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RESEARCH ARTICLE

Association of the s1799724 and rs1800629 Polymorphisms of the TNF-α Gene with Susceptibility to Cervical Cancer, a Systematic Review and Meta-Analysis Based on 24 Case-Control Studies

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Abstract

Objective: Some studies have recently focused on the association between TNF-α polymorphisms and cervical cancer; however, results have been inconsistent. In order to drive a more precise estimation, the present systematic review and meta-analysis is performed to investigate the relationship of the TNF-α rs1800629 and s1799724 polymorphisms with cervical cancer risk. **Methods:** An electronic search was conducted on PubMed, Web of Science, and Google scholar databases, for papers that describe the association between TNF-α polymorphisms and cervical cancer risk. **Results:** A number of 24 case-control studies in 22 publications were identified according to the inclusion criteria. The results showed that rs1800629 polymorphism was significantly associated with the increased cervical cancer risk under four genetic models (A vs. G: OR = 1.277, 95% CI: 1.104-1.477, p = 0.001; AA vs. GG: OR = 1.333, 95% CI: 1.062-1.674, p = 0.013; AG vs. GG: OR = 1.307, 95% CI: 1.064-1.605, p = 0.011; and AA+AG vs. GG: OR = 1.324, 95% CI: 1.104-1.587, p = 0.002). In stratified analysis, there was a significant association between rs1800629 polymorphism and cervical cancer risk in the subgroup of Caucasians and African, but not in Asians. However, no statistically significant association was observed between the s1799724 and cervical cancer risk under all genetic models. Furthermore, stratification by ethnicity indicated no association between the s1799724 and cervical cancer risk. **Conclusion:** the present meta-analysis suggests that the rs1800629 polymorphism of the TNF-α gene was significantly associated with cervical cancer risk, but not s1799724.

Keywords: TNF-α gene- cervical cancer- polymorphism- meta-analysis

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Introduction

Cervical cancer is the third most common female cancer (after breast and colon cancer) worldwide [1-2], and the number-one cause of cancer-related death in women in developing countries [3-4]. Cervical cancer is an important preventable cause of morbidity and mortality among women worldwide [5]. It is divided into two types: Cervical squamous cell carcinoma, which is derived from squamous cells and cervical adenocarcinoma, arising in

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the glandular cells of cervix. Cervical cancer incidence varies widely in different countries, ranging from around 3 to over 40 per 100,000 [6]. The higher incidence rates are seen mainly in developing countries, particularly in Africa, and the lowest rates occur in Western Europe and west Asia.

The major risk factor for cervical cancer is infection with human papillomavirus (HPV) [5]. However, several epidemiological studies have pointed out the importance of genetic risk factors in cervical cancer. Evidence revealed that familial clustering of cervical cancer and its precursor forms [7]. In 1999, Magnusson et al. reported a significant familial aggregation for cervical cancer [8]. Genes of the immune response system have been studied to investigate the potential association with cervical cancer as well as effect on the susceptibility toward HPV infection and the persistence of the infection. Genetic predisposition to cervical cancer is related to HLA class II. HLA, B7 and DQB1 are positively associated with cervical neoplasm [9]. However, several other candidate genes in the MHC regions except of the HLA such as TNF [10], LTA [11], TAP and TAP[12], which are part of different pathways, have been suggested to influence cervical cancer. Then, cervical cancer is a complex disease that results from the interaction between gene mutations and the environment [13].

TNF-α is one of the most intensively studied molecule in the field of immunology and cancer [14-15]. TNF-α is an important pleiotropic inflammatory cytokine exerting both homeostatic and pathophysiological function in the periphery and in the central nervous system (CNS), which plays a critical role in the pathogenesis of several autoimmune diseases [16, 17]. The TNF-α gene is located on the short arm of chromosome 6p21.1-p21.3 and various polymorphisms in this gene have been identified with susceptibility to cancers such as TNF-α-308G>A (rs1800629), TNF-α -857T>C (rs1799724), TNF-T-1031C (rs1799964) and TNF-α-238G>A (rs361525) [18]. In the past decade, the several epidemiologic studies investigated TNF-α polymorphisms on cervical cancer susceptibility. However, the results remain fairly inconsistent and inconclusive. To derive a more precise estimation of the association between TNF-α polymorphisms and cervical cancer risk, we conducted a meta-analysis of all available case-control studies relating the TNF-α rs1800629 and rs1799724 polymorphisms to the risk of developing cervical cancer.

Materials and Methods

Search Strategy

A systematic search of eligible studies on the association between TNF-□ gene polymorphisms and cervical cancer susceptibility was conducted in Medline, ISI Web of Science, Google Scholar, and Embase databases up to the end of April 2017. The following terms were included in the search: "cervical cancer'', -308 G>A, s1799724, rs1800629, ''single nucleotide polymorphisms'', ''SNPs'', "polymorphism", "variant", and "genotype", "SNP", and "allele". The extracted publications were limited to English. References of retrieved articles, review articles and similar meta-analysis were screened for other additional original articles. If there were multiple reports of the same study or overlapping data only the study with the largest sample sizes or the most recent one was include to the meta-analysis.

Inclusion and Exclusion Criteria

All studies included in this meta-analysis had to meet the following criteria: (1) full-text published studies; (2) studies with case-control or cohort design; (3) a study evaluated the association of TNF-α gene polymorphisms with cervical cancer risk; (4) available genotypes frequencies of TNF-α polymorphisms were provided to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). The exclusion criteria were as follows: (1) the study was not conducted on cervical cancer; (2) abstracts, case reports, letter to editor, and reviews; (3) studies with only case group (no control group); (4) studies without detail genotype frequencies, which were unable to calculate ORs; and (5) duplicate publications of data from the same study.

Data Extraction

Two independent authors extracted the information of each eligible study according to the inclusion criteria using a pre-designed form. The following items were extracted from each study: the first author, year of publication, number of cervical cancer patients and controls, genotype and allele frequency, minor allele frequencies (MAFs) in control subjects, and Hardy-Weinberg equilibrium test in control subjects. Any disagreements or conflicting evaluation were resolved by reaching a consensus through discussion or the involvement of a third party.

Statistical Analysis

The strength of association between the TNF-α polymorphisms and the cervical cancer risk was assessed by ORs with 95% CIs. The significance of pooled ORs was examined by Z-test. Five different genetic models were used in the current meta-analysis for TNF-α rs1800629 including the allelic model (A vs. G), the homozygote model (AA vs. GG), the heterozygote model (AG vs. GG), the dominant model (AA+AG vs. GG), and the recessive model (AA vs. AG+GG). The pooled ORs for TNF-α rs1799724 were performed in different genetic comparison models, including the allele model (T vs. C), the homozygote model (TT versus CC), the heterozygote model (TC versus CC), dominant model (TT+TC versus CC) and recessive model (TT versus TC+CC). Heterogeneity assumption was checked by a chi-square-based Q test, and I2 statistics was calculated to quantify the proportion of the total variation across studies due to heterogeneity [19, 20]. The heterogeneity was considered significant if either the Q statistic had $p < 0.1$ or $I2 > 50\%$. An I2 value of 0% represents no heterogeneity, with values of 25%, 50%, 75%, or more represent low, moderate, high, and ex¬treme heterogeneity,

respectively. A P value greater than 0.10 indicated a lack of heterogeneity among studies, so the fixed effect model (Mantel-Haenszel method) was used to calculate pooled OR. Otherwise, the fixed-effects model (Mantel-Haenszel approach) was used [20-21]. HWEs were calculated with goodness-of-fit tests (i.e., chi-square or Fisher's exact tests). A value of $p < 0.01$ signified a departure from HWE [22]. One-way sensitivity analyses were carried out by consecutively omitting one study at a time to assess the power of the meta-analysis findings. Publication bias was assessed both visually by using a funnel plot and statistically via Begg's funnel plots and Egger's bias test ($p < 0.05$ was considered statistically significant), which measures the degree of funnel plot asymmetry [23]. Sensitivity analysis was performed to evaluate the stability of the results by removing the studies. All the statistical analyses were performed by comprehensive meta-analysis (CMA) version 2.0 software (Biostat, USA). All p-values were two-tailed with a significant level at 0.05.

Results

Through electronic search, a total of 38 relevant studies concerning TNF-α rs1800629 and rs1799724 polymorphisms and cervical cancer risk were selected following an initial search, which 24 case control studies fit the inclusion criteria. Of the 14 excluded studies, two articles were reviews, seven were redundant studies, four were not involved with TNF-α polymorphism and one study was excluded because did not report allele frequencies for controls used for calculating ORs and 95% CIs. For the rs1800629 polymorphism, 4,780 cases and 4,620 controls were available from four studies, whereas for the rs1799724 polymorphism, 828 cases and 871 controls were available from six studies. Overall, eleven studies used Caucasians, ten used Asians, and three studies used African populations. The countries of eligible studies included Korea (one study), USA (four studies), Zimbabwe (one study), Portugal (one study), South Africa (one study), India (three studies), China (six studies), Sweden (one study), Argentina (two studies), Tunisia (one study), Poland (one study) and Mexico (one study). The results of HWE test for the distribution of the genotype in healthy control populations are shown in Table 1. The genotype distribution in six case-control studies was not in agreement with HWE ($p < 0.005$).

Quantitative Synthesis

TNF-α rs1800629

Table 2 listed the main results of the meta-analysis of TNF-α rs1800629 polymorphism and cervical cancer risk. When all the eligible studies were pooled into the meta-analysis of rs1800629 polymorphism, significantly increased risk of cervical cancer was observed in the allelic model (A vs. G: OR = 1.277, 95% CI = 1.104-1.477, P = 0.001, Figure 1A), the homozygote model (AA vs. GG: OR = 1.333, 95% CI = 1.062-1.674, P = 0.013), the heterozygote model (AG vs. GG: OR = 1.307, 95% CI =

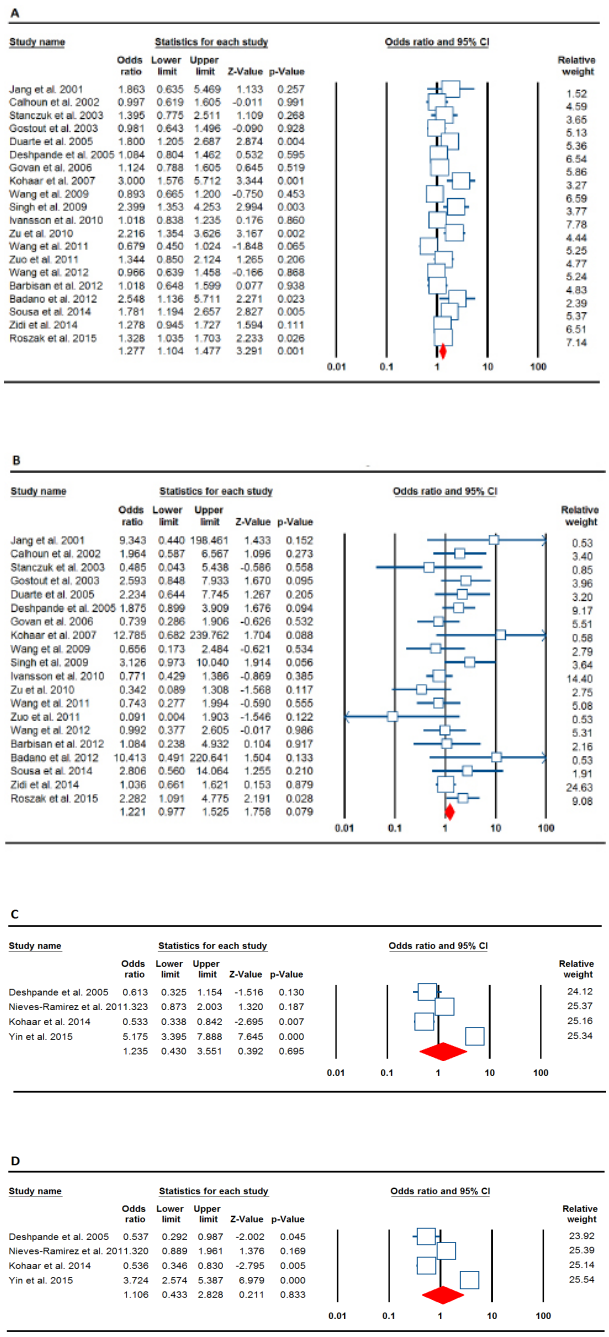

Figure 1. Forest Plots Showed Significant Association between TNF-α rs1800629 and rs1799724 Polymorphisms and Cervical Cancer Risk. A, rs1800629 (allele model, A vs. G); B, rs1800629 (recessive model, AA vs. AG+GG); C, rs1799724 (heterozygote model, TC vs. CC); D, rs1799724 (dominant model, TT+TC vs. CC)

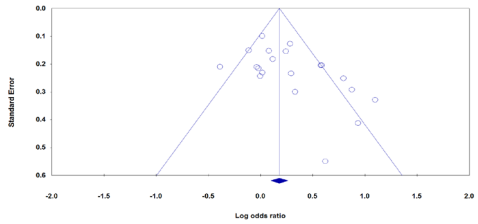

Figure 2. Begg's Funnel Plots of TNF-α rs1800629 Polymorphism and Cervical Cancer Risk under the Allele Model for Publication Bias Test. Each point represents a separate study for the indicated association

Table 1. Characteristics of Studies Included in TNFα rs1800629 and rs1799724 Polymorphisms and Cervical Cancer

First author	Country ethnicity	Case/Control	Cases					Controls					MAFs	HWE
			Genotype			Allele		Genotype			Allele			
TNFα rs1800629			GG	AG	AA	G	A	GG	AG	AA	G	A		
Jang et al. 2001 [24]	Korea (Asian)	51/92	46	3	2	95	7	85	7	0	177	7	0.038	0.704
Calhoun et al. 2002 [25]	USA(Caucasian)	127/107	91	27	9	209	45	73	30	4	176	38	0.177	0.678
Stanczuk et al. 2003 [26]	Zimbabwe (African)	103/101	74	28	1	176	30	81	18	2	180	22	0.108	0.41
Gostout et al. 2003 [12]	USA (Caucasian)	127/175	91	27	9	209	45	117	53	5	287	63	0.18	0.731
Duarte et al. 2005 [27]	Portugal (Caucasian)	195/244	138	50	7	326	64	200	40	4	440	48	0.098	0.236
Deshpande et al. 2005 [28]	USA (Caucasian)	258/411	188	54	16	430	86	297	100	14	694	128	0.155	0.13
Govan et al. 2006 [29]	South Africa (African)	244/228	174	62	8	410	78	172	46	10	390	66	0.144	0.005
Kohaar et al. 2007 [16]	India (Asian)	120/165	94	22	4	210	30	150	15	0	315	15	0.045	0.54
Wang et al. 2009 [30]	China (Asian)	456/800	386	67	3	839	73	666	126	8	1458	142	0.088	0.457
Singh et al. 2009 [31]	India (Asian)	150/162	122	17	11	261	39	147	11	4	305	19	0.058	≤0.001
Ivansson et al. 2010 [32]	Sweden (Caucasian)	1263/552	891	340	32	2122	404	396	138	18	930	174	0.157	0.169
Zu et al. 2010 [33]	China (Asian)	83/91	30	50	3	110	56	66	16	9	148	34	0.186	≤0.001
Wang et al. 2011 [34]	China (Asian)	186/200	149	30	7	328	44	144	46	10	334	66	0.165	0.019
Zuo et al. 2011 [35]	China (Asian)	239/110	158	81	0	397	81	83	25	2	191	29	0.131	0.941
Wang et al. 2012 [36]	China (Asian)	285/318	247	30	8	524	46	274	35	9	583	53	0.083	≤0.001
Barbisan et al. 2012 [37]	Argentina (Caucasian)	122/176	87	32	3	206	38	126	46	4	298	54	0.153	0.483
Badano et al. 2012 [14]	Argentina (Caucasian)	56/113	44	10	2	98	14	101	12	0	214	12	0.053	0.551
Sousa et al. 2014 [15]	Portugal (Caucasian)	223/205	152	65	6	369	77	164	39	2	367	43	0.104	0.849
Zidi et al. 2014 [38]	Tunisia (African)	130/260	55	33	43	143	117	141	35	84	317	203	0.39	≤0.001
Roszak et al. 2015 [39]	Poland (Caucasian)	362/399	217	123	22	557	167	263	125	11	651	147	0.184	0.397
TNFα rs1799724		4780/4620	CC	TC	TT	C	T	CC	TC	TT	C	T		
Deshpande et al. 2005 [28]	USA (Caucasian)	139/115	116	22	1	254	24	84	26	5	194	36	0.156	0.123
Nieves-Ramirez et al. 2011 [40]	Mexico [Caucasian)	191/205	93	82	16	268	114	114	76	15	304	106	0.258	0.636
Kohaar et al. 2014 [16]	India (Asian)	150/200	99	44	7	242	58	102	85	13	289	111	0.277	0.397
Yin et al. 2015 [41]	China (Asian)	348/351	215	87	46	517	179	301	44	6	646	56	0.08	0.006

1.064-1.605, P = 0.011), the dominant model (AA+AG vs. GG: OR = 1.324, 95% CI = 1.104-1.587, P = 0.002), but not under the recessive model (AA vs. AG+GG: OR = 1.221, 95% CI = 0.977-1.525, P = 0.079, Figure 1B). Stratified analysis by ethnicity showed no association between TNFα rs1800629 polymorphism and cervical cancer risk in Asians under all genetic models. However, significantly increased autism risk was observed in Africans (heterozygote model: AG vs. GG, OR = 1.670, 95% CI = 1.228-2.270, P = 0.001 and dominant model: AA+AG vs. GG, OR = 1.453, 95% CI = 1.111-1.902, P = 0.006) and Caucasians (allelic model: A vs. G, OR

Table 2. The Meta-Analysis of TNFα rs1800629 Polymorphism and Cervical Cancer Risk

Polymorphism	Study Number	Genetic Model	Type of Model	Heterogeneity		Odds Ratio			Publication Bias		
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall											
	20	A vs. G	Random	61.94	≤0.001	1.277	1.104-1.477	3.291	0.001	0.029	0.025
	20	AA vs. GG	Fixed	27.43	0.125	1.333	1.062-1.674	2.481	0.013	0.314	0.366
	20	AG vs. GG	Random	70.89	≤0.001	1.307	1.064-1.605	2.552	0.011	0.183	0.141
	20	AA+AG vs. GG	Random	67.34	≤0.001	1.324	1.104-1.587	3.03	0.002	0.097	0.056
	20	AA vs. AG+GG	Fixed	35.98	0.056	1.221	0.977-1.525	1.758	0.079	0.537	0.336
Asian											
	8	A vs. G	Random	78.48	≤0.001	1.403	0.970-2.029	1.798	0.072	0.035	0.062
	8	AA vs. GG	Fixed	43.54	0.088	1.089	0.670-1.770	0.343	0.731	1	0.54
	8	AG vs. GG	Random	82.21	≤0.001	1.469	0.895-2.411	1.521	0.128	0.173	0.267
	8	AA+AG vs. GG	Random	81.63	≤0.001	1.5	0.954-2.359	1.756	0.079	0.173	0.121
	8	AA vs. AG+GG	Random	50.71	0.048	1.04	0.487-2.217	0.1	0.92	0.901	0.647
African											
	3	A vs. G	Fixed	0	0.786	1.234	0.996-1.529	1.925	0.054	1	0.739
	3	AA vs. GG	Fixed	0	0.537	1.156	0.757-1.766	0.672	0.502	1	0.289
	3	AG vs. GG	Fixed	24.821	0.264	1.67	1.228-2.270	3.268	0.001	1	0.564
	3	AA+AG vs. GG	Fixed	0	0.585	1.453	1.111-1.902	2.725	0.006	1	0.766
	3	AA vs. AG+GG	Fixed	0	0.702	0.955	0.640-1.425	-0.225	0.822	1	0.185
Caucasian											
	9	A vs. G	Random	52.45	0.032	1.242	1.043-1.478	2.438	0.015	0.754	0.203
	9	AA vs. GG	Fixed	22.58	0.242	1.586	1.147-2.193	2.791	0.005	0.175	0.072
	9	AG vs. GG	Random	54.87	0.023	1.123	0.905-1.395	1.056	0.291	0.754	0.906
	9	AA+AG vs. GG	Random	52.8	0.031	1.201	0.982-1.469	1.787	0.074	0.916	0.501
	9	AA vs. AG+GG	Fixed	22.15	0.246	1.569	1.137-2.165	2.744	0.006	0.348	0.079

= 1.242, 95% CI = 1.043-1.478, P = 0.015; homozygote model: AA vs. GG, OR = 1.586, 95% CI = 1.147-2.193, P = 0.005; recessive model: AA vs. AG+GG, OR = 1.569, 95% CI = 1.137-2.165, P = 0.006).

TNF-α s1799724

Table 3 listed the main results of the meta-analysis of TNF-α s1799724 polymorphism and cervical cancer risk. When all the eligible studies were pooled into the meta-analysis of s1799724 polymorphism, there was no significant association between TNF-α s1799724 and cervical cancer under all five genetic models (allelic model: T vs. C, OR = 1.133, 95% CI = 0.452-2.838, P = 0.790; homozygote model: CT vs. CC, OR = 0.735, 95% CI = 0.356-1.518, P = 0.405; heterozygote model: TT vs. CC, OR = 1.235, 95% CI = 0.430-3.551, P = 0.695, Figure 1C; dominant model: TT+CT vs. CC, OR = 1.106, 95% CI = 0.433-2.828, P = 0.833, Figure 1D; and recessive model: TT vs. CT+CC, OR = 1.241, 95% CI = 0.306-5.045, P = 0.762). Stratified analysis by ethnicity showed no association between TNF-α s1799724 polymorphism and cervical cancer risk in Caucasian and Asian populations under all genetic models.

Heterogeneity test and sensitivity analysis

There was significant between-study heterogeneity for both TNF-α -308G>A and TNF-α -857T>C polymorphisms (Table 2). We have also performed sensitivity analysis to explore the potential influence of each individual study on the overall results by deleting one single study each time from the pooled analysis. However, no substantial change was observed in the overall studies, indicating that no individual study could affect the pooled OR significantly (data not shown).

Publication bias

To examine the publication bias of the currently available literature, both Begg's funnel plot and Egger's test were used. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models. Moreover, the Egger's test was used to provide statistical evidence for funnel plot symmetry. The results showed evidence of publication bias for TNF-α -308G>A under allele model (PBeggs = 0.029 and PEggers = 0.025), but not for TNF-α -857T>C (Figure 2).

Discussion

This systematic review and meta-analysis aimed to explore the association of s1799724 and rs1800629 polymorphisms of TNF-α and cervical cancer risk from 24 case-control studies with 5608 cases and 5491 healthy controls. Of the 24 included studies, only four involved TNF-α s1799724 with 828 cases and 871 controls.

Table 3. The Meta-Analysis of TNFα rs1799724 Polymorphism and Cervical Cancer Risk

Polymorphism	Study Number	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall											
	4	T vs. C	Random	95.98	≤0.001	1.133	0.452-2.838	0.266	0.79	0.734	0.444
	4	TT vs. CC	Fixed	48.17	0.122	0.735	0.356-1.518	-0.832	0.405	0.308	0.319
	4	TC vs. CC	Random	95.05	≤0.001	1.235	0.430-3.551	0.392	0.695	0.734	0.5
	4	TT+TC vs. CC	Random	94.54	≤0.001	1.106	0.433-2.828	0.211	0.833	0.308	0.293
	4	TT vs. TC+CC	Random	86.85	≤0.001	1.241	0.306-5.045	0.303	0.762	0.308	0.581
Asian											
	2	T vs. C	Random	98.25	≤0.001	1.591	0.255-9.924	0.497	0.619	NA	NA
	2	TT vs. CC	Fixed	69.36	0.071	0.882	0.455-1.709	-0.373	0.709	NA	NA
	2	TC vs. CC	Random	98.05	≤0.001	1.664	0.180-15.432	0.448	0.654	NA	NA
	2	TT+TC vs. CC	Random	97.73	≤0.001	1.418	0.212-9.475	0.361	0.718	NA	NA
	2	TT vs. TC+CC	Random	93.28	≤0.001	2.502	0.212-29.587	0.728	0.467	NA	NA
Caucasian											
	2	T vs. C	Random	86.4	0.007	0.813	0.346-1.909	-0.476	0.634	NA	NA
	2	TT vs. CC	Fixed	57.36	0.126	0.714	0.346-1.470	-0.915	0.36	NA	NA
	2	TC vs. CC	Random	74.77	0.046	0.936	0.442-1.981	-0.174	0.862	NA	NA
	2	TT+TC vs. CC	Random	83.05	0.015	0.869	0.361-2.092	-0.314	0.753	NA	NA
	2	TT vs. TC+CC	Fixed	65.5	0.089	0.944	0.471-1.890	-0.164	0.87	NA	NA

The present meta-analysis is the most comprehensive synthesis concerning polymorphisms on TNF-α and susceptibility to cervical cancer. According to our results, there was no an overall significant association of s1799724 polymorphism with cervical cancer risk under all genetic models. Furthermore, stratification by ethnicity indicated no association between the s1799724 and cervical cancer risk. However, the results showed that rs1800629 polymorphism was significantly associated with the increased cervical cancer risk under four genetic models (A vs. G: OR = 1.277, 95% CI: 1.104-1.477, p = 0.001; AA vs. GG: OR = 1.333, 95% CI: 1.062-1.674, p = 0.013; AG vs. GG: OR = 1.307, 95% CI: 1.064-1.605, p = 0.011; and AA+AG vs. GG: OR = 1.324, 95% CI: 1.104-1.587, p = 0.002). In stratified analysis, there was a significant association between rs1800629 polymorphism and cervical cancer risk in the subgroup of Caucasians and African, but not in Asians. According to the current meta-analysis, there was a variety in terms of s1799724 and rs1800629 polymorphisms of the TNF-α gene distribution in the different ethnicity. Compared to the previously published meta-analyses [24, 25] there are more studies included in the current meta-analysis, and the overall sample size is larger; therefore, our findings are more precise and reliable. In addition, the present meta-analysis there is the only study that has assessed both s1799724 and rs1800629 polymorphisms association with cervical cancer simultaneously. Additionally, our results were not consistent with a meta-analysis by Jin et al., 2015 on rs1800629 polymorphism with cervical cancer risk. They included 18 case–control studies with 2,775 cases and 2,759 controls of rs1800629. Their results suggested that rs1800629 polymorphism was associated with increased cervical cancer risk in both Asian and Caucasian populations. Additionally, Jin et al., 2015 not performed further subgroup by ethnicity in the African populations to detect significant difference [25]. In the present systematic review and meta-analysis, by including 20 case-control studies with 4,780 cases and 4,620 controls for quantitative synthesis, we found that the rs1800629 polymorphism was associated with cervical cancer risk in Caucasians and Africans, but not Asian populations.

Heterogeneity is a potential problem that may affect the accuracy of the meta-analyses results [26, 27]. Heterogeneity may be due to many factors, such as differences in the small sample size, diversity in design, inclusion criteria, diverse genotyping method, characteristics of controls, and a mixed population from different ethnicity [28, 29]. In present meta-analysis a significant heterogeneity was found for rs1800629 (under allele, heterozygote and dominant models) and rs1799724 (under allele, heterozygote, dominant and recessive models) polymorphisms in the overall population. Thus, we conducted subgroup analysis by ethnicity and found a statistically significant level of heterogeneity for rs1800629 in the Asian and Caucasian populations heterogeneity is still exist in, but not in Africans. A similar result was found for rs1799724. Therefore, both polymorphisms were the sources of the heterogeneity. It was suggested that different allelic frequencies in different ethnic groups may account for these discrepancies [30]. Moreover, in the sensitivity analysis, we have not found significant after omitting each study at a time, indicating the relative stability and credibility of the results of our meta-analysis.

This meta-analysis had significantly higher statistical power than the previous meta-analyses that analyzed the association between the TNF-α polymorphism and

cervical cancer risk, since the cancer patients involved in our meta-analysis were higher as many as the previous one. However, some limitation should be considered in this meta-analysis. First, the number of available studies for TNF-α rs1799724 polymorphism was limited to the four case-control studies, and, due to the limited sample size, the pooled results were less accurate and more studies with large sample size and high quality are needed for further analysis. Second, in the present meta-analysis we have included only published studies; therefore, publication bias might have occurred and the present meta-analysis results may have a substantial risk of being affected by bias. Third, the heterogeneity is difficult to exclude, in that it is influenced by complicated factors, such as age, sex, genetic diversities, different lifestyle, and clinical characteristics. In this study, a significant between study heterogeneity was found in most of the meta-analyses for both polymorphisms. Reduced heterogeneity was observed in some ethnicity after subgroup analyses, especially in African populations. However, due to the complexity of cervical cancer and potential confounding factors such as age, infection with HPV, lifestyle, difference in clinical and/or environmental factors might have contributed to the heterogeneity among individual studies. Finally, due to limited individual data for the adjustments of major confounders, we did not conduct a more precise analysis on other covariates such as age, lifestyle, HPV infection, and environmental factors.

In summary, this meta-analysis of 24 case-control studies suggested that the rs1800629 polymorphism of the TNF-α gene was significantly associated with cervical cancer risk, but not s1799724. Moreover, compared with Asians, African and Caucasian female with A allele of the TNFα rs1800629 had been found to have a greater susceptibility for the development of cervical cancer. Additionally, due to the limited number of studies and sample size included for TNF-α rs1799724 polymorphism, well-designed studies with large sample size and more ethnic groups are required to further verify and confirm current meta-analysis results.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.
2. Yazdi MF, Rafieian S, Gholi-Nataj M, Sheikhha MH, Nazari T, Neamatzadeh H. CYP2D6 Genotype and Risk of Recurrence in Tamoxifen Treated Breast Cancer Patients. Asian Pacific journal of cancer prevention : APJCP. 2015;16(15):6783-7.
3. Arbyn M, Castellsague X, de Sanjose S, Bruni L, Saraiya M, Bray F, et al. Worldwide burden of cervical cancer in 2008. Annals of oncology : official journal of the European Society for Medical Oncology. 2011;22(12):2675-86.
4. Sherris J, Herdman C, Elias C. Cervical cancer in the developing world. The Western journal of medicine. 2001;175(4):231-3.
5. Monk BJ, Herzog TJ. The new era of cervical cancer prevention: HPV vaccination. Gynecologic oncology. 2008;109(2 Suppl):S1-3.
6. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. World journal of clinical oncology. 2015;6(6):281-90.
7. Hemminki K, Dong C, Vaittinen P. Familial risks in cervical cancer: is there a hereditary component? International journal of cancer. 1999;82(6):775-81.
8. Magnusson PK, Sparen P, Gyllensten UB. Genetic link to cervical tumours. Nature. 1999;400(6739):29-30.
9. Engelmark M, Beskow A, Magnusson J, Erlich H, Gyllensten U. Affected sib-pair analysis of the contribution of HLA class I and class II loci to development of cervical cancer. Human molecular genetics. 2004;13(17):1951-8.
10. Jang WH, Yang YI, Yea SS, Lee YJ, Chun JH, Kim HI, et al. The -238 tumor necrosis factor-alpha promoter polymorphism is associated with decreased susceptibility to cancers. Cancer letters. 2001;166(1):41-6.
11. Niwa Y, Hirose K, Matsuo K, Tajima K, Ikoma Y, Nakanishi T, et al. Lymphotoxin-alpha polymorphism and the risk of cervical cancer in Japanese subjects. Cancer letters. 2005;218(1):63-8.
12. Gostout BS, Poland GA, Calhoun ES, Sohni YR, Giuntoli RL, 2nd, McGovern RM, et al. TAP1, TAP2, and HLA-DR2 alleles are predictors of cervical cancer risk. Gynecologic oncology. 2003;88(3):326-32.
13. Martínez-Nava G F-NJ, Madrid-Marina V, Madrid-Marina V, Torres-Poveda K. Cervical Cancer Genetic Susceptibility: A Systematic Review and Meta-Analyses of Recent Evidence. PLOS ONE. e0157344. 2016; .
14. Badano I, Stietz SM, Schurr TG, Picconi AM, Fekete D, Quintero IM, et al. Analysis of TNFalpha promoter SNPs and the risk of cervical cancer in urban populations of Posadas (Misiones, Argentina). Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2012;53(1):54-9.
15. Sousa H, Oliveira S, Santos AM, Catarino R, Moutinho J, Medeiros R. Tumour necrosis factor alpha 308 G/A is a risk marker for the progression from high-grade lesions to invasive cervical cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2014;35(3):2561-4.
16. Kohaar I, Thakur N, Salhan S, Batra S, Singh V, Sharma A, et al. TNFalpha-308G/A polymorphism as a risk factor for HPV associated cervical cancer in Indian population. Cellular oncology : the official journal of the International Society for Cellular Oncology. 2007;29(3):249-56.
17. Probert L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. Neuroscience. 2015;302:2-22.
18. Qidwai T, Khan F. Tumour necrosis factor gene polymorphism and disease prevalence. Scandinavian journal of immunology. 2011;74(6):522-47.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute. 1959;22(4):719-48.
22. Khoram-Abadi KM, Forat-Yazdi M, Kheirandish S, Saeidi N, Zarezade Z, Mehrabi N, et al. DNMT3B -149 C>T and -579 G>T Polymorphisms and Risk of Gastric and Colorectal Cancer: a Meta-analysis. Asian Pacific journal of cancer prevention : APJCP. 2016;17(6):3015-20.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-34.

24. Cai J, Yang MY, Hou N, Li X. Association of tumor necrosis factor-alpha 308G/A polymorphism with urogenital cancer risk: a systematic review and meta-analysis. Genetics and molecular research : GMR. 2015;14(4):16102-12.
25. Y. J. Association of Single Nucleotide Polymorphisms in Tumor Necrosis Factor-Alpha with Cervical Cancer Susceptibility. 2015 77-84. p.
26. Kamali M, Kargar S, Heiranizadeh N, Zare M, Kargar S, Zare Shehneh M, et al. Lack of any Association between the Hogg1 Ser326Cys Polymorphism and Breast Cancer Risk: a Systematic Review And Meta-Analysis Of 18 Studies. Asian Pacific journal of cancer prevention : APJCP. 2017;18(1):245-51.
27. Sobhan MR, Forat Yazdi M, Mazaheri M, Zare Shehneh M, Neamatzadeh H. Association between the DNA Repair Gene XRCC3 rs861539 Polymorphism and Risk of Osteosarcoma: a Systematic Review and Meta-Analysis. Asian Pacific journal of cancer prevention : APJCP. 2017;18(2):549-55.
28. Qi X, Wan Y, Zhan Q, Yang S, Wang Y, Cai X. Effect of CDKN2A/B rs4977756 polymorphism on glioma risk: a meta-analysis of 16 studies including 24077 participants. Mammalian genome : official journal of the International Mammalian Genome Society. 2016;27(1-2):1-7.
29. Mehdinejad M, Sobhan MR, Mazaheri M, Zare Shehneh M, Neamatzadeh H, Kalantar SM. Genetic Association between ERCC2, NBN, RAD51 Gene Variants and Osteosarcoma Risk: a Systematic Review and Meta-Analysis. Asian Pacific journal of cancer prevention : APJCP. 2017;18(5):1315-21.
30. Yang H, Gao Y, Feng T, Jin TB, Kang LL, Chen C. Meta-analysis of the rs4779584 polymorphism and colorectal cancer risk. PLoS One. 2014;9(2):e89736.