Int J Clin Exp Med 2016;9(2):2738-2747
www.ijcem.com /ISSN:1940-5901/IJCEM0017149

Original Article

Association between two common polymorphisms of TNF-α gene (-308 and -238) and the risk of head and neck carcinomas based on case-control studies

Xing Gao[1], Liwei Ma[2], Hongying Sun[3], Xinchun Jian[1]

[1]Department of Oral and Maxillofacial Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China; [2]Department of Oral Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China; [3]Department of Stomatology, Huashan Hospital, Fudan University, Shanghai, China

Received September 30, 2015; Accepted December 19, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Current data regarding association between TNF-α polymorphisms and the risk of head and neck squamous cell carcinomas (HNSCC) have shown controversial results. The current study aims to achieve a more accurate estimation of the association between TNF-α-308 and -238 gene polymorphisms and HNSCC susceptibility by a meta-analysis of all eligible studies. Methods: The meta-analysis was performed by reviewing ten studies on the TNF-α-308G/A polymorphism including 1833 HNSCC cases and 2542 controls and five studies on the TNF-α-238G/A polymorphism including 870 cases and 819 controls. Results: For TNF-α-308G/A polymorphism, a significant association was found under heterozygote model (AA vs. GA: OR = 2.48, 95% CI = 1.48-4.16, P<0.001; $P_{heterogeneity}$ = 0.68) in the overall analysis. Consistently, the subgroup analyses by tumor site, ethnicity and control source revealed that 308G/A polymorphism among heterozygote model was associated with HNSCC risk, especially in oral cancer (AA vs. GA: OR = 2.48, 95% CI = 1.30-4.73, P = 0.0006; $P_{heterogeneity}$ = 0.54) and Asians (AA vs. GA: OR = 3.50, 95% CI = 1.24-9.89, P = 0.02; $P_{heterogeneity}$ = 0.41). However, TNF-α-238G/A polymorphism were not found to be significantly associated with HNSCC risk in any genetic model. Conclusion: The findings of the meta-analysis indicated that an increased risk for the TNF-α-308G/A polymorphism was found in HNSCC, especially in oral cavity and Asian subgroup, suggesting that 308G/A polymorphism may be a genetic risk factor for HNSCC. However, 238G/A polymorphism were not observed to be associated with HNSCC risk. Further well-designed and large studies should be conducted to precluding the drawing of the conclusions.

Keywords: TNF-α, polymorphism, head and neck, oral cancer, meta-analysis

Introduction

Head and neck squamous cell carcinomas (HNSCC) including the oral cavity, pharynx, and larynx constitutes the sixth most common malignancy worldwide, and the etiology remains largely unknown [1]. Although increasing evidence suggests that environmental factors and chemical carcinogens, such as tobacco use and heavy alcohol consumption, are probable etiological factors contributing to HNSCC susceptibility, only a small fraction of individuals exposed to these carcinogens will develop HNSCC [2, 3]. HNSCC development is widely recognized as a stepwise process with involvement of a series of genetic alterations [4], and single-nucleotide polymorphisms (SNPs) for the associations between genomic regions and cancers in candidate genes offer a superior strategy for unravelling genetic complexity [5, 6].

Tumor necrosis factor alpha (TNF-α) gene, located on chromosome 6p21.231 in the polymorphic region of major histocompatibility complex, is one of the most important pro-inflammatory and tumour-related cytokines, which plays a pivotal role in the pathogenesis of a variety of inflammatory diseases and cancers for its regulating immune response [7]. TNF-α gene has different types of SNPs in the promoter regions, which can regulate the expression level of TNF-α gene. Commonly described variants of TNF-α gene SNPs consist of G to A transitions in the promoter region at positions -308G/A (rs1800629) and -238G/A (rs361525).

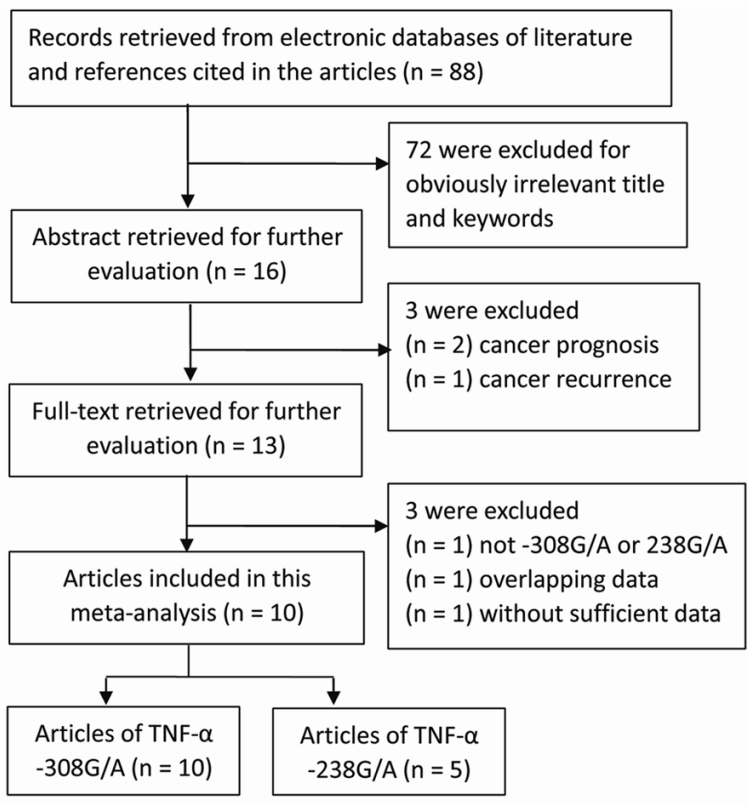

Figure 1. Flow diagram of the study selection process.

TNF-α A allele was found associated with higher constitutive and inducible TNF-α expression by affecting a consensus binding site of a transcription factor [8, 9]. The increased levels of TNF-α for a long duration can cause an uncontrolled infammation and have a significant harmful effect on the cells. TNF-α promoter -308G/A and -238G/A gene polymorphisms were found associated with the susceptibility to several types of cancers, including gastric, colorectal, prostate, and cervical cancers [10-13].

Thus far, several studies have been conducted in recent years to evaluate the association of TNF-α promoter -308G/A and -238G/A polymorphisms with HNSCC susceptibility [14-24]. However, the results remain inconclusive and controversial, partially because of the relatively small sample size of individual study and low statistical power of independent study. Meta-analysis allow stronger quantitative synthesis for identifying some models of genetic factors, which may aid in screening, early diagnosis and/or therapy in the clinic [4]. To the best of our knowledge, no previous meta-analysis was available on the association between TNF-α-308G/A and -238G/A SNPs and HNSCC susceptibility. Therefore, a meta-analysis was performed on all eligible case-control studies to derive a more precise estimation of the association, as well as to investigate the heterogeneity and potential bias.

Materials and methods

Literature search strategy

The electronic databases of PubMed, Embase, Medline, Web of Science, and China National Knowledge Infrastructure (CNKI) were searched for relevant publications to include in the meta-analysis, without any restriction on language and publication year (until 1 Sep 2015). The following search terms were used: ('tumor necrosis factor' OR 'TNF') AND ('polymorphisms' OR 'variants') AND ('cancer' OR 'carcinoma' OR "malignancy" OR "tumor" OR "tumour" OR "neoplasm") AND ('head and neck' or 'oral' or 'oropharyngeal' or 'laryngeal' or 'laryngopharyngeal' or 'hypopharyngeal'). The relevant articles were reviewed to evaluate their appropriateness for inclusion in the meta-analysis. Additional relevant publications were identified through the references cited in the retrieved articles or reviews on this topic.

Inclusion and exclusion criteria

The inclusion criteria for eligible articles were as follows: (i) human case-control studies; (ii) evaluation of TNF-α-308G/A and -238G/A polymorphism and HNSCC risk; (iii) available genotyping data for calculating odds ratio (OR) and 95% confidence interval (CI); and (iv) histologically confirmed diagnosis of HNSCC. Accordingly, the exclusion criteria were as follows: (i) not a case-control study; (ii) overlapping or duplicate publications; and (iii) no usable data reported.

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

First author, Year [ref]	Country	Ethnicity	Site	Control source	Genotyping	Sample size (n)		Matched factors
						Case	Control	
Chiu, 2001 [14]	Taiwan, China	Asian	Oral cavity	Hospital	PCR-RFLP	60	284	Age, areca-chewing
Liu, 2005 [15]	Taiwan, China	Asian	Oral cavity	Hospital	PCR-RFLP	192	146	Age, gender
Chen, 2005 [16]	Taiwan, China	Asian	Oral cavity	Population	PCR	137	102	NA
Gupta, 2007 [17]	India	Asian	Oral cavity	Population	PCR-RFLP	94	133	Age, gender
Yapijakis, 2009 [18]	Germany & Greece	Caucasian	Oral cavity	Hospital	PCR-RFLP	160	153	Age, gender
Kietthubthew, 2010 [19]	Thailand	Asian	Oral cavity	Population	PCR	107	157	Age, gender, smoking, alcohol drinking
Oh, 2010 [20]	USA	Caucasian	Mixed (larynx, oropharynx)	Population	PCR	281	849	Age, gender
Yang, 2011 [21]	Taiwan, China	Asian	Mixed (oral cavity, oropharynx, hypopharynx)	Hospital	PCR	205	198	Age, smoking, betel quid-chewing
Jin, 2013 [22]	USA	Caucasian	Oral cavity	Hospital	PCR-RFLP	325	335	Age, gender, smoking, and alcohol drinking
Singh, 2015 [23]	India	Asian	Oral cavity	Hospital	PCR-RFLP	272	185	Gender, alcohol drinking

PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism. NA, not available.

Table 2. Distribution of TNF-α genotype among cases and controls included in the meta-analysis

SNP (No. of case/control)	First author, Year	Case (n)					Control (n)					HWE of control
		GG	GA	AA	G	A	GG	GA	AA	G	A	
TNF-α-308	Chiu, 2001	47	12	1	106	14	232	50	2	514	54	0.69
(1833/2542)	Liu, 2005	175	16	1	366	18	120	24	2	264	28	0.53
	Chen, 2005	125	12	0	262	12	88	14	0	194	14	0.46
	Gupta, 2007	61	23	10	145	43	114	19	0	247	19	0.37
	Yapijakis, 2009	36	49	75	121	199	121	19	13	261	45	< 0.05
	Kietthubthew, 2010	83	14	NA	NA	NA	133	19	NA	NA	NA	NA
	Oh, 2010	215	58	8	484	74	641	195	13	1477	211	0.68
	Yang, 2011	180	23	2	383	27	155	43	0	353	43	0.09
	Jin, 2013	101	224	NA	NA	NA	138	207	NA	NA	NA	NA
	Singh, 2015	235	35	2	505	39	164	20	1	348	22	0.65
TNF-α-238	Liu, 2005	188	4	0	380	4	136	10	0	282	10	0.67
(870/818)	Gupta, 2007	94	0	0	188	0	133	0	0	266	0	< 0.05
	Kietthubthew, 2010	92	5	NA	NA	NA	141	11	NA	NA	NA	NA
	Yang, 2011	200	5	0	405	5	187	11	0	385	11	0.69
	Singh, 2015	252	20	0	524	20	180	5	0	365	5	0.53

HWE, Hardy-Weinberg, equilibrium. NA, not available.

Data extraction

According to the selection criteria, all relevant crude data were extracted from each eligible article independently by two researchers. Inconsistencies were discussed until a consensus was reached. The following information were extracted from each publication: first author' name, publication year, country origin, ethnicity, tumor site, source of control (hospital- or population-based control), genotyping methods, number of cancer cases and controls, characteristics ofcases and controls, genotype frequencies for cases and controls.

Statistic analysis

Hardy-Weinberg equilibrium (HWE) of control group in each study was measured using Pearson's goodness-of-fit x^2 test. The strength of association of TNF-α-308G/A and -238G/A polymorphisms with HNSCC susceptibility was determined by OR with 95% CI. In the overall and the subgroup meta-analysis, pooled ORs and 95% CIs of TNF-α both 308G/A and -238G/A were calculated from combination of each study by heterozygote model (AA vs. GA), homozygote model (AA vs. GG), dominant model (AA + GA vs. GG), and recessive model (AA vs. GA + GG). The allele comparison (A vs. G) was conducted as an additive mode. The statistical significance of the pooled OR was evaluated using the Z-test, and the heterogeneity of the ORs was tested by χ^2-based Q-test and I^2 statistics. If the result of heterogeneity test showed $P > 0.1$, ORs were pooled according to the fixed-effects model (Mantel-Haenszel model). Otherwise, the random-effects model (DerSimonian and Laird model) was selected. Additionally, the potential publication bias was examined by the Egger's test and Begg's funnel plot. The significance of the intercept was determined by the t test as suggested by Egger's test. For sensitivity analysis, each study was sequentially excluded and the summary ORs (95% CIs) were recalculated. All statistical analyses were performed with the software Review manager 5.0 (The Cochrane Collaboration, Oxford, UK) and STATA 12.0 (Stata Corporation, College Station, TX, USA), using two-sided *P* values.

Results

Characteristics of included studies

Of the 88 potentially relevant articles, 75 were excluded with reasons and 13 full-text articles were reviewed for detailed evaluation from the search of the published literature. During the data extraction according to the inclusion and exclusion criteria, one study by Vairaktaris et al [24] that was the overlapping data by the same authors' colleague was excluded; one study by Canova et al [25] that was not relevant to TNF-

Table 3. Summary of polled odds ratios (ORs) with 95% confidence interval (CI) of TNF-α-308 polymorphism and HNSCC risk in the meta-analysis

Group (No. of case/control)	Genotype	Test of association		Model	Test of heterogeneity	
		OR (95% CI)	*P*-value		I^2 (%)	*P*-value
Overall	AA vs. GA	**2.48 (1.48-4.16)**	< 0.001	Fixed	0	0.68
(1833/2542)	AA vs. GG	3.69 (0.98-13.89)	0.05	Random	78	< 0.05
	AA + GA vs. GG	1.32 (0.74-2.34)	0.35	Random	92	< 0.05
	AA vs. GA + GG	4.61 (0.79-27.05)	0.09	Random	87	< 0.05
	A vs. G	1.35 (0.63-2.92)	0.44	Random	95	< 0.05
Subgroup						
Oral SCC	AA vs. GA	**2.48 (1.30-4.73)**	0.006	Fixed	0	0.54
(1347/1495)	AA vs. GG	4.26 (0.74-24.59)	0.10	Random	74	< 0.05
	AA + GA vs. GG	1.56 (0.76-3.17)	0.22	Random	92	< 0.05
	AA vs. GA + GG	3.63 (0.89-14.89)	0.07	Random	61	< 0.05
	A vs. G	1.63 (0.58-4.55)	0.35	Random	95	< 0.05
Asian	AA vs. GA	**3.50 (1.24-9.89)**	0.02	Fixed	0	0.41
(1067/1205)	AA vs. GG	**3.81 (1.48-9.83)**	0.006	Fixed	44	0.13
	AA + GA vs. GG	0.97 (0.57-1.64)	0.90	Random	78	< 0.05
	AA vs. GA + GG	**3.76 (1.44-9.79)**	0.007	Fixed	39	0.16
	A vs. G	1.01 (0.54-1.90)	0.98	Random	85	< 0.05
Hospital-based case-control	AA vs. GA	**2.13 (1.10-4.13)**	0.03	Fixed	0	0.77
(1214/1301)	AA vs. GG	2.96 (0.51-17.16)	0.23	Random	74	< 0.05
	AA + GA vs. GG	1.38 (0.55-3.43)	0.49	Random	95	< 0.05
	AA vs. GA + GG	2.83 (0.74-10.78)	0.13	Random	56	0.06
	A vs. G	1.33 (0.39-4.56)	0.65	Random	96	< 0.05

Significant results are listed in bold.

α-308G/A and -238G/A polymorphism was excluded; and one study by Erdei et al [26] was excluded due to the control source being not healthy individuals. Consequently, ten eligible articles were identified in the final meta-analysis (**Figure 1**), and the characteristics of the eligible studies and detailed variant genotype distributions of TNF-α-308G/A and -238G/A are summarized in **Tables 1** and **2** respectively.

For TNF-α-308G/A polymorphism, ten eligible case-control studies including 1833 HNSCC cases and 2542 controls were identified. There was eight oral carcinoma study and two mixed HNSCC studies. Seven of the ten studies were conducted in Asians and three studies were conducted in Caucasians. There were six studies of hospital-based controls and four studies of population-based controls. For TNF-α-238G/A polymorphism, five eligible case-control studies including 870 HNSCC cases and 819 controls were identified. There was four oral carcinoma study and one mixed HNSCC studies. All five studies were conducted in Asians. There were three studies of hospital-based controls and two studies of population-based controls.

Quantitative assessment of TNF-α-308G/A SNP

The association of TNF-α-308G/A SNP with HNSCC risk were summarized in **Table 3**. In the overall analysis, a significant association was found in the heterozygote model (AA vs. GA: OR = 2.48, 95% CI = 1.48-4.16, *P*<0.001; $P_{\text{heterogeneity}}$ = 0.68). However, no significant associations were found in the other genetic model; homozygote (AA vs. GG: OR = 3.69, 95% CI = 1.48-4.16, *P* = 0.05), dominant (AA + GA vs. GG: OR = 1.32, 95% CI = 0.74-2.34, *P* = 0.35), recessive (AA vs. GA + GG: OR = 4.61, 95% CI = 0.79-27.05, *P* = 0.09) models, and allele comparison (A vs. G: OR = 1.35, 95% CI = 0.63-2.92, *P* = 0.44). In the stratified analysis by tumor site, a significant association was also found in oral cancer among heterozygote model (AA vs. GA: OR = 2.48, 95% CI = 1.30-4.73, *P* = 0.0006;

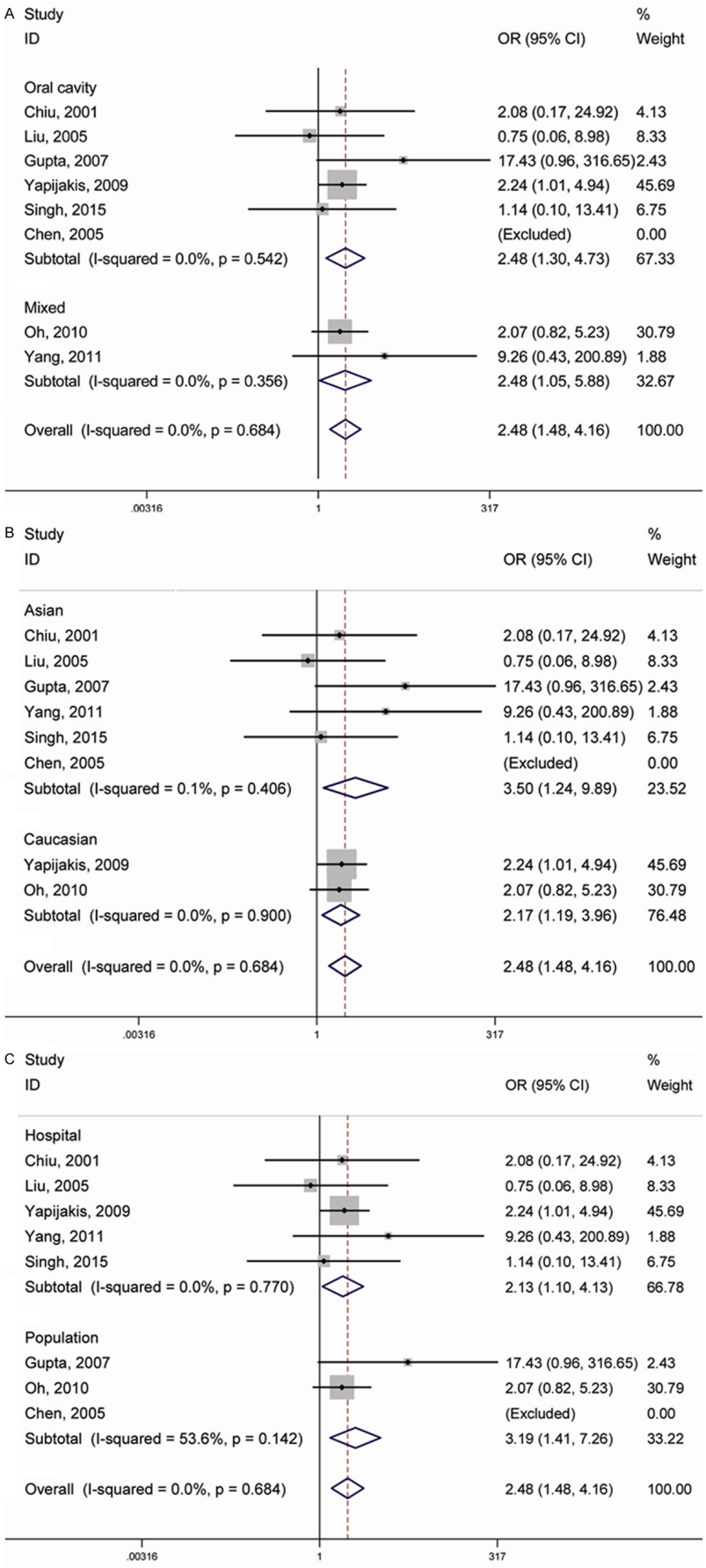
A
Study
ID
OR (95% CI)
%
Weight
Oral cavity
Chiu, 2001 2.08 (0.17, 24.92) 4.13
Liu, 2005 0.75 (0.06, 8.98) 8.33
Gupta, 2007 17.43 (0.96, 316.65) 2.43
Yapijakis, 2009 2.24 (1.01, 4.94) 45.69
Singh, 2015 1.14 (0.10, 13.41) 6.75
Chen, 2005 (Excluded) 0.00
Subtotal (I-squared = 0.0%, p = 0.542) 2.48 (1.30, 4.73) 67.33
Mixed
Oh, 2010 2.07 (0.82, 5.23) 30.79
Yang, 2011 9.26 (0.43, 200.89) 1.88
Subtotal (I-squared = 0.0%, p = 0.356) 2.48 (1.05, 5.88) 32.67
Overall (I-squared = 0.0%, p = 0.684) 2.48 (1.48, 4.16) 100.00
.00316
1
317
B
Study
ID
OR (95% CI)
%
Weight
Asian
Chiu, 2001 2.08 (0.17, 24.92) 4.13
Liu, 2005 0.75 (0.06, 8.98) 8.33
Gupta, 2007 17.43 (0.96, 316.65) 2.43
Yang, 2011 9.26 (0.43, 200.89) 1.88
Singh, 2015 1.14 (0.10, 13.41) 6.75
Chen, 2005 (Excluded) 0.00
Subtotal (I-squared = 0.1%, p = 0.406) 3.50 (1.24, 9.89) 23.52
Caucasian
Yapijakis, 2009 2.24 (1.01, 4.94) 45.69
Oh, 2010 2.07 (0.82, 5.23) 30.79
Subtotal (I-squared = 0.0%, p = 0.900) 2.17 (1.19, 3.96) 76.48
Overall (I-squared = 0.0%, p = 0.684) 2.48 (1.48, 4.16) 100.00
.00316
1
317
C
Study
ID
OR (95% CI)
%
Weight
Hospital
Chiu, 2001 2.08 (0.17, 24.92) 4.13
Liu, 2005 0.75 (0.06, 8.98) 8.33
Yapijakis, 2009 2.24 (1.01, 4.94) 45.69
Yang, 2011 9.26 (0.43, 200.89) 1.88
Singh, 2015 1.14 (0.10, 13.41) 6.75
Subtotal (I-squared = 0.0%, p = 0.770) 2.13 (1.10, 4.13) 66.78
Population
Gupta, 2007 17.43 (0.96, 316.65) 2.43
Oh, 2010 2.07 (0.82, 5.23) 30.79
Chen, 2005 (Excluded) 0.00
Subtotal (I-squared = 53.6%, p = 0.142) 3.19 (1.41, 7.26) 33.22
Overall (I-squared = 0.0%, p = 0.684) 2.48 (1.48, 4.16) 100.00
.00316
1
317

Figure 2. Forest plots of meta-analysis of TNF-α-308G/A polymorphism and head and neck cancer stratified by (A) tumor sites, (B) ethnicity and (C) control source in heterozygote model (CC vs. TC + TT).

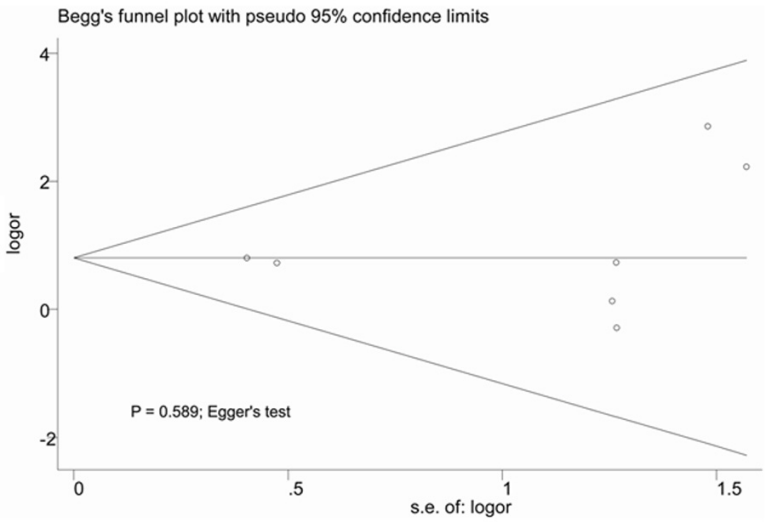

Figure 3. Begg's funnel plots of TNF-α-308G/A polymorphisms among heterozygote model. s.e. standard error; or, odds ratio.

$P_{heterogeneity}$ = 0.54), and no significant associations were also found in the other genetic model. Consistently, there was evidence for the association between TNF-α-308G/A SNP and HNSCC risk in the stratified analysis based on source of controls in the heterozygote model (AA vs. GA: OR = 2.13, 95% CI = 1.10-4.13, *P* = 0.03; $P_{heterogeneity}$ = 0.77). In the stratified analysis by ethnicity, significant associations were observed in Asians among three models; heterozygote model (AA vs. GA: OR = 3.50, 95% CI = 1.24-9.89, *P* = 0.02), homozygote (AA vs. GG: OR = 3.81, 95% CI = 1.48-9.83, *P* = 0.006), and recessive (AA vs. GA + GG: OR = 3.76, 95% CI = 1.44-9.79, *P* = 0.007) models. Forest plots for meta-analysis of these three stratified analyses in the significant heterozygote genetic model were shown in **Figure 2**. Because there was only two available studies of mixed HNSCC sites, two Caucasian studies, two studies of population-based controls, the stratified analyses were not emphasized in this study (**Figure 2**).

Quantitative assessment of TNF-α-238G/A SNP

The overall analysis of TNF-α-238G/A SNP and HNSCC risk revealed that no significant associations were found in the dominant model (AA + GA vs. GG: OR = 0.72, 95% CI = 0.26-1.99, *P* = 0.53; I^2 = 71, $P_{heterogeneity}$ = 0.01) and allele comparison (A vs. G: OR = 0.73, 95% CI = 0.18-2.95, *P* = 0.65; I^2 = 80, $P_{heterogeneity}$ = 0.006). Subgroup analyses were not performed due to the small number of studies. Although there were five eligible case-control studies on TNF-α-238G/A polymorphism, AA genotype was not identified in the five studies (**Table 2**). Thus, heterozygote model (AA vs. GA), homozygote model (AA vs. GG), and recessive model (AA vs. GA + GG) were not estimated.

Sensitivity analysis

A leave-one-out sensitivity analysis was performed by sequential removal of individual study. For TNF-α-308G/A polymorphism, the *P* values and corresponding pooled ORs with 95% CI were not significantly changed after the sequential removal of individual studies. In the heterozygote model (AA vs. GA) of TNF-α-308G/A, *P* values ranged from 0.0003 to 0.007 and ORs ranged from 2.11 to 2.69. ORs under heterozygote comparison stayed statistically significant. For TNF-α-238G/A polymorphism, sensitivity analysis was not performed due to the small number of studies included.

Publication bias

No evidence for publication bias was detected by either the Begg's test or the Egger's test for the genetic models of TNF-α-308G/A polymorphisms (*P* > 0.05). **Figure 3** showed that the representative shapes of funnel plots did not reveal any evidence of obvious asymmetry with Begg's test (*P* = 0.764) and Egger's test (*P* = 0.589) in heterozygote model of TNF-α-308G/A. Publication bias investigation was also not performed for TNF-α 238G/A due to the small number of studies included.

Discussion

An association between chronic inflammation and head and neck cancer with emphasis on oral cancer has been basically addressed [27,

28]. Patients with chronic inflammatory diseases such as oral lichen planus and discoid lupus erythematosus carry a significantly increased risk of developing cancer [29]. Host genetic factors are emerging as key determinants of disease for head and neck cancer [4], as genetic variations in pro-inflammatory and anti-inflammatory cytokine genes influence individual response to carcinogenic exposures. TNF-α is one of the most important pro-inflammatory cytokines involved in cell growth, differentiation, and apoptosis, which has been reported to play a vital role in the oral carcinogenesis [30]. As transcription of TNF-α is regulated by the promoter region of TNF-α gene polymorphisms, two well-characterised variations in the promoter region of the TNF-α gene, namely, -308G/A and -238G/A, were identified and extensively studied in cancer susceptibility [10-13].

To the best of our knowledge, this meta-analysis conducted for the first time all the available data on the association between TNF-α-308G/A and -238G/A polymorphisms and HNSCC risk. A meta-analysis with larger sample and subgroup analysis is better to estimate the association between these polymorphisms and HNSCC risk. For TNF-α-308G/A polymorphism, ten eligible studies involving 1833 HNSCC cases and 2542 controls were included in this meta-analysis. The results demonstrated that the TNF-α-308G/A polymorphism was significantly associated with HNSCC risk under heterozygote comparison. For TNF-α-238G/A polymorphism, five eligible case-control studies including 870 HNSCC cases and 819 controls were identified. The results demonstrated that the TNF-α-238G/A polymorphism was not significantly associated with HNSCC risk.

The 308G/A is the most commonly studied SNP site of TNF-α promoter region. Our study revealed that 308G/A polymorphism was associated with an increased risk of HNSCC, in accordance with the previous meta-analysis of other cancers, such as gastric, colorectal, prostate, cervical cancers [10-13]. TNF-α-308 gene polymorphism plays a vital role as host genetic factor predisposing to head and neck carcinogenesis and it could be used as a screening marker. Our data showed that no significant association between TNF-α-238G/A polymorphism and HNSCC risk was found in all genetic models, in line with the previous several meta-analyses [10-12].

A significant association is found overall analysis, meta-analysis can estimate whether the association is common among different subgroups. Subgroup analysis was performed of TNF-α-308G/A polymorphism according to tumor site, ethnicity and control source. In the subgroup analysis by tumor site, the significantly increased risk of HNSCC in oral cavity and mixed sites were observed among the 308G/A heterozygote. In the analysis of control source, the increased risk of HNSCC in hospital-based and population-based controls were observed among the 308G/A heterozygote. The results of two subgroup analyses were in agreement with that of overall analysis. In the analysis of ethnicity, significant associations in Asians were found in the heterozygote model, homozygote, and recessive models. These data suggested that TNF-α-308G/A polymorphism may be a genetic risk factor for HNSCC, though the functional explanation for such these associations remains undetermined. Moreover, the involvement of TNF-α-308G/A in HNSCC susceptibility may interact with other genes polymorphisms and with some particular environmental exposures.

Despite the efforts in performing a comprehensive analysis, some limitations need to be addressed in the current meta-analysis and the results should be considered with caution. First, the number of eligible studies available and the pooled sample size of individual studies were not adequate in both overall and stratified analyses, especially Caucasian studies and population-based studies; and it is possible that some relevant unpublished studies were missed. Second, the effect of the confounding ingredients in gene-environment exposures and life habits interactions such as environmental factors, and tobacco and alcohol use, were not estimated in the current study due to data available limitation. Therefore, to obtain a more accurate analysis of TNF-α polymorphisms on HNSCC risk, more well-designed studies with larger sample sizes and diverse ethnicities are warranted to validate our findings.

Regardless of these limitations, the current meta-analysis also has some strength. First, a systematic review of the association of the TNF-α polymorphisms with the HNSCC risk is statistically more powerful than any individual study. Secondly, the quality of eligible studies

included in the current meta-analysis was satisfactory without evidence of publication bias for the outcome and without obvious heterogeneity in the significant genetic models. Thirdly, sensitivity analysis was performed to reflect the influence of the individual dataset to the pooled ORs, and conducted to validate the credibility of outcomes in this meta-analysis. These strengths suggest that the associations between TNF-α polymorphisms and HNSCC risk of this meta-analysis are robust.

In summary, the current meta-analysis provided a more accurate estimation of the association between the TNF-α polymorphisms and HNSCC risk compared with independent studies. The findings of the meta-analysis indicated that an increased risk for the TNF-α-308G/A polymorphism was found in HNSCC, especially in oral cavity and Asian subgroup, suggesting that 308G/A polymorphism may be a genetic risk factor for HNSCC. However, 238G/A polymorphism were not observed to be associated with HNSCC risk. Further well-designed and large studies should be conducted to precluding the drawing of the conclusions.

Acknowledgements

This study was supported by National Natural Science Foundation of China (81470736, 81260166).

Disclosure of conflict of interest

None.

Address correspondence to: Xinchun Jian, Department of Oral and Maxillofacial Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China. E-mail: jianxinchun@hotmail.com; Hongying Sun, Department of Stomatology, Huashan Hospital, Fudan University, Shanghai, China. E-mail: liuweb@hotmail.com

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62: 10-29.

[2] Marron M, Boffetta P, Zhang ZF, Zaridze D, Wunsch-Filho V, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Smith E, Schwartz SM, Rudnai P, Purdue MP, Olshan AF, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, McClean M, Matos E, Mates IN, Lissowska J, Levi F, Lazarus P, La Vecchia C,Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Cadoni G, Chen C, Castellsague X,Boccia S, Benhamou S, Ferro G, Berthiller J, Brennan P, Møller H, Hashibe M. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol 2010; 39: 182-96.

[3] Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011; 11: 9-22.

[4] Lacko M, Braakhuis BJ, Sturgis EM, Boedeker CC, Suárez C, Rinaldo A, Ferlito A, Takes RP. Genetic susceptibility to head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2014; 89: 38-48.

[5] Chen SS, Song J, Tu XY, Zhao JH, Ye XQ. The association between MMP-12 82 A/G polymorphism and susceptibility to various malignant tumors: a meta-analysis. Int J Clin Exp Med 2015; 8: 10845-54.

[6] Zhang K, Gao L, Wu Y, Chen J, Lin C, Liang S, Su J, Ye J, He X. NAT1 polymorphisms and cancer risk: a systematic review and meta-analysis. Int J Clin Exp Med 2015; 8: 9177-91.

[7] Watts TH. TNF/TNFR family members in costimulation of T cell responses. Annu Rev Immunol 2005; 23: 23-68.

[8] Kroeger KM, Carville KS, Abraham LJ. The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. Mol Immunol 1997; 34: 391-9.

[9] Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 1997; 94: 3195-9.

[10] Rokkas T, Sechopoulos P, Pistiolas D, Kothonas F, Margantinis G, Koukoulis G. Population differences concerning TNF-α gene polymorphisms in gastric carcinogenesis based on meta-analysis. Ann Gastroenterol 2014; 27: 139-148.

[11] Min L, Chen D, Qu L, Shou C. Tumor necrosis factor-a polymorphisms and colorectal cancer risk: a meta-analysis. PLoS One 2014; 9: e85187.

[12] Ma L, Zhao J, Li T, He Y, Wang J, Xie L, Qin X, Li S. Association between tumor necrosis factor-alpha gene polymorphisms and prostate cancer risk: a meta-analysis. Diagn Pathol 2014; 9: 74.

[13] Jin Y. Association of single nucleotide polymorphisms in tumor necrosis factor-alpha with cervical cancer susceptibility. Cell Biochem Biophys 2015; 71: 77-84.

[14] Chiu CJ, Chiang CP, Chang ML, Chen HM, Hahn LJ, Hsieh LL, Kuo YS, Chen CJ. Association between genetic polymorphism of tumor necrosis

factor-alpha and risk of oral submucous fibrosis, a pre-cancerous condition of oral cancer. J Dent Res 2001; 80: 2055-9.

[15] Liu CJ, Wong YK, Chang KW, Chang HC, Liu HF, Lee YJ. Tumor necrosis factor-α promoter polymorphism is associated with susceptibility to oral squamous cell carcinoma. J Oral Pathol Med 2005; 34: 608-12.

[16] Chen WC, Tsai MH, Wan L, Chen WC, Tsai CH, Tsai FJ. CYP17 and tumor necrosis factor-a gene polymorphisms are associated with risk of oral cancer in Chinese patients in Taiwan. Acta OtoLaryngologica 2005; 125: 96-9.

[17] Gupta R, Sharma SC, Das SN. Association of TNF-α and TNFR1 promoters and 30 UTR region of TNFR2 gene polymorphisms with genetic susceptibility to tobacco-related oral carcinoma in Asian Indians. Oral Oncol 2008; 44: 455-63.

[18] Yapijakis C, Serefoglou Z, Vylliotis A, Nkenke E, Derka S, Vassiliou S, Avgoustidis D, Neukam FW, Patsouris E, Vairaktaris E. Association of Polymorphisms in Tumor Necrosis Factor Alpha and Beta Genes with Increased Risk for Oral Cancer. Anticancer Res 2009; 29: 2379-86.

[19] Kietthubthew S, Wickliffe J, Sriplung H, Ishida T, Chonmaitree T, Au WW. Association of polymorphisms in proinflammatory cytokine genes with the development of oral cancer in Southern Thailand. Int J Hyg Environ Health 2010; 213: 146-52.

[20] Oh SS, Chang SC, Cai L, Cordon-Cardo C, Ding BG, Greenland S, He N, Jiang Q, Kheifets L, Le A, Lee YC, Liu S, Lu ML, Mao JT, Morgenstern H, Mu LN,Pantuck A, Papp JC, Park SL, Rao JY, Reuter VE, Tashkin DP, Wang H, You NC, Yu SZ, Zhao JK, Belldegrun A, Zhang ZF. Single nucleotide polymorphisms of 8 inflammation-related genes and their associations with smoking-related cancers. Int J Cancer 2010; 127: 2169-82.

[21] Yang CM, Hou YY, Chiu YT, Chen HC, Chu ST, Chi CC, Hsiao M, Lee CY, Hsieh CJ, Lin YC, Hsieh YD, Ger LP. Interaction between tumor necrosis factor-α gene polymorphisms and substance use on risk of betel quid-related oral and pharyngeal squamous cell carcinoma in Taiwan. Arch Oral Biol 2011; 56: 1162-9.

[22] Jin L, Sturgis EM, Zhang Y, Huang Z, Song X, Li C, Wei Q, Li G. Association of tumor necrosis factor-alpha promoter variants with risk of HPV-associated oral squamous cell carcinoma. Mol Cancer 2013; 12: 80.

[23] Singh PK, Bogra J, Chandra G, Ahmad MK, Gupta R, Kumar V, Jain A, Ali Mahdi A. Association of TNF-α (-238 and -308) promoter polymorphisms with susceptibilityof oral squamous cell carcinoma in North Indian population. Cancer Biomark 2015; 15: 125-31.

[24] Vairaktaris E, Yapijakis C, Serefoglou Z, Avgoustidis D, Critselis E, Spyridonidou S, Vylliotis A, Derka S, Vassiliou S, Nkenke E, Patsouris E. Gene expression polymorphisms of interleukins-1 beta, -4, -6, -8, -10, and tumor necrosis factors-alpha, -beta: regression analysis of their effect upon oral squamous cell carcinoma. J Cancer Res Clin Oncol 2008; 134: 821-32.

[25] Canova C, Hashibe M, Simonato L, Nelis M, Metspalu A, Lagiou P, Trichopoulos D, Ahrens W, Pigeot I, Merletti F, Richiardi L, Talamini R, Barzan L, Macfarlane GJ, Macfarlane TV, Holcátová I, Bencko V, Benhamou S, Bouchardy C, Kjaerheim K, Lowry R, Agudo A, Castellsagué X, Conway DI, McKinney PA,Znaor A, McCartan BE, Healy CM, Marron M, Brennan P. Genetic associations of 115 polymorphisms with cancers of the upper aerodigestive tract across 10 European countries: the ARCAGE project. Cancer Res 2009; 69: 2956-65.

[26] Erdei E, Luo L, Sheng H, Maestas E, White KA, Mackey A, Dong Y, Berwick M, Morse DE. Cytokines and tumor metastasis gene variants in oral cancer and precancer in Puerto Rico. PLoS One 2013; 8: e79187.

[27] Bonomi M, Patsias A, Posner M, Sikora A. The role of inflammation in head and neck cancer. Adv Exp Med Biol 2014; 816: 107-27.

[28] Wang F, Arun P, Friedman J, Chen Z, Van Waes C. Current and potential inflammation targeted therapies in head and neck cancer. Curr Opin Pharmacol 2009; 9: 389-95.

[29] Feller L, Altini M, Lemmer J. Inflammation in the context of oral cancer. Oral Oncol 2013; 49: 887-92.

[30] Piva MR, DE Souza LB, Martins-Filho PR, Nonaka CF, DE Santana Santos T, DE Souza Andrade ES, Piva D. Role of inflammation in oral carcinogenesis (Part II): CD8, FOXP3, TNF-α, TGF-β and NF-κB expression. Oncol Lett 2013; 5: 1909-1914.