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Original Article

Association between tumor necrosis factor alpha rs1800629 polymorphism and risk of cervical cancer

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Abstract: Purpose: The objective of this study was to evaluate the influence of the *TNF-α* rs1800629 polymorphism on the risk of cervical cancer. Methods: A comprehensive search of EMBASE, PubMed, Wanfang database and China National Knowledge Infrastructure (CNKI) was conducted and the papers published were retrieved. The fixed effects or random effects model was appropriately used to calculate the odds ratio (OR) along with 95% confidence interval (CI). Results: Data from sixteen articles containing nineteen studies were summarized in this meta-analysis. In general, we observed a marginal association between the *TNF-α* rs1800629 polymorphism and cervical cancer risk under the AA + AG vs. GG comparison model (OR=1.17, 95% CI=1.00-1.38, *P*=0.019 for heterogeneity). Interestingly, significantly increased risk was observed in the allele model (A vs. G: OR=1.19, 95% CI=1.02-1.38, *P*=0.006 for heterogeneity). In the stratified analysis by ethnicity, we found significant results in Caucasians. Conclusions: Our results reveal that the Caucasian population may be at increased risk of developing invasive cervical cancer associated with the *TNF-α* rs1800629 polymorphism.

Keywords: *TNF-α*, rs1800629, cervical cancer

Introduction

As the third most common cancer diagnosed in females, cervical cancer has been a severe health threat worldwide [1]. Decades of research has focused on the identification of etiological factors that determine the progression of this invasive cancer. It is found that human papillomavirus (HPV), a highly immunogenic virus that activates strong humoral and cellular immune responses, plays a predominant role in the initiation of cervical cancer [2, 3]. Multiple cytokines described as mediators of the immunologic response have been associated with the malignancy [4, 5].

Tumor necrosis factor alpha (*TNF-α*) is an important inflammation regulator cytokine associated with the B-cell-mediated immune response [6]. It is secreted by macrophages and functions as a proinflammatory molecular in response to immune injury and infection [7, 8]. Currently, little is known about the physiological role of this cytokine in various human cancers. It is reported that lower expression of *TNF-α* induces invasion and transformation of cancer cells [9]. In addition, cancer type and serum level in tissues are key factors to determine how *TNF-α* acts in these cancers [10].

The *TNF-α* gene mapped on chromosome 6 is highly polymorphic. To date, there have been 16 single nucleotide polymorphisms identified in the *TNF-α* gene. A promotor polymorphism (rs1800629) which results in G to A transition at nucleotide position -308 of the transcriptional start site of the gene is directly and positively related to specific regulation of *TNF-α* synthesis at the transcriptional level [11]. Genotype-phenotype studies of the *TNF-α* rs1800629 polymorphism showed the G allele conferred two-fold lower effects on the transcription level when compared with the A allele [12]. But the transcription activity affected by the *TNF-α* rs1800629 polymorphism may vary due to different cell types [11-13].

The functional consequence of this polymorphism provided an impetus to researchers

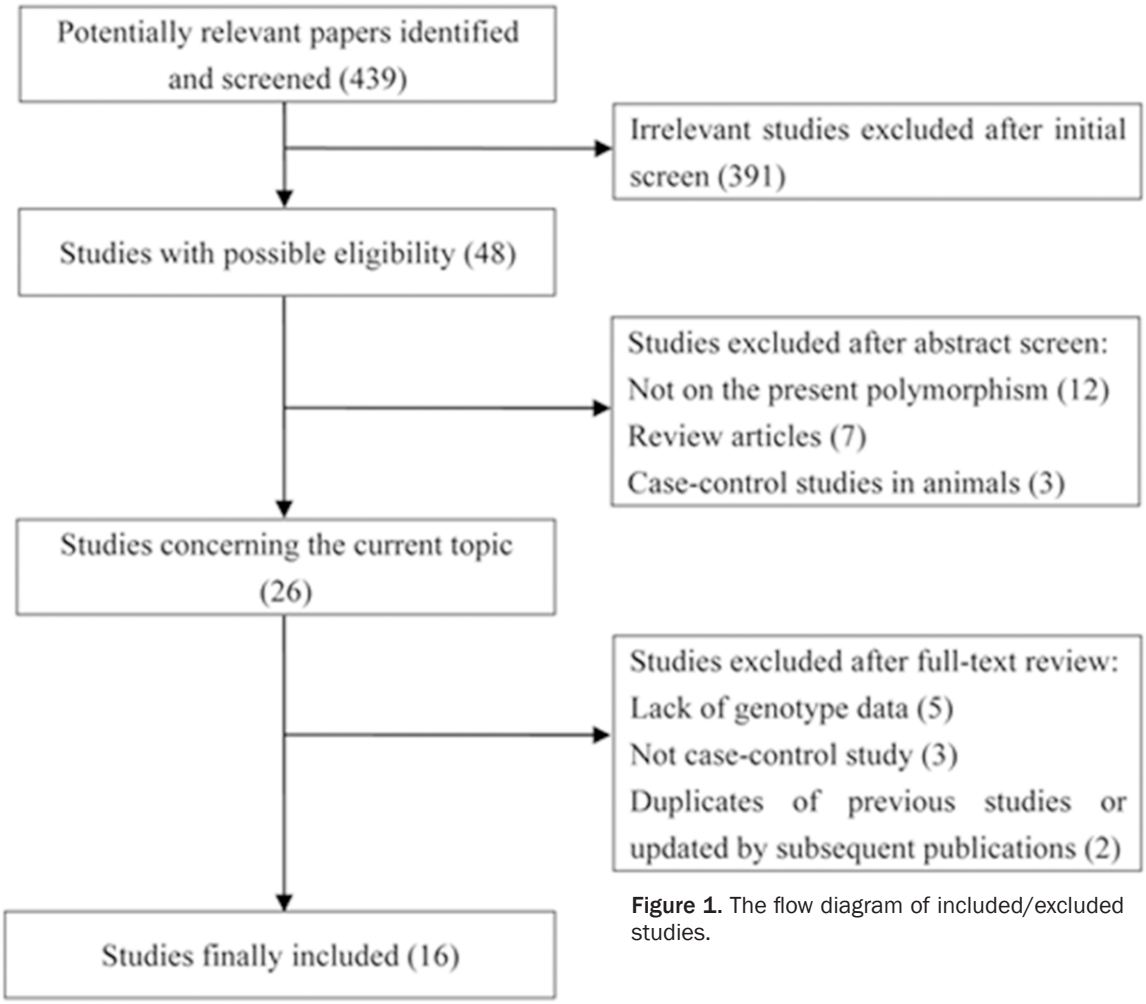

Figure 1. The flow diagram of included/excluded studies.

interested in the role of *TNF-α* rs1800629 polymorphism in cervical cancer [14-16]. In general, the case-control studies have produced mixed results, with little consensus in most cases on whether the *TNF-α* polymorphism is actually associated with cervical cancer risk or not. Most importantly, several previous meta-analyses have examined the association of *TNF-α* rs1800629 polymorphism with cervical cancer risk and showed similar results [17-20], with incomplete data or duplicates included in these studies. We thereby performed a meta-analysis based on the data summarized from all available studies to evaluate the influence of the *TNF-α* rs1800629 polymorphism on the risk of cervical cancer.

Materials and methods

Literature search and selection

The identification of relevant studies was carried out in EMBASE, PubMed, Wanfang database and China National Knowledge Infrastructure (CNKI). We retrieved the papers matching the following search terms: cervical cancer/polymorphism/polymorphisms/tumor necrosis factor-alpha/*TNF-α*/rs1800629. To assure the comprehensiveness of data, we also scanned the references of all retrieved articles. Selection of eligible studies for this meta-analysis was based on: (1) the paper must have a case-control design; (2) the influence of the *TNF-α* rs1800629 polymorphism on the risk of cervical cancer was evaluated; (3) the original article mut present adequate genotype data to calculate the odds ratio (OR) along with 95% confidence interval (CI); (4) when several studies were conducted on the same case series, we considered the most recent or the largest one with complete data.

Data extraction

Following the inclusion criteria mentioned above, two investigators selected all eligible

Table 1. Characteristics of all studies

First author	Year	Ethnicity	Country	HWE	Matching	Genotyping methods	Cases	Controls	Source of controls
Jang	2001	Asian	Korea	+	ND	PCR-RFLP	51	92	ND
Gostout	2003	Caucasian	USA	+	Residence area	PCR-RFLP	127	175	HB
Stanczuk	2003	African	Zimbabwe	+	ND	PCR-RFLP	103	139	HB
Deshpande*	2005	Caucasian	USA	+	ND	PCR-RFLP	115	213	HB
Deshpande*	2005	Caucasian	USA	+	ND	PCR-RFLP	143	194	HB
Govan&	2006	Mixed	South Africa	-	Age, ethnicity, residence area	PCR-RFLP	83	59	HB
Govan&	2006	African	South Africa	+		PCR-RFLP	161	169	HB
Kohaar	2007	Caucasian	India	+	Age, ethnicity	PCR-RFLP	120	165	HB
Singh	2009	Caucasian	India	-	Age, ethnicity	PCR-RFLP	150	162	HB
Wang	2009	Caucasian	Costa Rica	+	ND	PCR-RFLP	456	800	PB
Ivansson	2010	Caucasian	Sweden	+	Ethnicity	PCR-RFLP	1263	552	PB
Zu	2010	Asian	China	-	ND	PCR-RFLP	83	91	HB
Wang	2011	Asian	China	-	ND	PCR-RFLP	186	200	HB
Wang	2012	Asian	China	-	ND	PCR-RFLP	285	318	HB
Badano	2012	Caucasian	Argentina	+	age	PCR-RFLP	56	113	HB
Barbisan	2012	Caucasian	Argentina	+	ND	PCR-RFLP	122	176	HB
Huang	2012	Asian	China	+	ND	PCR-RFLP	42	87	HB
Sousa	2013	Caucasian	Portugal	+	ND	PCR-RFLP	223	205	PB

**&,* The same paper studied two distinct population; PB: population-based study; HB: hospital-based study; PCR-RFLP*:* polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium.

Table 2. Meta-analysis results

Genetic contrast models	Groups	OR	95 % CI	P_{OR}	Heterogeneity analysis	
					I^2	*P* values
AA vs. GG						
	Total	1.25	0.95-1.65	0.108	0.126	0.303
	Asian	1.01	0.58-1.75	0.976	0.000	0.527
	Caucasian	1.47	1.04-2.08[a]	0.028	0.306	0.164
	HB	1.39	1.00-1.94[b]	0.051	0.027	0.420
	PB	0.91	0.55-1.51	0.719	0.263	0.258
AG vs. GG						
	Total	1.13	0.95-1.34	0.160	0.433	0.026
	Asian	1.06	0.57-1.98	0.853	0.741	0.004
	Caucasian	1.09	0.91-1.30	0.336	0.305	0.165
	HB	1.15	0.91-1.46	0.234	0.505	0.016
	PB	1.11	0.87-1.41	0.406	0.432	0.172
A vs. G						
	Total	1.19	1.02-1.38[a]	0.029	0.516	0.006
	Asian	1.10	0.75-1.60	0.636	0.582	0.048
	Caucasian	1.25	1.02-1.54[a]	0.035	0.622	0.005
	HB	1.21	1.00-1.47[b]	0.054	0.524	0.011
	PB	1.11	0.83-1.47	0.494	0.672	0.048
AA + AG vs. GG						
	Total	1.17	1.00-1.38[b]	0.052	0.456	0.019
	Asian	1.09	0.68-1.75	0.711	0.639	0.026
	Caucasian	1.16	0.96-1.40	0.129	0.450	0.059
	HB	1.21	0.97-1.50	0.086	0.506	0.015
	PB	1.10	0.85-1.43	0.465	0.536	0.116
AA vs. AG + GG						
	Total	1.21	0.92-1.59	0.174	0.220	0.193
	Asian	0.90	0.53-1.55	0.716	0.211	0.280
	Caucasian	1.47	1.04-2.07[a]	0.030	0.304	0.165
	HB	1.34	0.96-1.85	0.084	0.187	0.249
	PB	0.88	0.53-1.46	0.622	0.126	0.319

[a]significant results; [b]borderline results; PB: population-based study; HB: hospital-based study; OR: odds ratio; 95% CI: 95% confidence interval; P_{OR}: *P* value for the pooled ORs.

papers, from which they recorded the following information in duplicate: first author's surname, journal year of publication, ethnicity (Caucasian, Asian or African), study country, matching characteristics, source of controls (population-based or hospital-based) and genotype frequencies. An expert in this field was consulted whenever there was conflict.

Statistical analysis

Summary OR and 95% CI was calculated for all studies of the *TNF-α* rs1800629 polymorphism and the risk of cervical cancer under AA vs. GG model, AG vs. GG model, allele A vs. allele G model, AA + AG vs. GG model, and AA vs. AG + GG model. Stratified analyses were performed in ethnicity (when the ethnicity was investigated in less than 3 papers, we categorized them into "other" group) and source of controls. Heterogeneity was measured by the X^2 test and by the I^2 statistic [21]. If the statistical significance level was reached ($P < 0.1$ or $I^2 > 50\%$), the values of each study were estimated using the random effects model [22]; otherwise the fixed effects model was more appropriate [23]. Publication bias was inspected by funnel plots. Egger's test was also performed to test the asymmetry or symmetry of the funnel plot [24].

Deviation from Hardy-Weinberg equilibrium (HWE) was checked using the Chi square good-

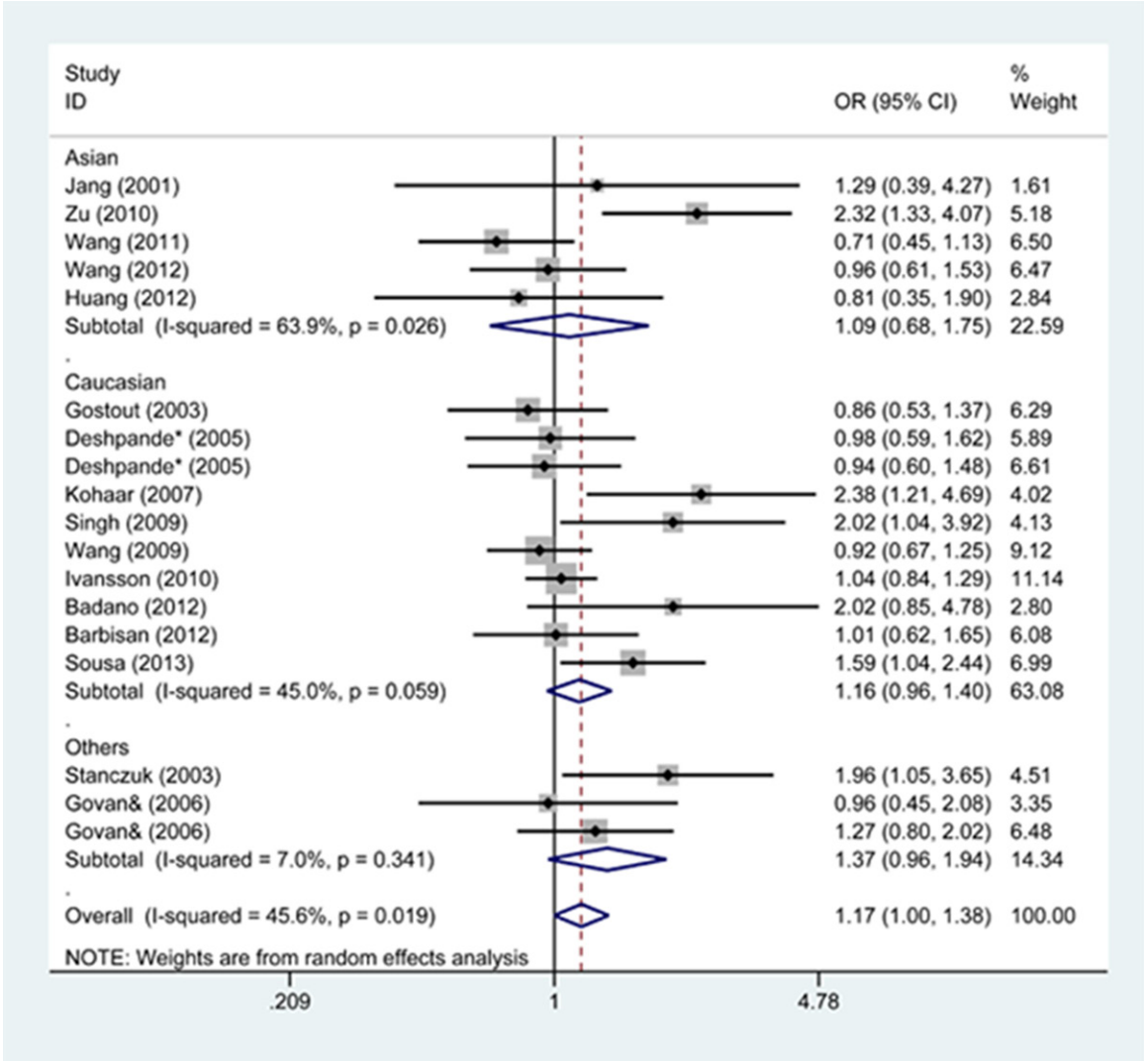

Figure 2. Forest plot of cervical cancer risk associated with the *TNF-α* rs1800629 polymorphism (AA + AG vs. GG) in the stratified analyses by cancer type. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

ness-of-fit test in each of the control populations. By sequentially omitting the single studies, we applied sensitivity analyses to detect the stability of our results. All analyses were performed using STATA version 12.0 (Stata Corporation, USA). The significant threshold was fixed at $P < 0.1$.

Results

Characteristics of the studies

As presented in **Figure 1**, we achieved a total of 16 papers [14-16, 25-37] after rigorous selection using the inclusion criteria. Of these, two articles [25, 27] investigated the association of the *TNF-α* rs1800629 polymorphism with cervical cancer risk in two different populations, which were retrieved as separate dataset. Therefore, for the final meta-analysis, we included 19 studies, providing 3,769 cases and 3,910 controls. The details describing these included studies are summarized in **Table 1**.

Meta-analysis results

The main meta-analysis results are listed in **Table 2**. When all of the eligible studies were pooled together, we observed a marginal association between the *TNF-α* rs1800629 poly-

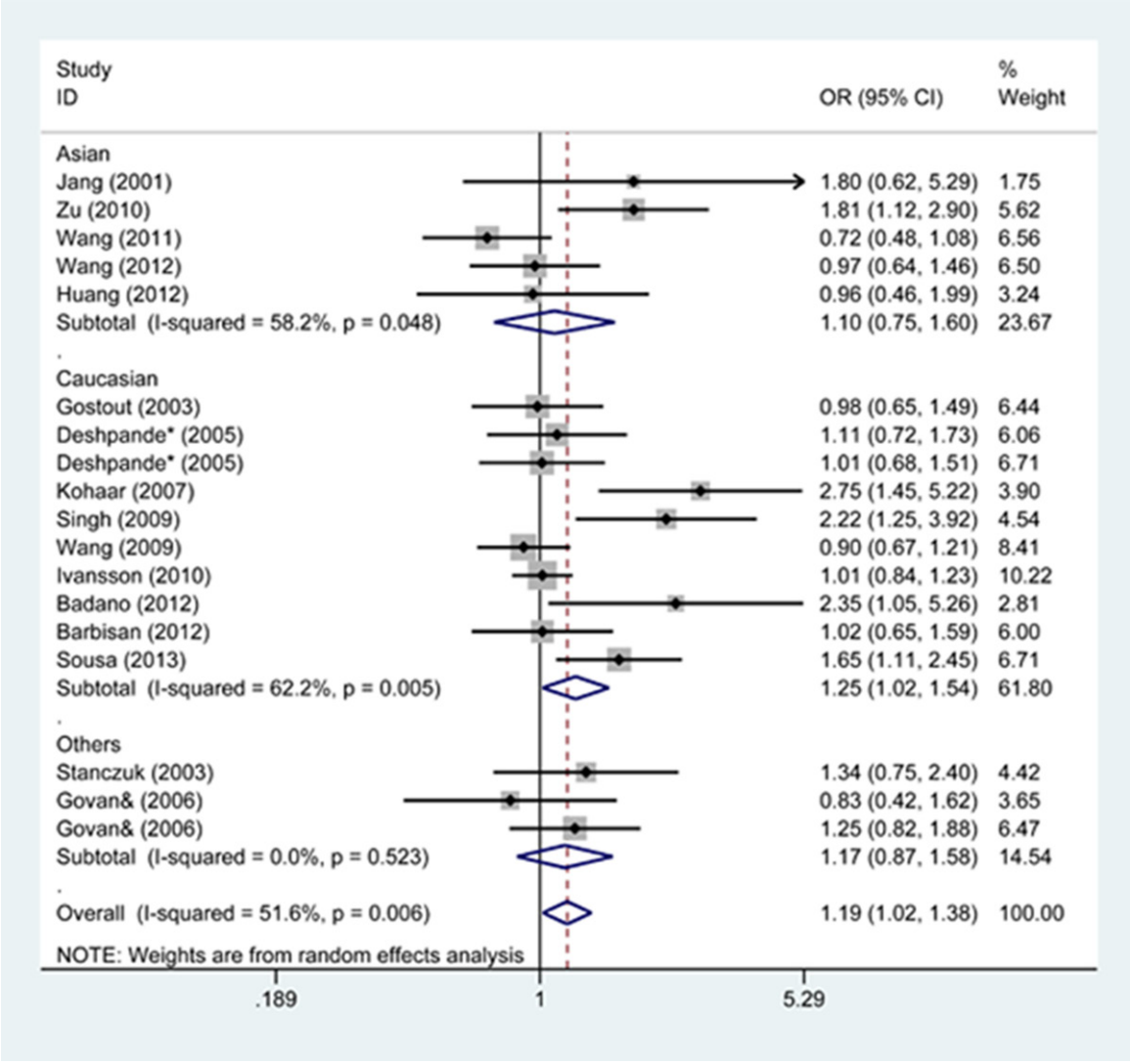

Figure 3. Forest plot of cervical cancer risk associated with the *TNF-α* rs1800629 polymorphism (A vs. G) in the stratified analyses by cancer type. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

morphism and cervical cancer risk under the AA + AG vs. GG comparison model (OR=1.17, 95% CI=1.00-1.38, *P*=0.019 for heterogeneity) (**Figure 2**). Interestingly, significantly increased risk was observed in the allele model (A vs. G: OR=1.19, 95% CI=1.02-1.38, *P*=0.006 for heterogeneity) (**Figure 3**).

In the stratified analysis by ethnicity, we found significant results in Caucasians. The association strength was more pronounced in the AA vs. GG and the AA vs. AG + GG comparison models (OR=1.47, 95% CI=1.04-2.08, *P*=0.164 for heterogeneity; OR=1.47, 95% CI=1.04-2.07, *P*=0.165 for heterogeneity, respectively) (**Figure 2**), and less pronounced in the A vs. G contrast model (OR=1.25, 95% CI=1.02-1.54, *P*=0.005 for heterogeneity) (**Figure 3**).

Finally, we estimated the association strength in stratification analysis according to source of controls. The AA vs. GG and A vs. G comparison models showed nonsignificant but borderline associations in the hospital-based studies (OR=1.39, 95% CI=1.00-1.94, *P*=0.420 for heterogeneity; OR=1.21, 95% CI=1.00-1.47, *P*=0.011 for heterogeneity, respectively) (**Table 2**).

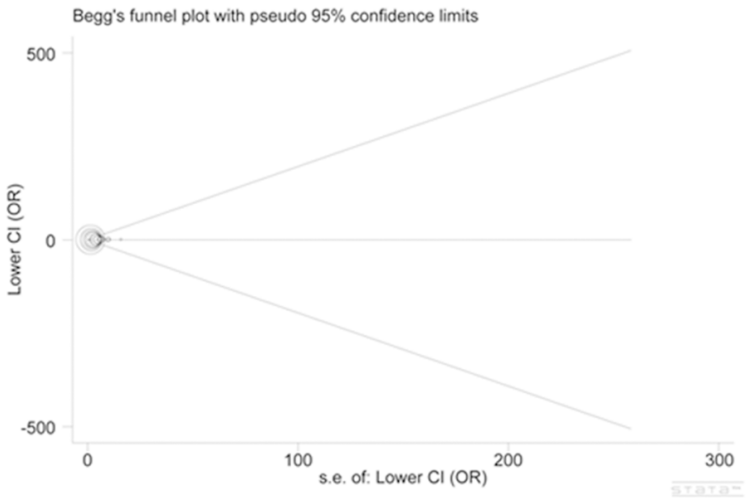

Figure 4. Begg's funnel plot for publication bias test (model: AA vs. GG). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of the odds ratio. Horizontal line, mean effect size.

Evaluation of heterogeneity

Significant heterogeneity was observed in this meta-analysis (**Table 2**). To identify the source of the between-study heterogeneity, we performed stratified analyses. As a result, we found both ethnicity and source of controls were contributing factors.

Sensitivity analysis and publication bias

We examined the stability of our results by performing the one-way sensitivity analysis. The sequential omission of the studies did not reflect any statistical alternation in the overall ORs, suggesting the evidence presented in this study was credible and compelling (data not shown). In terms of publication bias, no obvious asymmetry was revealed in the funnel plots for all comparison models. The Egger's test further confirmed the symmetry of the funnel plots with statistical evidence (P=0.494 for AA vs. GG) (**Figure 4**).

Discussion

To date, a variety of polymorphisms in numerous genes have been investigated in cervical cancer. In the current study, the risk of cervical cancer associated with the *TNF-α* rs1800629 polymorphism was evaluated in 7,679 subjects summarized from sixteen papers with the aid of meta-analysis. Overall, we found significant results in the A vs. G allele model and nonsignificant but borderline association in the AA + AG vs. GG model. In the stratified analysis by ethnicity, significantly increased risk of cervical cancer was observed in Caucasian population under the AA vs. GG and AA vs. AG + GG comparison models in addition to the allele model. Intriguingly, this significant association reduced to the borderline when performing the analysis according to source of controls.

As a result of the significant regulatory function in transcriptional activity of cytokine gene *TNF-α*, many clinical and epidemiological studies have focused on the rs1800629 polymorphism. The A allele and the G allele function differentially in their effects on the transcription level of *TNF-α*. Compared with the G allele, the A allele is a much stronger transcriptional activator correlated with high *TNF-α* production [11, 12]. This is the most likely explanation for the increased risk of various diseases in relation to the rs1800629 polymorphism, especially the A allele. More specifically, the carriage of the AA genotype was discovered to have seven-fold elevated risk of death from cerebral malaria [11]. A recent statistical analysis carried out by Sousa et al. also revealed that the A allele carriers were associated with an almost 2-fold increased risk for invasive cervical cancer development [16]. Similar to the previous discoveries, in our meta-analysis, we found a fixed 19% increased risk to develop cervical cancer in the subjects carrying the A allele.

Although the rs1800629 polymorphism is a known risk factor for cervical cancer, not all association studies concerning their association showed significant results. Govan et al. associated the *TNF-α* rs1800629 polymorphism with two South African ethnic population groups, failing to find any significant association [27]. Similar results were also found in Korean population [29], Swedish population [28] and Chinese population [32]. The reported genetic effects varied across the published studies may attribute to the insufficient detection power of these relatively small sample-sized single studies.

Previously, several meta-analyses have been performed and estimated the association of the *TNF-α* rs1800629 polymorphism and cervical cancer risk. The first report gathered all case-control studies published from January 1989 to October 2010, and suggested that the *TNF-α* rs1800629 polymorphism may contribute to cervical cancer susceptibility [18]. This finding was replicated in the following studies with either a larger or relatively smaller study size [17, 19, 20]. However, considering that the overlapped data were included and more importantly, additional studies were published subsequently, we performed the quantitative analysis to further assess the association, though consistent results were revealed in our study.

We observed significant association in Caucasian population, but not in Asian population. One possibility is that *TNF-α* rs1800629 is a low-penetrant polymorphism, and the current sample size lacks statistical power to detect the slight effects. Another explanation may be the obvious heterogeneity indicated across studies. Therefore, the present findings may have been biased by the heterogeneity which may arise from differences in genetic background and source of controls. Because some studies did not report how the control subjects were recruited or selected and whether the controls were well matched with the patients [29, 31].

There are several weaknesses in this study. Firstly, publication bias may have occurred, as only published data were included in the meta-analysis. Secondly, in the subgroup of Asians, specially the Africans (the two studies were merged into "other" group for insufficient data), and the limited study size made it impossible to derive a precise estimate or even to perform a meta-analysis to assess the association. Thirdly, the impact of gene-to-gene and gene-to-environment interactions was not addressed in the analysis. Therefore, additional studies are warranted to evaluate the effect of this functional polymorphism on cervical cancer risk.

In conclusion, the evidence presented in this meta-analysis supported the consideration of a potential effect of the *TNF-α* rs1800629 polymorphism on the increased cervical cancer risk in Caucasian population. The genetic association of the *TNF-α* rs1800629 polymorphism with cervical cancer risk requires to be further validated in larger studies in future.

Disclosure of conflict of interest

None.

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