, and higher inducible IL-6 responses compared with subjects homozygous for the C allele. In spite of that, there was evidence to support a positive association between −174G allele and higher IL-6 levels, C allele was essentially associated with PCa.[48] In consideration of that, −174G>C and −592G>C possessed the identical alleles

pattern, we speculated that the two polymorphisms might have similar effects on PCa. Integrating IL-6 with IL-6R could activate different signaling pathways of cancer, including the Janus tyrosine family kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, the extracellular signal-regulated kinase 1 and 2 (ERK1/2)-mitogen-activated protein kinase pathway, and the phosphoinositide 3-kinase (PI3-K) and protein kinase B (PKB/Akt) pathway.[49] In classic IL-6 signaling, upon binding of IL-6 to its receptor, JAK phosphorylates and activates STAT factors, a family of transcription factors. This allows dimerization of the STAT protein and subsequent exposition of its nuclear localization signal. STAT will then translocate to the nucleus for transcription initiation of downstream target genes.[50] The targets of STAT-3 include growth factors and cytokines that are involved in inflammation-related carcinogenesis, such as hypoxia-inducible factor-1α, vascular endothelial growth factor, matrix metalloproteinase-2, and -9. A negative feedback loop exists for IL-6 through upregulation of suppressor of cytokine signaling 3 gene transcription by STAT-3. The suppressor of cytokine signaling 3 protein leads to termination of cytokine signaling through inhibition of JAK by direct binding to the kinases.[50] IL-6 also activates the ERK1/2-mitogen-activated protein kinase signaling pathway, JAK phosphorylates SHP2 (Src homology two domain-containing tyrosine phosphatase 2), a protein-tyrosine phosphatase, which in turn leads to activation of Ras after IL-6 binding. This activation will subsequently trigger a cascade of events that result in successive elicitation of Raf, then mitogen-activated protein kinase kinase (MAPKK) and finally ERK.[50] In addition, IL-6 was addressed to be able to activate signal transduction through the PI3-K signaling pathway. When PI3-K is activated in response to ligand binding, the resulting second messenger recruits the protein kinase Akt to the plasma membrane and binds it with phosphorylation to translocate toward the nucleus and other subcellular components, where it regulates various biological processes, including anti-apoptosis and proliferation.[50] In view of that, multiple lines of evidence supported an important role of genetics in determining cancer risk; understanding polymorphisms associated with cancer risk may be valuable for providing personalized diagnosis and therapy of certain cancers.

Limitations

There were several limitations in our meta-analysis. First, it was a retrospective study subjected to recall or selection bias of eligible studies in meta-analysis. Second, only published studies were included in current meta-analysis, which could not provide sufficient evidences to verify our findings, especially for the analysis of BCa and RCC. Finally, our result was performed by crude estimation; therefore, a more precise analysis would be needed to adjust whether the original data were available, such as smoking, drinking, gene–gene, and gene–environment interactions. Meanwhile, the heterogeneity of *IL-6* polymorphism was relatively high, suggesting that there were potential and undiscovered factors in the included studies. Besides, some controls of eligible studies did not conform to HWE in this updated meta-analysis, which may influence the ultimate conclusion. All the limitations clearly require to be investigated in future research. In spite of the aforementioned limitations, this current meta-analysis has definitely shown noticeable associations between *IL-6* polymorphisms and urinary system cancer risk.

Conclusion

This meta-analysis is a relatively detailed comprehensive study to explore the associations between the three *IL-6* polymorphisms and urinary system cancer, including PCa, BCa, and RCC. In summary, the current meta-analysis showed established associations between *IL-6* −592G>C polymorphisms and urinary system cancer in overall group and most of the subgroups. In the almost whole subgroup of Asian population, a marginally significant association was explored between urinary system cancer and *IL-6* −174G>C polymorphism rather than −597G>A, which also validates that chronic inflammation may be a potential risk factor in urinary system cancer. A more well-designed prospective study based on large sample size, multiple SNPs, or haplotypes is needed to confirm the current findings.

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Disclosure

The authors report no conflicts of interest in this work.

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