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REVIEW

Association of IL-8 gene promoter -251 A/T and IL-18 gene promoter -137 G/C polymorphisms with head and neck cancer risk: a comprehensive meta-analysis

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Purpose: No consensus exists on the impact of polymorphisms in cytokines (such as interleukin IL-8 and IL-18) on cancer risk; moreover, there is very little evidence regarding head and neck cancer (HNC).

Methods: Thus, a meta-analysis including 22 studies with 4731 cases and 8736 controls was conducted to evaluate this association. The summary odds ratio (OR) and corresponding 95% confidence intervals (CIs) for C-X-C motif chemokine ligand 8 (CXCL8, which encodes IL-8) and IL-18 polymorphisms and HNC risk were estimated.

Results: The results showed a significantly increased risk of HNC susceptibility for IL18-137 G/C in five genetic models, but, interestingly, no significant association was found for the CXCL8-251 A/T polymorphism. When stratified by cancer type, an increased risk of nasopharyngeal cancer was found for both -137 G/C and -251A/T. When the studies were stratified by ethnicity and genotyping method, there were significant associations between Asian populations and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) studies for -137 G/C, and African populations for -251 A/T in some genetic models. A positive association was also found between the population-based groups in some models for -137 G/C; conversely, significantly decreased risk was found among the -251 A/T hospital-based group. Meta-regression was also conducted. The publication year, control source, and cancer type contributed to CXCL8 -251 A/T heterogeneity; however, no factors were found that contributed to IL-18 -137 G/C heterogeneity. Marginal significance was found in the recessive model for IL-18 -137 G/C by Egger's test, whereas no publication bias was detected for CXCL8 -251 A/T.

Conclusions: The results indicate that the IL-18 -137 G/C polymorphism is associated with HNC risk, especially nasopharyngeal cancer, in Asian populations and, when using PCR-RFLP, CXCL8 -251 A/T polymorphisms play a complex role in HNC development.

Keywords: interleukin-8, interleukin-18, polymorphism, head and neck cancer, meta-analysis

Introduction

Head and neck cancer (HNC), which encompasses malignant tumors of the larynx, pharynx, oral cavity, thyroid, and other related areas, is the 7th most common solid malignancy in the world, with approximately 686,000 new cases annually.[1] Although the exact pathogenetic mechanisms of HNC are still undefined, evidence indicates that HNC carcinogenesis is a complicated, multistep, and multifactorial process, involving genetic factors, tobacco smoking, alcohol consumption, viral infection, ultraviolet radiation, lifestyle, and environmental factors.[2–4] However, although many people are

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exposed to these extrinsic factors, only a small proportion develop HNC,[5] and a family history of HNC in first degree relatives elevates the risk.[6] This indicates the existence of genetic predisposition, and suggests that certain genetic factors, such as genes involved in inflammation, might be associated with the pathogenesis of HNC. Inflammation, which is associated with DNA damage, angiogenesis, proliferation, invasion, and metastasis, may play an important role in the oncogenesis and progression of HNC.[7,8] Recent studies suggest an association between HNC and increased pro-inflammatory cytokines. Among these cytokines, interleukin (IL)-8 and IL-18 have attracted increasing attention.[9–11]

As a member of the chemokine family, IL-8 is encoded by the C-X-C motif chemokine ligand 8 (CXCL8) gene, which is located on chromosome 4q-13-21 in humans. CXCL8 consists of a proximal promoter region, four exons, and three introns.[12] It is produced by a wide range of healthy cells (such as neutrophils, monocytes, endothelial cells, and fibroblasts), and several types of tumor cells.[13,14] Present evidence suggests that IL-8 promotes angiogenesis, tumorigenesis, tissue invasion, and metastasis.[15–17] Although CXCL8 contains several polymorphic sites, only three common polymorphisms have been reported in the coding sequence: +251 A/T, +396 G/T, and +781 C/T.[18] Polymorphisms may play important roles in some cancers, including ovarian, breast, bladder, and others.[19–22] An A/T single nucleotide polymorphism (SNP) is located at position -251 of CXCL8 in the transcription start site, which is associated with IL-8 expression.[23–26] A large number of studies have investigated associations between the CXCL8 -251 A/T (rs4073) gene polymorphism and the risk of human cancers, with conflicting conclusions.[27–32]

IL-18 is also a pro-inflammatory cytokine. A member of the IL-1 super-family, it is known as an inducer of interferon-γ.[33] IL-18 is produced by a number of cell types, such as activated blood and tissue monocytes/macrophages, Kupffer cells, T and B cells, osteoblasts, dendritic cells (DCs), microglia, and epithelial cells.[34] IL-18 induces the activation of natural killer cells and the proliferation of activated T cells, affecting both innate and acquired immunity.[35]

IL-18 is also associated with tumorigenesis, and has been reported to contribute to both anticancer and procancer processes.[36–39] The human IL-18 gene is located on chromosome 11q22.1–q22.3.[40] Three SNPs in the IL-18 promoter regions have been identified that could alter IL-18 expression (-137, -607, and -656).[41] However, the most commonly investigated and the most biochemically functional polymorphism is the -137 G>C (rs187238) polymorphism. Numerous studies have reported a role for the -137 G>C polymorphism in the susceptibility to various cancers, whereas the results of these studies mainly display that there is no association between IL-18 -137 G>C and cancer risk,[42,43] but, interestingly, in our present meta-analysis, we got a completely different result.

To our knowledge, no quantitative summary of the evidence regarding the association of CXCL8 and IL-18 polymorphisms with HNC risk has been reported, and existing studies regarding the association of CXCL8 or IL-18 with other types of cancers are contradictory. Therefore, we conducted a meta-analysis to quantitatively summarize the evidence and estimate relationships using subgroups analysis, meta regression, sensitivity analysis, and evaluation of publication bias.

Methods

Publication search and inclusion criteria

We searched the PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure databases for all potentially eligible articles up to November 31, 2017 on the association between CXCL8 and IL18 polymorphisms and HNC risk. The search terms used were "IL-8", "CXCL8", "IL-18", "polymorphism", "head and neck cancer", "nasopharyngeal cancer", "oral cancer", "laryngeal cancer", "esophageal cancer", "thyroid cancer", "tongue cancer", and "mouth neoplasm". We also screened the references of review articles and meta-analyses articles. Primary searches resulted in 176 abstracts (Figure 1). An additional six studies were added from meta-analyses and review articles, for a total of 182 studies. For inclusion, identified studies had to: (1) be case-controlled; (2) study the association between CXCL8 or IL-18 and HNC risk; (3) provide sufficient data to calculate a *P*-value and odds ratio (OR) with 95% confidence interval (CI); and (4) contain control subjects that conformed to the Hardy-Weinberg equilibrium (HWE).

Data extraction

Data were extracted independently by two investigators from studies that met the inclusion criteria. Discrepancies were resolved by discussion between the authors to reach an agreement. The following information was recorded for each study: first author, year of publication, region, cancer type, genotyping methods, source of controls, the number of cases and controls for each genotype, and HWE score in the control groups (Table 1).

Statistical analysis

Statistical analyses were performed using Stata 14.0 software (Stata Corporation, College Station, TX, USA). To evaluate the deviation of the CXCL8 and IL-18 polymorphisms from

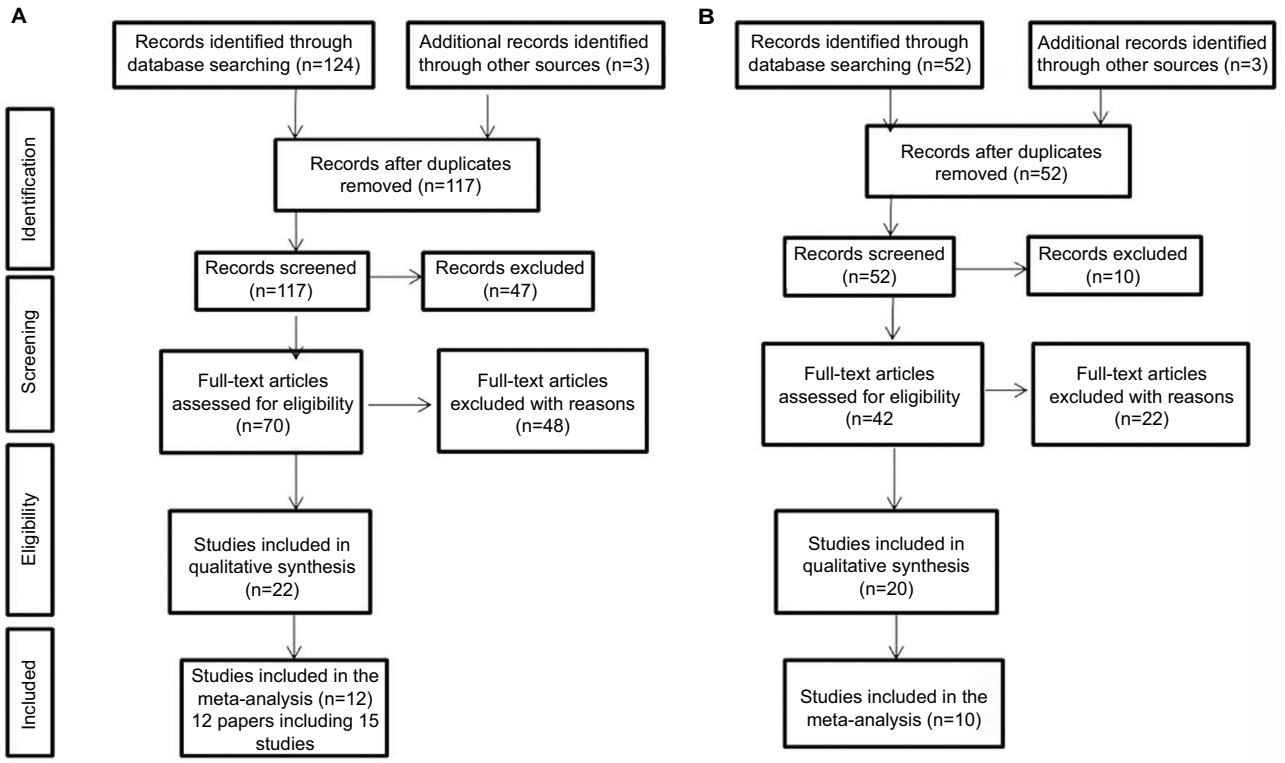


Figure 1 Flowchart for identification of IL-8 (**A**) and IL-18 (**B**) studies.

HWE, a chi-square test was used to evaluate the control subjects, in which $P<0.05$ suggested a significant deviation from HWE. The OR corresponding to the 95% CI was used to evaluate the association between CXCL8 and IL-18 polymorphisms and HNC risk. The present study was performed using allelic, homozygote, heterozygote, dominant, and recessive models. Stratified analyses based on cancer types, ethnicity, genotyping methods, and the sources of controls and DNA samples were quantified with ORs and 95% CIs. If a cancer type was included in only one study, it was combined into the "other cancers" group. The statistical heterogeneity was evaluated using the Q-test and I^2 statistics. When heterogeneity existed ($P<0.10$, $I^2>50\%$), the random effect model was used:[44] otherwise, the Mantel-Haenszel method was applied to calculate ORs in a fixed-effect model.[45] Stratified and meta-regression analyses were used to explore sources of heterogeneity. Moreover, sensitivity analysis was performed to assess the stability of the results by sequentially removing each study and evaluating the stability of the results. Publication bias was analyzed by Begg's funnel plot and Egger's test.[46,47]

Results

Study characteristics

After a comprehensive search, 182 relevant articles were initially retrieved. After screening the titles and abstracts, 160 articles were excluded, 13 papers were duplicated, 21 papers were reviews, 80 papers were not associated with SNPs in CXCL8 or IL-18, 27 papers were not about HNC, 16 papers lacked relative data, and three papers were not consistent with HWE (Figure 1). Finally, 22 articles but 25 case-control studies (15 for CXCL8 and 10 for IL-18) covering 4731 cases and 8736 controls met our inclusion criteria (Figure 1). In terms of genotyping methods, for CXCL8, five articles used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), two articles used TaqMan assays, and five articles used other methods; for IL18, four articles used PCR-RFLP, three articles used allele specific-PCR, and three articles used other methods. The genotype distributions of the studied SNPs in the control groups agreed with HWE ($P>0.05$). All Newcastle-Ottawa Scale (NOS) scores were greater than 5 stars, indicating good articles. The study characteristics are shown in Table 1.

Quantitative synthesis

As shown in Tables 2 and 3, when all eligible studies were pooled together, a significant association between the 137 G/C polymorphism and HNC was observed under all gene models: (C vs G: OR=1.31, 95% CI=1.09–1.57, $P_{\text{heterogeneity}}=0.002$; CC vs GG: OR=1.69, 95% CI=1.20–2.38, $P_{\text{heterogeneity}}=0.175$; GC vs GG: OR=1.27, 95% CI=1.01–

Table 1 Characteristics of literature included in the meta-analysis

Reference	Year	Region	Cancer type	Genotype methods	Sample size (case/ control)	Source of control	DNA sample	Genotype—case			Genotype—control			HWE
IL-8 -251 A/T								AA	AT	TT	AA	AT	TT	
Shimizu et al[48]	2008	Asian	Oral cancer	PCR-FRET	69/91	Population-based	Tissue	8	30	31	8	45	38	YES
Campa et al[49,a]	2007	European	Oral cancer	TaqMan	153/725	Population-based	Blood	41	72	40	158	370	197	YES
Campa et al[49,b]	2007	European	Pharynx cancer	TaqMan	107/725	Population-based	Blood	31	50	26	158	370	197	YES
Campa et al[49,c]	2007	European	Laryngeal cancer	TaqMan	313/725	Population-based	Blood	75	141	97	158	370	197	YES
Campa et al[49,d]	2007	European	Esophageal cancer	TaqMan	171/822	Population-based	Blood	35	93	43	173	429	220	YES
Ben Nasr[50]	2007	African	Nasopharyngeal cancer	AS-PCR	160/169	Population-based	Blood	37	74	49	23	71	75	YES
Kietthubthew[51]	2010	Asian	Oral cancer	Taq-Man	63/99	Population-based	Blood	10	21	32	16	49	34	YES
Zhang	2008	Asian	Esophageal cancer	PCR-RFLP	320/404	Population-based	Blood	50	175	95	74	200	130	YES
Liu[53]	2012	Asian	Oral cancer	PCR-RFLP	270/350	Population-based	Blood	42	131	97	66	164	120	YES
Wei[54]	2007	Asian	Nasopharyngeal cancer	PCR-RFLP	280/290	Population-based	Blood	54	137	89	42	122	126	YES
Tai[55]	2007	Asian	Nasopharyngeal cancer	PCR-RFLP	105/109	Population-based	Blood	11	52	42	17	53	39	YES
Liu[67]	2011	Asian	Esophageal cancer	PCR-HRM	351/384	Hospital-based	Blood	19	192	140	42	174	168	YES
Hu[68]	2012	Asian	Oral cancer	PCR-HRM	142/30	Hospital-based	Tissue	21	67	54	5	14	11	YES
Kiliç[56]	2016	European	Thyroid cancer	PCR-RFLP	101/109	Population-based	Blood	7	41	53	10	50	49	YES
A. Savage[57]	2004	Asian	Esophageal cancer	Single base extension	129/429	Population-based	Blood	26	55	48	75	207	147	YES
IL-18 -137 G/C								GG	GC	CC	GG	GC	CC	
Abdolahi[58]	2015	Asian	Thyroid cancer	PCR-RFLP	105/148	Population-based	Blood	59	33	6	85	56	7	YES
Babar[59]	2011	European	Esophageal cancer	TaqMan	193/1082	Population-based	Blood	105	74	14	582	414	86	YES
Farhat[60]	2008	African	Nasopharyngeal cancer	PCR-RFLP	163/164	Population-based	Blood	75	73	15	83	68	13	YES
Asefi[61]	2008	Asian	HNSCC	AS-PCR	111/212	Hospital-based	Blood	65	37	9	116	79	17	YES
Tsai[62]	2013	Asian	Oral cancer	TaqMan	567/559	Population-based	Blood	437	122	8	476	78	5	YES
Pratesi[63]	2005	European	Nasopharyngeal cancer	AS-PCR	89/130	Population-based	Blood	43	39	7	72	53	5	YES
Nong[64]	2009	Asian	Nasopharyngeal cancer	PCR-RFLP	250/270	Population-based	Blood	140	88	22	189	70	11	YES
Wei[65]	2007	Asian	Esophageal cancer	AS-PCR	235/250	Hospital-based	Blood	127	91	17	176	66	8	YES
Pan[69]	2013	Asian	Nasopharyngeal cancer	PCR-RFLP	190/200	Hospital-based	Blood	102	74	14	139	52	9	YES
Chung[66]	2015	Asian	Thyroid cancer	Sequencing	94/260	Hospital-based	Blood	70	18	6	187	70	3	YES

Note: Superscripted a, b, c and d are parts of one study by Campa et al.[49]

Abbreviations: HWE, Hardy Weinberg equilibrium; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; AS-PCR, alleles specific polymerase chain reaction; HNSCC, head and neck squamous cell carcinoma; PCR-HRM, polymerase chain reaction-high resolution melt; PCR-FRET, polymerase chain reaction-fluorescence resonance energy transfer.

Table 2 Stratified analyses about CXCL8 -251 A/T polymorphism

Category	n	Case/ controls	A allele vs T allele (allele model) OR (95% CI), *P*, *Ph*	AA vs TT (homozygous model) OR (95% CI), *P*, *Ph*	AT vs TT (heterozygous model) OR (95% CI), *P*, *Ph*	AA+AT vs TT (dominant model) OR (95% CI), *P*, *Ph*	AA vs AT+TT (recessive model) OR (95% CI), *P*, *Ph*
Total	15	2734/5461	1.03 (0.94–1.14), 0.491, 0.039	1.05 (0.85–1.28), 0.672, 0.042	1.02 (0.88–1.19), 0.749, 0.053	1.04 (0.90–1.20), 0.625, 0.041	1.04 (0.87–1.24), 0.643, 0.056
Cancer type							
Oral			0.96 (0.83–1.11), 0.596, 0.440	0.96 (0.72–1.29), 0.795, 0.580	0.88 (0.70–1.11), 0.280, 0.400	0.90 (0.72–1.11), 0.332, 0.446	1.04 (0.80–1.34), 0.777, 0.512
Nasopharyngeal			1.26 (0.89–1.79), 0.191, 0.022	1.49 (0.75–2.98), 0.255, 0.033	1.39 (1.01–1.92), 0.041, 0.242*	1.41 (0.93–2.13), 0.104, 0.073	1.29 (0.76–2.18), 0.348, 0.091
Esophageal			0.99 (0.88–1.11), 0.897, 0.988	0.88 (0.67–1.17), 0.386, 0.318	1.14 (0.95–1.38), 0.166, 0.351	1.09 (0.92–1.29), 0.347, 0.723	0.84 (0.60–1.17), 0.300, 0.087
Others			1.00 (0.82–1.23), 0.968, 0.203	1.06 (0.74–1.51), 0.754, 0.285	0.82 (0.65–1.04), 0.108, 0.622	0.88 (0.70–1.10), 0.262, 0.390	1.19 (0.93–1.53), 0.170, 0.412
Ethnicity							
Asian			0.99 (0.87–1.12), 0.857, 0.139	0.91 (0.69–1.20), 0.516, 0.112	1.04 (0.84–1.28), 0.709, 0.058	1.02 (0.84–1.24), 0.854, 0.069	0.89 (0.70–1.14), 0.371, 0.135
European			1.03 (0.92–1.15), 0.580, 0.428	1.09 (0.87–1.37), 0.436, 0.554	0.90 (0.75–1.09), 0.278, 0.616	0.95 (0.80–1.13), 0.581, 0.542	1.16 (0.96–1.40), 0.113, 0.563
African			1.63 (1.19–2.22), 0.002, —*	2.46 (1.31–4.64), 0.005, —*	1.60 (0.98–2.59), 0.059, —	1.81 (1.15–2.84), 0.010, —*	1.91 (1.08–3.39), 0.027, —*
Genotyping methods							
PCR-RFLP			0.99 (0.81–1.22), 0.936, 0.028	0.95 (0.64–1.42), 0.811, 0.063	1.11 (0.88–1.41), 0.386, 0.167	1.06 (0.81–1.39), 0.689, 0.053	0.91 (0.69–1.19), 0.482, 0.252
TaqMan			1.03 (0.90–1.17), 0.667, 0.287	1.09 (0.87–1.36), 0.458, 0.531	0.87 (0.69–1.11), 0.264, 0.212	0.93 (0.75–1.16), 0.539, 0.208	1.17 (0.97–1.41), 0.094, 0.676
Others			1.09 (0.88–1.35), 0.435, 0.082	1.09 (0.61–1.94), 0.774, 0.017	1.12 (0.85–1.48), 0.406, 0.192	1.13 (0.87–1.48), 0.359, 0.170	1.04 (0.60–1.80), 0.887, 0.012
Source of control							
Population-based			1.04 (0.94–1.17), 0.444, 0.021	1.11 (0.91–1.35), 0.318, 0.090	1.00 (0.85–1.17), 0.952, 0.053	1.02 (0.87–1.20), 0.793, 0.022	1.11 (0.95–1.29), 0.180, 0.268
Hospital-based			0.96 (0.78–1.18), 0.690, 0.922	0.59 (0.35–1.00), 0.052, 0.496	1.28 (0.96–1.71), 0.091, 0.514	1.14 (0.87–1.51), 0.342, 0.624	0.54 (0.32–0.89), 0.016, 0.312*
DNA sample							
Blood			1.04 (0.93–1.15), 0.484, 0.018	1.04 (0.84–1.30), 0.705, 0.019	1.03 (0.88–1.21), 0.691, 0.028	1.04 (0.89–1.22), 0.584, 0.020	1.04 (0.86–1.25), 0.701, 0.028
Tissue			0.97 (0.67–1.39), 0.861, 0.874	1.04 (0.47–2.30), 0.928, 0.659	0.87 (0.52–1.48), 0.610, 0.751	0.90 (0.55–1.49), 0.687 0.893	1.09 (0.52–2.30), 0.812, 0.553

Note: *95%CI did not include 0.

Abbreviations: OR, odds ratio; CI, confidence interval; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; *Ph*, *p*-value of the heterogenety.

Table 3 Stratified analyses about IL18 -137 G/C polymorphism

Category	n	Case/controls	C allele vs G allele (allele model) OR (95% CI), *P*, *Ph*	CC vs GG (homozygous model) OR (95% CI), *P*, *Ph*	GC vs GG (heterozygous model) OR (95% CI), *P*, *Ph*	GC+CC vs GG (dominant model) OR (95% CI), *P*, *Ph*	CC vs GG+GC (recessive model) OR (95% CI), *P*, *Ph*
Total	12	1997/3275	1.31 (1.09–1.57), 0.004, 0.002*	1.69 (1.20–2.38), 0.003, 0.175*	1.27 (1.01–1.59), 0.039, 0.004*	1.32 (1.06–1.65), 0.012, 0.002*	1.53 (1.13–2.06), 0.006, 0.321*
Cancer type							
Thyroid			1.03 (0.75–1.41), 0.864, 0.657	2.41 (0.58–10.09), 0.227, 0.114	077 (0.52–1.15), 0.198, 0.603	0.89 (0.61–1.29), 0.522, 0.968	2.60 (0.61–11.17), 0.199, 0.104
Esophageal			1.33 (0.70–2.50), 0.382, 0.001	1.56 (0.49–4.96), 0.451, 0.028	1.36 (0.72–2.59), 0.346, 0.011	1.39 (0.68–2.85), 0.363, 0.003	1.39 (0.55–3.52), 0.493, 0.072
Nasopharyngeal			1.48 (1.20–1.83), 0.000, 0.222*	2.01 (1.30–3.10), 0.002, 0.598*	1.53 (1.22–1.93), 0.000, 0.365*	1.60 (1.26–2.02), 0.000, 0.306*	1.72 (1.12–2.63), 0.012, 0.664*
Others			1.23 (0.70–2.17), 0.478, 0.015	1.19 (0.60–2.35), 0.626, 0.397	1.23 (0.61–2.46), 0.566, 0.017	1.24 (0.63–2.43), 0.538, 0.015	1.19 (0.61–2.33), 0.614, 0.531
Ethnicity							
Asian			1.40 (1.13–1.74), 0.002, 0.012*	2.03 (1.38–2.99), 0.000, 0.332*	1.33 (0.98–1.79), 0.066, 0.003	1.41 (1.06–1.86), 0.017, 0.004*	1.83 (1.28–2.61), 0.001, 0.469*
European			1.08 (0.80–1.44), 0.623, 0.211	1.25 (0.52–3.04), 0.620, 0.166	1.05 (0.79–1.38), 0.752, 0.509	1.05 (0.81–1.37), 0.711, 0.331	1.19 (0.54–2.58), 0.669, 0.203
African			1.15 (0.82–1.61), 0.413, —	1.28 (0.57–2.86), 0.552, —	1.19 (0.75–1.87), 0.458, —	1.20 (0.78–1.86), 0.406, —	1.18 (0.54–2.56), 0.680, —
Genotyping methods							
PCR-RFLP			1.38 (1.04–1.83), 0.024, 0.050*	1.84 (1.19–2.83), 0.006, 0.503*	1.39 (0.99–1.95), 0.056, 0.078	1.44 (1.03–2.03), 0.035, 0.053*	1.61 (1.06–2.46), 0.027, 0.663*
AS-PCR			1.32 (0.85–2.03), 0.214, 0.016	1.81 (0.86–3.81), 0.116, 0.169	1.28 (0.77–2.12), 0.345, 0.034	1.34 (0.79–2.27), 0.281, 0.018	1.64 (0.94–2.87), 0.080, 0.343
Others			1.21 (0.85–1.72), 0.296, 0.024	1.73 (0.65–4.58), 0.272, 0.063	1.10 (0.67–1.79), 0.713, 0.008	1.17 (0.76–1.79), 0.482, 0.017	1.73 (0.63–4.74), 0.283, 0.051
Source of control							
Population-based			1.27 (1.02–1.59), 0.035, 0.016*	1.47 (1.00–2.16), 0.050, 0.320	1.27 (1.00–1.61), 0.048, 0.075	1.30 (1.01–1.67), 0.038, 0.035*	1.35 (0.96–1.89), 0.085, 0.490
Hospital-based			1.36 (0.96–1.92), 0.081, 0.014	2.14 (1.11–4.12), 0.024, 0.137*	1.24 (0.74–2.08), 0.408, 0.002	1.34 (0.84–2.15), 0.215, 0.004	1.92 (1.04–3.52), 0.036, 0.181*

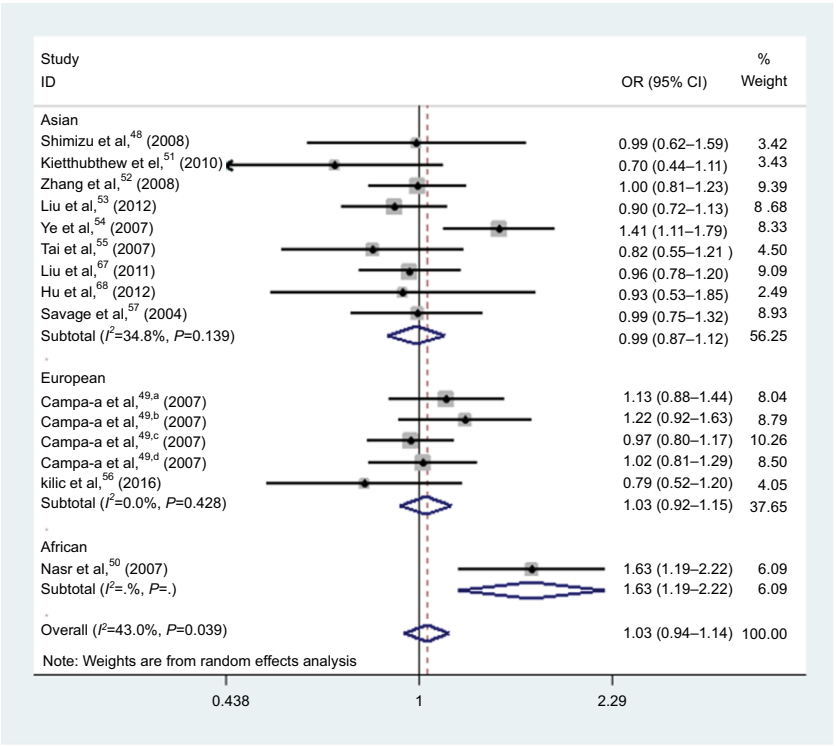
Note: *95%CI did not include 0.

Abbreviations: OR, odds ratio; CI, confidence interval; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; AS-PCR, alleles specific polymerase chain reaction; *Ph*, *p*-value of the heterogeneity.

1.59, $P_{heterogeneity}$=0.004; GC+CC vs GG: OR=1.32, 95% CI=1.06–1.65, $P_{heterogeneity}$=0.002;CC vs GG+GC: OR=1.53, 95%CI=1.13–2.06, $P_{heterogeneity}$=0.321), whereas no significant association was found between the 251 A/T polymorphism and HNC risk.

Furthermore, to evaluate the effect of specific factors on the results, we performed subgroup analysis, concentrating on cancer type, ethnicity, genotyping method, and DNA sample (Tables 2 and 3 and Figure 2). Stratified analysis revealed that the overall association was partly attributed to nasopharyngeal cancer for -251 A/T (AT vs TT: OR=1.39, 95%CI=1.01–1.92, $P_{heterogeneity}$=0.242) and -137 G/C (C vs G: OR=1.48, 95% CI=1.20–1.83, $P_{heterogeneity}$=0.222; CC vs GG: OR=2.01, 95% CI=1.30–3.10, $P_{heterogeneity}$=0.598; GC vs GG: OR=1.53, 95% CI=1.22–1.93, $P_{heterogeneity}$=0.365; GC+CC vs GG: OR=1.60, 95% CI=1.26–2.02, $P_{heterogeneity}$=0.306; CC vs GG+GC: OR=1.72, 95% CI=1.12–2.63, $P_{heterogeneity}$=0.664). In the subgroup analysis based on ethnicity, the results suggested a significantly increased risk of HNC in an African population with -251 A/T (A vs T: OR=1.63, 95% CI=1.19–2.22, $P_{heterogeneity}$=NA; AA vs TT: OR=2.46, 95% CI=1.31–4.64, $P_{heterogeneity}$=NA; AA+AT vs TT: OR=1.81, 95% CI=1.15–2.84, $P_{heterogeneity}$=NA; AA vs AT+TT: OR=1.91, 95% CI=1.08–3.39, $P_{heterogeneity}$=NA) and in an Asian population for -137 G/C (C vs G: OR=1.40, 95% CI=1.13–1.74, $P_{heterogeneity}$=0.012; CC vs GG: OR=2.03, 95% CI=1.38–2.99, $P_{heterogeneity}$=0.332; GC+CC vs GG: OR=1.41, 95% CI=1.06–1.86, $P_{heterogeneity}$=0.004; CC vs GG+GC: OR=1.83, 95% CI=1.28–2.61, $P_{heterogeneity}$= 0.469); however, no significant association was found in Asian or European populations for -251 A/T or in European or African populations for -137 G/C. In subgroup analysis by genotyping methods, a significantly elevated risk was found in the PCR-RFLP group for -137 G>C (C vs G: OR=1.38, 95% CI=1.04–1.83, $P_{heterogeneity}$=0.050; CC vs GG: OR=1.84, 95% CI=1.19–2.83, $P_{heterogeneity}$=0.503; GC+CC vs GG: OR=1.44, 95% CI=1.03–2.03, $P_{heterogeneity}$=0.053; CC vs GG+GC: OR=1.61, 95% CI=1.06–2.46, $P_{heterogeneity}$=0.663), but no significant association was found for -251 A/T with any genotyping method. Stratification by the control source showed significant associations between the population-based group (C vs G: OR=1.27, 95% CI=1.02–1.59, $P_{heterogeneity}$=0.016; GC+CC vs GG: OR=1.30, 95% CI=1.01–1.67, $P_{heterogeneity}$=0.035) and the hospital-based group (CC vs GG: OR=2.14, 95% CI=1.11–4.12, $P_{heterogeneity}$=0.137, CC vs GG+GC: OR=1.92, 95% CI=1.04–3.52, $P_{heterogeneity}$=0.181) and -137 G>C, whereas significantly decreased risk was found in the hospital-based group for -251 A/T (AA vs AT+TT: OR=0.54, 95% CI=0.32–0.89, $P_{heterogeneity}$=0.312).

A



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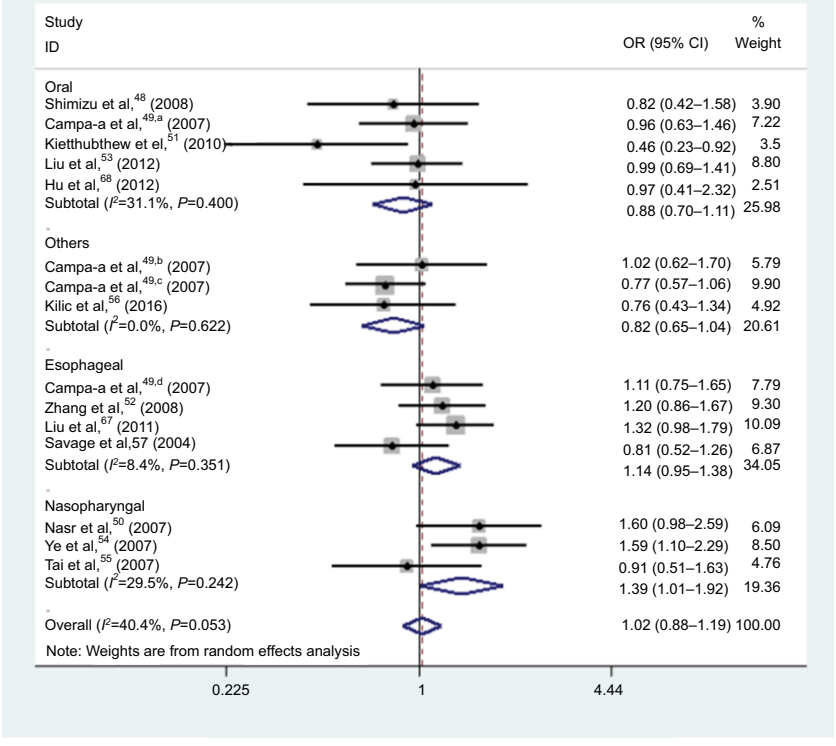
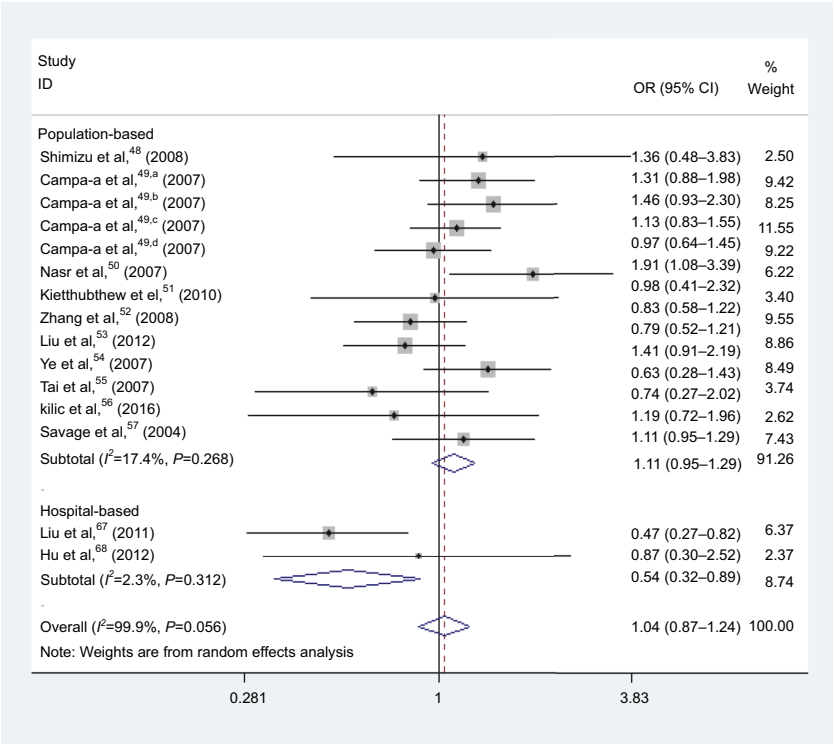


Figure 2 (*Continued*)

C



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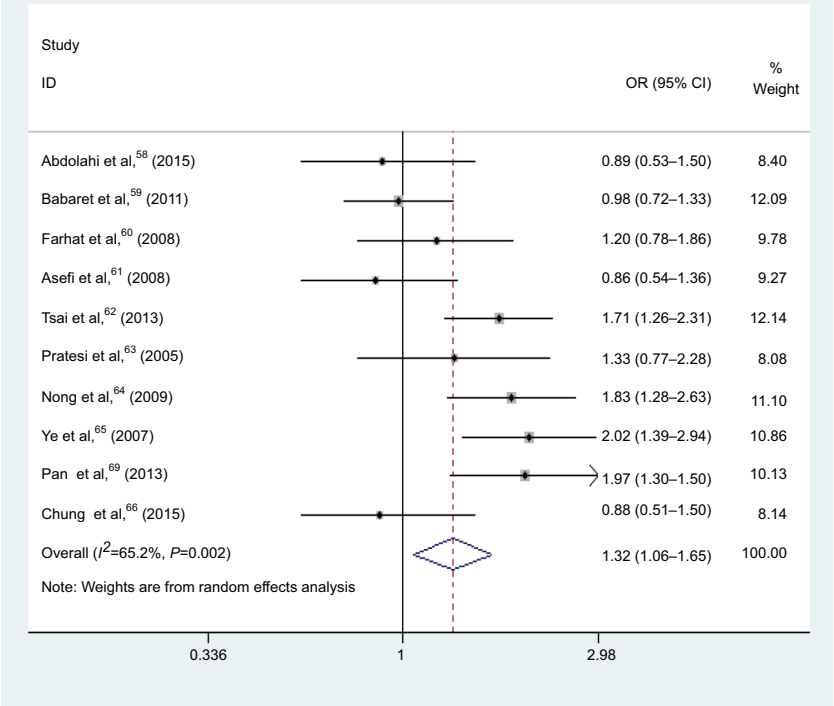

Figure 2 (*Continued*)

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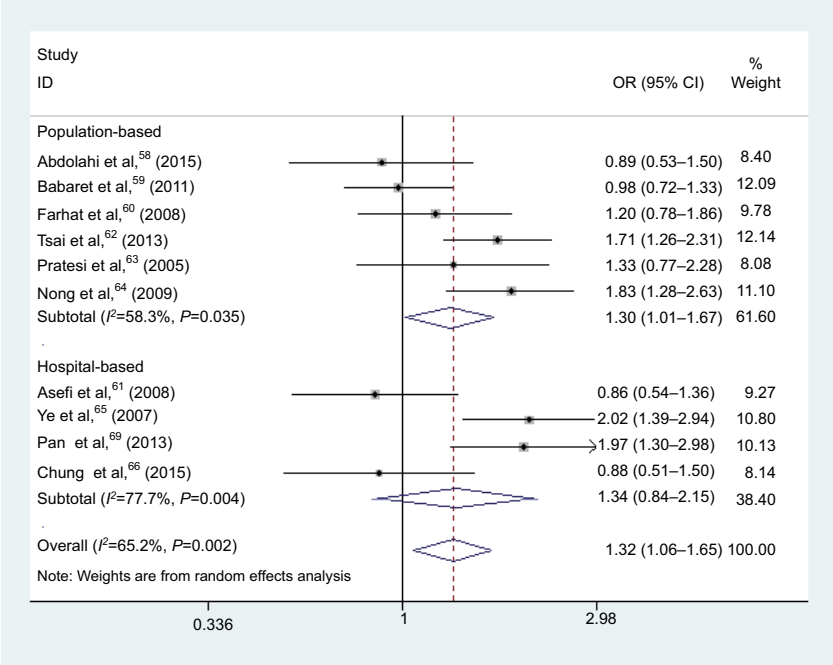

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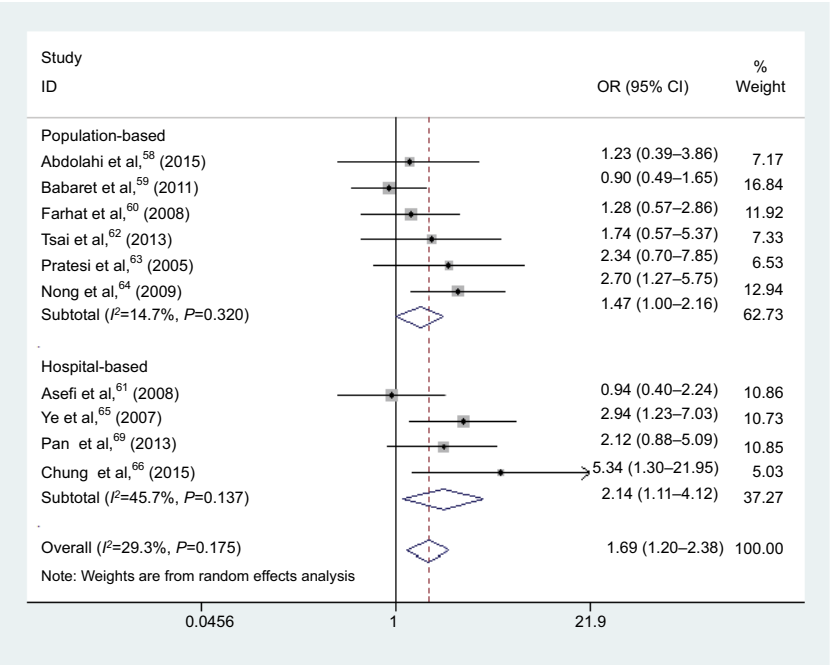
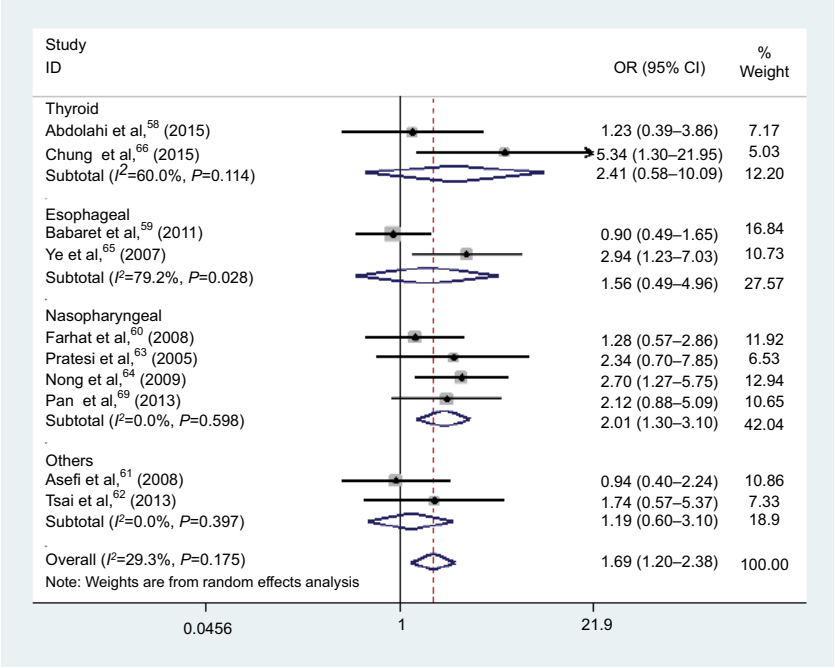


Figure 2 (*Continued*)

G



H

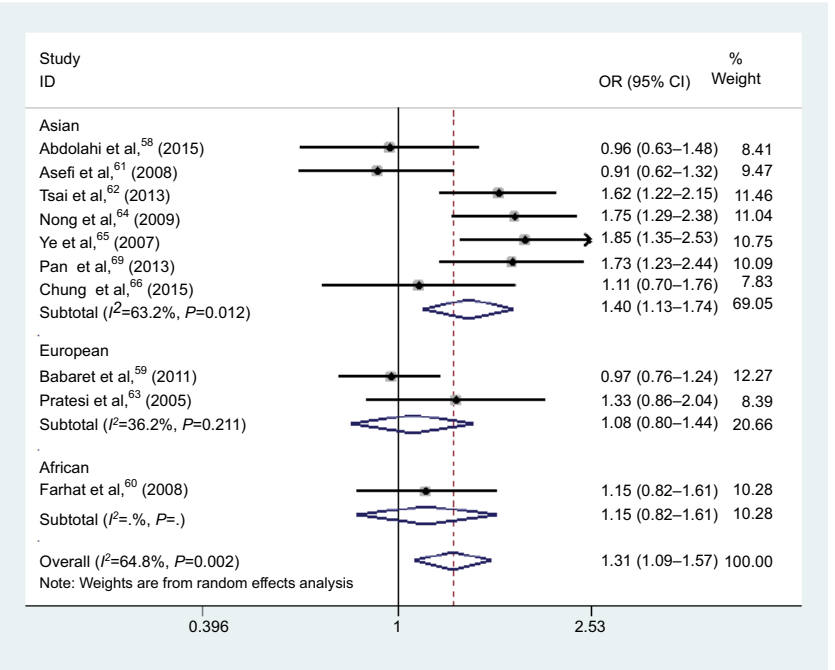


Figure 2 (*Continued*)

I

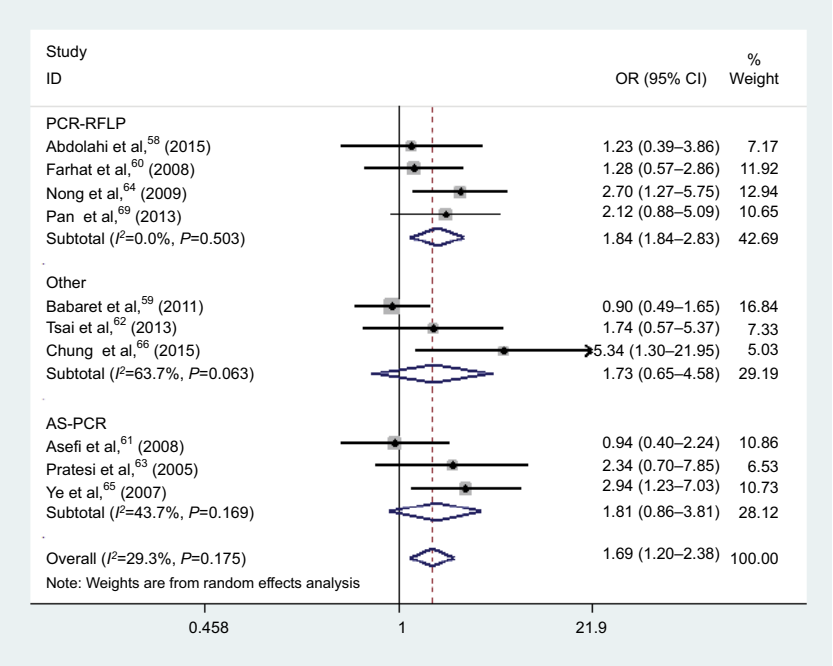


Figure 2 Forest plot of HNC risk associated with polymorphism if CXCL8 -251 A/T and IL-18 -137 G/C. (**A**) Forest plot of association between CXCL8 -251 A/T polymorphism and HNC risk in A vs T model in ethnicity. (**B**) Forest plot of association between CXCL8 -251 A/T polymorphism and HNC risk in AT vs TT model in cancer type. (**C**) Forest plot of association between CXCL8 -251 A/T polymorphism and HNC risk in AA vs AT/TT model in source of control. (**D**) Forest plot of association between IL-18 -137 G/C polymorphism and HNC risk in GC/CC vs GG model in overall analysis. (**E**) Forest plot of association between IL18 137 G/C polymorphism and HNC risk in GC/CC vs GG model in source of control. (**F**) Forest plot of association between IL-18 -137 G/C polymorphism and HNC risk in CC vs GG model in source of control. (**G**) Forest plot of association between IL-18 -137 G/C polymorphism and HNC risk in CC vs GG model in cancer type. (**H**) Forest plot of association between IL-18 -137 G/C polymorphism and HNC risk in G vs C model in ethnicity. (**I**) Forest plot of association between IL-18 -137 G/C polymorphism and HNC risk in CC vs GG model in genotyping methods.
Abbreviations: HNC, head and neck cancer; OR, odds ratio; CI, confidence interval.

Evaluation of heterogeneity

There was heterogeneity among the studies in all overall comparisons and subgroup analyses for CXCL8 -251 A/T and some overall comparisons and subgroup analyses (C vs G, GC vs GG, GC/CC vs GG) for IL-18 -137 G/C. To explore the sources of heterogeneity, we performed meta-regression using publication year, cancer type, ethnicity, source of controls, sample size (≤500 and >500 subjects) and genotyping method as covariables. The results suggested that the publication year (AA vs AT/TT: P=0.020; AA vs TT: P=0.041), source of control (AA vs AT/TT: P=0.024), and cancer type (AA/ATvs TT: P=0.047; AT vsTT: P=0.036) may contribute to the heterogeneity for CXCL8 -251 A/T; however, for IL18 -137 G/C, no factors contributing to the heterogeneity were found. Moreover, for CXCL8 -251 A/T, our meta-regression analyses revealed that the publication year could explain 88.38% (AA vs AT/TT), 54.62% (AA vs TT) of the τ^2, the source of controls could explain 73.22% (AA vs AT/TT) of the τ^2, and the cancer type could explain almost 100% (AA/AT vs TT; AT vs TT) of the τ^2.

Sensitivity analysis

To evaluate the sensitivity of the meta-analysis, we omitted one study at a time and checked for significant differences. There were no significant differences observed upon removal of any of the studies, indicating that the results are statistically reliable (Figure 3).

Publication bias

A Begg funnel plot was generated, and Egger's test was performed to evaluate the publication bias of the studies included in our analysis. Figure 3 displays funnel plots examining the CXCL8 -251 A/T and IL-18 -137 G/C polymorphisms and cancer risk. There was marginal significance in the recessive model (CC vs GC+GG: P=0.048) for *IL-18* -137 G/C in the Egger's test, while no publication bias was detected in any genetic comparison for *CXCL8* -251 A/T (Figure 4).

Discussion

To our knowledge, this is the first meta-analysis to assess the association of the *CXCL8* -251 A/T and *IL-18* -137

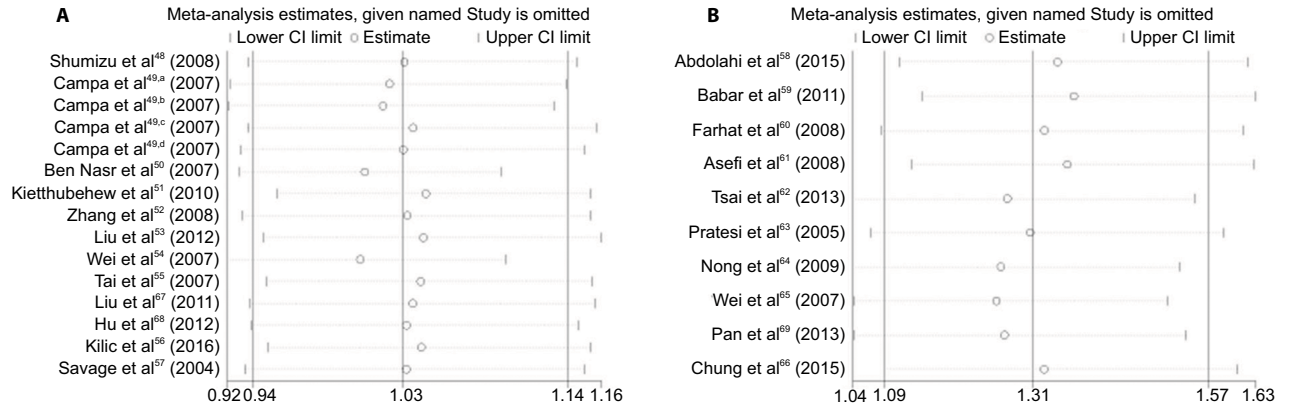


Figure 3 Sensitivity analysis of the overall ORs. The results were calculated through omitting each eligible study. (**A**) IL-8 -251 A/T in A versus T model; (**B**) IL-18 -137 G/C in C versus G model.
Note: Superscripted a, b, c and d are parts of one study by Campa et al.[49]
Abbreviations: OR, odds ratio; CI, confidence interval.

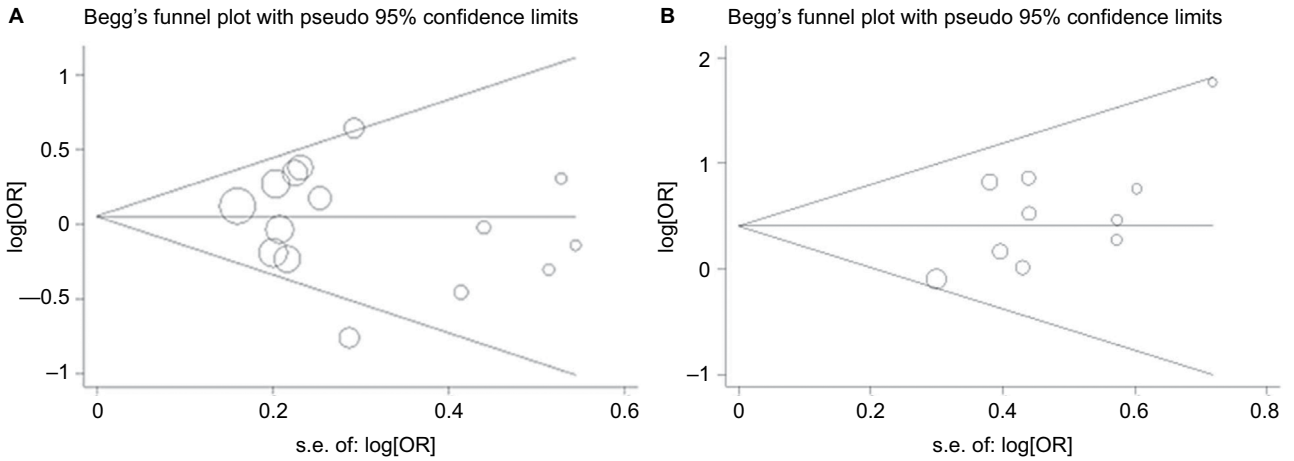


Figure 4 Begg's funnel of the Egger's test for publication bias test. Each point represents a separate study for the indicated association. (**A**) IL-8 -251 A/T in recessive model; (**B**) IL-18 -137 G/C in recessive model.
Abbreviations: OR, odds ratio; SE, standard error.

G/C polymorphisms with HNC risk. In our present study, a significantly elevated risk was observed for IL-18 -137 G/C, but no strong association between the CXCL8 -251 A/T polymorphism and HNC risk was found in the overall analysis.

Further subgroup analyses revealed that the association between *IL-18* -137 G/C and HNC risk was more predominant among nasopharyngeal cancer groups, Asian populations, studies using PCR-RFLP for genotyping, and population- and hospital-based studies. To elaborate more specifically, C alleles carriers and CC genotypes were significantly associated with an increased risk in nasopharyngeal cancer groups, Asian populations, and samples analyzed by PCR-RFLP. Moreover, an association between C allele carriers and increased risk was found in the population-based group, whereas, in the hospital-based group, an increased risk for HNC was found with the CC genotype.

Conversely, stratified analysis of CXCL8 -251 A/T provided evidence that A allele carriers and AA genotypes were associated with a significantly increased risk in African populations. Moreover, AT genotypes were associated with a significantly increased risk in the nasopharyngeal cancer group compared with the TT genotype, whereas the AA genotype was associated with a significantly decreased risk in hospital-based studies.

To some extent, our results are distinctly different from those of previous studies. Several studies in recent years have investigated these polymorphisms, with conflicting results. For CXCL8 -251 A/T, our pooled results are in accordance with some previous studies,[24,25] but contrast with studies reporting a positive association between the CXCL8 -251 A/T polymorphism and cancer risk.[19,48] On the other hand, for IL-18 -137 G/C, our pooled results were completely opposite to those reported by Yang et al[43] and Mi et al.[42]

Although the results of overall analysis are sometimes the same, similar or different trends may be found in subgroup analyses. For example, for CXCL8-251 A/T, stratification by ethnicity revealed a significant association for African populations with carriers of the A allele and homozygous AA genotypes, whereas, among non-African populations, there were no strong associations in any of the genetic models. Our results are in accordance with Gao et al,[28] who also observed significantly elevated risks in African populations. However, diverse results were observed in other previous studies, Wang et al[22] found that carriers of the -251 A allele among African and Asian populations were at a higher risk for cancer. Wang et al[27] found that there were significant risks among Asians for both A allele carriers and AA individuals; however, no significant associations were found in non-Asian populations. On the contrary, when the *IL-18* -137 G/C, data was stratified by ethnicity, C alleles carriers and CC genotypes in Asian populations were significantly associated with an increased risk of HNC. This result is consistent with the reports of Yang et al[43] and Mi et al,[42] who found that C alleles and CC genotypes elevated the risk of cancers. These results indicate that *CXCL8* -251 A/T and *IL-18* -137 G/C polymorphisms may be crucial in HNC patients of specific ethnicities. The reasons for these discrepancies are not known. We hypothesize that they may be attributable to gene–environmental interactions. Variation in the allele frequency of particular polymorphisms might differ among ethnicities as a result of disparate environmental effects, and it can be inferred from the different allele distribution, in accordance with natural selection principles, that the rare allele carriers in the African populations for *CXCL8* or Asian populations for *IL-18* might be eliminated compared to in other ethnicities. This might explain why a significant association was observed in certain ethnicities, but not others. It should be noted that, for decades, nasopharyngeal cancer was more common in African and Asian populations compared with other ethnicities, consistent with the associations between nasopharyngeal cancer and the two polymorphisms studied here in these populations.[49] The differences could also be due to small sample size or potential reporting bias in our study. For example, the African CXCL8 -251 A/T cohort contained approximately 329 subjects, and there is only one study in the African group.[50] Therefore, it was underpowered to find causal positive or negative associations.

Cancer type was also used as a stratifying factor, and we found significantly elevated risk for nasopharyngeal cancer in the heterozygote model (AT vs TT) for CXCL8-251 A/T and in all genetic models for *IL18* -137 G/C; however, we did not find any associations with any other cancer types in any genetic models. This is consistent with the results of Gao et al[28] and Wang et al.[22] These findings indicate that the A allele of *CXCL8* -251 A/T and the C allele of *IL-18* -137 G/C are risk factors for developing nasopharyngeal cancer. The mechanism for these findings is not well understood.

However, a number of studies have investigated the significant biochemical functions of CXCL8 or IL-18, and the effects of particular polymorphisms. The A/T and G/C SNPs studied here are, respectively, associated with the production of CXCL8, IL-8 transcriptional activity, and the expression of IL-8 and IL-18,[23–26,41] which are associated with cancer characteristics, such as increased proliferation, invasion, and migration.[16,51,52] Hence, the A allele, C allele, and CC genotype may contribute to tumorigenesis and metastasis.

Selection bias in control subject recruitment was a significant source of concern. When stratified by control source, we found significantly decreased risk among hospital-based studies for *CXCL8* -251 A/T (AA vs AT+TT), whereas, for IL-18 -137 G>C, we observed significantly increased risk for C allele carriers (C vs G, GC+CC vs GG) among the population-based group and for the CC genotype (CC vs GG, CC vs GG+GC) among the hospital-based group. Considering that hospital-based controls lack the representativeness of population-based controls, and the amount of studies used was small, we must be cautious with our conclusions. When stratified by genotyping methods, we did not find any statistical association in any genetic models for *CXCL8* -251 A/T; however, a strong association was found in all genetic models except the heterozygote model (GC vs GG) for *IL-18* -137 G/C. This is the first report of this association in the literature.

One of the major concerns in a meta-analysis is heterogeneity among the included studies, because imprecise results may be obtained as a result of non-homogeneous data. In our study, the Q-test and I^2 statistics were used to test the significance of heterogeneity. Significant heterogeneity was found in all pooled and subgroup analyses for CXCL8 -251 A/T and some for *IL-18* -137 G/C, and meta-regression was performed for the corresponding genetic models according to cancer type, ethnicity, source of controls, sample size, genotyping method, and publication year to explore its source. We found that publication year, source of controls, and cancer type were the main sources of heterogeneity for CXCL8 -251 A/T; however, these did not impact the overall summary effect. Meanwhile we did not find any factors contributing to heterogeneity in the three corresponding genetic models (C

vs G, GC vs GG and GC +CC vs GG) for *IL-18* -137 G/C. This is a common phenomenon in meta-regression analyses, and is permitted.

Importantly, sensitivity analyses indicated that the estimated summary effect was robust, and did not change when individual studies were excluded.

There were several limitations to this meta-analysis. First, in the stratified analyses, we could not perform subgroup analysis by age, smoking status, alcohol consumption, treatment, and other risk factors because of insufficient data in the included studies. A more precise analysis could be conducted if these data were comprehensive. Second, tumorigenesis depends on both genetic and environmental factors, but gene–gene and gene–environment interactions were not taken into account in our meta-analysis, again because of a lack of data. Third, heterogeneity is a potential problem which may preclude the acquisition of accurate results in a meta-analysis. Significant heterogeneity was observed in some genetic models, which may have resulted from the publication year, source of controls, and cancer type. Fourth, although most controls were selected from healthy populations, a few studies selected controls from inpatients with cancer-free histories or no family history of cancer and other diseases. In addition, we used Begg's funnel plot and Egger's test to assess the publication bias, and found a marginal significance in the recessive model for *IL-18* -137 G/C by Egger's test, possibly because only published studies were included in the meta-analysis. Last, most of the subjects included were of Asian and European ancestry, with only one study for each of CXCL8 -251A/T and IL-18 -137 G/C regarding African ethnicity; therefore, potential selective bias could exist which might contribute to insufficient statistical power.

In conclusion, the present meta-analysis suggests that the *IL-18* -137 G/C polymorphism contributes to the susceptibility of HNC, especially among nasopharyngeal cancer groups, Asian populations, studies using PCR-RFLP for genotyping, and population- and hospital-based studies in some genetic comparisons. The CXCL8 -251 A/T polymorphism acted as an important genetic factor for HNC development, especially among African populations and nasopharyngeal cancer groups, and, interestingly, a decreased risk was found in the hospital-based group. However, due to the limitations mentioned above, investigations, using unbiased methods, well-matched controls, and with larger sample size and examining the effect of gene–gene and gene–environment interactions, as well as more types of interleukins, should be conducted in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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