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Original Article

Lack of association between TNFα rs1800629 polymorphism and prostate cancer risk: a meta-analysis

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Abstract: Previous evidence has suggested that tumor necrosis factor α (TNFα) may be involved in the aetiology of prostate cancer, but the underlying association between TNFα-308G/A polymorphism (rs1800629) and prostate cancer risk is still ambiguous. This meta-analysis was performed to quantitatively summarize the evidence for such a relationship. Eligible studies were identified by searching electronic databases, including PubMed, EMBASE, and Wanfang, for case-control studies published up to 31 September 2015. The odds ratio (OR) corresponding to the 95% confidence interval (CI) was used to assess the different associations. Twelve studies with 5069 cases and 5360 controls were identified for this meta-analysis. Our meta-analysis of the pooled data reveals that there was no significant association between TNFα-308G/A polymorphism and susceptibility to prostate cancer (for A vs. G: OR=1.10, 95% CI 0.94-1.30, P=0.120; for AA vs. GG: OR=0.96, 95% CI 0.73-1.26, P=0.756; for AA vs. GA: OR=1.13, 95% CI 0.92-1.38, P=0.244; for AA vs. GA+GG: OR=1.21, 95% CI 0.95-1.24, P=0.703; for AA+GA vs. GG: OR=1.14, 95% CI 0.93-1.39, P=0.213). Our subgroup analysis by ethnicity further confirms that there are no significant associations for all comparison models. Taken together, this meta-analysis suggests that TNFα-308G/A polymorphism may not be associated with prostate cancer susceptibility. However, further well-designed studies with larger sample sizes and a representative population of prostate cancer patients and well-matched controls are warranted to confirm this finding.

Keywords: Prostate cancer, tumor necrosis factor-α, polymorphism, meta-analysis

Introduction

Prostate cancer is the fifth most common cancer in the world and the second most common cancer in men [1]. Despite the clinical importance of this disease, the mechanisms underlying the development and progression of prostate cancer are still not well understood, which may has been one of the most important reasons why no effective treatment modalities have been developed to cure this disease. Importantly, in recent years, an accumulation of genetic changes affecting the expression of certain critical genes has been thought to underlie the malignant transformation and progression of prostate cancer [2].

Tumor necrosis factor (TNF)-alpha, secreted by macrophages and T lymphocytes, is a potent proinflammatory cytokine and immune modulator and exhibits a wide range of biological activities, including protection from infection, immune surveillance against tumors and stimulation of inflammatory responses [3]. Intriguingly, it has been observed that TNF-α might play paradoxical roles in human cancers. Therapeutically, local accumulation of a high dose of TNF-α in tumor tissues seems to exhibit potent anti-neoplastic actions [4]. However, endogenous levels of TNF-α have been reported to contribute to the tissue remodeling for tumor growth and promote cancer metastasis [5].

As TNF-α production is partially governed by genetic factors [6], the role of polymorphisms of the TNF-α promoter in determining disease susceptibility or serving as a marker of disease severity has been a subject of intensive research in recent years. The TNF-α gene exhibits an important functional single nucleotide polymorphism (SNP) located at position -308 in its promoter region, which is often referred to

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

Study	Year	Country	Ethnicity	Source	Language of included article	Sample size		Age (Average)		Genotyping method	HWE	NOS score
						Case	Control	Case	Control			
OH	2000	USA	ND	ND	English	73	122	/	/	Allele-specific PCR	N	6
Wu	2004	China	Asian	PB	English	96	126	71	67	PCR	Y	7
Ge	2007	China	Asian	HB	Chinese	245	245	71	71	TaqMan	N	5
Danforth (1)	2008	USA	Caucasian	PB	English	1155	1389	65	65	TaqMan or MGB Eclipse assay	Y	7
Danforth (2)	2008	USA	Caucasian	PB	English	1111	1125	64	64	TaqMan or MGB Eclipse assay	Y	7
Saenz-Lopez	2008	Spain	Caucasian	HB	English	296	310	67	44	TaqMan	Y	7
Zabaleta (1)	2008	USA	Caucasian	HB	English	479	400	/	/	TaqMan	Y	7
Zabaleta (2)	2008	USA	African	HB	English	67	130	/	/	TaqMan	Y	7
Kesarwani	2009	India	Caucasian	PB	English	197	256	61	62	PCR-RFLP	Y	6
Moore	2009	Finland	Mixed	PB	English	949	857	59	58	PCR-RFLP	Y	7
Wang	2009	USA	Mixed	HB	English	251	250	65	65	TaqMan	Y	8
Berhane	2012	India	Caucasian	HB	English	150	150	67	66	ARMS-PCR	Y	5

ND: not document; HWE: Hardy-Weinberg equilibrium; Y: genotype frequency distribution agreed to HWE in controls; N: genotype frequency distribution disagreed to HWE in controls; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HB: hospital-based; PB: population-based; NOS: Newcastle-Ottawa Scale.

Table 2. Genotype counts of TNF-α-308G/A polymorphisms of studies included in the meta-analysis

Study	Case			Control			Case		Control	
	GG	GA	AA	GG	GA	AA	G	A	G	A
OH	20	53	0	81	38	3	93	53	200	44
Wu	74	20	2	103	22	1	168	24	228	24
Ge	204	39	2	195	48	2	447	43	438	52
Danforth (1)	793	336	26	926	418	45	1922	388	2270	508
Danforth (2)	792	294	25	806	286	33	1878	344	1898	352
Saenz-Lopez	221	70	5	256	52	2	512	80	564	56
Zabaleta (1)	322	148	9	272	118	10	792	166	662	138
Zabaleta (2)	56	9	2	94	33	3	121	13	221	39
Kesarwani	175	21	1	215	37	4	371	23	467	45
Moore	700	228	21	641	205	11	1628	270	1487	227
Wang	160	79	12	172	69	9	399	103	413	87
Berhane	120	24	6	131	18	1	264	36	279	21

as TNF-α-308G/A, rs1800629. This genetic variation results in two allelic forms in which the presence of guanine (G) defines the common variant, whereas the adenine (A) allele represents the less common variant [7]. A large body of evidence indicates that TNF-α play an important role in the pathogenesis of cancer. Notably, the SNP TNF-α-308G/A (rs1800629) has been confirmed as a risk factor for a range of human cancers [8-10].

Several original studies have investigated the association of TNF-α-308G/A (rs1800629) with prostate cancer [11-13]. However, the results from those studies are still inconclusive probably because of the relatively small sample size in each of published studies. Therefore, we performed this meta-analysis to achieve a more precise estimation of the association between TNF-α-308G/A (rs1800629) and the risk of prostate cancer.

Materials and methods

Data sources

We carried out a comprehensive search of the electronic databases, including Pubmed, EMBASE, and Wanfang, for all articles that had been published on the association between TNF-α-308G/A polymorphism and the risk of prostate cancer. The keywords "TNF" and "polymorphism" and "prostate cancer" were used for the literature search. All articles were updated on 31 September 2015. References of all primary studies and review articles were reviewed to identify additional relevant studies.

Inclusion and exclusion criteria

Studies meeting the following criteria were included in the meta-analysis: (1) case-control studies comparing prostate cancer cases with healthy or non-cancer controls; (2) studies evaluating the association between TNF-α-308G/A polymorphism and prostate cancer risk; and (3) sufficient genotype data of TNF-α-308G/A polymorphism were reported. The exclusion criteria were used as follows: (1) case-only studies; (2) case reports, letters, or reviews; (3) studies with incomplete data or no usable data; and (4) studies containing overlapping data.

Data extraction

Two investigators reviewed the titles, abstracts and full texts of relevant articles independently using a standardized screening guide. After data abstraction, discrepancies and differences between two investigators were resolved by consensus and discussion. To catch a glimpse of the included reports, we then summarized the characteristics of those studies, including first author's name, publication time, study country origin, ethnicity, source of controls, genotyping method, and sample size (**Table 1**) as well as genotype frequency distribution (**Table 2**).

Quality assessment

We evaluated the methodological quality of the included studies according to the Newcastle-Ottawa Scale (NOS) criteria. The NOS criteria are scored based on three aspects: (1) subject selection, 0-4; (2) comparability of subjects, 0-2; and (3) clinical outcomes, 0-3. Total NOS scores range from 0 to 9, with scores ≥ 7 indicating good quality.

Statistical analysis

The strength of the association between TNF-308G/A polymorphism and prostate cancer risk was measured by OR and 95% CI using

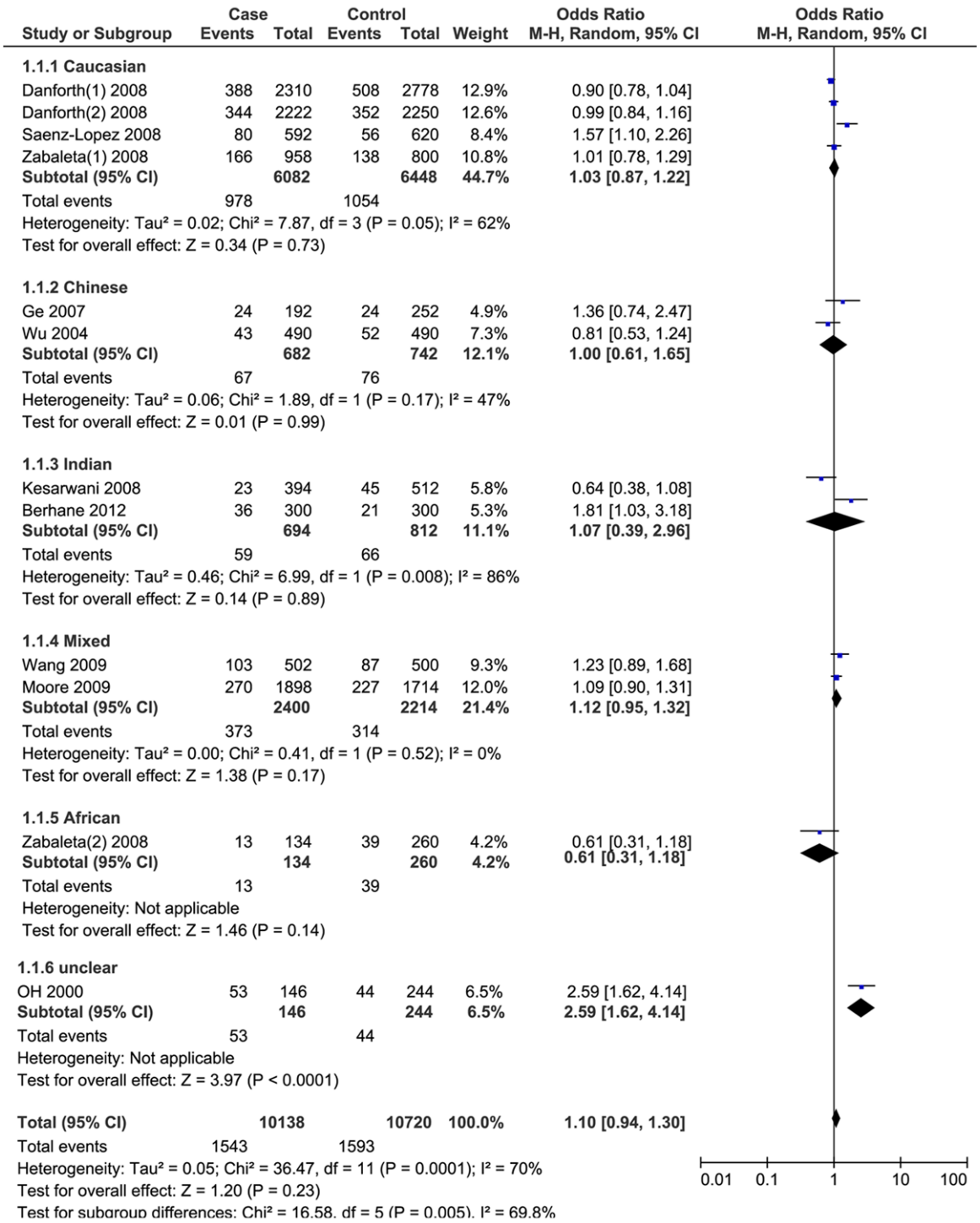

Figure 1. Meta-analysis for the relationship between TNF-α-308G/A polymorphisms and prostate cancer risk. The solid squares represent odds ratios (ORs) from individual studies; the diamonds are shown as overall effect. The combined ORs along with their 95% CIs were in the contrast of A allele vs. G allele and estimated using the random-effects method.

Review Manger (version 5.2, Cochrane Collaboration, Oxford, England). The statistical significance of pooled OR was determined using a Z-test. The genetic models used for the data analysis for the polymorphism were as follows: the allele model (A vs. G); the heterozygote

Table 3. Main results of pooled ORs in the meta-analysis

	N	A vs G		Test for heterog	AA vs GG		Test for heterog	AA vs GA		Test for heterog	AA vs GA+GG		Test for heterog	AA+GA vs GG		Test for heterog
		OR (95% CI)	P	Ph	OR (95% CI)	P	Ph	OR (95% CI)	P	Ph	OR (95% CI)	P	Ph	OR (95% CI)	P	Ph
Total	12	1.10 (0.94-1.30)	0.12	0.0001	0.96 (0.73-1.26)	0.75	0.007	1.13 (0.92-1.38)	0.24	0.615	0.95 (0.72-1.24)	0.73	0.436	1.14 (0.93-1.39)	0.21	0.157
Ethnicities																
Caucasian	4	1.03 (0.87-1.22)	0.73	0.05	0.76 (0.55-1.06)	0.11	0.431	1.03 (0.92-1.16)	0.57	0.152	1.03 (0.92-1.56)	0.57	0.049	0.76 (0.55-1.06)	0.14	0.501
Chinese	2	1.00 (0.61-1.65)	0.99	0.17	0.82 (0.19-3.50)	0.79	0.833	0.91 (0.62-1.33)	0.62	0.244	1.48 (0.32-6.79)	0.61	0.538	0.93 (0.64-1.36)	0.73	0.194
Indian	2	1.07 (0.39-2.96)	0.89	0.008	1.44 (0.07-28.81)	0.81	0.05	0.99 (0.48-2.03)	0.97	0.098	1.43 (0.08-26.06)	0.89	0.058	1.05 (0.41-2.70)	0.91	0.024
Mixed	2	1.12 (0.95-1.32)	0.17	0.52	1.61 (0.91-2.85)	0.09	0.736	1.07 (0.88-1.29)	0.51	0.404	1.57 (0.89-2.76)	0.12	0.662	1.10 (0.92-1.32)	0.34	0.429
African	1	0.61 (0.31-1.18)	0.14	NA	1.12 (0.18-6.90)	0.9	NA	0.46 (0.20-1.03)	0.06	NA	1.30 (0.21-7.99)	0.78	NA	0.51 (0.24-1.09)	0.08	NA
Unclear	1	1.59 (0.62-1.14)	0.25	NA	0.57 (0.03-11.44)	0.71	NA	1.65 (0.97-1.74)	0.35	NA	0.23 (0.01-4.56)	0.34	NA	1.24 (0.77-1.90)	0.34	NA
Source																
PB	5	1.03 (0.94-1.13)	0.49	0.202	1.18 (0.86-1.61)	0.32	0.171	1.16 (0.84-1.61)	0.36	0.296	0.85 (0.62-1.17)	0.32	0.189	0.98 (0.88-1.08)	0.65	0.392
HB	6	0.89 (0.69-1.45)	0.37	0.027	0.77 (0.45-1.21)	0.35	0.466	0.93 (0.71-1.22)	0.59	0.059	1.27 (0.75-2.14)	0.37	0.511	1.32 (0.85-1.99)	0.17	0.00001
Genotyping method																
TaqMan	7	1.02 (0.93-1.41)	0.82	0.051	1.07 (0.98-1.35)	0.12	0.308	1.29 (0.93-1.67)	0.43	0.117	0.89 (0.77-1.02)	0.39	0.009	1.03 (0.89-1.48)	0.28	0.623
PCR-RFLP	2	0.86 (0.74-1.01)	0.06	0.019	0.96 (0.90-1.03)	0.27	0.325	0.91 (0.81-1.01)	0.07	0.172	0.89 (0.78-1.01)	0.06	0.003	1.21 (0.87-1.77)	0.42	0.524
Others	3	1.08 (0.85-1.37)	0.51	0.065	0.89 (0.56-1.04)	0.14	0.051	0.96 (0.73-1.28)	0.79	0.243	1.04 (0.62-1.31)	0.77	0.005	0.96 (0.85-1.08)	0.47	0.709
HWE																
Y	10	1.08 (0.95-1.21)	0.53	0.065	1.20 (0.32-1.17)	0.38	0.016	1.17 (0.71-1.25)	0.53	0.108	0.94 (0.70-1.29)	0.67	0.457	1.15 (0.86-1.54)	0.79	0.645
N	2	1.01 (0.90-1.43)	0.83	0.499	0.98 (0.58-1.66)	0.93	0.003	1.03 (0.99-1.60)	0.62	0.086	0.90 (0.72-1.12)	0.35	0.102	1.10 (1.01-1.20)	0.34	0.073
Sample size																
>500	6	1.05 (0.89-1.52)	0.23	0.621	0.84 (0.63-1.12)	0.42	0.153	1.25 (0.70-2.25)	0.95	0.0001	0.90 (0.69-1.62)	0.87	0.332	1.11 (0.89-1.47)	0.34	0.664
<500	6	1.08 (0.99-1.17)	0.33	0.972	1.20 (0.99-1.47)	0.36	0.646	1.02 (0.95-1.22)	0.22	0.129	0.98 (0.73-1.35)	0.67	0.578	1.16 (0.93-1.42)	0.21	0.092

N: number of sample size; Test for heterog: test for heterogeneity; P: *p* value; Ph: *p* value for heterogeneity; HWE: Hardy-Weinberg equilibrium; Y: genotype frequency distribution agreed to HWE in controls; N: genotype frequency distribution disagreed to HWE in controls; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism;

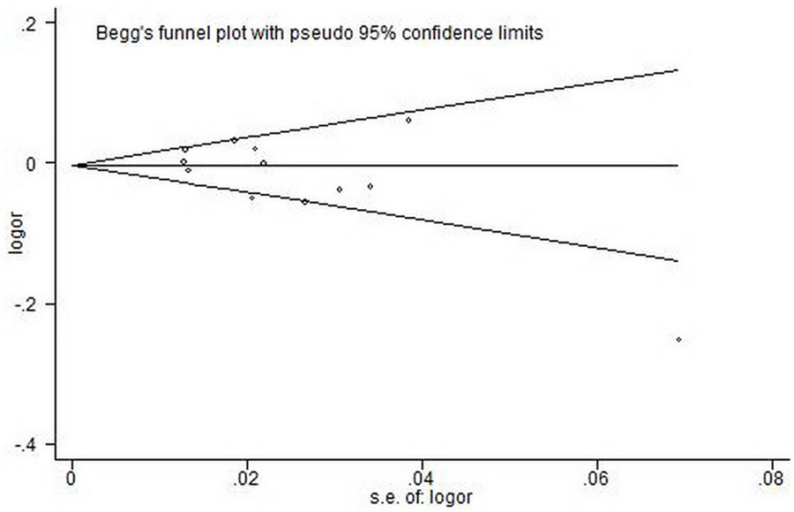

Figure 2. Funnel plot for the detection of the publication bias in this meta-analysis.

model (GA vs. GG); the homozygote model (AA vs. GG); the dominant model (GA+AA vs. GG); and the recessive model (AA vs. GA+GG). Heterogeneity between included studies was assessed by Q test and I^2 tests, and a *P* value of ≤0.10 was considered statistically significant. Pooled OR was analyzed by a fixed-effects model (the Mantel-Haenszel method) or a random-effects model (the DerSimonian and Laird method) according to the degree of the between-study heterogeneity. If the *P* value of the heterogeneity was >0.10, the pooled OR was calculated using the fixed-effects model; otherwise, the random-effects model was used [14]. Publication bias was analyzed by visual inspection of asymmetry in funnel plots. Additionally, Egger's tests were also carried out to assess the publication bias regarding our meta-analysis. Begg's and Egger's tests were both performed using Stata 12.0 software (Stata Corporation, College Station, Texas, USA). Sensitivity analysis was conducted by sequentially removing a single study each time from the meta-analysis in an attempt to identify any potential influence of an individual data set on the pooled OR.

Results

We performed a comprehensive literature search of the electronic databases, including PubMed, Embase, and Wanfang, and initially identified 107 relevant articles. After reviewing the full texts of those reports, 12 case-control studies from 10 articles with a total of 10429 subjects (5069 prostate cancer cases and 5360 controls) were finally included into the meta-analysis [11-13, 15-21]. The studies were conducted in USA, Finland, Spain, Indian, and China (**Table 1**). The sample sizes of cases from the twelve studies range from 67 to 1155, while the sample sizes of the controls in those studies vary from 122 to 1389 [10-16, 21, 22]. Genotype counts of TNF-α-308G/A polymorph isms of the studies included in the meta-analysis was shown in **Table 2**.

Meta-analysis

Our meta-analysis of the twelve studies showed that TNF-α-308G/A polymorphism was not significantly associated with the risk of prostate cancer under five genetic models (for A vs. G: OR=1.10, 95% CI 0.94-1.30, P=0.120; for AA vs. GG: OR=0.96, 95% CI 0.73-1.26, P=0.756; for AA vs. GA: OR=1.13, 95% CI 0.92-1.38, P=0.244; for AA vs. GA+GG: OR=1.21, 95% CI 0.95-1.24, P=0.703; for AA+GA vs. GG: OR=1.14, 95% CI 0.93-1.39, P=0.213) (**Figure 1**). Subgroup analysis based on ethnicity, sample size, resource, method and HWE further confirms that there is no significant association between TNF-α-308G/A polymorphism and the risk of prostate cancer for all comparison models (**Table 3**).

Sensitivity analysis

A single study that was initially included in the meta-analysis was then sequentially removed each time to evaluate the influence of the individual data-set on the pooled ORs. Consistently, the corresponding pooled ORs were not significantly altered (data not shown), indicating that our results were statistically robust.

Publication bias

Publication bias was investigated by Begg's funnel plot and the result from funnel plots was further assessed by Egger's test. As shown in **Figure 2**, there is no significant asymmetry in the dominant model (TT vs. CC/CT) of this

meta-analysis. Additionally, the finding from Egger's test further rules out the possibility of publication bias regarding our meta-analysis (P=0.170).

Discussion

TNF-α is a key mediator of inflammation and inflammation is believed to play an important role in prostate cancer development. However, the association of TNF-α308G/A polymorphism with susceptibility to prostate cancer is still not conclusive to date. Three of the 12 studies included in this meta-analysis reported that the A allele is associated with a high risk to prostate cancer. Nevertheless, the other 9 studies yet failed to demonstrate this relationship. These conflicting results may result from the relatively small sample size and different genetic and environmental background. Therefore, we performed this meta-analysis to precisely clarify the true association.

Our meta-analysis shows that there is no significant association between TNF-α-308G/A polymorphism and prostate cancer susceptibility overall. To rule out the influence of race, sample size, genotyping method, and HWE on the results of our meta-analysis, we performed subgroup analyses. Consistently, the results from those analyses also reveal no statistically significant association. These findings suggested that TNF-α-308G/A polymorphism might play no role in the etiology of prostate cancer. Multiple studies have also shown that the A allele of the common -308G/A polymorphism in the promoter region of the TNF gene is associated with increased TNF-α expression, which may contribute to the development of prostate cancer. For instance, Lopez et al examined the effect of the TNF-α-308G/A polymorphism on prostate cancer susceptibility [13]. They found that the A allele was associated with a 60% increased risk of prostate cancer in the white population from Spain. Actually, it might be not uncommon that the epidemiology results were not coincidence with the results of functional study. Because cancer is a complicated multigenetic disease, different genetic backgrounds may contribute to the discrepancy [22]. The influence of the TNF-α-308G/A polymorphism might be masked by the presence of other as-yet unidentified causal genes involved in breast cancer development.

Heterogeneity might be a potential problem when interpreting the results of all meta-analysis. Although we performed a careful literature search for published studies, used strict criteria for study inclusion, and carried out precise data extraction and careful data analysis, there is still significant between-study heterogeneity under most comparisons. After stratified analysis based on race/ethnicity, the heterogeneity was substantially decreased or removed. However, significant heterogeneity was still observed under some comparisons, which may be accounted for by the smoking status, drinking status, various pathological types, sampling error or other unknown factors. Unfortunately, further stratified analyses were not performed because of inadequate data.

It is worth noting that there may be some other limitations regarding our meta-analysis. First of all, control subjects were not uniformly defined. Misclassification bias was still possible because included studies may have recruited subjects who had other risks of developing cancer. Secondly, in the subgroup analysis, the number of each subgroup was relatively small and there is no enough statistical power to explore the real association. Therefore, further well-designed studies with larger sample sizes are needed to further examine the association.

In conclusion, this meta-analysis suggests that the TNF-α-308G/A polymorphism is not associated with prostate cancer development. However, it is necessary to conduct further studies with larger sample sizes using standardized unbiased genotyping methods, homogeneous prostate cancer patients and well matched controls. Moreover, gene-gene and gene-environment interactions should also be considered

in the analysis. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between the TNF-α-308G/A polymorphism and prostate cancer risk.

Disclosure of conflict of interest

None.

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