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Association between *interleukin-10* gene polymorphisms and risk of oral carcinoma: A meta-analysis

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Summary. Background. The single nucleotide polymorphisms (SNPs) of Interleukin-10 (*IL-10*) gene have been linked with the risk of oral carcinoma (OC) in a relatively small sample size. Our study aims to investigate the pooled associations by conducting a meta-analysis of published studies.

Methods. PubMed, Web of Science and Google Scholar databases were searched to identify eligible studies published in English before October 2019. The odds ratio (OR) with a 95% confidence interval (CI) was used to assess association. The publication bias was detected by Begg's test. Sensitivity and cumulative analyses were performed to evaluate the stability of crude results.

Results. The meta-analysis involved eight studies. Significant associations were certified between *IL-10* gene -1082A/G polymorphism and susceptibility of OC for A vs. G (OR=1.817, 95% CI: 1.481-2.230), AA vs. GG (OR=3.436, 95% CI: 2.281-5.175), dominant genetic model (OR=2.913, 95% CI: 1.939-4.376), and recessive genetic model (OR=1.886, 95% CI: 1.372-2.594) in overall population, East Asians and South Asians. In addition, the significant association between -592A/C polymorphism of the gene and susceptibility of OC were detected in South Asians.

Conclusions. The meta-analysis results support that the *IL-10* gene -1082G allele is a risk factor for OC in East Asians and South Asians, and *IL-10* gene -592C allele is a protective factor for the disease.

Key words: Oral carcinoma, IL-10, Polymorphism, Meta-analysis

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Introduction

Oral carcinoma (OC) is a group of tumors arising from the oral cavity, mouth, tongue, and pharynx. The incidence of OC with age-adjustment in the world is estimated at 4/100 000 (Bray et al., 2018). The American Cancer Society reported that 53,000 estimated new cases and 10,860 estimated deaths were expected in the United States in 2019 and the death rate of OC rose from 2012 through 2016 (Siegel et al., 2019). In India, Pakistan, Bangladesh, Sri Lanka, and other South-Asian countries, the incidence of OC ranks among the three top cancers (Sreekumar, 2019). OC patients in this region account for nearly a quarter of patients in the world. The high incidence of the disease have been widely concerned.

OC is considered to be a multi-factorial disease, and environmental, genetic and epigenetic factors are involved in its etiology (Ali et al., 2017; Irimie et al., 2018). The most important etiological factors of OC are tobacco and excess alcohol consumption. The consumption of alcohol and tobacco is closely linked not only with the development of the disease but also with the progression and prognosis. Furthermore, HPV

virus infection, poor oral hygiene, chronic trauma, betel nut chewing, immune system suppression, and male gender are risk factors for the disease (Talamini et al., 2000; Trivedy et al., 2002; Singhvi et al., 2007; Meurman, 2010). It should not be ignored that inherited mutated genes carrying the defect cause the susceptibility changes of OC (Ankathil et al., 1996). Many genetic factors associated with OC have been identified, including chromosome, allele, oncogene, tumor suppressor gene, single nucleotide polymorphism (SNP), point mutation, deletion, and other alterations.

As small molecular weight proteins, cytokines are secreted by immune cells activated in the immune system and are part of the immune surveillance system. As a type II cytokine, Interleukin-10 (IL-10) plays the roles of immunosuppression and anti-angiogenesis and plays the dual role of tumor promotion and tumor suppression (Mannino et al., 2015). Increased expression levels of IL10 have been reported in various types of cancer, including OC (Aziz et al., 2015).

The SNPs located in the promoter region of the *IL-10* gene can significantly affect the expression of this gene. Many studies have attempted to link the relationships between the polymorphous of *IL-10* gene and the risk of OC, but the results are controversial. Therefore, we conducted the meta-analysis of all published data (until October 2019) and attempted to investigate and clarify the associations.

Materials and methods

In this study, we followed the methods previously published by our group (Xuan et al., 2011, 2013, 2014).

Search strategy

We conducted a comprehensive search of Medline (PubMed), Google Scholar and Web of Science databases to identify suitable studies published before October 2019. The following keywords were used for searching: (''oral cancer'' OR ''oral carcinoma'') AND (''polymorphism*'' OR ''variant*'') AND (''Interleukin-10'' OR ''IL-10''). If a research group has multiple publications, we select the most recent and complete study. To make up for the shortage of automatic retrieval, we also carried out manual retrieval.

Inclusion criteria

The two investigators independently evaluated all the retrieved articles to identify the studies that were included in the meta-analysis. The selection criteria were as follows: 1) *IL-10* gene polymorphisms and OC; 2) case-control study; 3) All patients with OC were histopathologically confirmed; 4) data from original studies; 5) Human studies. If relevant information was not available after contacting the authors, the study was excluded.

Data extraction

Two researchers independently extracted the required data and a third researcher reviewed it. The relevant information were as follows: first author, publication year, the ethnicity of the study population, genotype information in patients and controls.

Statistical analysis

The main method was based on our previously published articles. Allele-count method was used to determine the allele frequencies of the three common polymorphisms (rs1800896, rs3021097, and rs1800872) of *IL-10* gene. According to the Genotypic distribution in controls, the inverse variance method was used to estimate the putative risk alleles (-1082G, -819C and -592C) frequency. The Hardy-Weinberg Equilibrium (*HWE*) can be used to determine if a population is in equilibrium for a specific gene. The Fisher exact test for HWE in controls can be performed by using routine fisher. We examined four genetic models include allele model, additive model, dominant model and recessive model. The associations were estimated by odds ratio (OR) and its 95% confidence interval (CI). The Z-test was used to determine the significance of the pooled OR and $P<0.05$ was considered statistically significant. Subgroup analyses were performed to evaluate the specific effects of ethnicity.

Cochran's Q test was used to assess heterogeneity of pooled studies, $P<0.1$ was considered statistically significant. I^2 value was also used to quantitatively assess heterogeneity ($I^2=(Q-df)/Q\times100\%$). A rough guide to interpretation is as follows: 0-25%, might not be important; 25-50%, may represent moderate heterogeneity; 50-75%, may represent substantial heterogeneity; 75-100%, considerable heterogeneity. The fixed-effects model was used in homogenous studies ($P<0.1$, $I^2<50\%$). Otherwise, the random-effects model was more appropriate. Sensitivity analysis and cumulative Meta-Analysis were performed to evaluate the stability of crude results. If more than seven studies were included, it was necessary to assess publication bias. Begg's test was used to estimate publication bias which was shown as a funnel plot. The p-value less than 0.05 indicates bias. All analyses were performed using STATA software (version 10.0, Stata Corporation, College Station, TX, USA) and R statistical software (version 3.6.1, http://www.r-project.org).

Results

Studies included in the meta-analysis

The process of study selection and exclusion are shown in Fig. 1. A total of 126 studies possibly related to this study were identified by electronic and manual retrieval. Then, two reviewers independently screened and identified potentially related studies. 17 studies on

the association between the *IL-10* gene polymorphism and risk of OC were identified in the process. However, after reading the full text of the above papers and trying to contact the authors, seven meta-analysis studies, one duplicate study, and one study in which information could not be obtained were removed from the meta-analysis. Finally, eight studies met the inclusion criteria, corresponding to 1,980 OC patients and 2,178 normal controls were considered in the meta-analysis (Vairaktaris et al., 2008; Yao et al., 2008; Tsai et al., 2014; Hsu et al., 2015; Hussain et al., 2016; Singh et al., 2017; Sharma et al., 2018; Goud et al., 2019). The main characteristics of the included studies are listed in Table 1.

Frequency of the IL-10 gene -1082 G, -819 C and -592 C alleles in controls

The pooled *IL-10* gene -1082 G allele frequency was 12.17% (95 CI: 8.77%–16.66%) in East Asian and was 19.94 % (95 CI: 16.34 %–24.10 %) in South Asian populations. The pooled *IL-10* gene -819 C allele frequency was 28.19 % (95 CI: 23.79 %–33.04 %) in South Asian populations. The pooled *IL-10* gene -592 C allele frequency was 28.98% (95 CI: 23.40%–35.25%) in East Asian and was 59.52 % (95 CI: 54.50 %–64.39%) in South Asian populations.

Association between IL-10 gene -1082 A/G polymorphism and risk of oral carcinoma

The association between *IL-10* gene -1082 A/G polymorphism and risk of OC was investigated in 1730 OC patients and 1928 controls. In overall population, the pooled results of all eligible studies indicated significant associations for A vs. G (OR=1.817, 95%CI: 1.481-2.230, P=1.065e-8, Fig. 2A), AA vs. GG (OR=3.436, 95%CI: 2.281-5.175, P=3.421e-9, Fig. 2B), dominant genetic model (OR=2.913, 95%CI: 1.939-4.376,

Table 1. Characteristics of the eligible studies for IL-10 gene polymorphisms in meta-analysis.

Study	Year	Ethnicity	rs1800896							rs1800871							rs1800872						
			Case			Control			HWE P	Case			Control			HWE P	Case			Control			HWE P
			AA	AG	GG	AA	AG	GG		TT	TC	CC	TT	TC	CC		AA	AC	CC	AA	AC	CC	
Vairaktaris et al.	2008	Caucasians	46	96	2	81	60	0	0.000	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Yao et al.	2008	East Asian	184	75	21	234	56	10	0.015	113	120	47	129	134	37	0.800	113	120	47	129	134	37	0.800
Tsai et al.	2014	East Asian	522	217	49	766	168	22	0.002	418	288	82	528	335	93	0.000	408	301	79	484	374	98	0.045
Hsu et al.	2015	East Asian	130	14	1	96	16	0	1.000	33	101	11	53	51	8	0.499	33	101	11	53	51	8	0.499
Hussain et al.	2016	South Asian	69	158	5	127	93	1	0.000	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Singh et al.	2017	South Asian	—	—	—	—	—	—	—	—	—	—	—	—	—	—	39	168	43	14	173	63	0.000
Sharma et al.	2018	South Asian	51	36	13	100	50	0	0.015	41	39	20	19	101	30	0.000	25	54	21	18	88	44	0.000
Goud et al.	2019	Southeast Asian	37	4	0	39	9	0	1.000	—	—	—	—	—	—	—	—	—	—	—	—	—	—

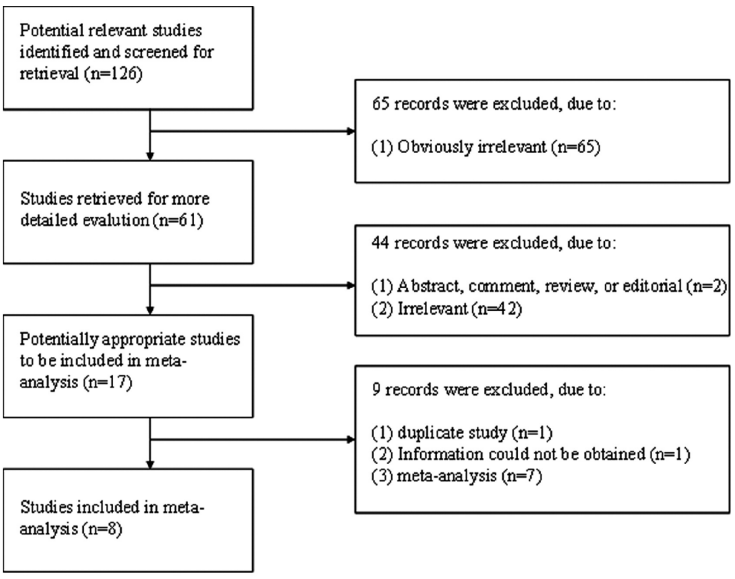

Fig. 1. Flow chart of study selection process.

P=2.605e-7, Fig. 2C), and recessive genetic model (OR=1.886, 95% CI: 1.372-2.594, P=9.619e-6, Fig. 2D). In the subgroup analysis by ethnicity, the above associations were detected in East Asians and South Asians. The detailed results are listed in Table 2.

Association between IL-10 gene - 819 T/C polymorphism and risk of oral carcinoma

There were no associations between *IL-10* gene -819 T/C polymorphism and risk of OC in overall population for T vs. C (OR=1.055, 95%CI: 0.761-1.464, P=0.746), TT vs. CC (OR=1.021, 95%CI: 0.553-1.885, P=0.947), dominant genetic model (OR=1.000, 95% CI: 0.907-1.446, P=0.254), and recessive genetic model (OR=0.964, 95%CI: 0.486-1.911, P=0.916). Similar results were detected in East Asians. The main results are listed in Table 2.

Association between IL-10 gene -592 A/C polymorphism and risk of oral carcinoma

In overall population, the significant associations between *IL-10* gene -592 A/C polymorphism and risk of OC were not detected for A vs. C (OR=0.968, 95% CI: 0.737-1.271, P=0.815), AA vs. CC (OR=0.761, 95%CI: 0.390-1.483, P=0.422), dominant genetic model (OR=0.896, 95% CI: 0.650-1.234, P=0.501), and recessive genetic model (OR=0.876, 95%CI: 0.508-1.513, P=0.635). In the stratified analysis by ethnicity, significant associations were found in South Asians but not in East Asians. The main results are listed in Table 2.

Sensitivity analysis

We conducted a sensitivity analysis to evaluate the stability of the crude results which pooled with the

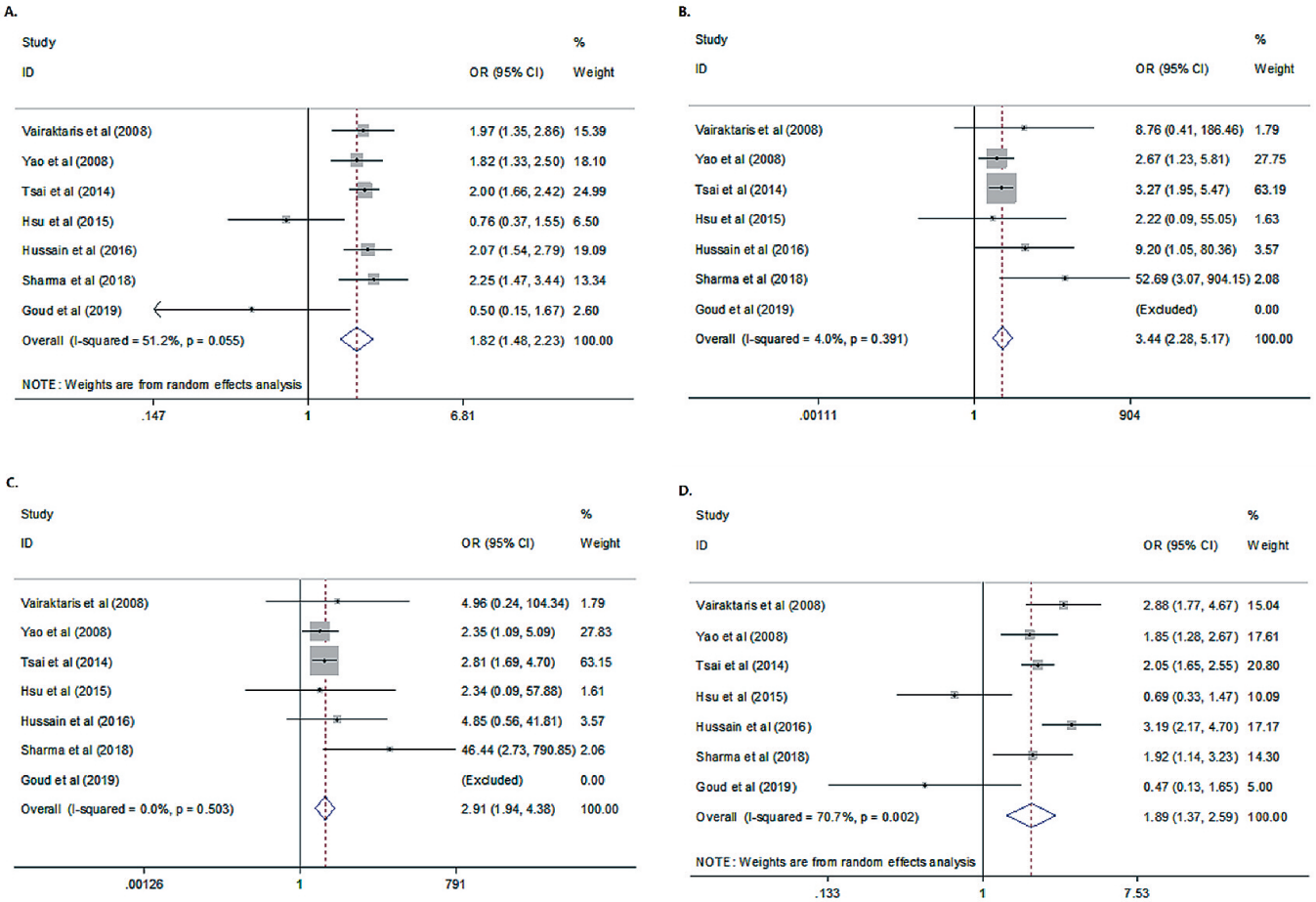

Fig. 2. Odds ratio (OR) and its 95% confidence interval (CI) of every included study and pooled results for the association between IL-10 gene A1082G polymorphism and risk of oral cancer (OC) in the overall population. **A.** A vs. G (OR=1.817, 95% CI: 1.481-2.230, random-effects model). **B.** AA vs. GG (OR=3.436, 95% CI: 2.281-5.175, fixed-effects model). **C.** dominant genetic model (OR=2.913, 95% CI: 1.939-4.376, fixed-effects model). **D.** recessive genetic model (OR=1.886, 95% CI: 1.372-2.594, random-effects model).

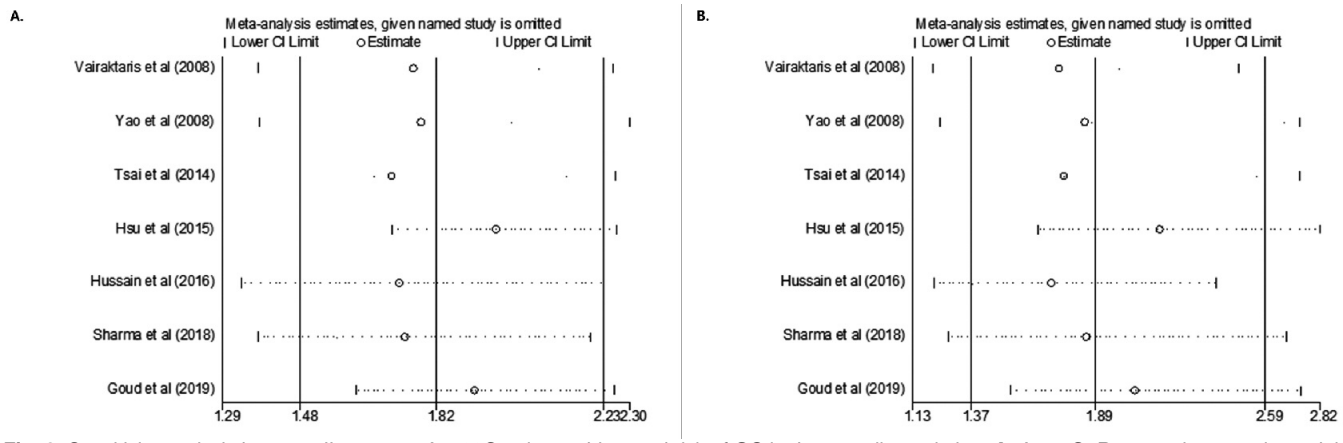

Fig. 3. Sensitivity analysis between IL-10 gene A1082G polymorphism and risk of OC in the overall population. **A.** A vs. G. **B.** recessive genetic model. This figure shows the impact of each study on the pooled OR. The overall OR is represented by a middle vertical axis and its 95% CI is represented by two vertical axes. The circle on the dotted line represents pooled OR, and the ends of the dotted line represent the values of 95% CI.

Table 2. Main results of the pooled ORs in meta-analysis.

		Sample Size		Test of heterogeneity			Test of associations				Test of publication bias	
		Case	Control	Q	P	I2 (%)	OR	95% CI	Z	P	z	P
IL-10 1082 A/G (rs1800896)												
Over all	A vs. G	1730	1928	12.31	0.055	51.2	1.817*	1.481-2.230	5.72	1.065e-8	1.20	0.230
	AA vs. GG			5.21	0.391	4.0	3.436	2.281-5.175	5.91	3.421e-9	0.38	0.707
	Dominant model			4.33	0.503	0.0	2.913	1.939-4.376	5.15	2.604e-7	0.38	0.707
	Recessive model			20.49	0.002	70.7	1.886*	1.372-2.594	3.90	9.619e-5	1.20	0.230
East Asian	A vs. G	1368	1213	6.63	0.036	69.8	1.634*	1.133-2.356	2.63	0.009	–	–
	AA vs. GG			0.22	0.896	0.0	3.055	1.996-4.677	5.14	2.747e-07	–	–
	Dominant model			0.15	0.927	0.0	2.658	1.741-4.058	4.53	5.898e-6	–	–
	Recessive model			7.43	0.024	73.1	1.589*	1.023-2.468	2.06	0.039	–	–
South Asian	A vs. G	371	332	0.09	0.762	0.0	2.128	1.669-2.713	6.09	1.129e-9	–	–
	AA vs. GG			0.92	0.339	0.0	17.476	3.119-97.920	3.25	0.001	–	–
	Dominant model			1.55	0.214	35.4	11.087	1.994-61.647	2.75	0.006	–	–
	Recessive model			2.36	0.125	57.6	2.553*	1.558-4.183	3.72	1.992e-4	–	–
IL-10 – 819 T/C (rs1800871)												
Over all	T vs. C	1313	1518	18.91	0.000	84.1	1.055*	0.761-1.464	0.32	0.746	–	–
	TT vs. CC			13.07	0.004	77.0	1.021*	0.553-1.885	0.07	0.947	–	–
	Dominant model			1.24	0.774	0.0	1.000	0.907-1.446	1.14	0.254	–	–
	Recessive model			40.99	0.000	92.7	0.964*	0.486-1.911	0.11	0.916	–	–
East Asian	T vs. C	1213	1368	5.49	0.064	63.6	1.228*	0.977-1.544	1.76	0.079	–	–
	TT vs. CC			2.05	0.359	2.4	1.254	0.965-1.630	1.69	0.090	–	–
	Dominant model			1.03	0.596	0.0	1.170	0.911-1.503	1.23	0.220	–	–
	Recessive model			12.73	0.002	84.3	1.453*	0.898-2.352	1.52	0.128	–	–
IL-10 – 592 A/C (rs1800872)												
Over all	A vs. CC	1563	1768	23.18	0.000	82.7	0.968*	0.737-1.271	0.23	0.815	0.24	0.806
	AA vs. CC			24.61	0.000	83.1	0.761*	0.390-1.483	0.80	0.422	0.00	1.000
	Dominant model			8.37	0.079	52.2	0.896*	0.650-1.234	0.67	0.501	0.00	1.000
	Recessive model			36.12	0.000	88.9	0.876*	0.508-1.513	0.47	0.635	0.24	0.806
East Asian	A vs. C	1213	1368	8.76	0.013	77.2	1.197*	0.897-1.599	1.22	0.222	–	–
	AA vs. CC			3.67	0.160	45.5	1.136*	0.873-1.477	0.95	0.343	–	–
	Dominant model			1.82	0.403	0.0	1.097	0.854-1.409	0.73	0.467	–	–
	Recessive model			16.00	0.000	87.5	1.398*	0.816-2.395	1.22	0.223	–	–
South Asian	A vs. CC\	350	400	0.08	0.771	0.0	0.680	0.553-0.835	3.68	2.332e-4	–	–
	AA vs. CC			0.38	0.538	0.0	0.285	0.167-0.488	4.58	4.650e-6	–	–
	Dominant model			0.01	0.920	0.0	0.625	0.440-0.888	2.62	0.009	–	–
	Recessive model			0.26	0.607	0.0	0.360	0.227-0.572	4.33	1.491e-05	–	–

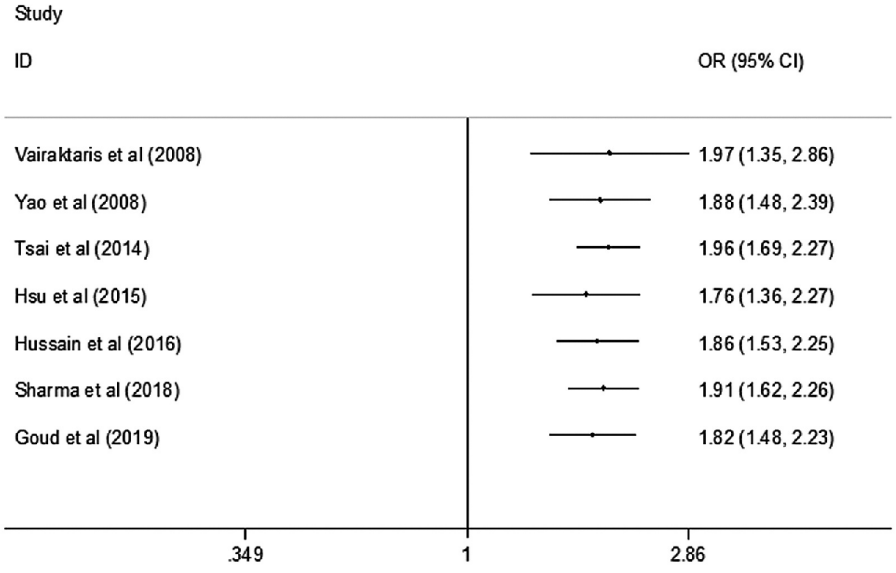

Fig. 4. Cumulative meta-analysis between IL-10 gene A1082G polymorphism and risk of OC in overall population for A vs. G. Studies are added one at a time in a specified order (according to date of publication) and the results are summarized as each new study is added.

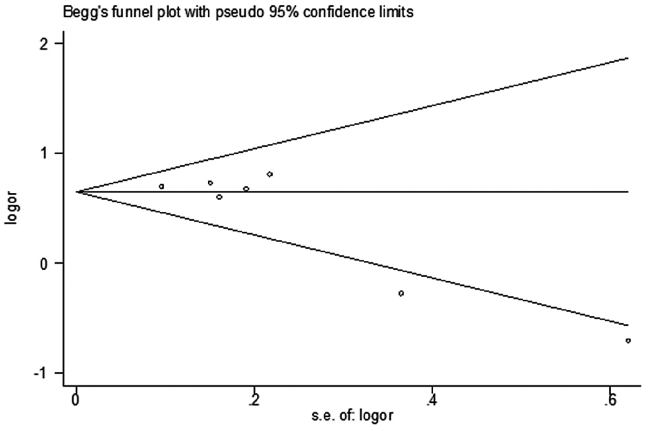

Fig. 5. Funnel plot of IL-10 gene A1082G polymorphism and risk of OC (A vs. G) in overall population (z=1.20, P=0.230).

random-effects model. When any single study was deleted, the corresponding pooled ORs were not substantially altered (Fig. 3A,B), suggesting that the results of this meta-analysis are stable.

Cumulative meta-analysis

In the association between *IL-10* gene -1082 A/G polymorphism and risk of OC, starting with a single study and adding the other studies one at a time according to the year of publications, the pooled OR did not change significantly during this process (Fig. 4).

Publication bias

Begg's test and funnel plot were performed to access the publication bias of the studies. The results suggest no evidence of publication biases (Table 2, Fig. 5).

Discussion

As one of head and neck cancers, OC has been a serious and growing health problem in the world and has climbed from the eighth most common cancer in 2003 to sixth in 2016 (Ettinger et al., 2019). It has been accepted that heavy alcohol and tobacco consumption are the two most important risk factors for OC and have synergistic effects (Petti, 2009). Chronic inflammation, HPV infection, ultraviolet exposure, malnutrition, and low intake of vegetables and fruits have also been identified as risk factors for OC (Lucenteforte et al., 2009; Adams et al., 2016). Therefore, OC is also considered to be mainly caused by environmental carcinogens. However, genetic predisposition remains a significant risk factor for the disease.

Inter-individual genetic variations play important roles in the ability of individuals to resist exogenous carcinogens or to inhibit the initiation, promotion or proliferation of carcinogenic agents (Basu, 2018). As the most common style of genetic variation, SNP represents the substitution of single nucleotides in DNA. SNPS in genes are involved in DNA damage repair, cell cycle regulation, cell apoptosis, cell signal transduction, and other molecular and cellular biological processes, which are closely related to the occurrence and development of cancers. The relationships between SNPS and cancer susceptibility have also been extensively studied, including OC (Taniyama et al., 2010). However, these studies have not been evaluated sufficiently, because the results of the studies are controversial.

IL-10 is an anti-inflammatory cytokine within the human immune response that inhibits monocyte/

macrophage, neutrophil cytokine production, and TH1-type lymphocyte responses (Murthy et al., 2000). Several inflammatory cytokines, including IL-10, are involved in mediating different steps in the carcinogenic pathway (Landskron et al., 2014). The *IL-10* gene is located on 1q31-32 with five exons and four introns. It spans a length of 5.2 kb and encodes a 178 amino acid protein. Several SNPs in *IL-10* have been identified (Mosser and Zhang, 2008). Promoter polymorphisms have been subject to the most scrutiny, particularly about influences on gene transcription and protein production. The three most common SNPs (A1082G rs1800896, T819C rs1800871, and A592C rs1800872) which are located in the promoter region have been reported to regulate IL-10 transcription and expression. Studies have indicated that about 75 percent of the differences in interleukin-10 expression are due to genetic variations. Studies also demonstrate that the salivary concentrations of IL-10 in OC individuals were higher than their healthy controls (Aziz., 2015). Therefore, the relationship between *IL-10* gene common polymorphisms and OC susceptibility has been widely investigated, especially in regions with a high incidence of the disease. However, the results of these studies are inconsistent. It is necessary to conduct a meta-analysis to assess the relationships and get relatively accurate conclusions. You et al performed a meta-analysis in 2015 and reported a significant result in the association between *IL-10* gene -1082A/G polymorphism and risk of OC (You et al., 2015). However, only four comparisons were included in their study and lack of assessment in the relationship between two other polymorphism sites (rs1800871 and rs1800872) and risk of OC in different ethnicities. Therefore, it is necessary to conduct an updated meta-analysis to fully and accurately evaluate the relationship between the three common SNPs in the promoter region of *IL-10* gene and susceptibility of OC. The sample size was enlarged in our study. Sensitivity analysis and cumulative meta-analysis were used to evaluate the stability of crude results which pooled with a random-effects model. Besides, the Funnel plot and Begg's test were used to test publication bias. Moreover, we performed subgroup analyses based on ethnicity.

In our study, we found the frequencies of the putative risk alleles varied significantly between South and East Asian populations. Subgroup analysis by ethnicity is necessary. In overall East Asia, and South Asia populations, the associations between the *IL-10* gene -1082A/G polymorphism and risk of OC were confirmed for A vs. G, AA vs. GG, recessive genetic model, and dominant genetic model. Nevertheless, we did not find any associations between the *IL-10* gene -819T/C polymorphism and risk of OC. What is interesting is that the *IL-10* gene -592A/C variant has been considered to be a protective factor for OC and *IL-10* gene -592C is a protective allele.

Two major limitations of our study should be summarized. First, our study only included papers published in English. Papers published in other languages were not included because relevant data were not identified, which may bias the current results. Second, significant heterogeneity was detected in some genetic models when we pooled ORs. In this case, a random-effects model was used to pool the data. Sensitivity analysis and cumulative meta-analysis were performed to evaluate the stability of the crude results.

In conclusion, our results support that the *IL-10* gene -1082G allele is a risk factor for OC in East Asians and South Asians, and *IL-10* gene -592C allele is a protective factor for the disease. These results clarified the controversy regarding the polymorphism of the *IL-10* gene and the risk of OC.

Competing Interests. The authors declare no competing interests.

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Contributions. Conception and design of the study: C.X. Acquisition of data: F.L., and HL. Analysis and interpretation of the data: C.X., F.L., C.Y.W., and J.Z. Writing and revision of the manuscript: C.X., and F.L. All authors reviewed the manuscript.

Availability of Data and Materials. The datasets used and/or analyzed during this current study are available from the corresponding author on reasonable request.

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