Association of tumor necrosis factor-α 308G/A polymorphism with urogenital cancer risk: a systematic review and meta-analysis

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ABSTRACT. We integrated all the eligible studies and investigated whether the TNF-α 308G/A polymorphism correlates with urogenital cancer risk. Tumor necrosis factor-α (TNF-α) is a risk factor for some urogenital cancers; however, in prostate and bladder cancers the results are controversial. PubMed, EMBASE, Web of Science, the Cochrane Library, the Chinese Biomedical Literature Database, and the Wanfang Database were searched for all case-control studies on the relationship between the TNF-α 308G/A polymorphism and susceptibility to urogenital cancer between January 1994 and January 2015. The pooled odds ratio with 95% confidence interval was calculated to assess the associations. A total of

504 articles were found, 39 of which involved 11,613 cases and 12,542 controls that fulfilled the inclusion criteria. Overall, the TNF-α 308G/A polymorphism was significantly associated with the risk of urogenital cancer. In the subgroup analysis for different cancer types, significant associations were found in cervical cancer and urothelial carcinoma, while our meta-analysis indicated that there were no significant associations between the TNF-α 308G/A polymorphism and prostate, bladder, or renal cancers. When stratified by ethnicity, significant associations were observed in Caucasian populations, whereas no significant associations were found in African-Americans, Asians, or mixed populations. Furthermore, carriers of the -308A allele among the hospital-based case-control group were at a high risk of urogenital cancer. Our meta-analysis showed that the TNF-α 308G/A polymorphism was significantly associated with urogenital cancer risk, particularly in the Caucasian and hospital-based populations.

Key words: Urogenital cancer; TNF-α; Polymorphism; Meta-analysis

INTRODUCTION

Urogenital cancers, including prostate, bladder, cervical, ovarian, renal cell, and endometrium cancers, are commonly diagnosed in human beings. Prostate cancer is the most commonly diagnosed cancer in men; in 2014, the estimated number of new cases was 233,000 and the number of deaths was 29,480. Bladder cancer is the fourth most common cancer in men with an estimated 56,390 new cases in 2014, and there are also high incidences of other urogenital cancers, such as cervical, ovarian, and renal cell cancers. Until now, the exact mechanism of carcinogenesis is uncertain, although several factors have been discovered and hypotheses proposed. Lichtenstein et al. (2000) found that there was a significant association between environmental and heritable factors and causation of cancer, and genetic factors might account for 42% of prostate cancer cases. Zaridze et al. (2008) considered genetic factors and gene polymorphisms to be critical causes of cancer risk.

With regard to urogenital cancer, several specific mechanisms of cancer development have also been proposed. Pashos et al. (2002) reported that risk factors such as cigarette smoking might have an effect on the development of bladder cancer. The association between cervical cancer and certain types of human papillomavirus (HPV) has already been confirmed. Inflammation may be associated with prostate cancer for two reasons: cytokines are frequently present in prostate biopsy and prostatectomy specimens; and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin have been confirmed by Veitonmaki et al. (2013) to reduce prostate cancer risk. Furthermore, chronic inflammation is also thought to play an important role in the development of other urogenital cancers.

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine primarily produced by macrophages that can induce cellular growth, death, and regeneration. The gene that encodes TNF-α has the chromosomal locus 6p21.3, and there are several polymorphisms in the upstream proximal promoter of TNF-α that may have an effect on its production and bioactivity. Recently, several studies focusing on the associations between TNF-α polymorphisms and urogenital cancer risk have been performed, producing results that suggest that the TNF-α 308G/A polymorphism

(one of several TNF-α polymorphisms) might be a risk factor for urogenital cancer development. For instance, Berhane et al. study (2012) showed a statistically significant increase in the risk of prostate cancer among individuals that carry the A allele of the TNF-α-308 gene. Badano et al. (2012) thought that the presence of the high producer allele TNF-α-308 A was correlated with an increased risk of cervical cancer in a Posadas population. However, results from other studies remain controversial (Nonomura et al., 2006; Danforth et al., 2008; Wang et al., 2011; Barbisan et al., 2012; Jones et al., 2013). Owing to these conflicting results, we conducted this meta-analysis to provide a comprehensive assessment of the associations between the TNF-α 308G/A polymorphism and the risk of urogenital cancer.

MATERIAL AND METHODS

Search strategy

Databases including PubMed, EMBASE, Web of Science, the Cochrane Library, the Chinese Biomedical Literature Database, and the Wanfang Database were searched for all case-control studies that mainly focused on the relationship between the TNF-α 308G/A polymorphism and susceptibility to cancer. The following search terms were used: (‘cancer’ OR ‘carcinoma’) AND (‘TNF alpha’ OR ‘tumor necrosis factor alpha’ OR ‘tumor necrosis factor α’ OR ‘TNFα’) AND (‘polymorphism’ OR ‘single nucleotide polymorphism’ OR ‘SNP’ OR ‘variation’). The articles retrieved were then selected by reviewers to identify studies focusing on urogenital cancers. There was no language restriction on the literature search. Secondary searches of unpublished literature were conducted by searching the reference lists of the selected studies, and reviews were also examined to find more eligible studies.

Inclusion and exclusion criteria

The inclusion criteria were: 1) the study must have been a case-control study; 2) the study must have evaluated urogenital cancer risk and the TNF-α 308G/A polymorphism; and 3) the study must have provided sufficient data, including number or frequency of alleles and genotypes. Studies were excluded if they: 1) were reviews, case reports, or non-case-control studies or meta-analyses; 2) did not report sufficient available data; or 3) duplicated reports.

Data extraction

Data from the eligible studies were independently extracted according to the inclusion and exclusion criteria by two authors, and a consensus was attempted. For each study, the following characteristics were collected: authors, year of publication, ethnicity, group, sample size, and alleles and genotypes of the TNF-α 308G/A polymorphism. Moreover, we evaluated whether the genotype distributions followed the Hardy-Weinberg equilibrium (HWE).

Data synthesis and statistical analysis

Odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated to assess

the association between the TNF-α 308G/A polymorphism and urogenital cancer risk in an allele contrast model (A *vs* G), a homozygote model (AA *vs* GG), a heterozygote model (GA *vs* GG), a dominant model (AA/GA *vs* GG), and a recessive model (AA *vs* GA/GG). Subgroup analysis was performed according to type of urogenital cancer, ethnicity, and control source. Heterogeneity was checked by a chi-square-based Q statistic test and quantified by I^2 metric value. If $I^2 > 50\%$, suggesting that an obvious heterogeneity existed, ORs were pooled by the random-effect model, otherwise, the fixed-effect model was used. Sensitivity analysis was performed by excluding the studies not in HWE, and publication bias was evaluated by funnel plots and Egger's test. All meta-analyses were performed using Stata 12.0 and P-values < 0.05 were considered statistically significant.

RESULTS

Study characteristics

A total of 504 articles were preliminarily reviewed, of which 39 studies with 11,613 cases and 12,542 controls fulfilled the inclusion criteria (Table 1). Three hundred and fifty-one studies remained after 153 replicated articles had been eliminated. Two hundred and ninety-two studies did not focus on urogenital cancer and 8 studies were case-only or case-case studies. Twelve articles were also excluded because they did not provide sufficient data. As a result, a total of 39 articles were included in our meta-analysis (Figure 1). There are 13 studies (Oh et al., 2000; McCarron et al., 2002; Wu, 2004; Jinchao, 2007; Danforth et al., 2008; Sáenz-López et al., 2008; Zabaleta et al., 2008; Kesarwani, 2009; Moore et al., 2009; Wang et al., 2009a; Zhang et al., 2010; Berhane et al., 2012; Jones et al., 2013) focusing on prostate cancer, 19 studies (Jang et al., 2001; Calhoun et al., 2002; Gostout et al., 2003; Stanczuk et al., 2003; Deshpande et al., 2005; Duarte et al., 2005; Govan, 2006; Kohaar et al., 2007; Singh, 2009; Wang et al., 2009b; Ivansson, 2010; Zu, 2010; Wang et al., 2011; Zuo et al., 2011; Badano et al., 2012; Barbisan et al., 2012; Hang and Xu, 2012; Wang et al., 2012; Sousa et al., 2014) on cervical cancer, 6 studies (Tsai et al., 2001; Jeong et al., 2004; Kim et al., 2005; Leibovici et al., 2005; Nonomura et al., 2006; Ahirwar et al., 2008) on bladder cancer, 1 study (Jang et al., 2001) on renal cell cancer, and 1 study (Wu, 2013) on urothelial carcinoma. Five articles (Stanczuk et al., 2003; Govan, 2006; Zabaleta et al., 2008; Berhane et al., 2012; Jones et al., 2013) involved African-American patients, 16 articles (Oh et al., 2000; Calhoun et al., 2002; McCarron et al., 2002; Gostout et al., 2003; Deshpande et al., 2005; Duarte et al., 2005; Leibovici et al., 2005; Kohaar et al., 2007; Danforth et al., 2008; Sáenz-López et al., 2008; Zabaleta et al., 2008; Wang et al., 2009b; Ivansson, 2010; Badano et al., 2012; Barbisan et al., 2012; Sousa et al., 2014) involved Caucasian patients, 16 (Jang et al., 2001; Tsai et al., 2001; Jeong et al., 2004; Wu, 2004; Kim et al., 2005; Nonomura et al., 2006; Jinchao, 2007; Ahirwar et al., 2008; Kesarwani, 2009; Singh, 2009; Zu, 2010; Wang et al., 2011; Zuo et al., 2011; Hang and Xu, 2012; Wang et al., 2012; Wu et al., 2013) involved Asian patients, and 3 (Moore et al., 2009; Wang et al., 2009a; Zhang et al., 2010) involved mixed populations. The distributions of genotypes in the controls of 7 studies (McCarron et al., 2002; Govan, 2006; Ahirwar et al., 2008; Singh, 2009; Zu, 2010; Wang et al., 2011; Wang et al., 2012) were not consistent with HWE. The general demographic characteristics of studies included in this meta-analysis are summarized in Table 1.

Table 1. General characteristics of studies included in the meta-analysis.

Author	Cancer type	Ethnicity	Study design	Sample size		Case		Control		HWE P value
				Case	Control	A/G	AA/GA/GG	A/G	AA/GA/GG	
Jones et al. (2013)	Prostate cancer	African-American	HCC	279	535	113/445	5/103/171	181/889	14/153/368	0.69
Berhane et al. (2012)	Prostate cancer	African-American	HCC	150	150	36/264	6/24/120	21/279	1/18/131	0.66
Zhang et al. (2010)	Prostate cancer	Mixed	PCC	169	176	53/116†	48/128†			
Kesarwani et al. (2009)	Prostate cancer	Asian	PCC	197	256	23/371	1/21/175	45/467	4/37/215	0.12
Danforth et al. (2008)	Prostate cancer	Caucasian	HCC	2266	2514	732/3800	51/630/1585	860/4168	78/704/1732	0.53
Zabaleta et al. (2008)*	Prostate cancer	Caucasian	HCC	479	400	166/792	9/148/322	138/662	10/118/272	0.51
Zabaleta et al. (2008)*	Prostate cancer	African-American	HCC	67	130	13/121	2/9/56	39/221	3/33/94	0.96
Sáenz-López et al. (2008)	Prostate cancer	Caucasian	PCC	296	310	80/512	5/70/221	56/564	2/52/256	0.72
Wu et al. (2004)	Prostate cancer	Asian	PCC	96	126	24/168	2/20/74	24/228	1/22/103	0.88
McCarron et al. (2002)	Prostate cancer	Caucasian	PCC	239	220	78/400	6/66/167	83/357	13/57/150	0.02
Moore et al. (2009)	Prostate cancer	Mixed	PCC	949	857	270/1628	21/228/700	227/1487	11/205/641	0.23
Wang et al. (2009a)	Prostate cancer	Mixed	PCC	251	250	103/399	12/79/160	87/413	9/69/172	0.53
Jinchao Ge (2007)	Prostate cancer	Asian	HCC	245	245	43/447	2/39/204	52/438	2/48/195	0.61
Oh et al. (2000)	Prostate cancer	Caucasian	HCC	146	122	106/186	0/106/40	44/200	3/38/81	0.55
Barbisan et al. (2012)	Cervical cancer	Caucasian	PCC	122	176	38/206	3/32/87	54/298	4/46/126	0.93
Badano et al. (2012)	Cervical cancer	Caucasian	PCC	56	113	14/98	2/10/44	12/214	0/12/101	0.55
Jang et al. (2001)	Cervical cancer	Asian	PCC	51	92	7/95	2/3/46	7/177	0/7/85	0.70
Ivansson et al. (2010)	Cervical cancer	Caucasian	PCC	1263	552	404/2122	32/340/891	174/930	18/138/396	0.17
Huang et al. (2012)	Cervical cancer	Asian	PCC	42	87	9/33†	23/64†			
Wang et al. (2009b)	Cervical cancer	Caucasian	PCC	456	800	73/839	3/67/386	142/1458	8/126/666	0.46
Zu et al. (2010)	Cervical cancer	Asian	HCC	83	91	56/110	3/50/30	34/148	9/16/66	0.00
Kohaar et al. (2007)	Cervical cancer	Caucasian	HCC	120	165	30/210	4/22/94	15/315	0/15/150	0.54
Singh et al. (2009)	Cervical cancer	Asian	HCC	150	162	39/261	11/17/122	19/305	4/11/147	0.00
Calhoun et al. (2002)	Cervical cancer	Caucasian	HCC	127	107	45/209	9/27/91	38/176	4/30/73	0.68
Deshpande et al. (2005)	Cervical cancer	Caucasian	HCC	258	411	86/430	16/54/188	128/694	14/100/297	0.13
Wang et al. (2011)	Cervical cancer	Asian	PCC	186	200	44/328	7/30/149	66/334	10/46/144	0.02
Govan et al. (2006)	Cervical cancer	African-American	HCC	244	228	78/410	8/62/174	66/390	10/46/172	0.01
Stanczuk et al. (2003)	Cervical cancer	African-American	PCC	103	101	30/176	1/28/74	22/180	2/18/81	0.41
Duarte et al. (2005)	Cervical cancer	Caucasian	HCC	195	244	64/326	7/50/138	48/440	4/40/200	0.24
Gostout et al. (2003)	Cervical cancer	Caucasian	HCC	127	175	45/209	9/27/91	63/287	5/53/117	0.73
Sousa et al. (2014)	Cervical cancer	Caucasian	PCC	223	205	77/369	6/65/152	43/367	2/39/164	0.85
Wang et al. (2012)	Cervical cancer	Asian	HCC	285	318	46/524	8/30/247	53/583	9/35/274	0.00
Zuo et al. (2011)	Cervical cancer	Asian	PCC	239	110	81/397	0/81/158	29/191	2/25/83	0.94
Wu et al. (2013)	Urothelial carcinoma	Asian	HCC	300	594	58/542	7/44/249	91/1097	4/83/507	0.77
Nonomura et al. (2006)	Bladder cancer	Asian	HCC	141	173	5/277	0/5/136	1/345	0/1/127	0.97
Leibovici et al. (2005)	Bladder cancer	Caucasian	PCC	485	443	151/307†	134/309†			
Kim et al. (2005)	Bladder cancer	Asian	HCC	153	153	16/290	2/12/139	24/282	1/22/130	0.95
Ahirwar et al. (2008)	Bladder cancer	Asian	PCC	136	200	29/243	5/19/112	36/364	7/22/171	0.00
Tsai et al. (2001)	Bladder cancer	Asian	PCC	114	150	20/208	1/18/95	27/273	1/25/124	0.83
Jeong et al. (2004)	Bladder cancer	Asian	HCC	113	109	17/209	1/15/97	19/199	0/19/90	0.32
Jang et al. (2001)	Renal cancer	Asian	PCC	39	92	4/74	0/4/35	7/177	0/7/85	0.70

HWE = Hardy-Weinberg equilibrium; HCC = hospital-based case-control studies; PCC = population-based case-control studies; *two independent case-control study sets. †AA+AG/GG.

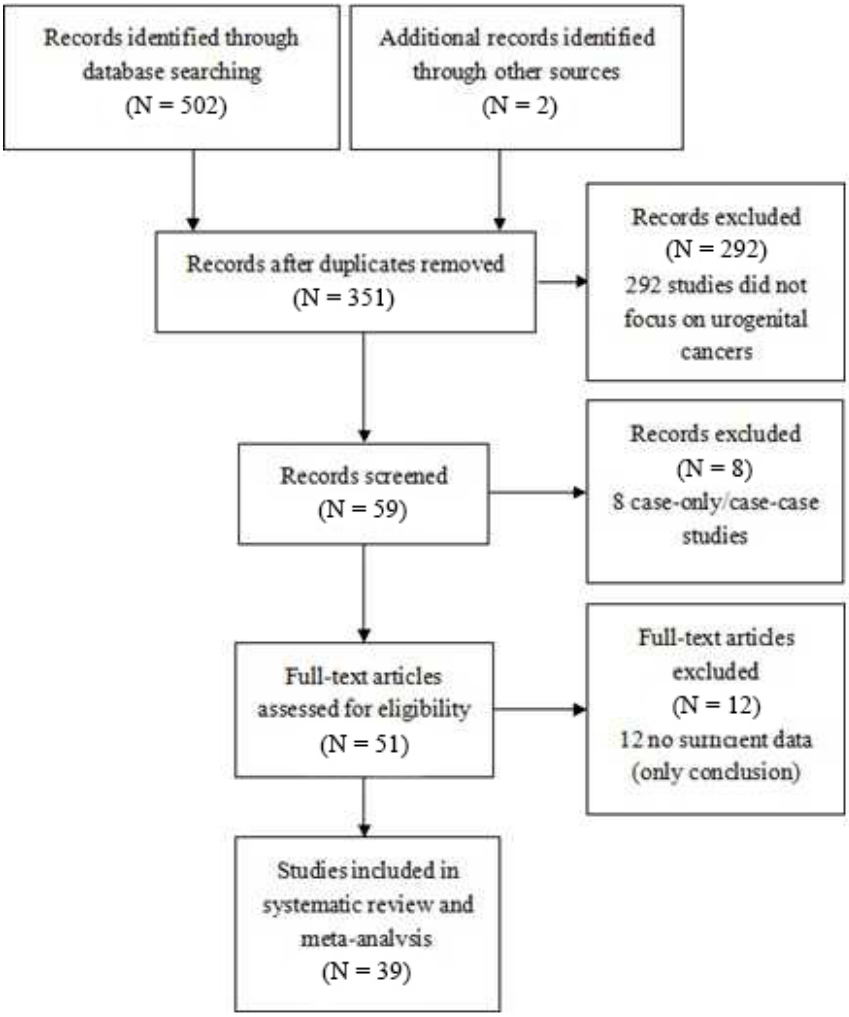

Figure 1. Study selection and inclusion process.

Meta-analysis results

Overall, there was significant association between the TNF-α 308G/A polymorphism and urogenital cancer risk (A *vs* G: OR = 1.18, 95%CI = 1.06-1.32, P = 0.002; GA *vs* GG: OR = 1.19, 95%CI = 1.04-1.37, P = 0.012; GA/AA *vs* GG: OR = 1.20, 95%CI = 1.07-1.36, P = 0.003) (Table 2). In the subgroup analysis of caner type, the OR (95%CI) in cervical cancer was 1.28 (1.08-1.52) in the allele contrast model, 1.27 (1.02-1.60) in the heterozygote model, and 1.29 (1.06-1.58) in the dominant model. In urothelial carcinoma, the OR (95%CI) was 3.56 (1.03-12.29) in the homozygote model and 3.52 (1.02-12.13) in the recessive model. These results indicate that there were significant associations between the TNF-α 308G/A polymorphism and cervical cancer and urothelial carcinoma (Table 2). However, as shown in Table 2, no significant associations were

found between the TNF-α 308G/A polymorphism and prostate, bladder, and renal cancers. When stratified by ethnicity, there was significant association in Caucasian populations (A *vs* G: OR = 1.25, 95%CI = 1.05-1.48, P = 0.011; GA *vs* GG: OR = 1.25, 95%CI = 1.02-1.55, P = 0.033; GA/AA *vs* GG: OR = 1.27, 95%CI = 1.05-1.54, P = 0.012), whereas no significant associations were found in African-Americans, Asians, or mixed populations (Table 2). With regard to the subgroup analysis of control sources, significant difference was found between patients and hospital-based controls in the allele contrast (OR = 1.25, 95%CI = 1.05-1.47, P = 0.01) and dominant (OR = 1.29, 95%CI = 1.04-1.60, P = 0.023) models, but not in the population-based case-control group (Table 2).

Table 2. Results of genetic models for the TNF-α 308G/A polymorphism and urogenital cancer.

Group	N	A *vs* G			AA *vs* GG			GA *vs* GG			GA+AA *vs* GG			AA *vs* GA+GG		
		OR (95%CI)	P	Model	OR (95%CI)	P	Model	OR (95%CI)	P	Model	OR (95%CI)	P	Model	OR (95%CI)	P	Model
Overall	39	1.18 (1.06,1.32)	0.002	R	1.10 (0.92,1.30)	0.302	F	1.19 (1.04,1.37)	0.012	R	1.20 (1.07,1.36)	0.003	R	1.06 (0.89,1.26)	0.533	F
Cancer type																
Prostate cancer	12	1.12 (0.95,1.32)	0.177	R	1.10 (0.92,1.30)	0.371	F	1.19 (1.04,1.37)	0.124	R	1.18 (0.97,1.45)	0.101	R	0.87 (0.68,1.11)	0.267	F
Cervical cancer	19	1.28 (1.08,1.52)	0.004	R	1.28 (0.99,1.67)	0.064	F	1.27 (1.02,1.60)	0.034	R	1.29 (1.06,1.58)	0.013	R	1.23 (0.94,1.59)	0.127	F
Urothelial carcinoma	1	1.29 (0.91,1.82)	0.148	R	3.56 (1.03,12.29)	0.044	F	1.08 (0.73,1.60)	0.705	R	1.19 (0.82,1.74)	0.358	R	3.52 (1.02,12.13)	0.046	F
Bladder cancer	6	0.97 (0.68,1.38)	0.869	R	1.33 (0.53,3.36)	0.545	F	0.92 (0.57,1.48)	0.728	R	1.01 (0.75,1.35)	0.955	R	1.32 (0.53,3.33)	0.551	F
Renal cancer	1	1.37 (0.39,4.81)	0.626	R	2.47 (0.15,40.64)	0.527	F	1.39 (0.38,5.04)	0.619	R	1.39 (0.38,5.04)	0.619	R	2.39 (0.15,39.28)	0.541	F
Ethnicity																
Asian	16	1.16 (0.94,1.43)	0.168	R	1.25 (0.85,1.83)	0.261	F	1.13 (0.84,1.53)	0.418	R	1.13 (0.87,1.46)	0.364	R	1.17 (0.80,1.70)	0.461	F
Caucasian	16	1.25 (1.05,1.48)	0.011	R	0.99 (0.79,1.24)	0.937	F	1.25 (1.02,1.55)	0.033	R	1.27 (1.05,1.54)	0.012	R	0.98 (0.78,1.22)	0.837	F
African-American	4	1.13 (0.88,1.45)	0.344	R	1.03 (0.58,1.82)	0.932	F	1.27 (0.91,1.76)	0.155	R	1.26 (0.93,1.71)	0.136	R	0.96 (0.54,1.69)	0.878	F
Mixed	3	1.12 (0.95,1.32)	0.168	R	1.62 (0.92,2.85)	0.097	F	1.07 (0.88,1.29)	0.512	R	1.12 (0.94,1.32)	0.207	R	1.57 (0.89,2.76)	0.117	F
Control source																
Hospital	19	1.25 (1.05,1.47)	0.01	R	1.12 (0.90,1.40)	0.299	F	1.24 (0.98,1.57)	0.072	R	1.29 (1.04,1.60)	0.051	R	1.08 (0.87,1.34)	0.498	F
Population	20	1.12 (0.98,1.27)	0.106	R	1.04 (0.79,1.38)	0.772	F	1.13 (1.00-1.29)	0.058	R	1.13 (1.00,1.27)	0.051	R	1.02 (0.77,1.35)	0.886	F

R = random-effect model. F = fixed-effect model.

In our study, we found that there was evidence of heterogeneity in the association between the TNF-α 308G/A polymorphism and urogenital cancer risk overall among the 39 stratified studies in some genetic models. Therefore, the random-effect model was used to evaluate OR and 95%CI.

We performed a sensitivity analysis by excluding the studies that did not comply with the HWE to estimate the sensitivity of our study. These studies were omitted, while the overall statistical significance did not change, indicating that the results were stable. Therefore, we conclude that our meta-analysis data were relatively stable and credible.

To estimate the publication bias of our meta-analysis, the Begg's test was performed and the results did not reveal any evidence of obvious asymmetry, indicating that there was minimal publication bias (A *vs* G: P = 0.20; AA *vs* GG: P = 0.22; GA *vs* GG: P = 0.47; GA/AA *vs* GG: P = 0.33; AA *vs* GA/GG: P = 0.33). The funnel plot was symmetrical, which also indicates that there was no publication bias in our study (Figure 2).

DISCUSSION

The etiology of urogenital cancers (including prostate, bladder, and cervical cancers, and renal cell carcinoma) (Alibek et al., 2012) is complicated, and several risk factors are involved in their development and progression. Environmental factors (Lichtenstein et al., 2000; Sharma et al., 2013; Porru et al., 2014), dietary habits (Isa et al., 2013; Askari et al., 2014), chronic inflammation (Deivendran et al., 2014; Neveu et al., 2014; Parida et al., 2014), infectious agents (Alibek et al., 2012), and genes and gene polymorphisms (Bozdogan et al., 2014; Wu et al., 2013; Zhou et al., 2014) are considered to be contributors, among which chronic inflammation and cytokines are thought to play the most important role in tumor promotion and progression (Coussens et al., 2002; Alibek et al., 2012).

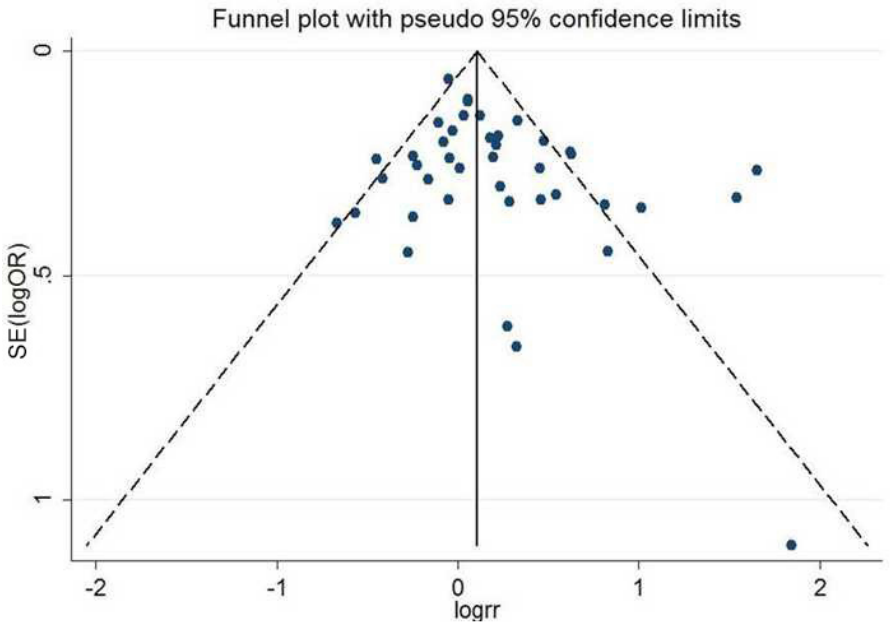

Figure 2. Funnel plot of the TNF-α 308G/A polymorphism and urogenital cancer risk.

TNF is an important infectious agent in inflammation progression as well as urogenital cancer development. The TNF-α 308G/A polymorphism is a G/A polymorphism at nucleotide (nt) -308, and is associated with the development of several urogenital cancers, including prostate cancer (Zabaleta et al., 2008; Moore et al., 2009; Jones et al., 2013), cervical cancer (Singh, 2009; Zuo et al., 2011), bladder cancer (Jeong et al., 2004; Kim et al., 2005; Leibovici et al., 2005), and renal cell carcinoma (Jang et al., 2001). For example, Jeong et al. (2004) studied 113 patients with bladder cancer and 109 healthy subjects and found that the genotype of the 308 nucleotide in the TNF-α promoter had a statistically significant effect on TNF-α production and was related to the bladder tumor grade. Kohaar et al. (2007) demonstrated that a single-nucleotide polymorphism (SNP) at -308 (G/A) of the TNFα promoter increased the risk of HPV infection and development in cervical cancer in Indian women. Although many studies have been performed to investigate the associations between the TNF-α 308G/A polymorphism and urogenital cancers, the results of these studies are controversial (Wu, 2004; Nonomura et al., 2006; Danforth et al., 2008; Wang et al., 2011; Barbisan et al., 2012; Jones et al., 2013). In Wu et al. study (2004), 126 healthy people and 96 patients with prostate cancer were examined and their results suggested that prostate cancer appears to be associated with the p53 gene codon 72 polymorphisms, but not with the TNF-α gene. Ahirwar et al. (2008) suggested that TNF-α is not associated with bladder cancer risk and bacillus Calmette-Guérin (BCG) therapy. Therefore, it is necessary to integrate all the eligible studies to produce a comprehensive study that determines the exact relationship between the TNF-α 308G/A polymorphism and urogenital cancers. Furthermore, to our knowledge, no comprehensive study has previously been conducted to address this issue. Owing to the conflicting results, we conducted this meta-analysis to provide a comprehensive assessment of the associations between the TNF-α 308G/A polymorphism and risk of urogenital cancer.

In our meta-analysis, a significant association was found between the TNF-α 308G/A polymorphism and urogenital cancer risk, indicating that the -308A allele might be a genetic risk factor for susceptibility to urogenital cancer. In the subgroup analysis of cancer type, our study suggested that the TNF-α 308G/A polymorphism led to an increased incidence of cervical cancer risk in the allele contrast model (OR = 1.28, 95%CI = 1.08-1.52, P = 0.004), the heterozygote model (OR = 1.27, 95%CI = 1.02-1.60, P = 0.034), and the dominant model (OR = 1.29, 95%CI = 1.06-1.58, P = 0.013), which was consistent with several of the studies we included (Duarte et al., 2005; Kohaar et al., 2007; Singh, 2009; Zuo et al., 2011; Badano et al., 2012; Sousa et al., 2014), but not with some of the other studies (Jang et al., 2001; Calhoun et al., 2002; Gostout et al., 2003; Deshpande et al., 2005; Ivansson, 2010; Wang et al., 2011; Barbisan et al., 2012; Wang et al., 2012). Furthermore, previous meta-analyses have produced the same conclusion. Interestingly, the genotypes of the TNF-α 308G/A polymorphism among the urogenital cancer patients in Wang et al. (2011) and Wang et al. (2012) studies did not follow HWE, which might be the main reason for the significant differences. Our results also suggest that the TNF-α 308G/A polymorphism is significantly associated with urothelial carcinoma. However, only one study (Wu et al., 2013) has investigated the relationship between the TNF-α 308G/A polymorphism and urothelial carcinoma. This study also suggests that TNF-α 308A/A or IL-8 251T/T genotypes and arsenic methylation have a significant joint dose-response effect on urothelial carcinoma risk. Therefore, more large-scale studies should be conducted. With regard to prostate, bladder, and renal cancers, no significant associations with the TNF-α 308G/A polymorphism were found in our meta-analysis. Previous meta-analyses performed on prostate cancer are consistent with our study, while for bladder cancer, a meta-analysis conducted by Yang et al. (2012) demonstrated that the TNF-α 308AA+GA genotype might be a marker for the tumor-invasive stage of bladder cancer. When we compared our study with Yang et al. study (2012), we found that two studies (Nonomura et al., 2006; Ahirwar et al., 2008) were not included in Yang et al. study (2012) when they compared genotypes between patients and control subjects using the dominant model (AA/GA *vs* GG). Furthermore, one study was not included in our study owing to its insufficient data, which might also have contributed to this controversial result.

In the subgroup analysis of ethnicity, significant association was found in Caucasian populations, while there was no significant association in African-Americans, Asians, and mixed populations, indicating that ethnicity might be an important risk factor in the development and progression of urogenital cancer. Several factors may contribute to this difference, including racial background, living environment, and life habits. Moreover, the unclear interaction of identified and unidentified genes may also be involved in carcinogenesis.

In addition, we performed the subgroup analysis using different sources of controls, and the results indicate that there is a significant association in hospital-based controls, but not in population-based controls. In our opinion, there might be some bias in the control subjects of the hospital-based group, in which latent infections and micro progression in the development of urogenital cancers could not be eliminated. Therefore, these subjects might not have been representative of the general population.

Despite a comprehensive analysis of the association between the TNF-α 308G/A polymorphism and the risk of developing urogenital cancer, there are some limitations that should be addressed. First, the association between the TNF-α 308G/A polymorphism and some urogenital cancers, such as endometrial, ovarian, and penis cancer, were not performed by researchers, and were not involved in our meta-analysis, which might have led to some bias in the final conclusion. Second, the studies that we included and the raw data we used did not provide sufficient information about the interaction between the TNF-α 308G/A polymorphism and other

risk factors, such as other gene polymorphisms, living habits, and other exposures. Without these considerations, we cannot draw an exact conclusion. Third, some urogenital cancers only occur in women (such as cervical and ovarian cancers) or men (prostate cancer), and others cannot occur in both population (such as bladder and renal cancers). Therefore, subgroup analysis based on gender should also be conducted if studies performed on bladder and renal cancers are to provide relevant data. Finally, although sensitivity analysis was conducted by excluding the studies that did not comply with the HWE, and the results showed no sensitivity in our study, the results would have been more credible if all the studies we included had complied with the HWE. Therefore, larger-scale and better-designed studies are necessary to determine the association between the TNF-α 308G/A polymorphism and the risk of urogenital cancer.

In conclusion, in this meta-analysis we pooled all the available data related to the TNF-α 308G/A polymorphism and urogenital cancer risk, and our results suggest that the TNF-α 308G/A polymorphism is significantly associated with the increased risk of urogenital cancer. Furthermore, significant association was also found in Caucasian populations. More studies are required to overcome the aforementioned limitations to further assess the association between the TNF-α 308G/A polymorphism and increased susceptibility to urogenital cancer.

Conflicts of interest

The authors declare no conflict of interest.

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