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HEAD AND NECK

Significant association of the cytokine variants with head and neck cancer risk: evidence from meta-analysis

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Abstract

Aim To evaluate the possible relevance of the IL-18-137 G>C (rs187238), IL-18-607 C>A (rs1946518) and IL-4-590 C>T (rs2243250) polymorphisms to the genetic susceptibility of head and neck cancer.

Methods Data were retrieved from PubMed, EMBASE, Web of Science and CNKI databases, and the results were independently analysed by two reviewers using Stata 14.0 software.

Results After searching for and assessing the literature, a total of thirteen studies involving 2,959 patients newly diagnosed as head and neck cancer and 3,622 controls from healthy donors were analysed. The results suggested that a strong relationship between patients and healthy controls was observed in the IL-18-137 G>C polymorphism in consistence with the result (CC vs. GG + GC: OR = 1.63, $P = 0.004$; CC vs. GG: OR = 1.82, $P = 0.001$). When stratified by cancer type, ethnicity and the source of control samples, significant and elevated risks were obtained in the genetic susceptibility to Asian patients with NPC in all genetic models and in those studies using the PCR-RFLP test method. In addition, comparable results were obtained for the IL-18-607 C>A polymorphism, especially for Asian patients with NPC.

Conclusions It should be a potential association between IL-18 variants and nasopharyngeal carcinoma. Furthermore, IL-18 gene variants might be considered as a critical role in predicting the occurrence of nasopharyngeal carcinoma in Asian population. However, the IL-4-590 C>T polymorphism does not influence the development of head and neck cancer.

Keywords Interleukin-18-137 G>C (rs187238) · Interleukin-18-607 C>A (rs1946518) · Interleukin-4-590 C>T (rs2243250) · Head and neck cancer · Polymorphism · Meta-analysis

Introduction

As the sixth most common malignancy in the world, head and neck cancer (HNC) occurs in epithelial tissues of various origins consisting of the oral and maxillofacial cavities, pharynx and larynx [1, 2]. Among the different types of HNC, oral cancer and nasopharyngeal carcinoma (NPC) are the most common [3, 4]. More than 90% of these malignancies are squamous cell carcinoma (SCC) [5]. HNC has become a serious global health problem, with estimated more than 550,000 new cases and 300,000 deaths every year [6]. In 2015, there were 106,540 newly diagnosed cases of HNC and 11,710 expected related deaths in the USA alone [7]. Epidemiological evidence indicates that the overall 5-year survival of HNC patients has not significantly improved in the past decade [8]. Pathogenetic mechanisms of head and neck organs are involved into a multifactorial process arising from genetic alterations in oncogenes and tumour suppressor genes as well as due to the interaction of environmental factors such as smoking, alcohol intake and betel quid chewing, as well as lack of oral hygiene. According to previous studies, HPV infection has also emerged as a risk factor for the transformation of normal tissues into malignant lesions [9–11]. Recently, chronic inflammation stimulated by exposure to chemical, bacterial and viral agents has been proved that it has an important effect on the development and progression of cancer. Immune dysfunction induced

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by certain autoimmune reactions, also enhances the occurrence of various cancers, including head and neck cancer [12–16]. Cytokines are low-molecular-weight regulatory polypeptides of the immune system, which accumulate in the immune microenvironment. Functional single nucleotide polymorphisms (SNPs) on cytokine-encoding genes can strongly induce the proliferation of malignant cell by immune system disorders and enhance the capability of malignant transformation and tumour growth [12–16]. SNPs on the gene encoding the pro-inflammatory interleukins IL-18 are located on chromosome 11q22 [17], which induce alterations in its promoter region (-607 C>A, -137 G>C), and these genetic polymorphisms are responsible for the progression of some malignancies, such as esophageal squamous cell carcinoma [18]. The anti-inflammatory cytokines IL-4 is associated with humoral immune responses and induces a potent cytotoxic response against tumors, which is secreted by Th2 cells [19, 20]. It is also an autocrine growth factor, responsible for the induction of IgE production by B cell, and it can antagonize the function of IFN-γ and inhibit the activation of macrophages [21]. A key SNP on the promoter region of the IL-4 gene (-590 C>T), referred to as rs2243250 [22], is relevant to cancer. On the other hand, increased serum levels of IL-18 have been tested in cancers of various origins (colon, gastrointestinal tract and breast carcinomas) [21, 23–25]. To date, there have been a few studies investigating the association of IL-18-137 G>C, IL-18-607 C>A and IL-4-590 C>T polymorphisms with HNC risk, but the results have been inconsistent. Until now, there has been no specific meta-analysis or systematic review on the risk of HNC in relation to polymorphisms in IL-18 nor IL-4 polymorphism. Given that, we propose to perform a meta-analysis to better understand the relationship between HNC risk and SNPs on the IL-18 and IL-4 genes.

Methods

Search strategy

A search strategy based on combinations of the key words such as: “IL-18” or “interleukin-18”; “IL-4”, or “interleukin-4”; “polymorphism” or “variant”; “head and neck cancer” and “oral cancer”, “nasopharyngeal cancer”, “pharynx cancer”, or “larynx cancer”, was applied on all studies selected before June 2017, using PubMed, EMBASE, Web of Science and CNKI databases without language restriction. Combined phrases with information on specific genes or SNPs from studies were also used. References cited in selected original studies and previous meta-analyses and review articles were scanned to avoid missing to be included in.

Inclusion criteria

The inclusion criteria were as follows: (a) case–control study design, (b) relevance of polymorphisms in IL-18 and IL-4 to head and neck cancer risk/susceptibility, and (c) sufficient genotype data or data allowed to be calculated.

Exclusion criteria

The exclusion criteria were as follows: (a) review articles, (b) absence of the proposed SNPs or completed data on genotypes, (c) repeated publications by the same author or team, (d) studies based on animals or cell lines, and (e) unreliable and unreasonable materials and methods.

Data extraction

The extracted data included: the first author’s name (first name for record), year of publication, country, ethnicity (Asian or Caucasian), sources of controls, cancer types, genotyping methods, allele counts in HNC cases and controls, p for the Hardy–Weinberg equilibrium (HWE) using Fisher’s exact test, and Newcastle-Ottawa Scale (NOS) scores. Importantly, some details about patients, such as stage classification of cancer were also obtained. All the information was collected by two investigators independently. A third reviewer was required (Li) when the results were inconsistent.

Quality assessment

All the information was collected by two investigators independently. A third reviewer was required (Li) when the results were inconsistent. NOS scores were used to assess the quality of individual case–control studies. In brief, assessment scores ranged from 0 points (worst) to 9 points (best). A final score > 6 was considered as high quality.

Statistical analysis

The potential association of the three functional SNPs with head and neck cancer risk was assessed by odds ratio (OR) with 95% confidence interval (95% CI). $P < 0.05$ was defined significant. For rs1946518 polymorphism, the pooled ORs were calculated for the allele model (A vs. C), dominant model (CA + AA vs. CC), recessive model (AA vs. CC + CA) and codominant model (CA vs. CC, AA vs. CC). The same genetic models were also applied in rs187238

and rs2243250 polymorphisms. Necessarily, subgroup analyses of ethnicity, cancer types, source of controls and genotyping methods were also performed and statistically evaluated. Cochran's Q statistic and I^2 method was applied in heterogeneity [26]. $I^2 = 0$–50% meant no heterogeneity and $I^2 = 50$–75% meant moderate heterogeneity, and $I^2 > 75\%$ suggested high heterogeneity. The fixed-effect model (also called the Mantel–Haenszel method) was chosen for meta-analysis only when the heterogeneity tests yielded significant results ($p > 0.1$ or $I^2 < 40\%$) [27]. Otherwise, the random-effects model (also called the DerSimonian and Laird method) [28] was selected. All analyses were conducted using Stata 14.0 (Stata Corporation, College Station, TX, USA).

Results

Studies characteristics

The flowchart of the search process is presented in Fig. 1 and followed the method described in previous publications [29, 30]. A total of 204 studies were retrieved through databases searches using several combinations of keywords. After removing repeated records, an additional 130 studies were excluded for irrelevant title. Then, two papers of meta-analyses, one of case-only study and one lacking of specific data, were excluded. The remaining 14 full-text articles got assessed further for eligibility. Among the excluded studies, the data derived from two different studies had been pooled into one manuscript. Finally, thirteen studies satisfied the inclusion criteria of this analysis, being the basis of three independent study panels (Table 1). Of those, eight studies on IL-18-137 G>C polymorphism [29–36], nine studies on IL-18-607 C>A polymorphism [29–37], and four studies on IL-4-590 C>T polymorphism [38–41], respectively. Nine studies involved Asian populations [29–31, 33, 35, 36, 38, 39, 41], and four studies involved Caucasian populations [32, 34, 37, 40]. Regarding cancer type, five studies reported on nasopharyngeal carcinoma [29, 30, 32–34], seven reports on oral cancer/ oral squamous cell carcinoma (OSCC) [35–41], and one reported on HNC [31] and pharyngeal squamous cell carcinoma (PSCC) [41]. In terms of the genotyping method, seven studies adopted polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) [23, 29, 30, 32, 33, 37, 38, 40], two studies adopted the TaqMan assay (Applied Biosystems) [36, 41], two studies used PCR [35, 39], and two studies used alleles specific-PCR (AS-PCR) [31, 34]. Only three studies deviated from HWE in the three SNPs, respectively.

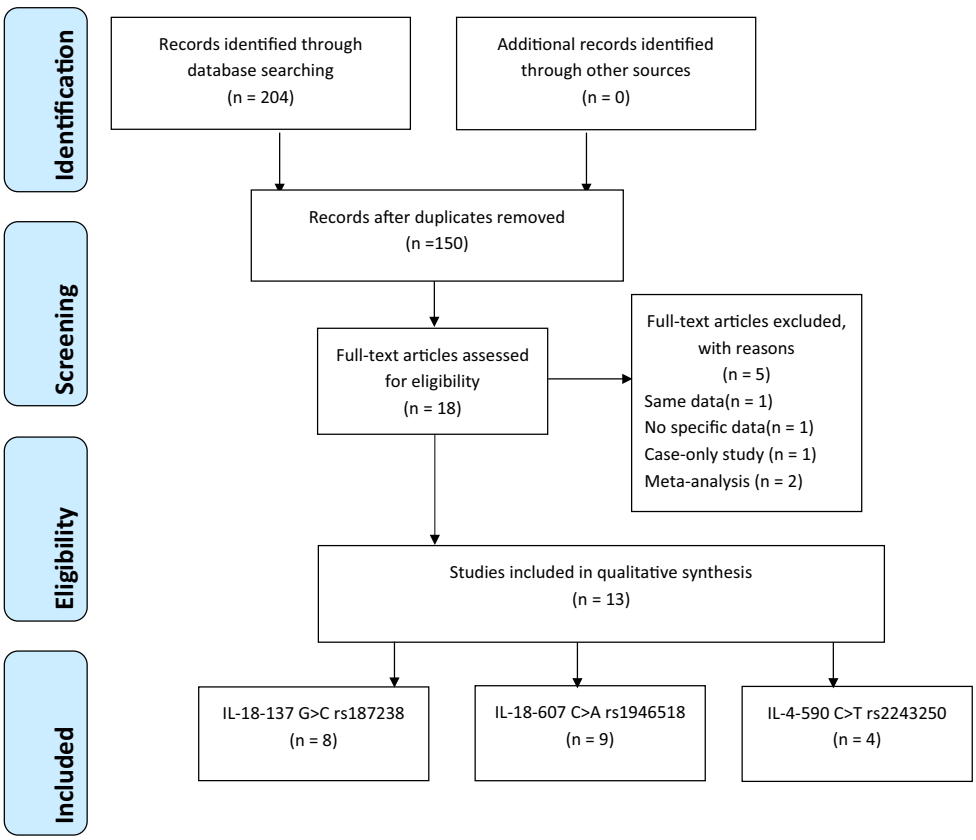

Fig. 1 The flow chart of inclusion and exclusion

Table 1 Characteristics of Studies Included in this Meta-analysis

First author	Year	Country	Ethnicity	SNP	Cancer type	Stage classification		Genotyping method	Source of controls	Age (mean + SD) year		Gender *N* (male/female)		Case	Control	Genotype distribution						*P* for HWE	NOS
																Case			Control				
						Stage I + II	Stage III + IV			Case	Control	Case	Control			GG	GC	CC	GG	GC	CC		
Singh	2014	India	Asian	IL-18-137	Oral cancer	175	93	PCR	Hospital	47.67 ± 12.67	43.1 ± 8.31	219/53	142/43	272	185	221	51	0	122	63	0	0.005	5
Pan	2013	China	Asian	IL-18-137	Nasopharyngeal carcinoma	NA	NA	PCR-RFLP	Hospital	48 ± 8	47 ± 8	135/55	140/60	190	200	102	74	14	139	52	9	0.16	5
Tsai[a]	2013	Taiwan	Asian	IL-18-137	Oral cancer	248	319	TaqMan	Population	54.25 ± 0.47	51.86 ± 0.62	545/22	456/103	57	559	437	122	8	476	78	5	0.37	6
Du	2012	China	Asian	IL-18-137	Nasopharyngeal carcinoma	NA	NA	PCR-RFLP	Hospital	49.8 ± 10.5	NA	NA	NA	150	180	88	51	11	131	43	6	0.3	5
ASEFI	2009	Iran	Asian	IL-18-137	Head and neck cancer			AS-PCR	Hospital	56.7 ± 13.7	53.3 ± 12.2	86/25	165/47	111	212	65	37	9	116	79	17	0.50	6
Nong	2009	China	Asian	IL-18-137	Nasopharyngeal carcinoma	81	169	PCR-RFLP	Population	48.6 ± 8.9	47.7 ± 9.1	176/74	179/91	250	270	140	88	22	189	70	11	0.17	7
Farhat	2008	Tunisia	Caucasian	IL-18-137	Nasopharyngeal carcinoma	10	150	PCR-RFLP	Population	41.97 ± 16	42.09 ± 15.55	116/47	116/48	163	164	75	73	15	83	68	13	0.86	6
Pratesi	2006	Italy	Caucasian	IL-18-137	Nasopharyngeal carcinoma	30	53	AS-PCR	Population	< 50:45 > 50:42	< 50:97 > 50:33	70/19	100/30	89	130	43	39	7	72	53	5	0.21	6

First author	Year	Country	Ethnicity	SNP	Cancer Type	Stage Classification		Genotyping method	Source of controls	Age (Mean + SD) year		Gender *N* (male/female)		Case	Control	Genotype distribution						P for HWE	NOS
																Case			Control				
						Stage I + II	Stage III + IV			Case	Control	Case	Control			CC	CA	AA	CC	CA	AA		
Singh	2014	India	Asian	IL-18-607	Oral cancer	175	93	PCR	Hospital	47.67 ± 12.67	43.1 ± 8.31	219/53	142/43	272	185	79	154	39	65	96	24	0.21	5
Tsai[a]	2013	Taiwan	Asian	IL-18-607	Oral cancer	248	319	TaqMan	Population	54.25 ± 0.47	51.86 ± 0.62	545/22	456/103	567	559	140	262	165	135	276	148	0.78	6

Table 1 (continued)

First author	Year	Country	Ethnicity	SNP	Cancer Type	Stage Classification		Genotyping method	Source of controls	Age (Mean + SD) year		Gender *N* (male/female)		Case	Control	Genotype distribution						P for HWE	NOS
						Stage I + II	Stage III + IV			Case	Control	Case	Control			Case			Control				
																CC	CA	AA	CC	CA	AA		
Pan	2013	China	Asian	IL-18-607	Nasopharyngeal carcinoma	NA	NA	PCR-RFLP	Hospital	48 ± 8	47 ± 8	135/55	140/60	190	200	40	97	53	56	93	51	0.31	5
Du	2012	China	Asian	IL-18-607	Nasopharyngeal carcinoma	NA	NA	PCR-RFLP	Hospital	49.8 ± 10.5	NA	NA	NA	150	180	36	80	34	47	93	40	0.64	5
ASEFI	2009	Iran	Asian	IL-18-607	Head and neck cancer	43	68	AS-PCR	Hospital	56.7 ± 13.7	53.3 ± 12.2	86/25	165/47	111	212	43	53	15	82	101	29	0.81	6
Nong	2009	China	Asian	IL-18-607	Nasopharyngeal carcinoma	81	169	PCR-RFLP	Population	48.6 ± 8.9	47.7 ± 9.1	176/74	179/91	250	270	47	132	71	69	133	68	0.81	6
Farhat	2008	Tunisia	Caucasian	IL-18-607	Nasopharyngeal carcinoma	10	150	PCR-RFLP	Population	41.97 ± 16	42.09 ± 15.55	116/47	116/48	163	164	41	94	28	53	77	34	0.54	7
Vairaktaris	2007	Greece	Caucasian	IL-18-607	Oral cancer	76	60	PCR-RFLP	NA	58.6 ± 10.2	57.5 ± 18.8	NA	NA	149	89	55	66	28	35	32	22	0.01	6
Pratesi	2006	Italy	Caucasian	L-18-607	Nasopharyngeal carcinoma	30	53	AS-PCR	Population	< 50:45 > 50:42	< 50:97 > 50:33	70/19	100/30	89	130	26	42	21	43	64	23	0.92	6
Yang	2014	Taiwan	Asian	IL-4-590	PSCC	330	262	TaqMan	Population	51.8 ± 9.8	52 ± 11.3	126/3	583/40	129	623	4	43	82	23	218	382	0.23	6
Yang	2014	Taiwan	Asian	IL-4-590	OSCC	330	262	TaqMan	Population	52.0 ± 10.9	52 ± 11.3	430/33	583/40	463	623	13	148	302	23	218	382	0.23	6
P Gaur	2011	India	Asian	IL-4-590	OSCC	32	108	PCR-RFLP	NA	51.4 ± 13.6	NA	119/21	NA	140	120	18	55	67	9	35	76	0.10	6

Table 1 (continued)

First author	Year	Country	Ethnicity	SNP	Cancer Type	Stage Classification		Genotyping method	Source of controls	Age (Mean + SD) year		Gender *N* (male/female)		Case	Control	Genotype distribution						P for HWE	NOS
						Stage I + II	Stage III + IV			Case	Control	Case	Control			Case			Control				
																CC	CT	TT	CC	CT	TT		
Vairaktaris	2006	Greece	Caucasian	IL-4-590	OSCC	NA	NA	PCR-RFLP	NA	58.4 ± 10.2	54.2 ± 11.6	126/30	120/42	156	162	84	46	26	99	48	15	0.016	5
Tsai[b]	2005	China	Asian	IL-4-590	OSCC	NA	NA	PCR	Population	53.27 ± 12.27	53.02 ± 10.08	120/10	60/45	130	105	9	21	100	2	28	75	0.74	7

NA not afford

[a]Tsai: Tsai HT, et al.

[b]Tsai: Tsai MH, et al.

Meta-analysis

After reviewing the literature, a total of 2959 patients of HNC and 3,622 controls from healthy population were incorporated into this meta-analysis. The pooled counts of three genotypes of the proposed SNP variants are shown in Table 2.

Association between rs187238 polymorphism and HNC risk

With regard to rs187238 polymorphism, eight studies with a total of 1,792 patients and 1,900 cancer-free controls were analysed. Significant results were found in the following genetic models: CC vs. GG + GC: OR = 1.63, $P = 0.004$; CC vs. GG: OR = 1.82, $P = 0.001$, without heterogeneity (Table 2). However, none of other three models yielded significant association (all $P > 0.05$). And heterogeneities existed in other three genotype models, after they were analysed based on subgroups, the differences in ethnicity and cancer type may be responsible for these heterogeneities. In addition, significant and elevated risks were obtained in the genetic susceptibility to Asian patients with NPC in all genetic models and in those studies using the PCR-RFLP test method, but not in Caucasian patients with any types of HNC (Dominant model: OR = 1.89, $P = 0.000$; Recessive model: OR = 2.07, $P = 0.004$; Allele model: OR = 1.84, $P = 0.000$; GC vs. GG: OR = 1.79, $P = 0.000$; CC vs. GG: OR = 2.50, $P = 0.000$) (Table 2; Fig. 2).

Association of rs1946518 polymorphism with head and neck cancer risks

The results of the analysis of rs1946518 polymorphism presented as forest plots provided obvious evidence of association between the SNP and head and neck cancer susceptibility between cases and controls (CA + AA vs. CC: OR 1.18, 95% CI 1.02–1.36, $P = 0.022$; A vs. C: OR 1.10, 95% CI 1.00–1.20, $P = 0.043$ and CA vs. CC: OR 1.18, 95% CI 1.01–1.37, $P = 0.032$) (Table 2). Overall, the data from 1941 cases and 1989 controls were analysed. No heterogeneity was observed among the studies in any of the genetic models (Table 2). The pooled ORs were used in a fixed effects model. After stratified analysis, IL-18-607 C>A was found to be relevant to increased risk in only Asian populations with NPC for three models (CA + AA vs. CC: OR 1.36, $P = 0.021$; AA vs. CC: OR 1.39, $P = 0.045$ and CA vs. CC: OR 1.36, $P = 0.033$), but without any replication in Caucasian patients nor oral cancer (Table 2; Fig. 3).

Table 2 Subgroup analyses

Subgroup	*n*	Case/control	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)
IL-18-137 G>C			Dominant model				Recessive model				Allele model				GC VS. GG				CC VS. GG			
Total	8	1792/1900	1.29	0.91–1.82	0.159	82.3	1.63	1.16–2.27	0.004	0.0	1.28	0.95–1.73	0.101	82.6	1.24	0.88–1.76	0.223	80.8	1.82	1.30–2.56	0.001	0.0
Ethnicity (cancer type)																						
Asian	6	1540/1606	1.29	0.82–2.04	0.272	87.3	1.71	1.16–2.53	0.007	0.0	1.30	0.87–1.92	0.197	87.3	1.25	0.79–1.97	0.336	86.2	1.93	1.30–2.87	0.001	0.0
Nasopharyngeal	3	590/650	1.89	1.49–2.39	0.000	0.0	2.07	1.26–3.39	0.004	0.0	1.84	1.51–2.24	0.000	0.0	1.79	1.40–2.29	0.000	0.0	2.50	1.52–4.13	0.000	0.0
Oral cancer	2	839/744	0.88	0.24–3.27	0.850	96.0	1.59	0.52–4.88	0.421	.	0.91	0.29–2.87	0.875	95.5	0.88	0.24–3.27	0.849	95.9	1.74	0.57–5.37	0.333	.
Caucasian	2	252/294	1.25	0.89–1.63	0.196	60.2	1.41	0.74–2.69	0.300	0.0	1.21	0.93–1.58	0.150	0.0	1.21	0.85–1.72	0.300	0.0	1.54	0.79–3.00	0.207	0.0
Nasopharyngeal	2	252/294	1.25	0.89–1.75	0.196	0.0	1.41	0.74–2.69	0.300	0.0	1.21	0.93–1.58	0.150	0.0	1.21	0.85–1.72	0.300	0.0	1.54	0.79–3.00	0.207	0.0
Genotyping method																						
PCR-RFLP	4	1320/1373	1.70	1.37–2.11	0.000	8.3	1.77	1.17–2.67	0.007	0.0	1.62	1.28–2.06	0.000	48.9	1.63	1.31–2.03	0.000	0.0	2.08	1.37–3.17	0.001	0.0
AS-PCR	2	200/342	1.04	0.68–1.60	0.852	31.7	1.30	0.66–2.55	0.442	1.6	1.08	0.74–1.57	0.686	41.9	0.99	0.66–1.45	0.965	3.5	1.28	0.64–2.55	0.479	30.5
PCR	2	366/445	0.61	0.32–1.19	0.148	73.0	–	–	–	–	0.74	0.34–1.60	0.447	84.6	0.53	0.35–0.80	0.002	25.6	–	–	–	–
Source of controls																						
Population	4	1069/1123	1.58	1.30–1.91	0.000	0.0	1.71	1.10–2.68	0.018	0.0	1.51	1.20–1.90	0.001	48.9	1.52	1.25–1.86	0.000	0.0	1.94	1.23–3.05	0.004	0.0
Hospital	4	723/777	1.09	0.54–2.21	0.81	90.2	1.51	0.91–2.52	0.111	0.0	1.09	0.61–1.95	0.763	89.5	1.06	0.53–2.14	0.868	89.2	1.68	1.00–2.80	0.049	29.3
IL-18-607 C>A			Dominant model				Recessive model				Allele model				CA VS. CC				AA VS. CC			
Total	9	1941/1989	1.18	1.02–1.36	0.022	0.0	1.16	1.00–1.35	0.051	0.0	1.10	1.00–1.20	0.043	0.0	1.18	1.01–1.37	0.032	0.0	1.18	0.99–1.42	0.069	0.0
Ethnicity (cancer type)																						
Asian	6	1540/1606	1.16	0.99–1.37	0.067	0.0	1.23	1.04–1.45	0.015	0.0	1.11	1.00–1.22	0.052	0.0	1.14	0.96–1.35	0.136	1.5	1.22	0.99–1.49	0.062	0.0

Table 2 (continued)

Subgroup	*n*	Case/control	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)
Naso-pharyn-geal	3	590/650	1.36	1.05–1.78	0.021	0.0	1.12	0.87–1.45	0.37	0.0	1.17	1.00–1.37	0.052	0.0	1.36	1.03–1.80	0.033	0.0	1.39	1.01–1.91	0.045	0.0
Oral cancer	2	839/744	1.07	0.86–1.34	0.552	36.5	1.36	1.08–1.72	0.01	0.0	1.08	0.93–1.24	0.312	0.0	1.03	0.81–1.31	0.795	50.0	1.13	0.85–1.50	0.405	0.0
Caucasian	3	401/383	1.25	0.92–1.70	0.150	0.0	0.90	0.64–1.29	0.578	25.1	1.07	0.87–1.31	0.525	0.0	1.35	1.02–1.37	0.077	0.0	1.07	0.72–1.60	0.737	0.0
Naso-pharyn-geal	2	252/294	1.33	0.91–1.92	0.137	0.0	1.01	0.66–1.55	0.963	44.7	1.13	0.89–1.44	0.320	0.0	1.36	0.92–2.01	0.126	0.0	1.23	0.752–2.01	0.41	0.0
Genotyping method																						
PCR-RFLP	5	902/903	1.33	1.08–1.65	0.008	0.0	1.01	0.81–1.25	0.941	0.0	1.12	0.98–1.28	0.092	0.0	1.39	1.11–1.74	0.004	0.0	1.23	0.94–1.60	0.129	0.0
AS-PCR	2	200/342	1.07	0.74–1.55	0.709	0.0	1.19	0.74–1.90	0.467	0.0	1.09	0.84–1.40	0.520	0.0	1.03	0.70–1.52	0.871	0.0	1.21	1.00–1.43	0.485	0.0
Source of controls																						
Population	4	1069/1123	1.16	0.96–1.41	0.135	17.8	1.27	1.04–1.53	0.016	19.7	1.10	0.98–1.24	0.103	0.0	1.13	0.92–1.39	0.241	39.7	1.20	0.95–1.53	0.127	0.0
Hospital	4	723/777	1.23	0.98–1.54	0.080	0.0	1.08	0.83–1.40	0.582	0.0	1.11	0.96–1.29	0.148	0.0	1.23	0.97–1.56	0.094	0.0	1.24	0.91–1.69	0.173	0.0
IL-4-590 C>T C>T			Dominant model				Recessive model				Allele model				CT VS. CC				TT VS. CC			
Total	5	1018/1633	0.97	0.60–1.57	0.912	43.1	1.09	0.78–1.54	0.606	65.9	1.04	0.79–1.36	0.792	67.4	0.97	0.69–1.36	0.871	26.6	0.98	0.50–1.89	0.945	62.0
Ethnicity (cancer type)																						
Asian	4	862/1471	0.81	0.43–1.53	0.512	42.7	1.00	0.70–1.41	0.980	65.7	0.95	0.71–1.29	0.753	66.8	0.86	0.54–1.35	0.505	40.1	0.78	0.38–1.60	0.490	53.0
OSCC	3	733/848	0.69	0.29–1.62	0.393	58.6	0.95	0.56–1.61	0.851	77.0	0.90	0.58–1.39	0.633	77.4	0.69	0.28–1.70	58.2	0.422	0.65	0.25–1.70	0.379	65.9
Genotyping method																						
TaqMan	2	592/1246	1.29	0.72–2.30	0.394	0.0	1.16	0.94–1.43	0.171	0.0	1.14	0.95–1.37	0.151	0.0	1.18	0.65–2.15	0.587	0.0	1.35	0.75–2.43	0.318	0.0
PCR-RFLP	2	296/282	0.93	0.39–2.20	0.862	70.7	1.00	0.28–3.59	0.999	89.2	0.93	0.38–2.23	0.865	91.0	1.04	0.67–1.60	0.871	0.0	0.97	0.22–4.36	0.968	86.3
Source of controls																						
Population	3	722/1351	0.93	0.41–2.09	0.858	44.6	1.18	0.97–1.44	0.107	0.0	1.13	0.95–1.34	0.169	0.0	0.88	0.52–1.50	0.645	59.3	1.00	0.47–2.17	0.991	38.2

Table 2 (continued)

Subgroup	*n*	Case/control	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)
NA	2	296/282	0.93	0.39–2.20	0.862	70.7	1.00	0.28–3.59	0.999	89.2	0.93	0.38–2.23	0.865	91.0	1.04	0.67–1.60	0.871	0.0	0.97	0.22–4.36	0.968	86.3

NA not afford
[a]Tsai: Tsai HT, et al.
[b]Tsai: Tsai MH, et al.

No difference between rs2243250 polymorphism and head and neck cancer risk

For rs2243250 polymorphism, five studies with 1018 patients and 1633 healthy donors were included. Heterogeneities existed in all genotype models. ORs were calculated using a random effects model. No relevance was found in IL-4-590 C>T susceptibility to HNC in any genotypes. In terms of the analyses based on subgroups, the differences in genotyping method may be helpful to explain these heterogeneities, and there was no any association obtained under any genetic model (all $P > 0.05$) (Table 2).

Sensitivity analysis

The estimated pooled OR change slightly showed in sensitivity analysis, which indicated that our results were statistically stable, by removing one study at a time from the analysis (Figs. 4, 5).

Publication bias

Begg's test and Egger's test (figures not shown) were performed to assess the publication bias among overall selected studies. As a result, there was no obvious evidence of publication bias in IL-18 and IL-4-590 gene polymorphisms under the dominant model ($P > 0.05$) (Figs. 6, 7).

Discussion

IL-18 and IL-4 levels have been found to be significantly increased in HNSCC cell lines [19, 42]. Recent reports confer that IL-4 may achieve the ability in inducing the growth of HNSCC cell lines through a paracrine mechanism [43]. Similar results have also been found in ovarian carcinomas, prostate cancer, melanoma and various types of lymphomas [22, 43–46]. The number of T cells expression by IL-4 in oral cancer patients is significantly higher than that in normal controls [23, 47]. Evidence has been shown that IL-4 could directly increase the proliferation rate of HNSCC cell lines [19]. There was a slight increase observed in the frequency of the T allele in oral cancer patients, compared to controls in a study on Chinese populations. Increased levels of IL-18 have been observed in many cancers, such as esophageal, colon, and skin carcinoma [48, 49]. A previous study has suggested that the overexpression of IL-18 could downregulate cyclin D1 expression and affect the caspase-dependent cell death, which decreased cell viability and induced apoptosis, respectively, in human tongue SCC cells [50]. However, the mechanisms of how IL-18-137 G>C, IL-18-607 C>A and IL-4 -590 C>T mutations influence

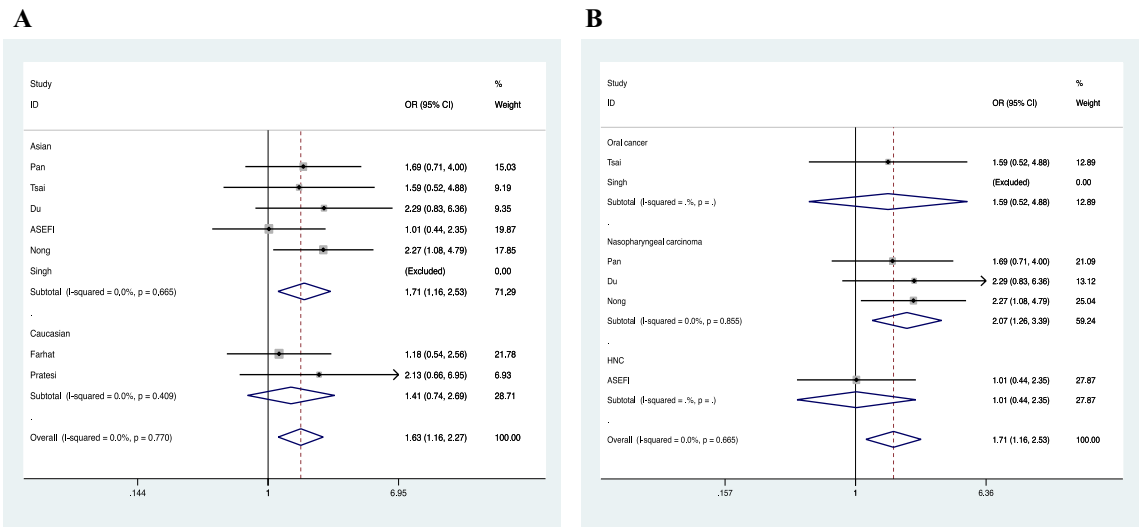

Fig. 2 Meta-analysis of the association between IL-18-137 G>C polymorphism and susceptibility to HNC subgroup by **a** ethnicity; **b** cancer type in Asian population under recessive model

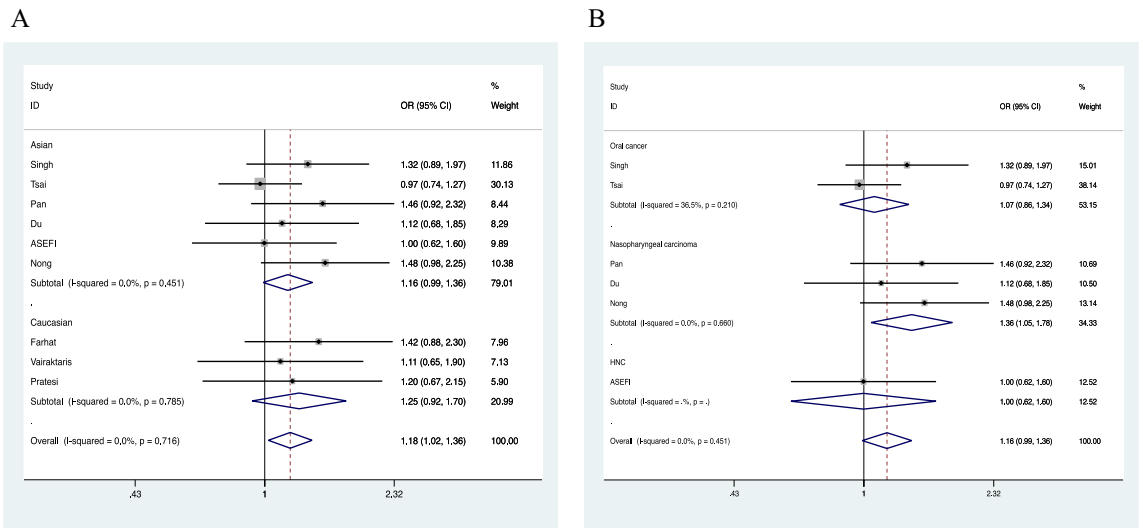

Fig. 3 Meta-analysis of the association between IL-18-607 C>A polymorphism and susceptibility to HNC subgroup by **a** ethnicity; **b** cancer type in Asian population under dominant model

the risk of HNC and the extent to which the variants are responsible for HNC risk are still unclear. Previous studies have shown that the specific associations between IL-18-137 G>C, IL-18-607 C>A and IL-4-590 C>T polymorphisms and HNC risk are controversial. Therefore, it is worth conducting a meta-analysis from all available studies to figure out these specific associations. In the present meta-analysis, thirteen case–control studies were involved, consisting of 2959 patients and 3622 healthy donors. There was a slight association between IL-18-137 G>C and HNC risk in some genetic models. Interestingly, in the stratified analyses, a significant increase of risk was found in Asian patients diagnosed with NPC and assessed with the PCR-RFLP method in overall genetic models. Furthermore, for the IL-18-607 C>A polymorphism, the results indicated that a high frequency of the A variant was found in HNC patients, indicating that the genetic variant could have an effect on the progression of head and neck cancer by influencing the maturation of IL-18 or by altering the interaction of IL-18-607 with its corresponding genes or targets. Moreover, the subgroup analyses showed a significant increase in the risk to Asian patients with nasopharyngeal carcinoma. In general, we found strong associations between SNPs on the IL-18 gene and head and neck cancer, especially for nasopharyngeal carcinoma in Asian population. In contrast, there was no

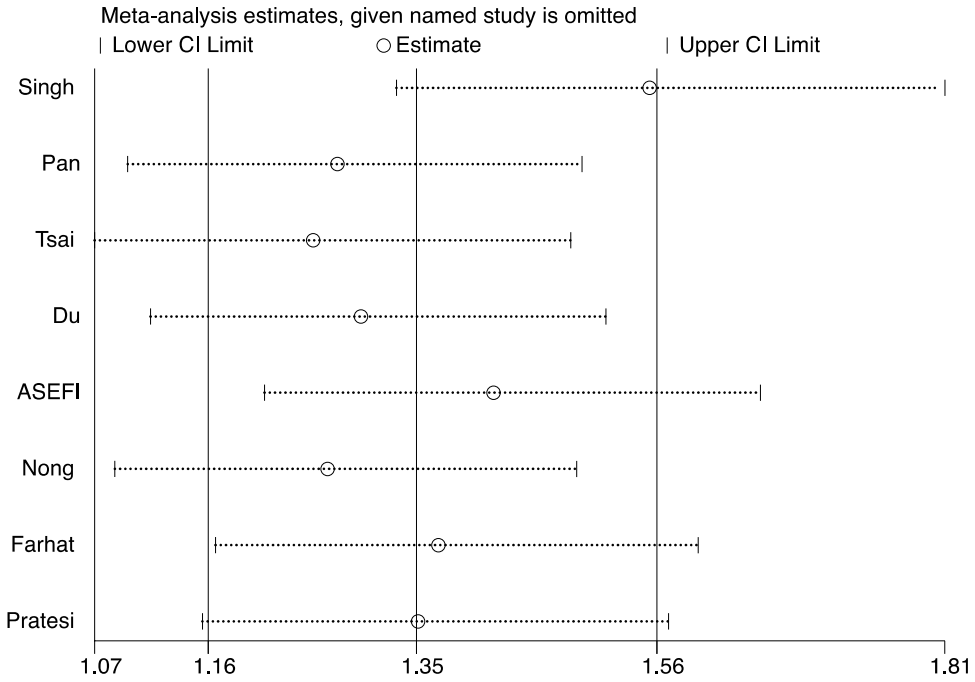

Fig. 4 Sensitivity analysis of the summary odds ratio coefficients on the relationships of IL-18-137 G>C polymorphism with the risk of HNC risk under the dominant model

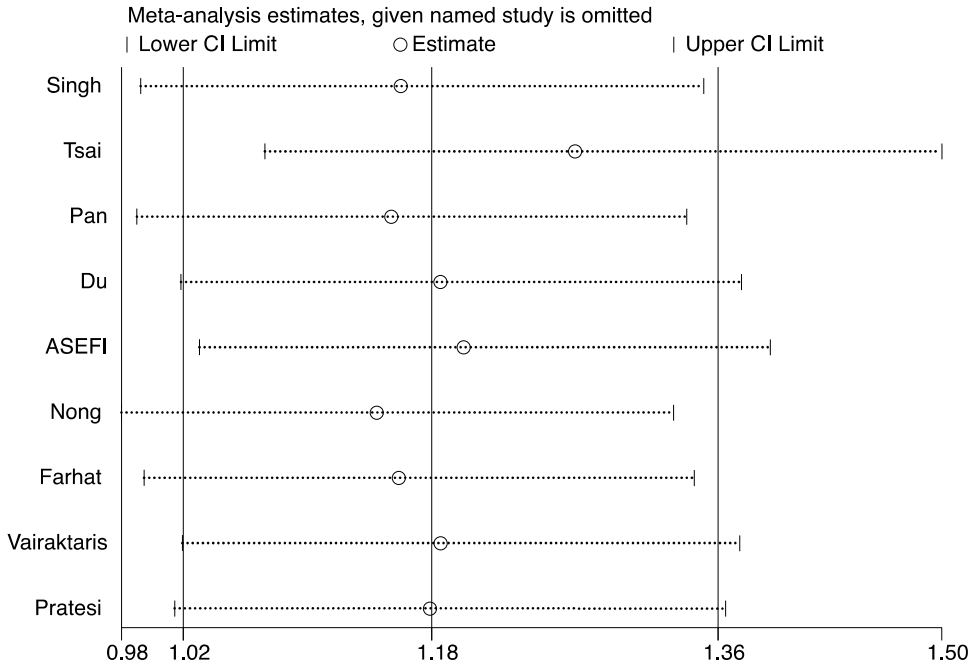

Fig. 5 Sensitivity analysis of the summary odds ratio coefficients on the relationships of IL-18-607 C>A polymorphism with the risk of HNC risk under the dominant model

any significant association of HNC risks with the IL-4 -590 C>T polymorphism.

To the best of our knowledge, this is the most comprehensive quantitative assessment of polymorphisms in these two key cytokines, related to inflammation that is specifically focused on their functions in the pathogenetic process of head and neck cancer. It is noteworthy that there are certain limitations of our analyses. First, heterogeneities exist in some genetic models. It is known that heterogeneity in a systematic review refers to the variability among studies [51]. In our study, differences in factors such as ethnicity, cancer type, cancer stage, age and gender among the selected studies could have resulted in heterogeneity. Meanwhile, the lack of unified methods to collect and analyze samples could change these results. Second, small-study effects are unavoidable in such a meta-analysis with a small sample size and a limited number of papers. Third, we could not

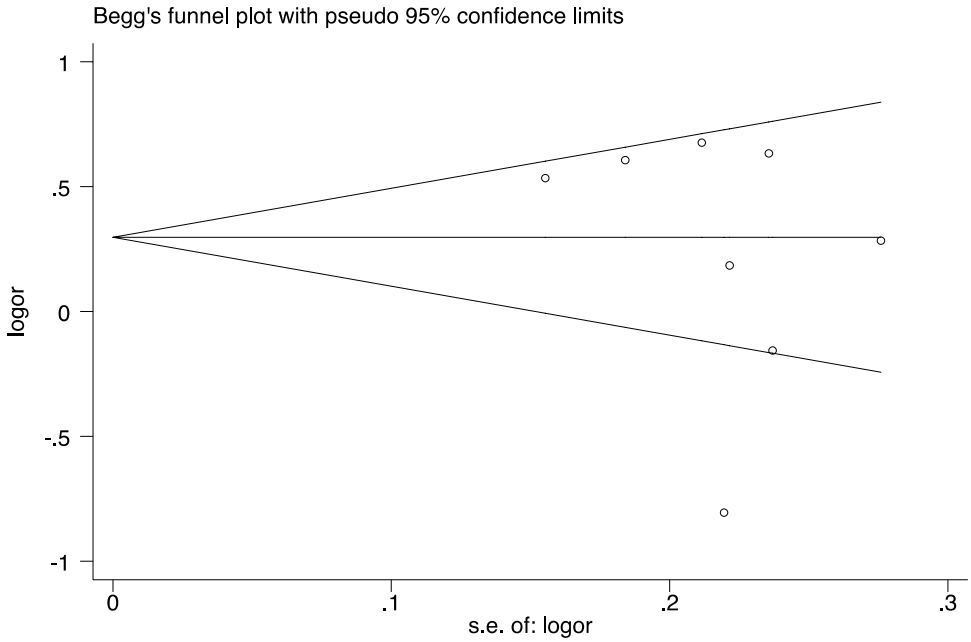

Fig. 6 Funnel plot for the meta-analysis of the association between IL-18-137 G>C polymorphism and oral cancer risk under the dominant model

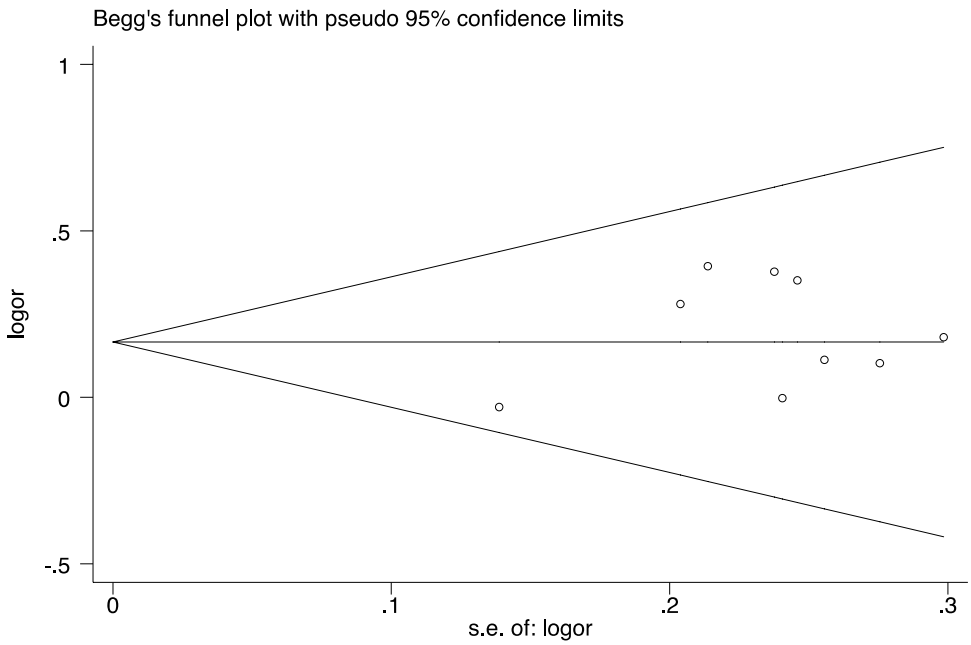

Fig. 7 Funnel plot for the meta-analysis of the association between IL-18-607 C>A polymorphism and oral cancer risk under the dominant model

determine the interaction between the environmental factors and genetic mutation and distribution or disease stage, age and gender. Nevertheless, we believe that these quantitative results can provide some evidence on how these key variants in cytokines play roles in the pathogenesis and progression of head and neck cancer.

In conclusion, the current data reveal that rs187238 and rs1946518 polymorphisms are more likely to represent potentially valuable genetic biomarkers that are related to indicate the susceptibility to nasopharyngeal carcinoma. Furthermore, IL-18 gene variants may serve as important biomarkers in predicting the occurrence of nasopharyngeal carcinoma in Asian population. However, the IL-4-590 C>T (rs2243250) polymorphism does not influence the development of head and neck cancer. Nevertheless, more high-quality studies with completed data, including multiple populations from different ethnic backgrounds and more efficient, strict and unified genotyping methods are required for further evaluation.

Compliance with ethical standards

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Conflict of interest We declare that we have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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