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Original Article

Association of interleukin-18 Gene-607C/A polymorphisms with head and neck cancer risk: a meta-analysis

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Abstract: We performed a meta-analysis to derive a more precise evaluation of the association between Interleukin-18 (IL-18)-607C/A polymorphism and overall head and neck cancer (HNC) risk and evaluated influence of cancer types, ethnicity and source of controls. A systematic literature search was performed using PubMed, Embase Cochran Library, Chinese National Knowledge Infrastructure (CNKI), China biomedical literature database (CBM), Wanfang database and VIP. Totally, we identified 10 studies including 2,042 cancer cases and 2,013 controls to evaluate the association of IL-18-607C/A polymorphism with risk for HNC. Overall, there was significant association between IL-18-607C/A polymorphism and the risk of HNC (A vs. C: OR=1.10, 95% CI: 1.01-1.20, P=0.03; CA vs. CC: OR=1.18, 95% CI: 1.02-1.37, P=0.02; CA+AA vs. CC: OR=1.19, 95% CI: 1.04-1.36, P=0.01). In the subgroup analysis, the association was found for nasopharyngeal carcinoma (C vs. A: OR=1.16, 95% CI: 1.01-1.32, P=0.03; AA vs. CC: OR=1.34, 95% CI: 1.02-1.75, P=0.03; CA vs. CC: OR=1.36, 95% CI: 1.08-1.70, P=0.01; CA+AA vs. CC: OR=1.35, 95% CI: 1.09-1.68, P=0.01), but not for oral cancer and thyroid cancer. According to the ethnicity, the results showed that the relationship between IL-18-607C/A gene polymorphism and HNC susceptibility mainly occurred in the Asian population (C vs. A: OR=1.11, 95% CI: 1.01-1.22, P=0.03; AA vs. CC: OR=1.23, 95% CI: 1.01-1.50, P=0.04; CA+AA vs. CC: OR=1.17, 95% CI: 1.01-1.37, P=0.04), not in European population and African population. In conclusion, our meta-analysis showed that IL-18-607C/A polymorphism was associated with susceptibility to HNC. In the future, large and well-designed case-control studies are needed to validate our findings.

Keywords: Interleukin-18, -607C/A, polymorphisms, head and neck cancer, risk, meta-analysis

Introduction

Head and neck cancer (HNC) is the sixth most common cancer worldwide, and 900,000 new cases were diagnosed and 35,000 died of HNC per year. Most cases are squamous cell carcinomas of the head and neck (HNSCC), which derives from the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx [1]. Although its pathogenesis is not yet fully understood, more evidence suggested that HNC is a disease involving multiple genetic factors, and further studies have demonstrated that the genetic susceptibility of HNC is closely related to many genetic mutations [2].

Interleukin-18 (IL-18) is a promoting factor in inflammatory cascade reaction, which is considered to be a kind of inducing factor of interferon-g (IFN-g) [3]. The human IL-18 gene is located on chromosome 11q22.2-q22.3, which has been identified with 11 different polymorphisms. Current research focuses mainly on -607C/A (rs1946518) and -137G/C (rs187238) [4]. At the site of -607C/A, due to changes in cytosine and adenine disturb the binding sites of cyclic AMP response element binding protein (CREB), which affects the expression of IL-18 protein and immune status and leads to carcinoma [5, 6]. It was confirmed that IL-18 can arrest the cell division in the S phase and regulate the cell cycle progression or trigger the apoptotic pathway, which is a key event in the process of HNC occurrence [7, 8].

Considering the relatively small sample size in most studies and even controversial results in some studies, it is possible to perform a quanti-

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

First author	Year	Cancer types	Ethnicity	Control	Cases			Control			WHE
					CC	CA	AA	CC	CA	AA	
Abdolahi [9]	2015	TC	Asian	PB	31	55	15	54	76	17	0.21
Asefi [10]	2009	Mixed	Asian	HB	43	53	15	82	101	29	0.81
Du [18]	2012	NPC	Asian	HB	36	80	34	47	93	40	0.64
Farhat [11]	2008	NPC	African	PB	41	94	28	53	77	34	0.54
Nong [12]	2009	NPC	Asian	HB	47	132	71	69	133	68	0.81
Pan [17]	2013	NPC	Asian	HB	40	97	53	56	93	51	0.33
Pratesi [13]	2006	NPC	European	PB	26	42	21	43	64	23	0.92
Singh [14]	2014	OC	Asian	HB	79	154	39	65	96	24	0.21
Tsai [15]	2013	OC	Asian	PB	140	262	165	135	276	148	0.78
Vairaktaris [16]	2007	OC	European	PB	55	66	28	35	32	22	0.01

TC: thyroid cancer; NPC: nasopharyngeal carcinoma; OC: oral cancer; Mixed: head and neck cancer; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium.

Table 2. Total and stratified analyses of the IL-18-607C/A polymorphism on HNC risk

	N	C vs. A		AA vs. CC		CA vs. CC		AA vs. CA+CC		CA+AA vs. CC	
		OR	p_h	OR	p_h	OR	p_h	OR	p_h	OR	p_h
Total	10	1.10 (1.01-1.20)	0.94	1.20 (1.00-1.43)	0.89	1.18 (1.02-1.37)	0.66	1.09 (0.94-1.26)	0.88	1.19 (1.04-1.36)	0.79
Cancer types											
NPC	5	1.16 (1.01-1.32)	0.92	1.34 (1.02-1.75)	0.86	1.36 (1.08-1.70)	0.82	1.09 (0.88-1.33)	0.71	1.35 (1.09-1.68)	0.90
OC	3	1.06 (0.93-1.21)	0.61	1.08 (0.83-1.40)	0.57	1.07 (0.86-1.33)	0.28	1.07 (0.86-1.34)	0.38	1.08 (0.87-1.32)	0.45
TC	1	1.22 (0.84-1.75)	-	1.54 (0.68-3.50)	-	1.26 (0.72-2.21)	-	1.33 (0.63-2.81)	-	1.31 (0.76-2.25)	-
Mixed	1	1.00 (0.71-1.39)	-	0.99 (0.48-2.04)	-	1.00 (0.61-1.64)	-	0.99 (0.50-1.93)	-	1.19 (1.04-1.36)	-
Ethnicity											
Asian	7	1.11 (1.01-1.22)	0.88	1.23 (1.01-1.50)	0.86	1.15 (0.98-1.35)	0.52	1.13 (0.96-1.33)	1.00	1.17 (1.01-1.37)	0.56
European	2	1.06 (0.81-1.39)	0.32	1.08 (0.64-1.80)	0.24	1.20 (0.78-1.84)	0.67	0.99 (0.63-1.57)	0.13	1.15 (0.77-1.71)	0.85
African	1	1.08 (0.79-1.48)	-	1.06 (0.56-2.03)	-	1.58 (0.95-2.62)	-	0.79 (0.46-1.38)	-	1.42 (0.88-2.30)	-
Control											
PB	5	1.07 (0.95-1.21)	0.82	1.11 (0.87-1.41)	0.73	1.11 (0.90-1.35)	0.40	1.07 (0.87-1.31)	0.39	1.11 (0.92-1.34)	0.67
HB	5	1.14 (1.01-1.30)	0.85	1.32 (1.01-1.71)	0.85	1.28 (1.03-1.57)	0.77	1.11 (0.89-1.38)	0.99	1.28 (1.05-1.56)	0.71

TC: thyroid cancer; NPC: nasopharyngeal carcinoma; OC: oral cancer; Mixed: head and neck cancer; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium. p_h: *p* value for heterogeneity.

tative synthesis of the evidence with rigorous methods. Here, we performed a meta-analysis on 10 published case-controls to derive a more precise evaluation of the association between IL-18-607C/A polymorphism and overall HNC risk and evaluated influence of cancer types, ethnicity and source of controls.

Materials and methods

Publication search

A systematic literature search was performed using Pubmed, Embase Cochran Library, Chinese National Knowledge Infrastructure (CNKI), China biomedical literature database (CBM), Wanfang database and VIP, covering all articles published up to October 2015. We used the following terms: "IL-18" "rs1946518", "-607C/A", "polymorphism", "oral cancer", "pharyngeal cancer", "laryngeal cancer", "nasopharyngeal carcinoma", "head and neck cancer". References of the retrieved publications were also screened. Only published studies with full-text articles were included. When overlapping articles were found, we only included the publications that reported the most extensive information.

Inclusion criteria

The inclusion criteria were as follows: (1) published in English or in Chinese; (2) case-control studies of HNC with IL-18-607C/A polymorphism; (3) supply the available genotype frequencies in cancer cases and controls. The

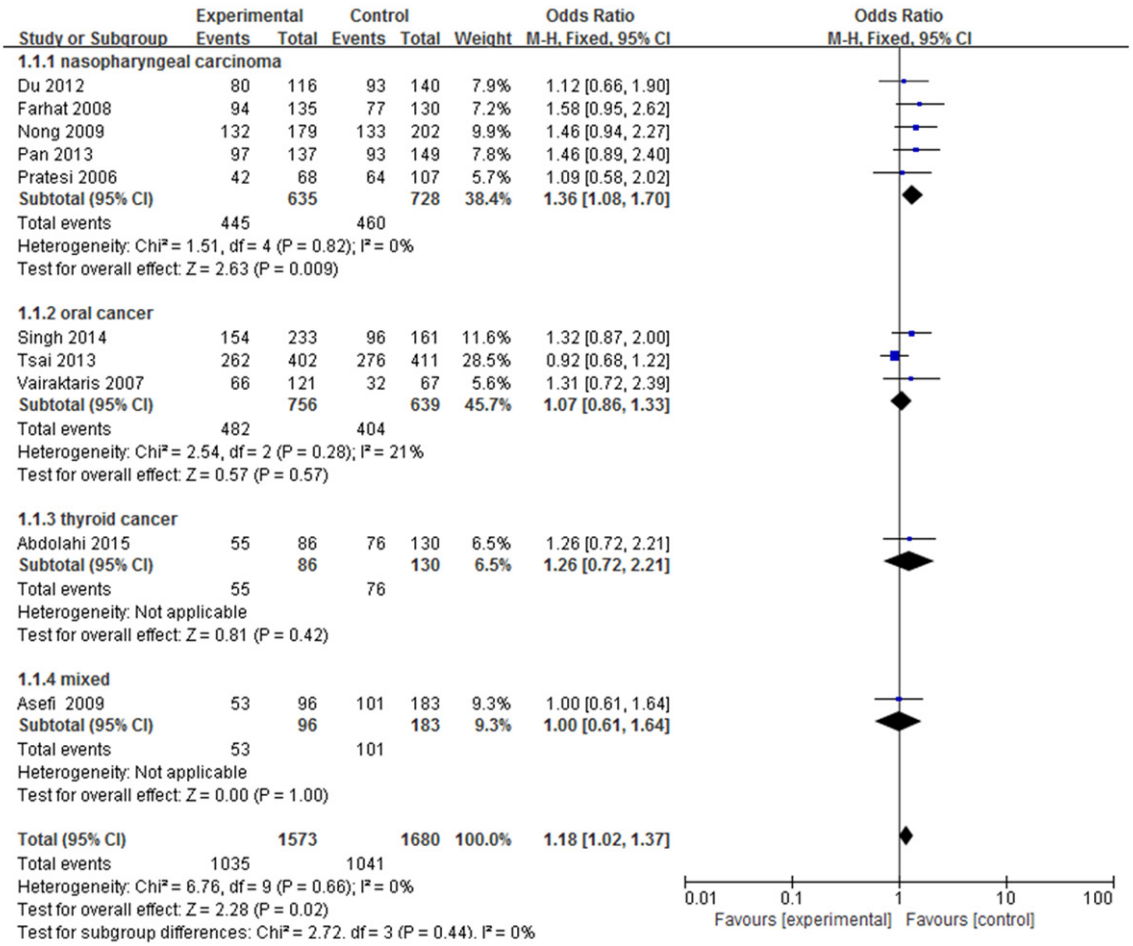

Figure 1. Meta-analysis with a fixed effects model for the ORs of HNC risk in different cancer types associated with IL-18-607C/A (CA vs. CC).

major reasons for exclusion of studies were (1) reviews and letters; (2) studies without detailed genotype frequencies. (3) Do not conforming to Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators (Cheng Yuan and Zhuo Chen) independently reviewed the articles and disagreements were resolved by discussion and consensus. We extracted the following information from each study: first author's surname, publication year, ethnicity, tumor type, source of controls, and the number of cases and controls for each genotype. Different ethnicities were categorized as Asian, European, and African. Cancer types were classified as nasopharyngeal carcinoma (NPC), oral cancer (OC), thyroid carcinoma (TC) and mixed. All eligible studies were defined as hospital-based (HB) and population-based (PB) according to the source of controls. HWE were calculated by Chi-square test (P<0.01 was considered as significant disequilibrium) based on the two polymorphisms genotyping distribution in controls.

Statistical analysis

Odds ratio (OR) with 95% confidence intervals (CIs) was used to assess the strength of association between IL-18-607C/A polymorphisms and HNC risk, based on the genotype frequencies in cases and controls. The pooled ORs were calculated for five models respectively: an allelic genetic model (A vs. C); a homozygous genetic model (AA vs. CC); a heterozygous genetic model (CA vs. CC); a recessive genetic model (AA vs. CA+CC) and a dominant genetic model (CA+AA vs. CC). The between-study heterogeneity of studies was performed though

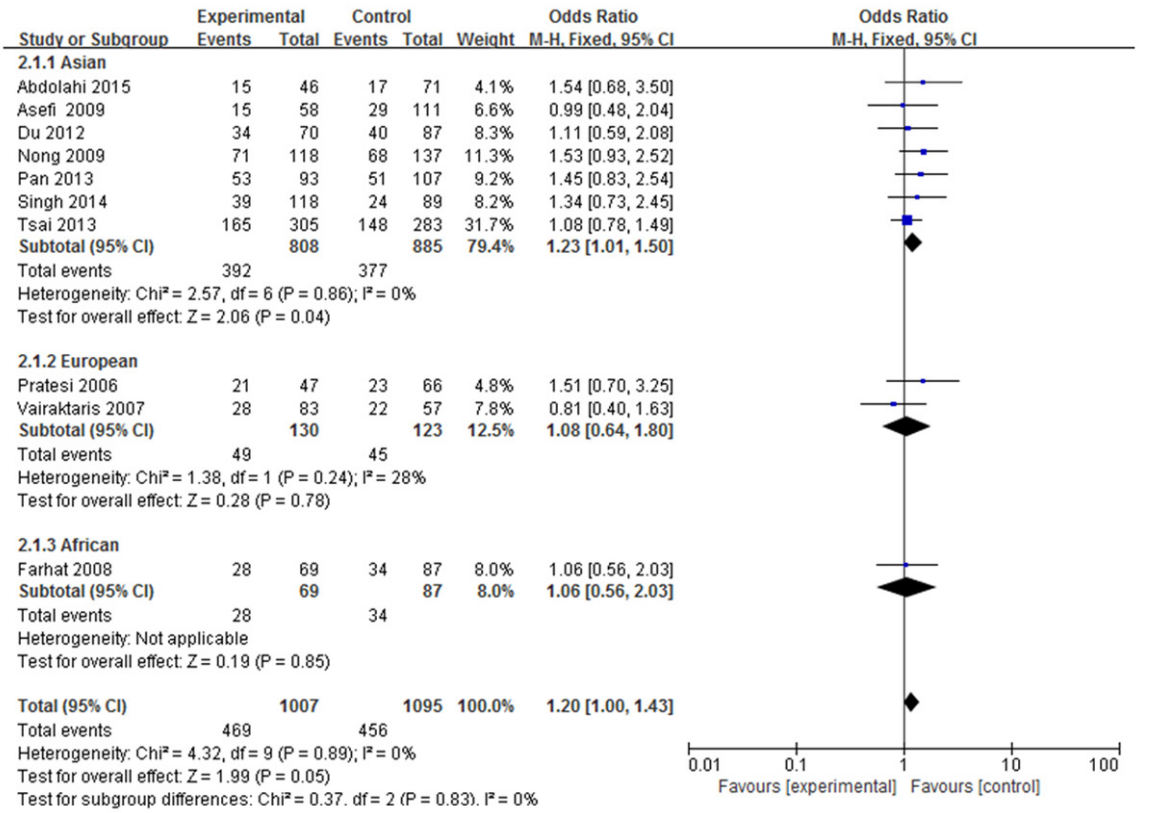

Figure 2. Meta-analysis with a fixed effects model for the ORs of HNC risk in different ethnicity associated with IL-18-607C/A (AA vs. CC).

Chi-square-based Q statistic test. If between-study heterogeneity was considered to be not significant (P>0.1), the fixed effects model was used, otherwise, the random effects model based on Mantel-Haenszel method was applied. Subgroup analyses were conducted among variables, such as cancer types, ethnicities, source of controls. Sensitivity analysis was conducted by removing one data set at a time to identify individual study' effect on pooled results and test the reliability of results. Funnel plots were used to access the potential publication bias by the method of Egger's linear regression test. All analyses were performed by Stata 12.0 and Review Manager 5.3, using two side *P* values.

Results

Characteristics of studies

Overall, we identified 10 studies [9-18] including 2,042 cancer cases and 2,013 controls to evaluate the association of IL-18-607C/A polymorphism with risk for HNC. The characteristics of these studies were listed in **Table 1**. There were 5 studies of NPC, 3 studies of OC, 1 study of TC and 1 study of mixed HNC; in the subgroup of ethnicity, 7 were carried out in Asian population, 2 were in European population and 1 was in African population, and in the subgroup of source of controls, 5 were carried out in PB and 5 were in HB. The distribution of genotypes in the controls conformed to HWE.

Main results

The evaluation of association between IL-18-607C/A polymorphism and HNC risk was presented in **Table 2**. Overall, there was significant association between IL-18-607C/A polymorphism and the risk of HNC (A vs. C: OR=1.10, 95% CI: 1.01-1.20, P=0.03; CA vs. CC: OR=1.18, 95% CI: 1.02-1.37, P=0.02; CA+AA vs. CC: OR=1.19, 95% CI: 1.04-1.36, P=0.01). In the subgroup of cancer types, there was significant association between IL-18-607C/A polymorphism and the risk of NPC (C vs. A: OR=1.16, 95% CI: 1.01-1.32, P=0.03; AA vs. CC: OR=1.34, 95% CI: 1.02-1.75, P=0.03; CA vs. CC: OR=1.36,

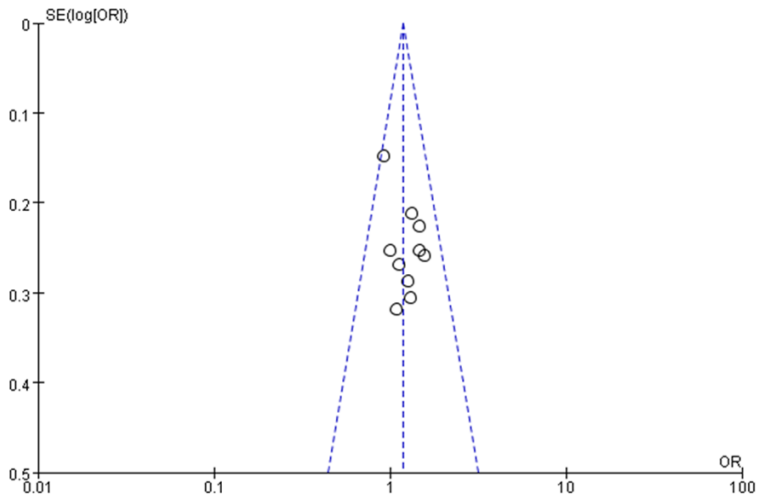

Figure 3. Funnel plot for publication bias of the meta-analysis of HNC risk and IL-18-607C/A polymorphism (CA vs. CC).

95% CI: 1.08-1.70, P=0.01; CA+AA vs. CC: OR=1.35, 95% CI: 1.09-1.68, P=0.01). But there is no significant relationship with TC and OC. According to the ethnicity, the results showed that the relationship between IL-18-607C/A gene polymorphism and HNC susceptibility mainly occurred in the Asian population (C vs. A: OR=1.11, 95% CI: 1.01-1.22, P=0.03; AA vs. CC: OR=1.23, 95% CI: 1.01-1.50, P=0.04; CA+AA vs. CC: OR=1.17, 95% CI: 1.01-1.37, P=0.04), not in European population and African population (**Figures 1** and **2**).

Evaluation of heterogeneity

There was no significant heterogeneity in all gene model (A vs. C: I^2=0%, P=0.94; AA vs. CC: I^2=0%, P=0.89; CA vs. CC: I^2=0%, P=0.66; AA vs. CA+CC: I^2=0%, P=0.88; CA+AA vs. CC: I^2=0%, P=0.79), so fixed effects model was applied in all comparison.

Sensitivity analysis

We used sensitivity analysis to estimate individual study's influence on the pooled ORs, and the result of sensitivity analysis showed no other single study influenced the summary OR qualitatively, suggesting stability of the meta-analyses.

Publication bias

Funnel plots are shown in **Figure 3** for heterozygous genetic model (CA vs. CC). Arrangement of data points did not reveal any evidence of obvious asymmetry. Formal evaluation using Egger's regression asymmetry tests for heterozygous genetic model and the result still did not show any evidence of publication bias (t=1.88, P=0.098).

Discussion

To our knowledge, this is the first meta-analysis to explore the association between IL-18-607C/A polymorphism and the risk of HNC. In the present meta-analysis, 10 eligible studies including 2,042 cases and 2,013 controls were identified and analyzed. The results demonstrated that IL-18-607C/A (rs1946518) polymorphism was associated with a statistical increased risk of HNC susceptibility in allelic genetic model, heterozygous genetic model and dominant genetic model. When stratified by different types of cancer, we found an association between IL-18-607C/A polymorphism and NPC risk under allelic genetic model, homozygous genetic model, heterozygous genetic model and dominant genetic model. When stratified by different ethnicity, the results showed an association between IL-18-607C/A polymorphism and HNC risk in Asian population under allelic genetic model, homozygous genetic model and dominant genetic model.

Considering the potential mechanism of IL-18 in cancer cell proliferation, metastasis, immune escape and angiogenesis, IL-18 has become one of key factors to control cancer development. In our study, a variety of genetic models suggested a high risk of between IL-18-607C/A and HNC. As a multifunctional cytokine, IL-18 can enhance the activity of T cells and NK cells and secretion of INF-γ [19]. In addition, it can also affect the differentiation of CD4+ and CD8+T cells and the synergy with other cytokines, such as inducing IFN-γ and stimulating Th1 type immune response [20]. In recent years, the abnormal expression of IL-18 gene was associated with many kinds of cancer, and serum IL-18 may be a clinical indicator for many kinds of cancer [21], but Jebreel [22] found that

there was no significant difference between the levels of serum HNSCC in IL-18 and healthy subjects. The relationship between serum IL-18 level and HNC remains to be confirmed, but the polymorphism of IL-18-607C/A affected the activation and expression of IL-18 gene, which was closely related to the occurrence of HNC [5].

Further subgroup analyses also found an association between the IL-18-607C/A polymorphism and HNC risk among studies using hospital-based controls.

Some other limitations in our meta-analysis should be acknowledged. Firstly, in the subgroup analyses, the sample size of different types of cancer and ethnicity was relatively small, such as TC and African population not having enough statistical power to explore the real association. Secondly, only English and Chinese language studies were included might have led to publication bias. Thirdly, the exclusion of unpublished data was generally associated with an overestimation of the true effect.

In conclusion, our meta-analysis showed that IL-18-607C/A polymorphism was associated with susceptibility to HNC, especially for NPC, but no significant relationship with the occurrence of OC and TC. In addition, there is a significant relationship with the risk of Asian population, while the relationship between the European and African populations is not obvious. Therefore, the further study of -607C/A IL-18 genotype or gene phenotype in Asian populations will provide a theoretical basis for exploring the pathogenesis of HNC.

Disclosure of conflict of interest

None.

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