Association Between Head and Neck Cancers and Polymorphisms 869T/C, 509C/T, and 915G/C of the Transforming Growth Factor-β1 Gene: A Meta-Analysis of Case-Control Studies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE 1 **Yanli Qu**
CF 2 **Jilong Feng**
BD 2 **Lijun Wang**
AE 1 **Huan Wang**
CD 1 **Hangyu Liu**
BF 1 **Xiaohu Sun**
AD 1 **Ji Li**
ADG 1 **Hong Yu**

1 Department of Radiation Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning, P.R. China
2 Department of Radiation Oncology, Fifth Peoples' Hospital of Shenyang, Shenyang, Liaoning, P.R. China

Corresponding Author: Hong Yu, e-mail: 2328901858@qq.com
Source of support: Liaoning Provincial Natural Science Foundation (No. 20180550537). Expression of PD-1 and PD-L1 Immunologic Markers in Predicting the Efficacy of Radiotherapy for Non-Small Cell Lung Cancer; Liaoning Provincial Doctor Launch Fund (No. 201601414). Association of Cytokine Gene Polymorphism with Radiosensitivity and Prognosis in Nasopharyngeal Carcinoma; Liaoning Provincial Natural Science Foundation (No. 1553581931102). Relationship between LAIR1 Gene Expression and Radiosensitivity and Prognosis in Non-Small Cell Lung Cancer

Background: Worldwide, head and neck cancers are the eighth most common malignancy. Single nucleotide polymorphisms (SNPs) are associated with susceptibility to cancer and sensitivity to radiotherapy and chemotherapy. The inflammatory cytokine, transforming growth factor-β1 (TGF-β1), is involved in the progression of malignancy. This study aimed to systematically review the literature and undertake a meta-analysis of case-control studies on the association between 869T/C, 509C/T, and 915G/C polymorphisms of the TGF-β1 gene and head and neck cancers.

Material/Methods: The published literature in the English and Chinese languages were searched to identify relevant studies reporting TGF-β1 gene polymorphisms and head and neck cancer. The PubMed, Embase, Wanfang Data, and CNKI databases were searched. Data were extracted from eligible studies, and meta-analysis was performed using Stata version 12.0 software.

Results: Ten case-control studies were identified. There was a significant association between the 869T/C polymorphism of the TGF-β1 gene and susceptibility to head and neck cancer. Subgroup analysis showed that the 869T/C polymorphism was not significantly associated with the histological type of head and neck cancer, but was significantly associated with susceptibility to head and neck cancer in the Asian population. The 509C/T polymorphism of the TGF-β1 gene was not significantly associated with susceptibility to nasopharyngeal cancer (NPC), but the 915G/C polymorphism was associated with susceptibility to oral cancer.

Conclusions: Data from this meta-analysis showed that the 869T/C and 915G/C polymorphisms of the TGF-β1 gene might be associated with susceptibility to head and neck cancer.

MeSH Keywords: **Head and Neck Neoplasms • Meta-Analysis • Transforming Growth Factor beta**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917506

📄 3287   ▦ 4   📊 9   📑 51

Background

Worldwide, the group of head and neck cancers are the eighth most common cancers and comprise between 5–10% of all cancers [1]. There are an estimated 834,860 new cases worldwide, with approximately 431,131 annual deaths from head and neck cancer [1]. More than 90% of head and neck cancers are squamous cell carcinoma, or head and neck squamous cell carcinoma (HNSCC), which has the eighth highest mortality rate of all cancers [2,3]. Exposure to tobacco, excessive alcohol consumption, infection with Epstein-Barr virus (EBV) or human papillomavirus (HPV), and environmental exposure to carcinogens are the main causes of head and neck cancer. However, the risk of developing head and neck cancer varies even in populations with the same exposure to carcinogens, which might be explained by genetic susceptibility [4,5]

Single nucleotide polymorphisms (SNPs) account for the majority of genetic mutations and are an important genetic cause for differences in cancer predisposition, sensitivity to radiotherapy and chemotherapy, and survival in cancer patients. These potential functions of SNPs in influencing cancer susceptibility, chemotherapy resistance, and therapeutic efficacy have been validated in several studies [6,7]. A previously reported study analyzed more than 200 publications that reported the gene polymorphisms that influenced the risk of developing HNSCC [8]. The genetic polymorphisms of HNSCC can be classified into several groups according to the biological functions of genes they regulate [8]. Polymorphisms have been reported to involve genes involved in biotransformation and detoxification enzymes (ADH) [9,10], the DNA repair pathway (XRCC1) [11], the apoptosis pathway (PUMA) [11], HPV-related HNSCC pathways [12], mitochondrial DNA (np16362 [T/C] mtDNA) [13], the bilirubin-related pathway (UGT1A1) [14] and E2F transcription factors [15].

Infection with HPV and EBV are risk factors for HNSCC. Transforming growth factor-β1 (TGF-β1) has an important role in inflammation and the immune responses that control the clearance of HPV and its escape from immune surveillance. The TGF-β1 T869C variant genotype has been reported to be significantly associated with HPV16-positive oropharyngeal cancer, but no significant association has been reported for the C509T or G915C polymorphisms of the TGF-β1 gene [12]. Activation of the TGF-β1 gene is increased in patients with EBV-positive nasopharyngeal carcinoma (NPC) when compared with healthy EBV-seropositive individuals [16]. Previous studies have shown that TGF-β1 levels increase during EBV infection, and TGF-β1 levels in patients with NPC significantly decrease at the end of the treatment [17]. Inflammation has been considered as an important factor in the pathogenesis of human cancers [18], including oral cancers [19]. Expression levels of inflammatory factors and genes that encode inflammatory cytokines may reflect tumor progression [20].

TGF-β1 is an inflammatory cytokine that inhibits cell proliferation and induces apoptosis in the early stages of neoplasia. The TGF-β1 gene is upregulated, and serum levels of TGF-β1 are increased in colon cancer [21,22], prostate cancer [23], and lung cancer [24]. Genetic variations in the promoter region of the TGF-β1 gene may affect transcription and protein synthesis. The functions of TGF-β1 are inhibited during the late stages of cancer due to the inactivation of tumor suppressor gene P53 and alterations in the TGF-β1 signaling pathway, resulting in tumor cell invasion and metastasis [25–27]. Previous studies have reported an association between polymorphisms of the TGF-β1 gene and carcinogenesis in NPC [28], lung cancer [29], esophageal cancer [30], prostate cancer [31], colon cancer [32], and gastric cancer [33]. TGF-β1 gene polymorphisms have been reported to be associated with the occurrence and progression of HNSCC [34]. Therefore, this study aimed to systematically review the literature and undertake a meta-analysis of case-control studies on the 869T/C, 509C/T, and 915G/C polymorphisms of the TGF-β1 gene and their associations with head and neck cancer.

Material and Methods

Search strategies

The databases searched included PubMed, Embase, Wanfang Data, and CNKI, up to 31st October 2018. The literature search terms included TGF-β1 gene polymorphisms, TGF, transforming growth factor, head and neck cancer, oral cancer, nasopharyngeal cancer, laryngeal cancer, hypopharyngeal cancer, and oropharyngeal cancer. The publications that were identified had their references manually checked.

Inclusion and exclusion criteria

The inclusion criteria were case-control studies that investigated the relationship between the TGF-β1 gene polymorphisms, 869T/C, 509C/T, and 915G/C, and predisposition to head and neck cancer. Published studies were identified that were in the English or Chinese language, and that provided the odds ratio (OR) and 95% confidence interval (CI). The exclusion criteria were studies that lacked a control group, duplicate publications, and studies with incomplete or insufficient data.

Data retrieval

Data were extracted from the identified publications by two independent researchers. The data recorded included the authors, year of publication, country of origin of the data, race or ethnicity of the patients, type of cancer, and the numbers of each polymorphism in the patient and case-control groups.

Statistical analysis

The heterogeneity test (I^2 test) was performed on the included studies. If the studies were homogenous, the data were combined and analyzed with a fixed-effects model. Otherwise, a random-effects model was used. The ORs and 95% CIs for the combined data analysis were calculated and processed for the sensitivity analysis. Egger's test was used to evaluate publication bias. Stata version 12.0 software (StataCorp, College Station, TX, USA) was used to analyze the data. The significance level of the tests was α=0.05.

Results

Results of the literature retrieval and the basic characteristics of the studies

A total of 124 studies were retrieved by searching for the keywords. Following the exclusion of studies that did not meet the inclusion criteria, ten case-control studies underwent meta-analysis [28,35–43]. The publication screening process is shown in Figure 1. The basic patient characteristics and the transforming growth factor-β1 TGF-β1 genotype distributions for the 869T/C rs1800470, 509C/T rs1800469, and 915G/C rs1800471 polymorphisms in the studies are shown in Table 1.

There were eight studies that reported an association with the 869T/C polymorphism of the TGF-β1 gene, including 1,607 patient cases and 1,981 control cases. The patient cases included 1,363 cases of nasopharyngeal carcinoma (NPC), 244 cases of oropharyngeal cancer, 1,675 control cases for NPC, and 306 control cases for oropharyngeal cancer. Fives studies reported the association with the TGF-β1 gene 509C/T polymorphism, including four studies of NPC and one study of oropharyngeal cancer, involving 1,355 patient cases and 1,579 control cases. Among these data, there were 1,207 cases of NPC and 1,424 controls. The study sample size ranged from 42 to 158 in the three studies that reported an association with the TGF-β1 gene 915G/C polymorphism, involving 340 cases of patients with cancer and 368 controls. Cases of oropharyngeal cancer were reported in three studies.

Correlation between the 869T/C polymorphism of the TGF-β1 gene and susceptibility to head and neck cancer

We analyzed each genotype generated by the 869T/C polymorphism of the TGF-β1 gene (Tables 2, 3, Figure 2), and no differences were found. The allele comparison (C *vs.* T) showed: OR=1.141; 95% CI, 0.927–1.406; P=0.213. The results for the dominant gene analysis (TC+CC *vs.* TT) were: OR=1.179; 95% CI, 0.925–1.521; P=0.203. The results for the recessive gene analysis (CC *vs.* TT+TC) were: OR=1.209; 95% CI, 0.857–1.705; P=0.28.
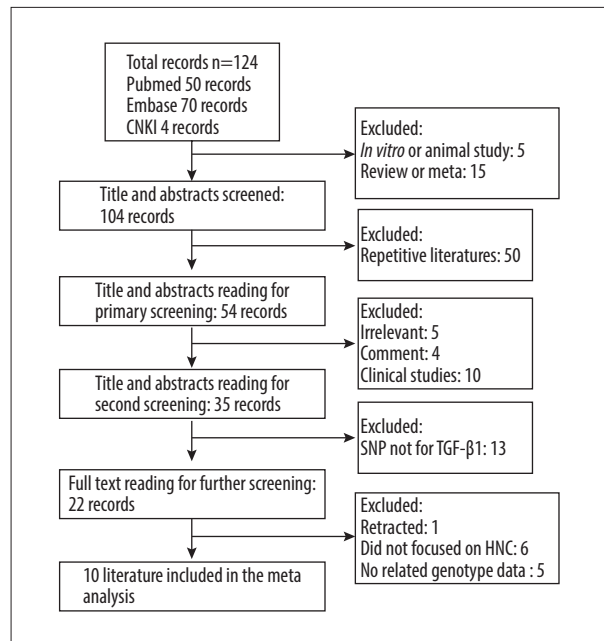
Figure 1. The review of the literature and findings.

The results for the homologous gene analysis (CC *vs.* TT) were: OR=1.298; 95% CI, 0.859–1.962; P=0.216. However, analysis of all combined data showed a significant correlation between the 869T/C polymorphism of the TGF-β1 gene and susceptibility to head and neck cancer (OR=1.181; 95% CI, 1.035–1.348; P=0.014).

Subgroup analysis

We conducted a subgroup analysis to include the different subtypes of head and neck cancer, different races, and different sample sizes. Only NPC and oropharyngeal cancer were identified in the studies selected. No significant differences were found between any two different genotypes for these two disease subtypes (P=0.131 and P=0.103, respectively).

The results for the allele and dominant gene analysis in the Asian population (C *vs.* T) were: OR=1.321; 95% CI, 0.974–1.93; P=0.074. For (TC+CC *vs.* TT) the findings were: OR=1.418; 95% CI, 0.921–2.184; P=0.112. The results for the recessive gene and homologous genotypes (CC *vs.* TT+TC) were: OR=1.564; 95% CI, 0.983–2.490; P=0.059. For CC *vs.* TT the findings were: OR 1.844; 95% CI, 0.920–3.497; P=0.061.

No significant differences were found in the subgroup analysis of each genotype in Asian populations, but the general analysis showed a significant difference (OR=1.431; 95% CI, 1.191–1.720; P=0.000) (Figure 3). No differences were also found between analyses for any of the genotypes or by the general analysis in non-Asian populations (P=0.320). A subgroup analysis based on sample size showed that for the

Table 1. Basic characteristics and the genotype distributions of TGF-β1 in the selected studies.

Gene	Author	Year	Country	Cancer type	Number	Case TT	Case TC	Case CC	Control TT	Control TC	Control CC	P(hwe)
869T/C	Yanli Qu	2016	China	NPC	193/231	51	75	36	65	114	52	0.88
869T/C	Ye-Sheng Wei	2007	China	NPC	108/120	16	49	43	30	61	29	0.85
869T/C	Sunhong Hu	2012	China	NPC	522/712	129	266	127	187	354	171	0.89
869T/C	Wafa Khaali	2016	Morocco	NPC	384/361	132	165	64	119	149	67	0.10
869T/C	N.K Carneiro	2013	Brazil	Oral	62/62	22	29	11	20	19	23	0.79
869T/C	Poonam Gaur	2011	India	Oral	140/120	51	58	31	70	39	11	0.21
869T/C	Khaled S.	2011	SaudiArabia	NPC	156/251	51	67	38	83	120	48	0.69
869T/C	Han-Jan Hsu	2014	Taiwan	Oralprecancer	42/124	1	37	4	8	113	3	0.000

Gene	Author	Year	Country	Cancer type	Number	Case CC	Case TC	Case TT	Control CC	Control TC	Control TT	P(hwe)
509C/T	Yanli Qu	2016	China	NPC	193/231	62	116	53	121	83	39	0.84
509C/T	Ye-Sheng Wei	2007	China	NPC	108/120	17	46	45	29	60	31	0.99
509C/T	Sunhong Hu	2012	China	NPC	522/712	208	224	80	203	337	172	0.16
509C/T	Wafa Khaali	2016	Morocco	NPC	384/361	127	153	44	120	148	56	0.37
509C/T	Esther Erdei	2013	America	Oral	148/155	73	54	21	76	57	22	0.04

Gene	Author	Year	Country	Cancer type	Number	Case GG	Case GC	Case CC	Control GG	Control GC	Control CC	P(hwe)
915G/C	Poonam Gaur	2011	India	Oral	140/120	55	58	27	59	44	17	0.080
915G/C	Han-Jan Hsu	2014	Taiwan	Oralprecancer	42/124	25	17	0	115	8	1	0.06
915G/C	Han-Jan Hsu	2014	Taiwan	Oral	158/124	84	74	0	115	8	1	0.06

subgroup with sample size >100, the results for the allele and dominant genotype analyses (C *vs.* T) were: OR=1.203; 95% CI, 0.959–1.510; P=0.110). For (TC+CC *vs.* TT) the findings were: OR=1.202; 95% CI, 0.908–1.591; P=0.199. The results for the recessive genotype and homologous genotype analyses (CC *vs.* TT+TC) were: OR=1.266; 95% CI, 0.933–1.718; P=0.129. The findings for CC *vs.* TT were: OR=1.369; 95% CI, 0.918–2.043; P=0.124. Similar to the results based on patient race, no differences were found between the different genotypes, but the general analysis obtained a significant difference overall (OR=1.230; 95% CI, 1.078–1.404; P=0.002) (Figure 4).

The relationship between TGF-β1 gene polymorphisms and NPC

Only one-fifth of cases of head and neck cancer were oropharyngeal cancer in the studies that we selected. To avoid selection bias, we analyzed the relationship between TGF-β1 gene polymorphisms and susceptibility to NPC (Figure 5). The results showed that TGF-β1 gene polymorphisms were not correlated with NPC. The previous general analysis results showed that polymorphisms at this site were correlated with patient race and sample size. Therefore, we conducted a racial subgroup analysis on the cases of NPC (Table 4).

The results for each genotype in the Asian populations included the allele analysis (C *vs.* T) (OR=1.139; 95% CI, 0.857–1.512; P=0.370) and the dominant gene analysis (TC+CC *vs.* TT) (OR=1.118; 95% CI, 0.792–1.577; P=0.527). The results for the recessive gene analysis (CC *vs.* TT+TC) were (OR 1.212; 95% CI, 0.810–1.813; P=0.350) and for the homologous gene analysis (CC *vs.* TT) were (OR 1.276; 95% CI, 0.742–2.180; P=0.371).

The results for each genotype in the non-Asian populations included the allele analysis (C *vs.* T) (OR=0.997; 95% CI, 0.840–1.184; P=0.977) and the dominant gene analysis

Table 2. Results of the meta-analysis for the association between TGF-β1 gene polymorphisms and head and neck cancers.

869T/C	N	Sample size Case/control	C vs. T OR (95% CL)	Pb	Pc	I²%	TC+CC vs. TT OR (95% CL)	Pb	Pc	I²%
Total	8	1607/1981	1.141 [0.927–1.406]	0.213	0.000	74.3	1.179 [0.915–1.521]	0.203	0.028	55.5
Type of cancer										
NPC	5	1363/1675	1.071 [0.912–1.257]	0.404	0.079	52.2	1.039 [0.875–1.235]	0.660	0.359	8.3
Oral	3	244/306	1.222 [0.590–2.528]	0.590	0.000	86.9	1.648 [0.720–3.773]	0.237	0.070	62.4
Ethnicities										
Asian	5	761/1001	1.321 [0.974–1.793]	0.074	0.001	79.4	1.418 [0.921–2.184]	0.112	0.011	69.4
Caucasian	3	602/674	0.931 [0.729–1.190]	0.568	0.149	47.5	0.965 [0.761–1.223]	0.767	0.767	0.0
Sample size										
>100	6	1259/1489	1.203 [0.959–1.510]	0.110	0.000	77.7	1.202 [0.908–1.591]	0.199	0.013	65.6
≤100	2	104/186	0.892 [0.458–1.735]	0.736	0.059	71.9	1.026 [0.452–2.330]	0.950	0.296	8.5
Publication bias tests										
Egger's P				0.343				0.258		
509C/T	N	Sample size Case/control	T vs. C OR (95% CL)	Pb	Pc	I²%	CT+TT vs. CC OR (95% CL)	Pb	Pc	I²%
Total	5	1335/1559	1.111 [0.749–1.647]	0.601	0.000	93.3	1.024 [0.669–1.567]	0.914	0.000	86.9
Type of cancer										
NPC	4	1215/1520	1.047 [0.748–1.466]	0.789	0.000	86.7	1.118 [0.758–1.648]	0.575	0.006	76.2
Publication bias tests										
Egger's P				0.445				0.408		
915G/C	N	Sample size Case/control	C vs. G OR (95% CL)	Pb	Pc	I²%	GC+CC vs. GG OR (95% CL)	Pb	Pc	I²%
Total	3	340/368	3.800 [1.125–12.843]	0.032	0.000	91.7	5.113 [1.224–21.367]	0.025	0.000	91.9
Publication bias tests										
Egger's P				0.226				0.327		

TGF-β1 – transforming growth factor-β1; CI – confidence interval; OR – odds ratio. Note: *P*b Value of the Z test for odds ration test. *P*c Value of the Q test for hetergeneity test. *P* Value of the Egger's test for publication bias.

(TC+CC *vs.* TT) (OR=0.977, 95% CI: 0.760–1.255; P=0.853). The results for the recessive gene analysis (CC *vs.* TT+TC) were (OR=1.057; 95% CI, 0.667–1.650; P=0.808) and for the homologous gene analysis (CC *vs.* TT) were (OR 1.012, 95% CI: 0.687–1.490; P=0.952). No significant differences were observed between the genotypes in the Asian and non-Asian populations. As the sample size of NPC cases in our selected studies was >100, we did not conduct a sample size analysis.

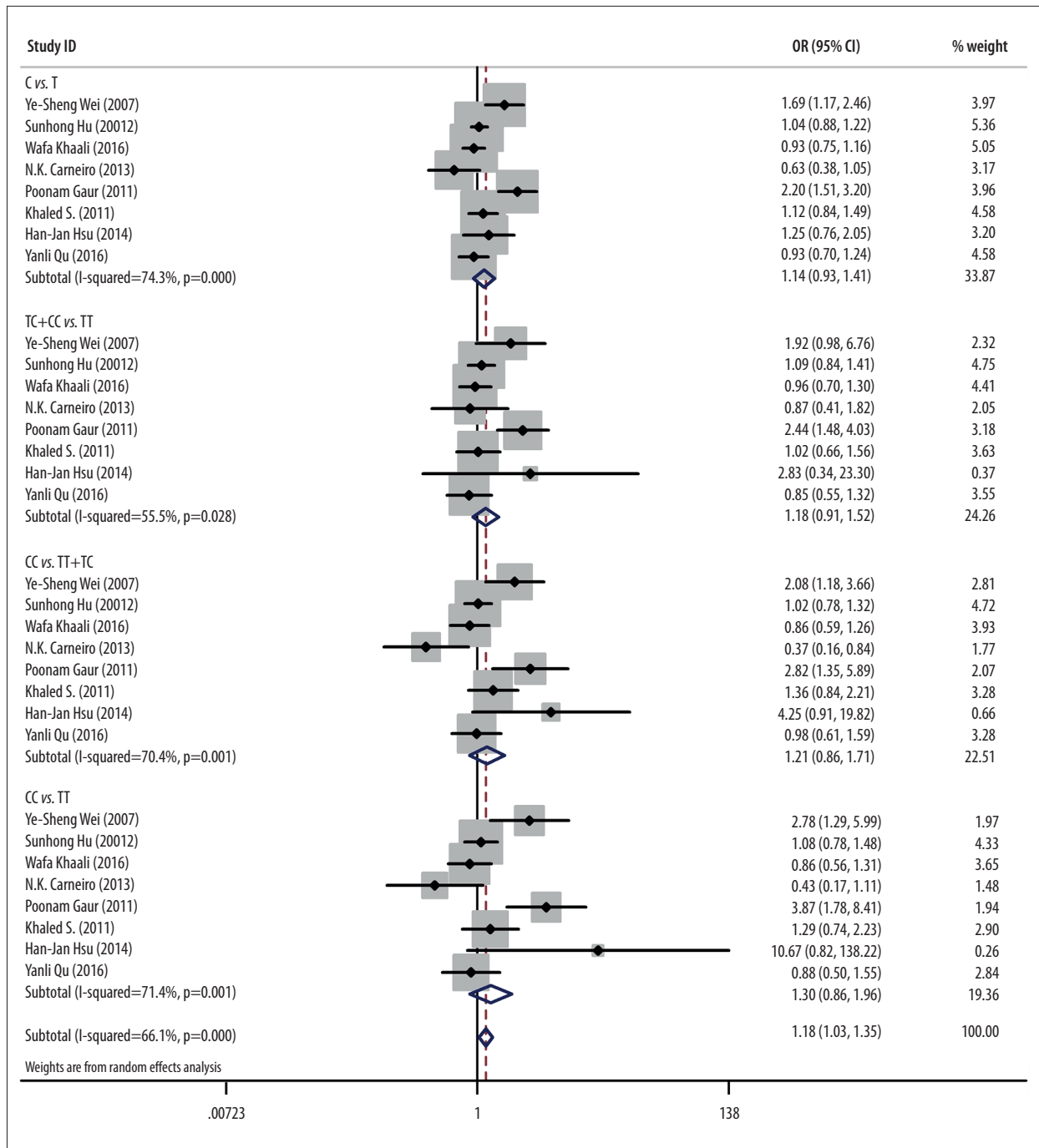### Correlation between the 509C/T polymorphism of the TGF-β1 gene and susceptibility to head and neck cancer

Five studies that reported the association between the 509C/T polymorphism of the TGF-β1 gene and head and neck cancers were identified in this study. Only one study reported the findings in patients with oral cancer. All the other studies involved cases of NPC. Therefore, we only analyzed the relationship

Table 3. Results of meta-analysis on the association between the TGF-β1 gene polymorphisms and head and neck cancers.

869T/C	N	CC *vs.* TT+TC				CC *vs.* TT				All			
		OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%
Total	8	1.209 [0.857–1.705]	0.28	0.001	70.4	1.298 [0.859–1.962]	0.216	0.001	71.4	1.181 [1.035–1.348]	0.014	0.000	66.1
Type of cancer													
NPC	5	1.131 [0.875–1.463]	0.346	0.105	47.7	1.138 [0.836–1.548]	0.411	0.099	48.8	1.077 [0.978–1.186]	0.131	0.075	33.2
Oral	3	1.537 [0.324–7.290]	0.589	0.000	87.1	2.134 [0.345–13.218]	0.415	0.001	86.1	1.469 [0.925–2.333]	0.103	0.000	78.9
Ethnicities													
Asian	5	1.564 [0.983–2.490]	0.059	0.009	70.2	1.844 [0.972–3.497]	0.061	0.002	76.6	1.431 [1.191–1.720]	0.000	0.000	70.3
Caucasian	3	0.824 [0.456–1.489]	0.521	0.025	72.9	0.874 [0.539–1.420]	0.587	0.137	49.7	0.929 [0.804–1.074]	0.320	0.017	28.9
Sample size													
>100	6	1.266 [0.933–1.718]	0.129	0.017	63.6	1.369 [0.918–2.043]	0.124	0.004	71.2	1.230 [1.078–1.404]	0.002	0.000	66.4
≤100	2	1.140 [0.104–12.17]	0.915	0.006	86.7	1.714 [0.075–38.984]	0.735	0.021	81.3	0.920 [0.545–1.552]	0.754	0.009	62.6
Publication bias tests													
Egger's P		0.095				0.05							

509C/T	N	TT *vs.* CC+CT				TT *vs.* CC				All			
		OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%
Total	5	1.108 [0.603–2.036]	0.521	0.000	91.5	1.138 [0.542–2.390]	0.733	0.000	92.4	1.090 [0.865–1.374]	0.464	0.000	90.4
Type of cancer													
NPC	4	1.176 [0.727–1.902]	0.508	0.001	80.6	1.123 [0.601–2.096]	0.716	0.000	84	1.133 [0.937–1.370]	0.198	0.000	79.1
Publication bias tests													
Egger's P		0.771				0.678							

| 915G/C	N	CC *vs.* GG+GC				CC *vs.* GG				All			
		OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%	OR (95% CL)	*P*b	*P*c	I²%
Total	3	1.343 [0.710–2.538]	0.364	0.574	0.0	1.598 [0.812–3.146]	0.175	0.734	0.0	2.815 [1.581–5.012]	0.000	0.000	81.1
Publication bias tests													
Egger's P		0.263				0.417							

TGF-β1 – transforming growth factor-β1; CI – confidence interval; OR – odds ratio. Note: *P*b Value of the Z test for odds ration test. *P*c Value of the Q test for hetergeneity test. *P* Value of the Egger's test for publication bias

Study ID	OR (95% CI)	% weight
C vs. T		
Ye-Sheng Wei (2007)	1.69 (1.17, 2.46)	3.97
Sunhong Hu (20012)	1.04 (0.88, 1.22)	5.36
Wafa Khaali (2016)	0.93 (0.75, 1.16)	5.05
N.K. Carneiro (2013)	0.63 (0.38, 1.05)	3.17
Poonam Gaur (2011)	2.20 (1.51, 3.20)	3.96
Khaled S. (2011)	1.12 (0.84, 1.49)	4.58
Han-Jan Hsu (2014)	1.25 (0.76, 2.05)	3.20
Yanli Qu (2016)	0.93 (0.70, 1.24)	4.58
Subtotal (I-squared=74.3%, p=0.000)	1.14 (0.93, 1.41)	33.87
TC+CC vs. TT		
Ye-Sheng Wei (2007)	1.92 (0.98, 6.76)	2.32
Sunhong Hu (20012)	1.09 (0.84, 1.41)	4.75
Wafa Khaali (2016)	0.96 (0.70, 1.30)	4.41
N.K. Carneiro (2013)	0.87 (0.41, 1.82)	2.05
Poonam Gaur (2011)	2.44 (1.48, 4.03)	3.18
Khaled S. (2011)	1.02 (0.66, 1.56)	3.63
Han-Jan Hsu (2014)	2.83 (0.34, 23.30)	0.37
Yanli Qu (2016)	0.85 (0.55, 1.32)	3.55
Subtotal (I-squared=55.5%, p=0.028)	1.18 (0.91, 1.52)	24.26
CC vs. TT+TC		
Ye-Sheng Wei (2007)	2.08 (1.18, 3.66)	2.81
Sunhong Hu (20012)	1.02 (0.78, 1.32)	4.72
Wafa Khaali (2016)	0.86 (0.59, 1.26)	3.93
N.K. Carneiro (2013)	0.37 (0.16, 0.84)	1.77
Poonam Gaur (2011)	2.82 (1.35, 5.89)	2.07
Khaled S. (2011)	1.36 (0.84, 2.21)	3.28
Han-Jan Hsu (2014)	4.25 (0.91, 19.82)	0.66
Yanli Qu (2016)	0.98 (0.61, 1.59)	3.28
Subtotal (I-squared=70.4%, p=0.001)	1.21 (0.86, 1.71)	22.51
CC vs. TT		
Ye-Sheng Wei (2007)	2.78 (1.29, 5.99)	1.97
Sunhong Hu (20012)	1.08 (0.78, 1.48)	4.33
Wafa Khaali (2016)	0.86 (0.56, 1.31)	3.65
N.K. Carneiro (2013)	0.43 (0.17, 1.11)	1.48
Poonam Gaur (2011)	3.87 (1.78, 8.41)	1.94
Khaled S. (2011)	1.29 (0.74, 2.23)	2.90
Han-Jan Hsu (2014)	10.67 (0.82, 138.22)	0.26
Yanli Qu (2016)	0.88 (0.50, 1.55)	2.84
Subtotal (I-squared=71.4%, p=0.001)	1.30 (0.86, 1.96)	19.36
Subtotal (I-squared=66.1%, p=0.000)	1.18 (1.03, 1.35)	100.00

Weights are from random effects analysis

.00723   1   138

Figure 2. The association between the 869T/C polymorphism of the TGF-β1 gene and head and neck cancer.

between 509C/T polymorphism of the TGF-β1 gene and NPC. Because the I^2 value was >50%, we chose a random-effects model for the statistical analysis. The results for each genotype were as follows (Tables 2, 3, Figure 6): T *vs.* C (OR=1.047; 95% CI, 0.748–1.466; P=0.789); TC+TT *vs.* CC (OR=1.118; 95% CI, 0.758–1.648; P=0.575); TT *vs.* CC+CT (OR=1.176; 95% CI, 0.727–1.902; P=0.508); and TT *vs.* CC (OR=1.123; 95% CI, 0.601–2.096; P=0.716). No difference was found for the general

analysis (OR=1.133; 95% CI, 0.937–1.370; P=0.198). Therefore, the meta-analysis did not support a correlation between the 509C/T polymorphism of the TGF-β1 gene and NPC.
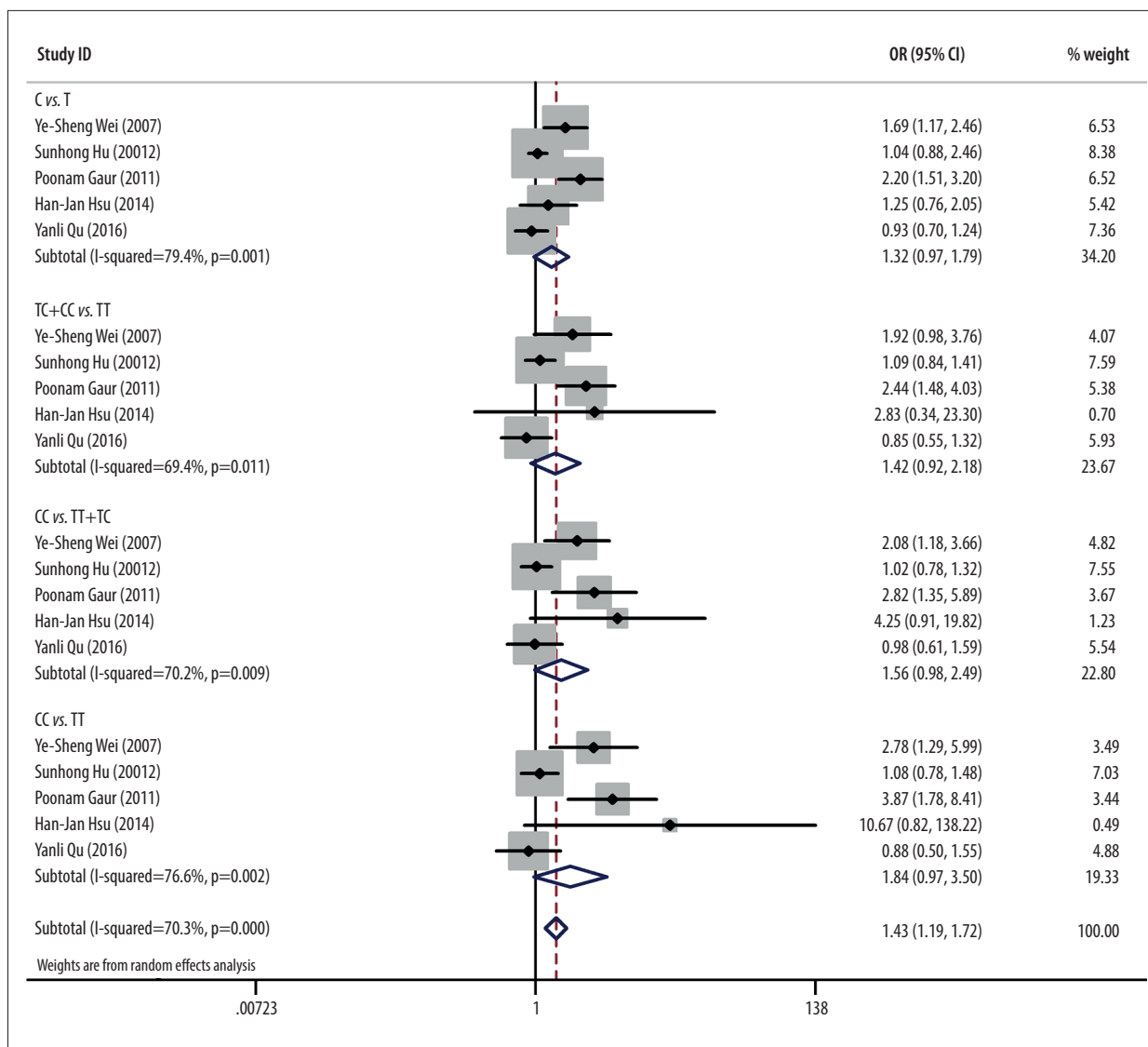
Figure 3. The association between the 869T/C polymorphism of the TGF-β1 gene and the Asian population.
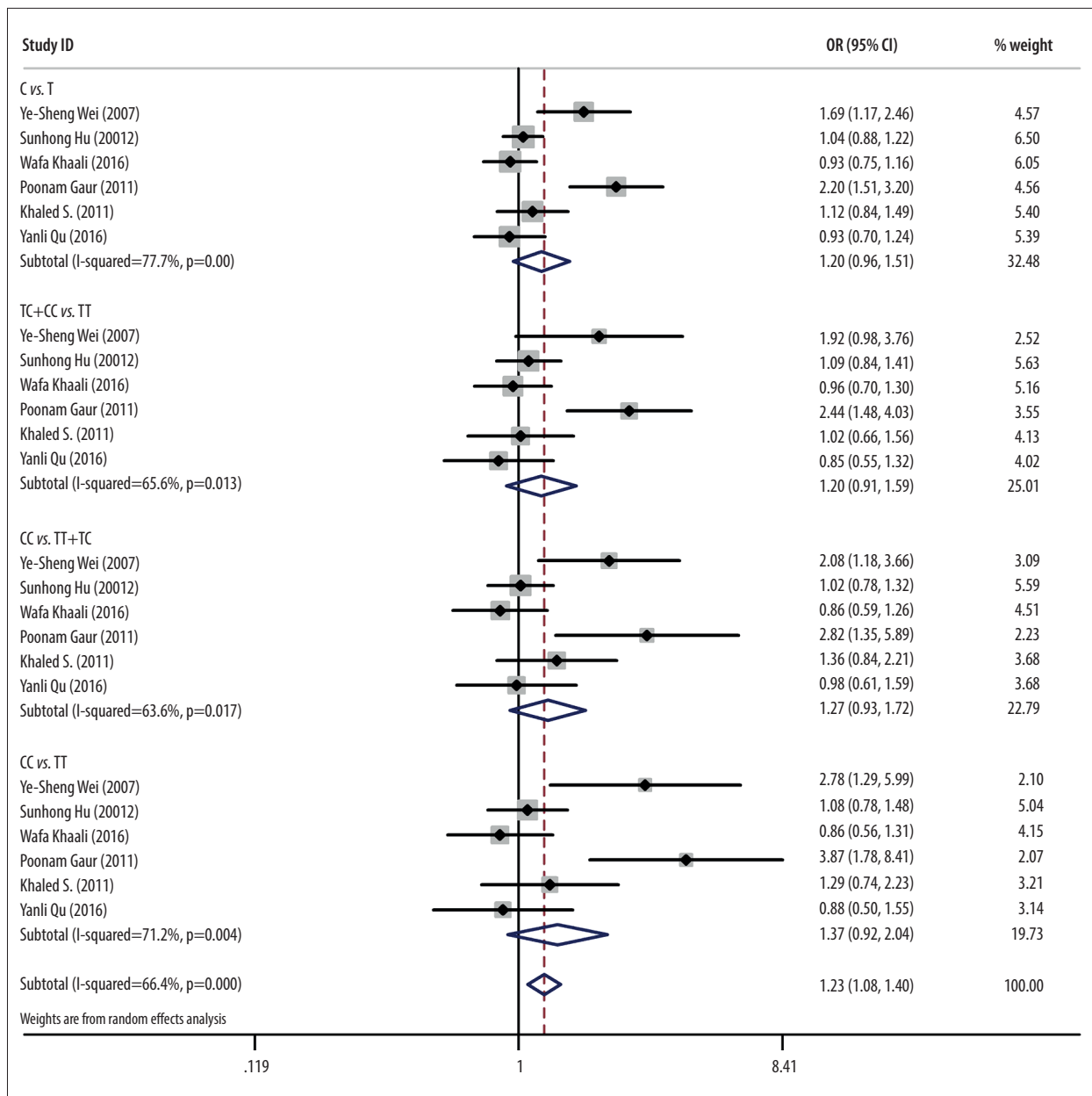
Correlation between the 915G/C polymorphism of the TGF-β1 gene and susceptibility to head and neck cancer

All three studies that included the 915G/C polymorphism of the TGF-β1 gene were conducted in Asian populations and reported the findings in patients with oral cancer. The statistical results demonstrated a significant correlation between the 915G/C polymorphism of the TGF-β1 gene and oral cancer (OR=2.815; 95% CI, 1.581–5.012; P=0.000). The allele and dominant genotype (C vs. G) analysis results showed a significant difference (OR=3.800; 95% CI, 1.125–12.843; P=0.032), and GC+CC vs. GG (OR=5.113; 95% CI, 1.224–21.367; P=0.025). The results for the recessive genotype and homologous gene (CC vs. GG+GC) showed no significant difference (OR=1.343; 95% CI, 0.710–2.538; P=0.364) and (CC vs. GG) (OR=1.598; 95% CI, 0.812–2.146; P=0.175) (Figure 7).

Publication bias and sensitivity analysis

Egger's test was used to determine publication bias. The P-value for the allele and genotype (C vs. T) analysis was P=0.343; TC+CC vs. TT was P=0.258; CC vs. TT+TC was P=0.095; and CC vs. TT was P=0.05. The results for Egger's test for each genotype of the 509C/T polymorphism and the 915G/C polymorphism for T vs. C was P=0.445; TC+TT vs. CC was P=0.408; TT vs. CC+CT was P=0.771; TT vs. CC was P=0.678; and C vs. G was P=0.226; GC+CC vs. GG was P=0.327; CC vs. GG+GC was P=0.263; and CC vs. GG wasP=0.417, respectively. These results indicated a relatively little publication bias in each group. The sensitivity test showed that the results for the three polymorphisms were stable (Figure 8), with a relatively small publication bias in each group (Figure 9).
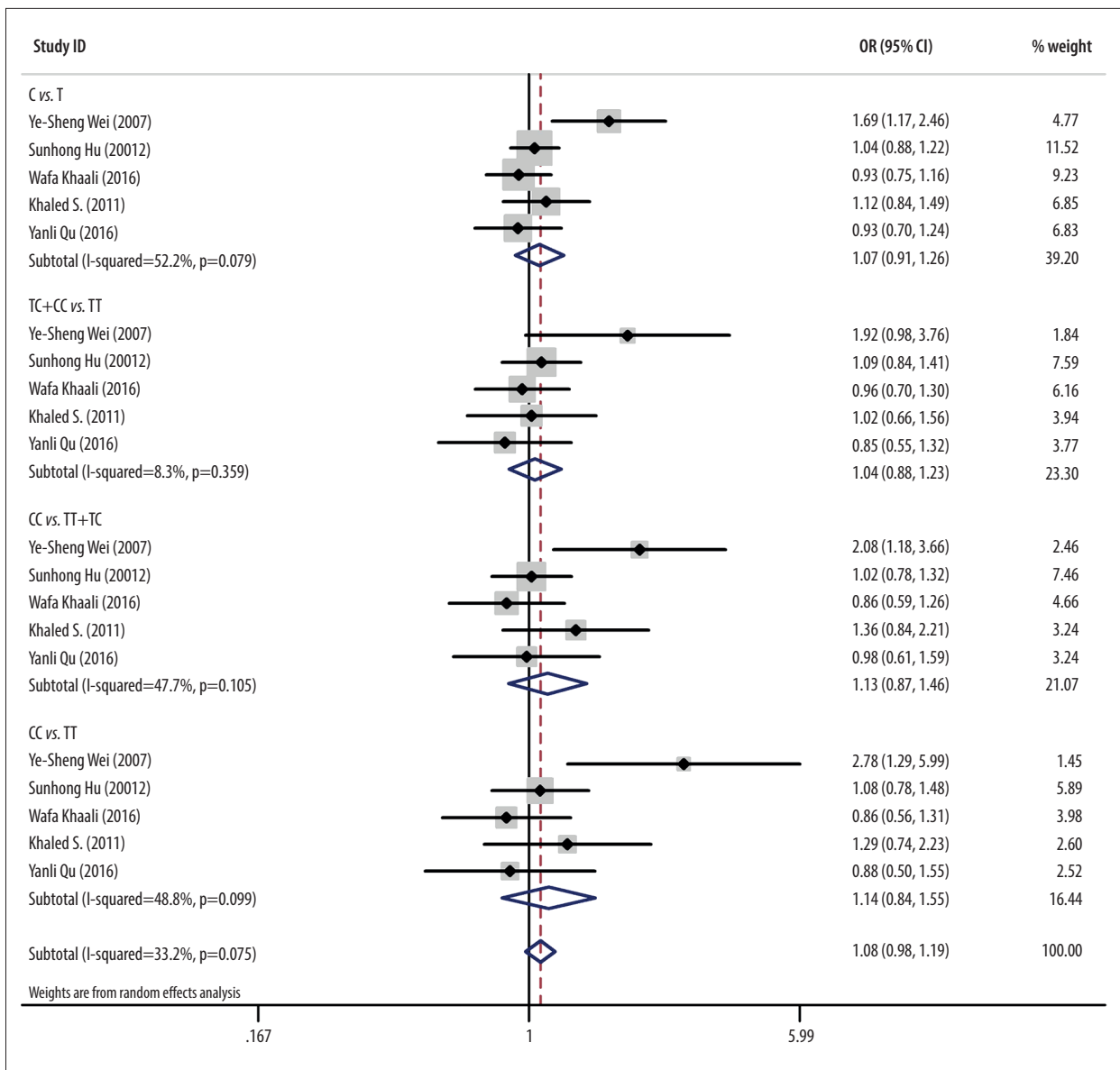
Figure 4. The association between the 869T/C polymorphism of the TGF-β1 gene and sample size.

Discussion

The susceptibility to difference cancers, and sensitivity to cancer treatments, varies between individuals in the same environment and may be explained not only by different physical conditions but also by genetic susceptibility. Changes in gene expression are key events in the occurrence and progression of cancer. Previously published studies have shown that cancer can be associated with chronic inflammation, tissue injury, and the activation of local host responses that induce cell proliferation [44].

Transforming growth factor-β1 (TGF-β1) is an inflammatory cytokine that has important roles in the carcinogenesis and the development of solid malignant tumors. Lu et al. [45] showed that both *in vivo* and *in vitro* levels of TGF-β1 were increased in tumor cells from head and neck cancer, indicating that overexpression of TGF-β1 may provide an oncogenic microenvironment. Also, TGF-β1 may contribute to the aggressive behavior of cancers through a local and systemic immunosuppression effect [26]. Several single nucleotide polymorphisms (SNPs) have been evaluated for their possible roles in inflammatory diseases and cancer predisposition. TGF-β1 SNPs are believed to influence downstream gene expression and further affect

Study ID	OR (95% CI)	% weight
C vs. T		
Ye-Sheng Wei (2007)	1.69 (1.17, 2.46)	4.77
Sunhong Hu (20012)	1.04 (0.88, 1.22)	11.52
Wafa Khaali (2016)	0.93 (0.75, 1.16)	9.23
Khaled S. (2011)	1.12 (0.84, 1.49)	6.85
Yanli Qu (2016)	0.93 (0.70, 1.24)	6.83
Subtotal (I-squared=52.2%, p=0.079)	1.07 (0.91, 1.26)	39.20
TC+CC vs. TT		
Ye-Sheng Wei (2007)	1.92 (0.98, 3.76)	1.84
Sunhong Hu (20012)	1.09 (0.84, 1.41)	7.59
Wafa Khaali (2016)	0.96 (0.70, 1.30)	6.16
Khaled S. (2011)	1.02 (0.66, 1.56)	3.94
Yanli Qu (2016)	0.85 (0.55, 1.32)	3.77
Subtotal (I-squared=8.3%, p=0.359)	1.04 (0.88, 1.23)	23.30
CC vs. TT+TC		
Ye-Sheng Wei (2007)	2.08 (1.18, 3.66)	2.46
Sunhong Hu (20012)	1.02 (0.78, 1.32)	7.46
Wafa Khaali (2016)	0.86 (0.59, 1.26)	4.66
Khaled S. (2011)	1.36 (0.84, 2.21)	3.24
Yanli Qu (2016)	0.98 (0.61, 1.59)	3.24
Subtotal (I-squared=47.7%, p=0.105)	1.13 (0.87, 1.46)	21.07
CC vs. TT		
Ye-Sheng Wei (2007)	2.78 (1.29, 5.99)	1.45
Sunhong Hu (20012)	1.08 (0.78, 1.48)	5.89
Wafa Khaali (2016)	0.86 (0.56, 1.31)	3.98
Khaled S. (2011)	1.29 (0.74, 2.23)	2.60
Yanli Qu (2016)	0.88 (0.50, 1.55)	2.52
Subtotal (I-squared=48.8%, p=0.099)	1.14 (0.84, 1.55)	16.44
Subtotal (I-squared=33.2%, p=0.075)	1.08 (0.98, 1.19)	100.00

Weights are from random effects analysis

.167   1   5.99

Figure 5. The association between the 869T/C polymorphism of the TGF-β1 gene and nasopharyngeal carcinoma.

the susceptibility to head and neck cancer. Previous studies have investigated TGF-β1 or TGF-β1 genetic polymorphisms as a predictive cancer marker [46,47]. In the classic TGF-β/Smad signaling pathway, TGF-β1 is phosphorylated after binding to its receptor, and phosphorylates Smad2 and Smad3, and then binds to Smad4. This cytoplasmic complex is transferred to the cell nucleus and interacts with other transcription factors, with abnormalities in this complex resulting in abnormal cell proliferation [48,49]. It has previously been reported that TGF-β1 is overexpressed in many types of cancers, and the levels are correlated with tumor invasion [21-24]. Expression of TGF-β1 and Smad7 in the tumor tissues are increased in head and neck cancer tissues, while Smad4 is downregulated [50]. TGF-β1 gene polymorphisms are also correlated with treatment response

and the prognosis [51]. Therefore, it is possible to hypothesize that TGF-β1 gene polymorphisms affect serum levels of TGF-β1 and Smad, leading to the inactivation of the TGF-β1/Smad signaling pathway, which might result in changes that influence the prognosis of head and neck cancer.

In this meta-analysis, TGF-β1 gene polymorphisms and susceptibility to head and neck cancer were investigated. The 869T/C polymorphism was associated with the development of head and neck cancer. Further subgroup analysis showed that this association was more significant in the Asian population. The subtypes of head and neck cancers included in this study were nasopharyngeal cancer (NPC) and oral cancer. No significant differences were found in the analysis of each genotype.
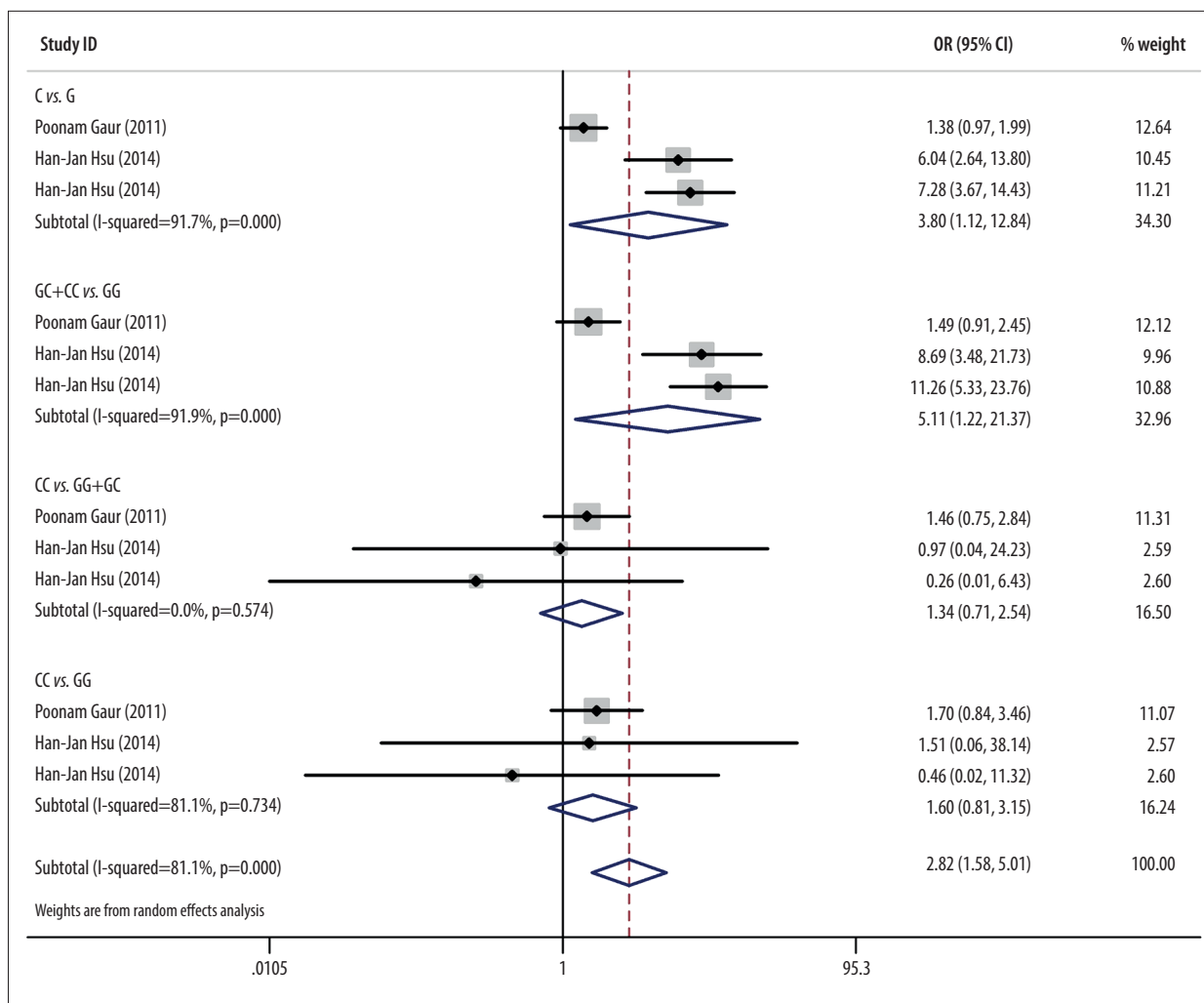
Table 4. Meta-analysis on the association between the TGF-β1 869 T/C gene polymorphisms and nasopharyngeal carcinoma in different ethnicities.

Gene type	Asian				Non-Asian				All			
	OR 95% CI	Pb	Pc	I² (%)	OR 95% CI	Pb	Pc	I² (%)	OR 95% CI	Pb	Pc	I² (%)
C vs. T	1.139 (0.857–1.512)	0.370	0.032	70.9	0.997 (0.840–1.184)	0.977	0.316	0.6	1.071 (0.912–1.257)	0.404	0.079	52.2
TC+CC vs. TT	1.118 (0.792–1.577)	0.527	0.141	48.9	0.977 (0.760–1.255)	0.853	0.817	0.0	1.039 (0.875–1.235)	0.660	0.359	8.3
CC vs. TT+TC	1.212 (0.810–1.813)	0.350	0.070	62.4	1.057 (0.677–1.650)	0.808	0.144	53.1	1.131 (0.875–1.463)	0.346	0.105	47.7
CC vs. TT	1.276 (0.747–2.180)	0.371	0.048	67.2	1.012 (0.687–1.490)	0.952	0.255	22.8	1.138 (0.836–1.548)	0.411	0.099	48.8

TGF-β1 – transforming growth factor-β1; CI – confidence interval; OR – odds ratio. *P*b Value of the Z test for odds ration test.
*P*c Value of the Q test for hetergeneity test. *P* Value of the Egger's test for publication bias.
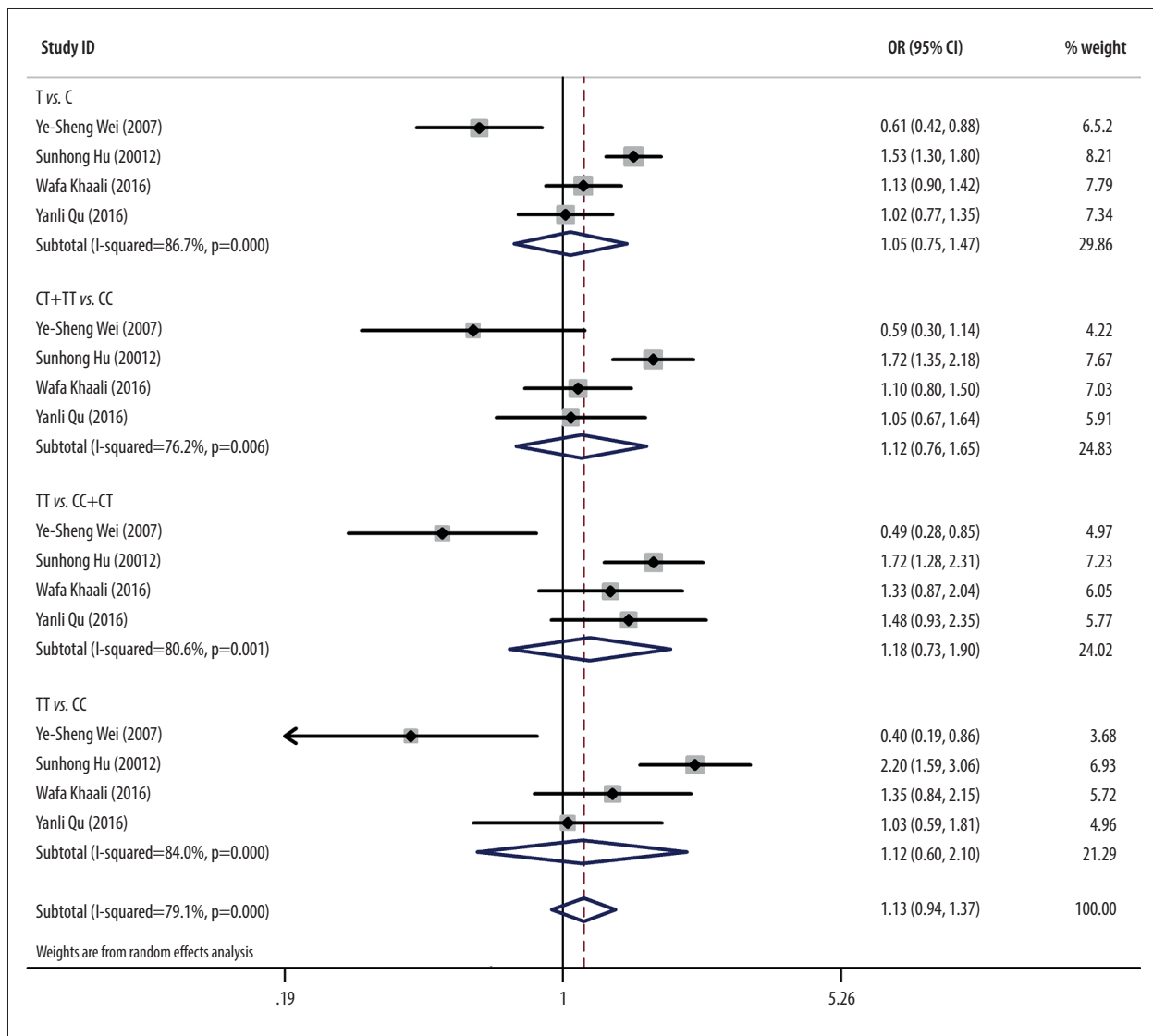
Figure 6. The association between the 509C/T polymorphism of the TGF-β1 gene and nasopharyngeal carcinoma.

Figure 7. The association between the 915G/C polymorphism of the TGF-β1 gene and oral cancer.

However, a significant difference was found in the general analysis, suggesting that TGF-β1 gene polymorphisms were correlated with different subtypes of head and neck cancer. However, subgroups analysis of the different tumor stages of head and neck cancer was not performed.

Four publications reported the 869T/C and 509C/T polymorphisms of the TGF-β1 gene in NPC. However, no association was observed in the analysis if these two polymorphic sites of the TGF-β1 gene and NPC. Wei et al. [28] previously reported that both 869T/C and 509C/T polymorphisms of the TGF-β1 gene were associated with a predisposition to NPC. Hu et al. [36] discovered that the allele mutation at position 509T reduced the risk of NPC, while a T to C mutation at position 869 was not associated with carcinogenesis in NPC. However, the findings from a study reported by Qu et al. [35] of the population of Northern China and the findings from a study by Khaali et al. [37] of patients in the population of North America population showed that neither the 869T/C

polymorphism of the TGF-β1 gene nor the 509C/T polymorphism were associated with the genesis of NPC. Differences in biological behavior and in the mechanisms underlying the genesis of NPC when compared with other tumors explain these findings. Therefore, further studies are needed to determine the genetic effects of these two sites. Also, racial differences exist between genotypes. The population of Southern China is at increased risk of NPC, whereas its incidence is relatively low in Northern China and North America.

In this study, the meta-analysis showed that the 915G/C polymorphism of the TGF-β1 gene was associated with susceptibility to oral cancer. The 915G/C polymorphism resides in the 25th codon of the TGF-β1 gene. In three studies, the 915G/C polymorphism and oral cancer were associations in the Asian population. However, Gaur et al. [42] reported that the TGF-β1 C allele is not a risk factor for oral cancer. Hsu et al. [40] showed that the G/C genotype increased the risk of oral cancer. A study by Hsu et al. [41] further validated the pivotal role of the
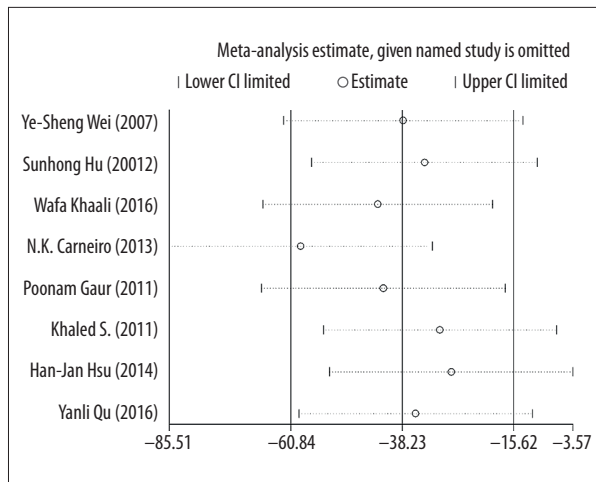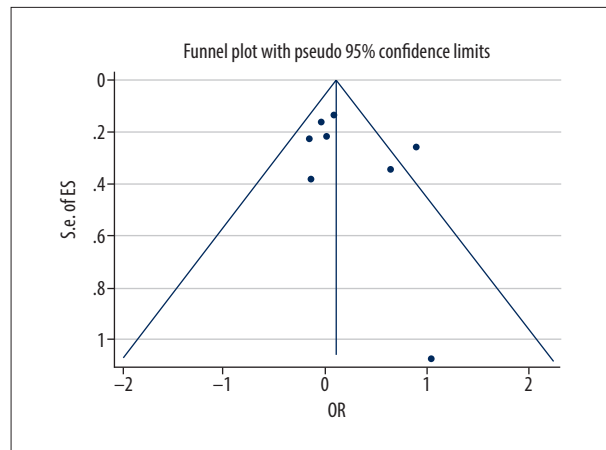
Figure 8. Sensitivity analysis of 869T/C polymorphism of the TGF-β1 gene.

Figure 9. Funnel plots of the 869T/C polymorphism of the TGF-β1 gene.

TGF-β1 gene C allele in precancerous lesions and oral cancer. The meta-analyses in the present study showed that the C dominant allele was a risk factor for oral cancer, which may be explained by the role of the G allele in increasing serum level of TGF-β1 levels, inhibiting epithelial cell proliferation and transformation. The polymorphism causes the G allele to be transformed to the C allele, leading to a substitution of arginine by proline at the protein level. This substitution may change the overall hydrophobic nature of the core sequence. Therefore, the α-helical structure is impaired and transported to the endoplasmic reticulum, leading to proliferation and transformation of epithelial cells, which increases the risk for oral cancer [45]. Chen et al. [17] reported low TGF-β1 expression in NPC, which was upregulated after clinical treatment. Changes in TGF-β1 levels associated with the inflammatory reaction are closely associated with the side effects of the treatment.

This study had several limitations. First, the publication sample size for the meta-analysis was small. There were only three published studies on the 915G/C polymorphism of the TGF-β1 gene that were included, which are likely to be insufficient to

determine its association with oral cancer. Second, only Chinese and English publications were screened, and studies published in other languages and unpublished data were not included. Future studies should include a larger sample size to validate the findings from this meta-analysis.

Conclusions

A meta-analysis of the published literature supported an association between the 869T/C polymorphism of the TGF-β1 gene and head and neck cancer, particularly in the Asian population. The 915G/C allele genotype and the dominant TGF-β1 genotype were associated with oral cancer, but the recessive and homozygous genotypes were not. The meta-analysis data did not support an association between the 509C/T polymorphism and head and neck cancers, including nasopharyngeal carcinoma (NPC).

Conflict of interest

None.

References:

1. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin, 2018; 68: 394–424

2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. Cancer J Clin, 2019; 69: 7–34

3. Ferlay J, Soerjomataram I, Dikshit R et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 2015; 136: E359–86

4. Brunotto M, Zarate AM, Bono A et al: Risk genes in head and neck cancer: A systematic review and meta-analysis of last 5 years. Oral Oncol, 2014; 50: 178–88

5. Munshi T, Heckman CJ, Darlow S: Association between tobacco waterpipe smoking and head and neck conditions: A systematic review. J Am Dent Assoc, 2015; 146: 760–66

6. Lundberg M, Pajusto M, Koskinen WJ et al: Association between transforming growth factor beta1 genetic polymorphism and response to chemoradiotherapy in head and neck squamous cell cancer. Head Neck, 2009; 31: 664–72

7. Zhou YL, Zhang WC, Chen XB et al: [The association between polymorphism of transforming growth factor-beta1 and radiochemotherapy response and survival in esophageal squamous cell carcinoma patients]. Zhonghua Yu Fang Yi Xue Za Zhi, 2011; 45: 583–87 [in Chinese]

8. Lacko M, Braakhuis BJ, Sturgis EM et al: Genetic susceptibility to head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys, 2014; 89: 38–48

9. McKay JD, Truong T, Gaborieau V et al: A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. PLoS Genet, 2011; 7: e1001333

This work is licensed under Creative Common Attribution-
NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

8401

Indexed in: [Current Contents/Clinical Medicine]   [SCI Expanded]   [ISI Alerting System]
[ISI Journals Master List]   [Index Medicus/MEDLINE]   [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS]

10. Qin HD, Shugart YY, Bei JX et al: Comprehensive pathway-based association study of DNA repair gene variants and the risk of nasopharyngeal carcinoma. Cancer Res, 2011; 71: 3000–8

11. Flores-Obando RE, Gollin SM, Ragin CC: Polymorphisms in DNA damage response genes and head and neck cancer risk. Biomarkers, 2010; 15: 379–99

12. Guan X, Sturgis EM, Lei D et al: Association of TGF-beta1 genetic variants with HPV16-positive oropharyngeal cancer. Clin Cancer Res, 2010; 16: 1416–22

13. Peng Z, Xie C, Wan Q et al: Sequence variations of mitochondrial DNA D-loop region are associated with familial nasopharyngeal carcinoma. Mitochondrion, 2011; 11: 327–33

14. Lacko M, Roelofs HM, Te MR et al: Genetic polymorphism in the conjugating enzyme UGT1A1 and the risk of head and neck cancer. Int J Cancer, 2010; 127: 2815–21

15. Lu M, Liu Z, Yu H et al: Combined effects of E2F1 and E2F2 polymorphisms on risk and early onset of squamous cell carcinoma of the head and neck. Mol Carcinog, 2012; 51(Suppl.1): E132–41

16. Xu J, Menezes J, Prasad U, Ahmad A: Elevated serum levels of transforming growth factor beta1 in Epstein-Barr virus-associated nasopharyngeal carcinoma patients. Int J Cancer, 1999; 84: 396–99

17. Chen HW, Chang YC, Lai YL et al: Change of plasma transforming growth factor-beta1 levels in nasopharyngeal carcinoma patients treated with concurrent chemo-radiotherapy. Jpn J Clin Oncol, 2005; 35: 427–32

18. Fernandez-Mateos J, Seijas-Tamayo R, Klain J et al: Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma. Sci Rep, 2017; 7: 6887

19. Feller L, Altini M, Lemmer J: Inflammation in the context of oral cancer. Oral Oncol, 2013; 49: 887–92

20. Serefoglou Z, Yapijakis C, Nkenke E, Vairaktaris E: Genetic association of cytokine DNA polymorphisms with head and neck cancer. Oral Oncol, 2008; 44: 1093–99

21. Stanilova S, Stanilov N, Julianov A et al: Transforming growth factor-beta1 gene promoter −509C/T polymorphism in association with expression affects colorectal cancer development and depends on gender. PLoS One, 2018; 13: e201775

22. Chruscik A, Gopalan V, Lam AK: The clinical and biological roles of transforming growth factor beta in colon cancer stem cells: A systematic review. Eur J Cell Biol, 2018; 97: 15–22

23. Shariat SF, Kattan MW, Traxel E et al: Association of pre- and postoperative plasma levels of transforming growth factor beta(1) and interleukin 6 and its soluble receptor with prostate cancer progression. Clin Cancer Res, 2004; 10: 1992–99

24. Domagala-Kulawik J, Hoser G, Safianowska A et al: Elevated TGF-beta1 concentration in bronchoalveolar lavage fluid from patients with primary lung cancer. Arch Immunol Ther Exp (Warsz), 2006; 54: 143–47

25. Siegel PM, Massague J: Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. Nat Rev Cancer, 2003; 3: 807–21

26. Tang B, Vu M, Booker T et al: TGF-beta switches from tumor suppressor to prometastatic factor in a model of breast cancer progression. J Clin Invest, 2003; 112: 1116–24

27. Jung B, Staudacher JJ, Beauchamp D: Transforming growth factor beta superfamily signaling in development of colorectal cancer. Gastroenterology, 2017; 152: 36–52

28. Wei YS, Zhu YH, Du B et al: Association of transforming growth factor-beta1 gene polymorphisms with genetic susceptibility to nasopharyngeal carcinoma. Clin Chim Acta, 2007; 380: 165–69

29. Bai L, Yu H, Wang H et al: Association single-nucleotide polymorphisms of inflammation-related factors associated with risk of lung cancer. Med Oncol, 2013; 30: 414

30. Wei YS, Xu QQ, Wang CF et al: Genetic variation in transforming growth factor-beta1 gene associated with increased risk of esophageal squamous cell carcinoma. Tissue Antigens, 2007; 70: 464–69

31. Omrani MD, Taghipour-Bazargani S, Salari-Lak S, Bagheri M: Association of codon 10 polymorphism of the transforming growth factor beta 1 gene with prostate cancer and hyperplasia in an Iranian population. Urol Int, 2009; 83: 329–32

32. Zhang Y, Liu B, Jin M et al: Genetic polymorphisms of transforming growth factor-beta1 and its receptors and colorectal cancer susceptibility: A population-based case-control study in China. Cancer Lett, 2009; 275: 102–8

33. Guo W, Dong Z, Guo Y et al: Polymorphisms of transforming growth factor-beta1 associated with increased risk of gastric cardia adenocarcinoma in north China. Int J Immunogenet, 2011; 38: 215–24

34. Lundberg M, Leivo I, Saarilahti K et al: Transforming growth factor beta 1 genotype and p16 as prognostic factors in head and neck squamous cell carcinoma. Acta Otolaryngol, 2012; 132: 1006–12

35. Qu YL, Yu H, Chen YZ et al: Relationships between genetic polymorphisms in inflammation-related factor gene and the pathogenesis of nasopharyngeal cancer. Tumour Biol, 2014; 35: 9411–18

36. Hu S, Zhou G, Zhang L et al: The effects of functional polymorphisms in the TGFbeta1 gene on nasopharyngeal carcinoma susceptibility. Otolaryngol Head Neck Surg, 2012; 146: 579–84

37. Khaali W, Moumad K, Ben DE et al: No association between TGF-beta1 polymorphisms and risk of nasopharyngeal carcinoma in a large North African case-control study. BMC Med Genet, 2016; 17: 72

38. Al-Hadyan KS, Al-Harbi NM, Al-Qahtani SS, Alsbeih GA: Involvement of single-nucleotide polymorphisms in predisposition to head and neck cancer in Saudi Arabia. Genet Test Mol Biomarkers, 2012; 16: 95–101

39. Carneiro NK, Oda JM, Losi GR et al: Possible association between TGF-beta1 polymorphism and oral cancer. Int J Immunogenet, 2013; 40: 292–98

40. Hsu HJ, Yang YH, Shieh TY et al: Role of cytokine gene (interferon-gamma, transforming growth factor-beta1, tumor necrosis factor-alpha, interleukin-6, and interleukin-10) polymorphisms in the risk of oral precancerous lesions in Taiwanese. Kaohsiung J Med Sci, 2014; 30: 551–58

41. Hsu HJ, Yang YH, Shieh T et al: TGF-beta1 and IL-10 single nucleotide polymorphisms as risk factors for oral cancer in Taiwanese. Kaohsiung J Med Sci, 2015; 31: 123–29

42. Gaur P, Mittal M, Mohanti BK, Das SN: Functional genetic variants of TGF-beta1 and risk of tobacco-related oral carcinoma in high-risk Asian Indians. Oral Oncol, 2011; 47: 1117–21

43. Erdei E, Luo L, Sheng H et al: Cytokines and tumor metastasis gene variants in oral cancer and precancer in Puerto Rico. PLoS One, 2013; 8: e79187

44. Balkwill F, Mantovani A: Inflammation and cancer: Back to Virchow? Lancet, 2001; 357: 539–45

45. Lu SL, Reh D, Li AG et al: Overexpression of transforming growth factor beta1 in head and neck epithelia results in inflammation, angiogenesis, and epithelial hyperproliferation. Cancer Res, 2004; 64: 4405–10

46. De Ruyck K, Van Eijkeren M, Claes K et al: TGFbeta1 polymorphisms and late clinical radiosensitivity in patients treated for gynecologic tumors. Int J Radiat Oncol Biol Phys, 2006; 65: 1240–48

47. Zhao L, Sheldon K, Chen M et al: The predictive role of plasma TGF-beta1 during radiation therapy for radiation-induced lung toxicity deserves further study in patients with non-small cell lung cancer. Lung Cancer, 2008; 59: 232–39

48. Han G, Wang XJ: Roles of TGFbeta signaling Smads in squamous cell carcinoma. Cell Biosci, 2011; 1: 41

49. Wu F, Weigel KJ, Zhou H, Wang XJ: Paradoxical roles of TGF-beta signaling in suppressing and promoting squamous cell carcinoma. Acta Biochim Biophys Sin (Shanghai), 2018; 50: 98–105

50. Liu DQ, Zhang J, Song HN et al: [Expression of Smad4 and Smad7 of BMP signaling pathway in oral squamous cell carcinoma]. Shanghai Kou Qiang Yi Xue, 2013; 22: 492–97 [in Chinese]

51. Zhang L, Yang M, Bi N et al: Association of TGF-beta1 and XPD polymorphisms with severe acute radiation-induced esophageal toxicity in locally advanced lung cancer patients treated with radiotherapy. Radiother Oncol, 2010; 97: 19–25