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# Interleukin-10 polymorphisms and nasopharyngeal carcinoma risk: a meta-analysis

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**ABSTRACT.** It has been reported that interleukin-10 (IL-10) promoter genes (1082 A/G, 819 T/C, 592 A/C) are associated with nasopharyngeal

 

carcinoma (NPC). However, the results remain controversial and ambiguous. To resolve inconsistencies in published data, we performed a meta-analysis to ascertain the association between IL-10 polymorphisms and NPC risk. Two case-control studies and two cohort studies were quantitatively analyzed to evaluate IL-10 promoter gene polymorphisms and NPC risk. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for each genetic model and allelic comparison. A random-effect model or a fixed-effect model was used to calculate the overall combined risk estimates. Overall, the variant genotypes (AA and AG) of the IL-10-1082 A/G polymorphism were associated with elevated risk of NPC compared with the GG homozygote (AG *vs* GG: OR = 1.77; 95%CI = 1.39-2.26; AG + GG *vs* AA: OR = 1.78; 95%CI = 1.42-2.22); no significant associations were observed in allelic contrast and the recessive model. Strong positive association was seen in the cohort studies but not in the case-control studies. No statistically significant association was detected between IL-10-819 T/C and IL-10-592 A/C polymorphisms and NPC. Additionally, publication bias was not found. Based on the current evidence, this meta-analysis suggests that IL-1082 A/G polymorphism may increase the risk of NPC, but IL-10-819 T/C and IL-10-592 A/C polymorphisms do not. Further multicenter studies that are better controlled are required to confirm these findings.

**Key words:** Interleukin-10; Meta-analysis; Nasopharyngeal carcinoma; Polymorphism; Promoter genes.

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is rare in most parts of the world, but is more prevalent in southern China, especially in Guangdong, where genetic abnormalities and Epstein-Barr virus (EBV) infection are critical in the pathogenesis of the disease (Chan et al., 2002, Jia et al., 2006). In 2008, there were an estimated 84,400 cases of NPC and 51,600 deaths (DeSantis et al., 2013).

Epidemiological studies have shown that NPC is a multifactorial disease and the risk factors include EBV infection, genetic components, salted fish consumption, cigarette smoking, alcohol consumption, and occupational exposure to wood and formaldehyde (Yu et al., 1987; Chow et al., 1993; Cheng et al., 1999; Zeng et al., 2002; Young et al., 2004; Jia et al., 2005; O'Neil et al., 2008). Accumulating data have shown that genetic polymorphisms show statistically significant associations with the xenobiotic enzymes that metabolize carcinogenic compounds, and underlie individual variations in cancer risk (Hiyama et al., 2008). At an international level, the wide geographic variation of NPC in terms of incidence and mortality suggests that carcinogenesis might be related to genetic component factors.

Interleukin-10 (IL10) is an important immunoregulatory cytokine with pleiotropic effects (Howard and O'Garra, 1992; Moore et al., 1993) and plays a substantial role in immune processes (Lalani et al., 1997; Moore et al., 2001). IL10 is mainly produced by macrophages, T-helper-2 cells, and B lymphocytes, which can both stimulate and suppress immune responses, such as cytokine production, antigen presentation, macrophage activation and antigen-specific T-cell proliferation

(Mocellin et al., 2005). Research into IL-10 gene polymorphism, especially in the promoter region, has revealed that the IL-10 gene is located on chromosome lq31-32, and is composed of five exons and four introns. Several single nucleotide polymorphisms (SNPs) have been identified in the IL-10 gene promoter region. Three SNP sequences, -1082 A/G (rs1800896), -819 T/C (rs3021097), and -592 A/C (rs1800872), have been reported to regulate the transcriptional start site, which influences the transcription of IL-10 messenger RNA and the expression of IL-10 *in vitro* (Edwards-Smith et al., 1999; Kingo et al., 2005). IL-10 SNP is associated with cancer susceptibility and affects the severity, disease progression, and IL-10 expression level (Zhou et al., 2008; Chen et al., 2010, Zhuang et al., 2010). In recent years, the varied role of IL10 has been well documented to have a beneficial effect in some diseases, and has been reported to play a critical role in cancer development and metastasis (Mocellin et al., 2005). Increased circulating IL10 has been reported in patients with different types of cancer, including hepatocellular carcinoma, infectious and autoimmune cancers, and leukemia (De Vita et al., 2000; Uwatoko et al., 2002; Guzowski et al., 2005; Tseng et al., 2006; de Deus et al., 2012, Li et al., 2012, Yao et al., 2013).

To date, multiple epidemiologic studies regarding the potential association of the IL-10 gene with NPC risk have been published (Wei et al., 2007; Tsai et al., 2013). The results of these studies are conflicting and ambiguous (Pratesi et al., 2006; Farhat et al., 2008); the studies have small sample sizes and the conclusions drawn might not be reliable. The purpose of this meta-analysis was to determine whether genetic variants of the IL-10 gene polymorphisms are positively or negatively associated with a predisposition to NPC.

## METHODS

### Literature search and inclusion criteria

PubMed, Web of Science, and Embase databases (updated to April 2014) were searched to identify relevant studies investigating the association between IL-10 polymorphisms and risk of NPC. The following search terms were used: “nasopharyngeal carcinoma” or “NPC”; ‘‘undifferentiated carcinoma of nasopharyngeal type’’ or “UCNT”; “nasopharyngeal cancer”; ‘‘neoplasms’’; ‘‘carcinoma’’; ‘‘cancer’’; ‘‘tumor’’; “Interleukin-10” or “IL-10”; “1082 G/A”; “819 T/C”; “592 A/C”; ‘‘single-nucleotide polymorphisms’’ or ‘‘SNP’’; and ‘‘polymorphisms’’ or “polymorphism” or “genetic polymorphism” or “allele” or “genotype”, without restriction on time period, sample size, population, language, or type of report. Reference lists of reviews or studies identified in the literature search were hand-searched for additional studies. If duplicated data were presented in several studies, only the most recent, largest, or most complete study was included. Studies meeting the following criteria were included: i) they should evaluate the association between IL-10 polymorphisms and NPC; ii) they should be case-control designed, cross-sectional, or cohort designed studies; iii) they should contain sufficient data on allelic frequencies or genotypes; and iv) they should provide the adjusted odds ratios (ORs) with the corresponding 95% confidence interval (CI) or other available data for estimating OR (95%CI).

### Data extraction and outcome measure

Two reviewers (Yun-fang Yu and Wen-bin Guo) independently extracted data about the characteristics of selected studies using a standardized data extraction form, and the data were

checked by other investigators. Data were abstracted as follows: first author, year of publication, study design, country, genotyping method, source of controls, number of participants, patient age, adjustment for covariates, and outcome data. To ensure the accuracy of extracted information, two investigators blinded to the identity information of the studies judged inclusion and exclusion. Disagreements were resolved by discussion and consensus with a third author (Cun-dong Liu).

### Statistical analyses

We computed a pooled OR and relevant 95%CI used as a common measure of the association between the polymorphisms of the IL-10 gene and risk of NPC. Statistical heterogeneity was evaluated using the Cochran Q test (significance level at < 0.10). The $I^2$ statistic (Higgins et al., 2003), which is a quantitative measure of inconsistency across studies, was also calculated. The random-effects model [DerSimonian and Laird method (DerSimonian and Laird, 1986)] was taken into account when heterogeneity was observed among the studies. Otherwise, a fixed effects model [Mantel-Haenszel method (Mantel and Haenszel, 1959)] was applied. When heterogeneity was present, subgroup and sensitivity analyses were applied. Potential publication bias was assessed by both Begg's (Begg and Mazumdar, 1994) and Egger's (Egger et al., 1997) unweighted regression tests. P values < 0.05 indicate publication bias and P > 0.05 indicates no bias. Statistical analyses were carried out with STATA version 11.0 (Stata Corporation, College Station, Texas, USA). All the P values were two-sided. ORs (95%) were calculated with SPSS 13.0 (SPSS Inc., Chicago, Ill., USA). To ensure the reliability and accuracy of the results, two authors independently uploaded the data.

## RESULTS

### Identification of eligible studies

We identified 35 potential studies from PubMed, Web of Science, and Embase databases, 27 articles of which were excluded for failing to satisfy all the inclusion criteria. Of these, the majority were excluded after reviewing titles and abstracts, mainly because they were animal studies, abstracts of committee reports or comments, review article, and not about IL-10 polymorphisms and NPC risk. This left eight for full-text review. In the review, four articles were excluded for the following reasons: two articles had data unavailable for analysis, one was a review article, and one duplicated previous data. Ultimately, a total of four studies (Pratesi et al., 2006; Wei et al., 2007; Farhat et al., 2008; Tsai et al., 2013) were included in our meta-analysis. A detailed flowchart of the selection process is shown in Figure 1.

### Study characteristics

The main study characteristics of all included studies are presented in Table 1. These studies were published between 2006 and 2013. Sample size ranged from 89 to 552 (total 1641). Of the four articles initially found, two were case-control studies of Chinese (Wei et al., 2007) and Tunisian (Farhat et al., 2008) populations, and two were cohort studies of Chinese (Tsai et al., 2013) and Italian (Pratesi et al., 2006) populations. Among these studies, four were pooled for 1082 A/G (rs1800896) variants, three for 819 C/T (rs3021097), and three for 592 A/C (rs1800872). Three

were for NPC and one was for undifferentiated carcinoma of nasopharyngeal type (UCNT). All of the genotyping used polymerase chain reaction (PCR) restriction fragment length polymorphism analysis. Genetic distributions of IL-10 gene polymorphisms are presented in Tables 2, 3, and 4.

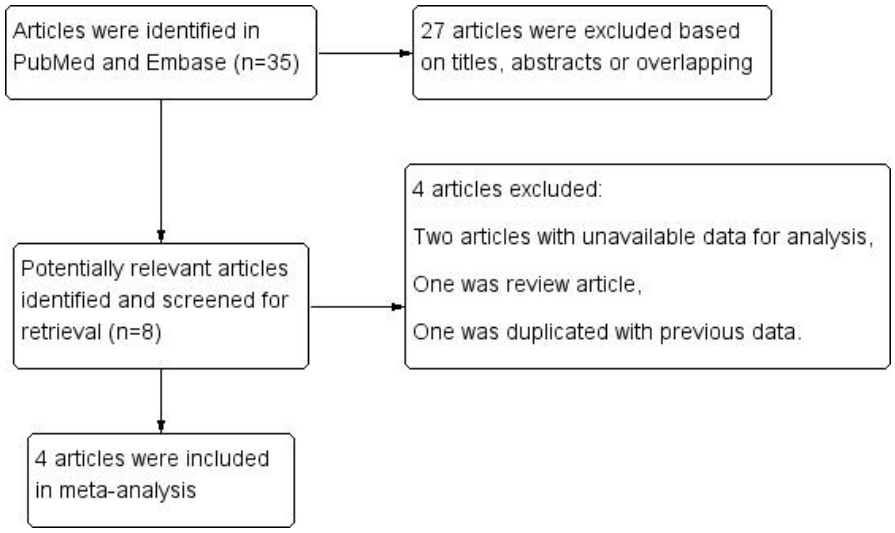


**Figure 1.** Flowchart from identification of eligible studies to final inclusion.

**Table 1.** Characteristics of the included studies.

| Author | Study design | Ethnicity | Country | Method | Source of controls | No. of case/control | Age | | Gender (M/F) | | Smoking% case/control |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Case | Control | Case | Control | |
| Pratesi et al. (2006) | Cohort | European | Italy | AS-PCR | PB | 89/130 | NA | NA | 70/19 | 100/30 | NA |
| Wei et al. (2007) | Case-control | Asian | China | PCR-RFLP | HB | 198/210 | 48.7 ± 0.8 | 47.9 ± 10.1 | 143/55 | 139/71 | 145/151 |
| Farhat et al. (2008) | Case-control | African | Tunisia | AS-PCR | PB | 160/156 | 41.9 ± 15.7 | 40.4 ± 14.8 | 116/44 | 149/48 | NA |
| Tsai et al. (2013) | Cohort | Asian | China | PCR-RFLP | HB | 176/522 | 48.2 ± 11.1 | 48.9 ± 9.8 | 128/48 | 379/143 | 77/209 |

HB = hospital based; PB = population based.

**Table 2.** Genotype distributions of Interleukin-10 (IL-10) 1082 A/G (rs1800896) polymorphism of enrolled studies.

| Author | Case | | | Control | | |
|---|---|---|---|---|---|---|
| | AA | AG | GG | AA | AG | GG |
| Pratesi et al. (2006) | 29 | 41 | 19 | 46 | 58 | 26 |
| Wei et al. (2007) | 123 | 61 | 14 | 167 | 38 | 5 |
| Farhat et al. (2008) | 58 | 80 | 22 | 70 | 60 | 26 |
| Tsai et al. (2013) | 117 | 49 | 10 | 419 | 92 | 11 |

**Table 3.** Genotype distributions of Interleukin-10 (IL-10) 819 T/C (rs3021097) polymorphism of enrolled studies.

| Author | Case | | | Control | | |
|---|---|---|---|---|---|---|
| | TT | TC | CC | TT | TC | CC |
| Pratesi et al. (2006) | 48 | 36 | 5 | 70 | 54 | 6 |
| Wei et al. (2007) | 82 | 81 | 35 | 94 | 92 | 24 |
| Tsai et al. (2013) | 88 | 69 | 19 | 285 | 185 | 52 |

**Table 4.** Genotype distributions of Interleukin-10 (IL-10) 592 A/C (rs1800872) polymorphism of enrolled studies.

| Author | Case | | | Control | | |
|---|---|---|---|---|---|---|
| | AA | AC | CC | AA | AC | CC |
| Pratesi et al. (2006) | 48 | 36 | 5 | 70 | 54 | 6 |
| Wei et al. (2007) | 82 | 81 | 35 | 94 | 92 | 24 |
| Tsai et al. (2013) | 93 | 66 | 17 | 261 | 205 | 56 |

## Overall analysis

A total of 1641 participations were included in the four studies. Table 2 and Figure 2A-D show the association of NPC risk with IL-10-1082 A/G (rs1800896) polymorphism. The pooled ORs indicate that there was an increased risk of NPC in individuals with variant allele and genotypes of IL-10-1082 A/G (heterozygote contrast, AG *vs* GG: $OR_{fixed\text{-}effects}$ = 1.77; 95%CI, 1.39-2.26; $P_{OR}$ = 0.000; $P_{Het}$ = 0.413; dominant model, AG + GG *vs* AA: $OR_{fixed\text{-}effects}$ = 1.78; 95%CI, 1.42-2.22; $P_{OR}$ = 0.000; $P_{Het}$ = 0.142). No significant associations were observed in allelic contrast and recessive model (allelic contrast, AA *vs* GG: $OR_{random\text{-}effects}$ = 1.76; 95%CI, 0.92-3.37; $P_{OR}$ = 0.086, $P_{Het}$ = 0.042, recessive model, GG *vs* AA + AG: $OR_{random\text{-}effects}$ = 1.58; 95%CI, 0.84-2.98; $P_{OR}$ = 0.157; $P_{Het}$ = 0.046).

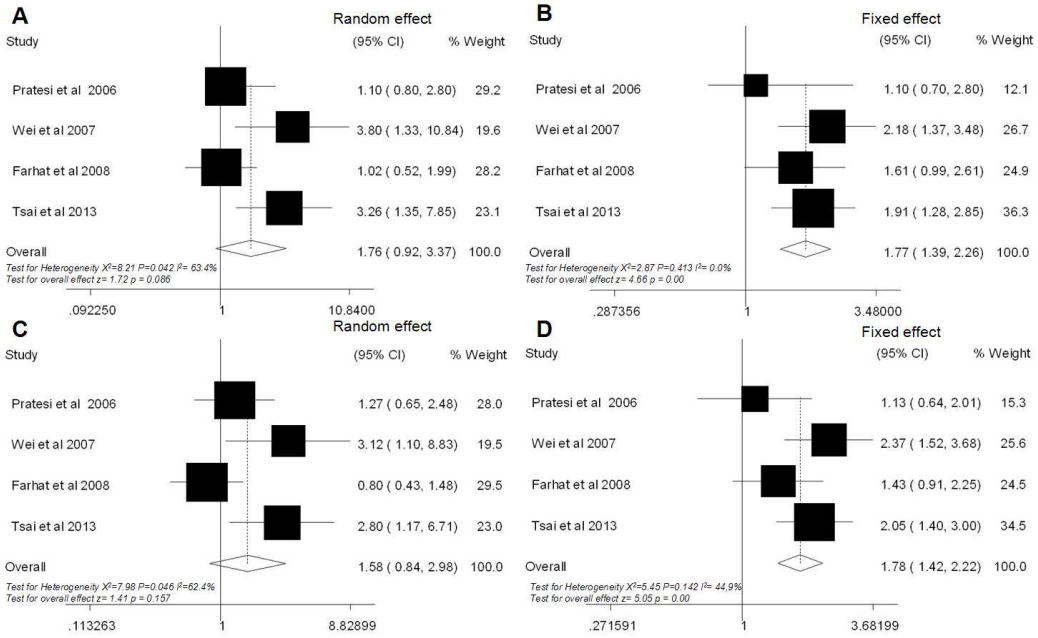


**Figure 2.** Forest plots of NPC risk associated with the IL-10-1082 A/G polymorphism. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled OR and 95%CI. (A) AA *vs* GG; (B) AG *vs* GG; (C) GG *vs* AA+G; (D) AG+GG *vs* AA.

The detailed results of the association between IL-10 polymorphism 819 C/T (rs3021097) and NPC risk are presented in Table 3 and Figure 3 (A-D) (Pratesi et al., 2006; Wei et al., 2007; Tsai et al., 2013). In all genetic models, the overall results of the pooled data did not show any statistical significance (allelic contrast, CC *vs* TT, $OR_{fixed\text{-}effects}$ = 1.36, 95%CI = 0.93-2.00, $P_{OR}$ =0.112, $P_{Het}$ = 0.688; homozygote contrast, TC *vs* TT, $OR_{fixed\text{-}effects}$ = 1.11, 95%CI = 0.85-1.45, $P_{OR}$ = 0.439, $P_{Het}$ = 0.796; dominant model, TC + CC *vs* TT: $OR_{fixed\text{-}effects}$ = 1.14, 95%CI = 0.90-1.44, $P_{OR}$ = 0.263, $P_{Het}$ = 0.847; recessive model, CC *vs* TC+TT: $OR_{fixed\text{-}effects}$ = 1.34, 95%CI = 0.92-1.94, $P_{OR}$ = 0.131, $P_{Het}$ = 0.576).

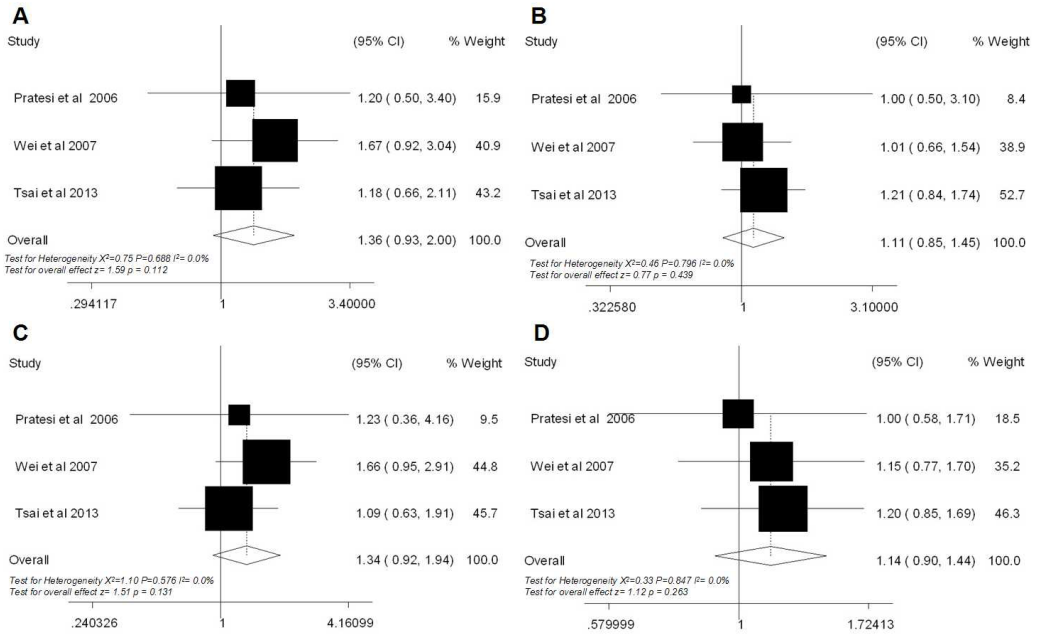


**Figure 3.** Forest plots of NPC risk associated with the IL-10-819 T/C polymorphism. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled OR and 95%CI. (**A**) CC *vs* TT; (**B**) TC *vs* TT; (**C**) CC *vs* TC+TT; (**D**) TC+CC *vs* TT.

As listed in Table 4 and Figure 4A-D, no evidence was found of the association between IL-10 polymorphism 592 A/C (rs1800872) and NPC risk from the three studies (Pratesi et al., 2006; Wei et al., 2007; Tsai et al., 2013) (allelic contrast, CC *vs* AA, $OR_{fixed\text{-}effects}$ = 1.19, 95%CI = 0.81-1.75, $P_{OR}$ = 0.376, $P_{Het}$ = 0.291; homozygote contrast, AC *vs* AA, $OR_{fixed\text{-}effects}$ = 0.97, 95%CI = 0.71-1.31, $P_{OR}$ = 0.833, $P_{Het}$ = 0.941; dominant model, AC + CC *vs* AA: $OR_{fixed\text{-}effects}$ = 0.99, 95%CI = 0.78-1.25, $P_{OR}$ = 0.912, $P_{Het}$ = 0.689; recessive model, CC *vs* AC+AA: $OR_{fixed\text{-}effects}$ = 1.23, 95%CI = 0.84-1.79, $P_{OR}$ = 0.295, $P_{Het}$ = 0.309).

## Heterogeneity and sensitivity analyses

Table 5 shows the results of the sensitivity and subgroups analyses of IL-10-1082 A/G (rs1800896) polymorphism and NPC risk. Two cohort studies were conducted in Europeans

and Asians including 265 cases and 652 controls. Pooled ORs showed that IL-10-1082 A/G polymorphism correlated with an increased risk of NPC, as suggested by the four following gene contrast models (AA *vs* GG, $OR_{fixed\text{-}effects}$ = 3.47, 95%CI = 1.77-6.82, $P_{OR}$ = 0.000; AG *vs* GG, $OR_{fixed\text{-}effects}$ = 2.02, 95%CI = 1.49-2.74, $P_{OR}$ = 0.000; AG+GG *vs* AA, $OR_{fixed\text{-}effects}$ = 2.18, 95%CI = 1.63-2.91, $P_{OR}$ = 0.000; GG *vs* AA+AG, $OR_{fixed\text{-}effects}$ = 2.93, 95%CI = 1.50-5.72, $P_{OR}$ = 0.002). In the subgroups analyses stratified by hospital based (Asians) (Wei et al., 2007; Tsai et al., 2013) and population based (Pratesi et al., 2006; Farhat et al., 2008), significant results were identified in the homozygote contrast and dominant model (AA *vs* GG and AG+GG *vs* AA), and no significant associations were observed in allelic contrast or the recessive model. However, for the case-control studies (Wei et al., 2007; Farhat et al., 2008) subgroup no significant associations were observed.

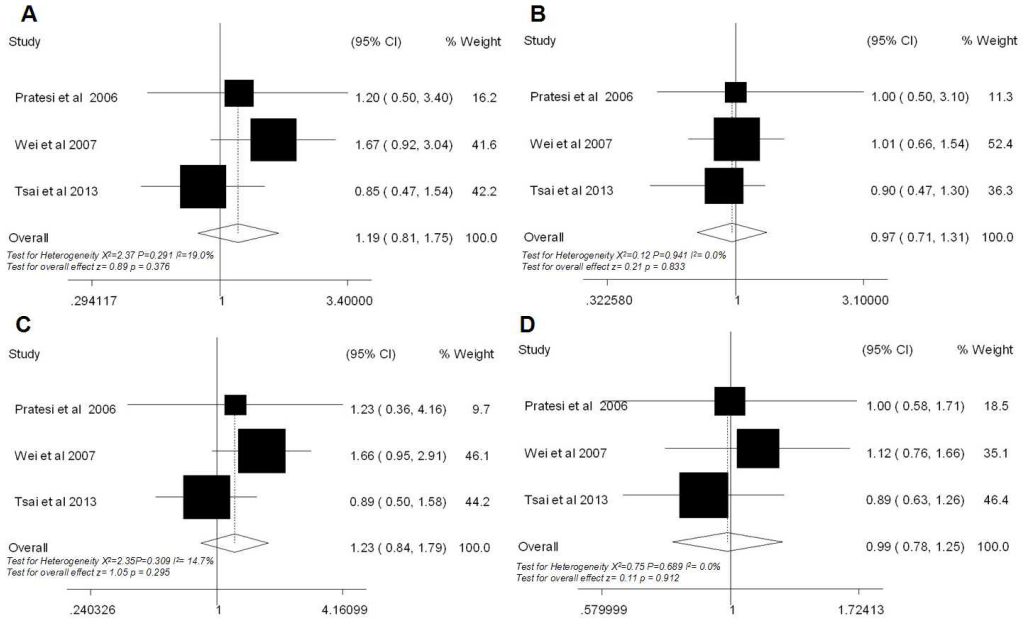


**Figure 4.** Forest plots of NPC risk associated with the IL-10-592 A/C polymorphism. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled OR and 95%CI. (**A**) CC *vs* AA; (**B**) AC *vs* AA; (**C**) CC *vs* AA+AC; (**D**) AC+CC *vs* AA.

## Publication bias

The Begg and Egger tests were performed to evaluate publication bias in the IL-10-1082 A/G polymorphism and NPC risk literature, and a funnel plot was produced. Both Begg's (rank correlation test) and Egger's funnel plot asymmetry test (regression method) in the meta-analysis indicated that there was no significant publication bias (AA *vs* GG: Begg's test P = 0.734, Egger's test P = 0.061 Figure 5). The shapes of the funnel plots for other gene models were also symmetrical. There was no publication bias in our meta-analysis.

**Table 5.** Summary of pooled ORs of Interleukin-10 (IL-10) 1082 A/G (rs1800896) polymorphism and NPC risk by subgroup analysis.

| Comparisons | Number of studies | OR (95%CI) | $P_{OR}$ | $P_{Het}$ | Model |
|---|---|---|---|---|---|
| Hospital based (Asians) | 2 (Wei et al., 2007; Tsai et al., 2013) | | | | |
| AA *vs* GG | | 1.81 (0.63-5.23) | 0.274 | 0.049 | Random |
| AG *vs* GG | | 1.66 (1.18-2.35) | 0.004 | 0.177 | Fixed |
| AG + GG *vs* AA | | 1.71 (1.25-2.35) | 0.001 | 0.090 | Fixed |
| GG *vs* AA + AG | | 1.70 (1.00-2.90) | 0.051 | 0.159 | Fixed |
| Population based | 2 (Pratesi et al., 2006; Farhat et al., 2008) | | | | |
| AA *vs* GG | | 1.85 (0.51-6.65) | 0.349 | 0.038 | Random |
| AG *vs* GG | | 1.88 (1.35-2.63) | 0.000 | 0.375 | Fixed |
| AG + GG *vs* AA | | 1.85 (1.35-2.54) | 0.000 | 0.118 | Fixed |
| GG *vs* AA + AG | | 1.47 (0.39-5.58) | 0.567 | 0.027 | Random |
| Cohort studies | 2 (Pratesi et al., 2006; Tsai et al., 2013) | | | | |
| AA *vs* GG | | 3.47 (1.77-6.82) | 0.000 | 0.826 | Fixed |
| AG *vs* GG | | 2.02 (1.49-2.74) | 0.000 | 0.673 | Fixed |
| AG + GG *vs* AA | | 2.18 (1.63-2.91) | 0.000 | 0.629 | Fixed |
| GG *vs* AA + AG | | 2.93 (1.50-5.72) | 0.002 | 0.875 | Fixed |
| Case-control studies | 2 (Wei et al., 2007; Farhat et al., 2008) | | | | |
| AA *vs* GG | | 1.06 (0.67-1.68) | 0.796 | 0.873 | Fixed |
| AG *vs* GG | | 1.42 (0.96-2.11) | 0.082 | 0.378 | Fixed |
| AG + GG *vs* AA | | 1.31 (0.92-1.86) | 0.137 | 0.529 | Fixed |
| GG *vs* AA + AG | | 0.99 (0.63-1.55) | 0.949 | 0.319 | Fixed |

OR = odds ratio; CI = confidence interval.

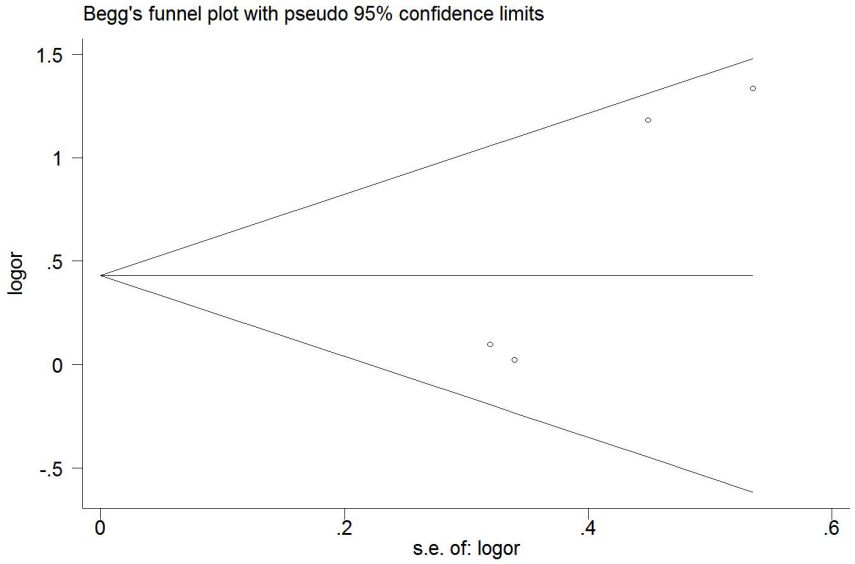


**Figure 5.** Funnel plot for publication bias test (AA *vs* GG). Each point represents a separate study for the indicated association.

## DISCUSSION

The present meta-analysis included 1641 participants from two case-control studies and two cohort studies, including a pool of 623 cases and 1018 controls, and explored the association

between the IL-10 polymorphisms and NPC risk. To our knowledge, this meta-analysis was the first comprehensive assessment of the relationship between IL-10 polymorphisms and NPC risk. In the overall analysis, we found an association between the IL-10-1082 A/G polymorphism and NPC (heterozygote contrast, AG *vs* GG: $OR_{fixed\text{-}effects}$ = 1.77; 95%CI, 1.39-2.26; $P_Z$ = 0.000; $P_{Het}$ = 0.413; dominant model, AG + GG *vs* AA: $OR_{fixed\text{-}effects}$ = 1.78; 95%CI, 1.42-2.22; $P_Z$ = 0.000; $P_{Het}$ = 0.142), and across sensitivity analyses there was no significant publication bias; heterogeneity existed under the allelic contrast and recessive model ($P_{het}$ < 0.05) after random effect models were selected to combine these pooled ORs, and no significant associations were observed. In the subgroup analyses, a strong positive association was also indicated in the cohort studies when the subgroup analyses were stratified according to study design. Moreover, in the subgroup analyses stratified with hospital based (Asians) and population based, significant results were identified in the homozygote contrast and dominant model. However, the data obtained in this case-control study indicate that none of the IL-10-1082 A/G studied is likely to have major effects on NPC susceptibility by subgroup analysis.

In NPC, some studies found an increasing production of IL-10 suggesting a possible involvement in the tumor growth; however, the opposite has also been reported. This meta-analysis, which still remains controversial and ambiguous, has pooled all the available results. We identified several reasons for the lack of association. First, the number of studies and sample sizes were relatively small, which means more investigations involving more subjects are needed to clarify the relationship. Second, the frequency distribution of the gene polymorphisms was significantly different among different ethnic groups. For example, the variation in genotype frequency among ethnic groups may contribute to the lack of a significant association overall. Third, some confounding factors, such as study design, source of controls, length of treatment, gender, cigarette smoking, and alcohol consumption, which are known risk factors for NPC and might affect its incidence, were not recognized or taken into account; this might have led to inaccurate results. For the IL-10-819 T/C and IL-10-592 A/C polymorphisms, no statistically significant association with NPC was detected in the overall population by any of the genetic models, and substantial heterogeneity was not observed.

NPCs are very different from other head and neck cancers because of their specific multifactorial etiology (Chan et al., 2002). There is evidence to suggest that NPC has a complex etiology involving a consistent association with EBV, patient's geographical origin, and environmental and hereditary factors; a dose-response relationship between EBV antibody titers and NPC risk has been demonstrated (Yu et al., 1987; DeSantis et al., 2013). Of the studies we included, one study (Pratesi et al., 2006) found that G-bearing genotypes of IL-10-1082 A/G were significantly higher in patients with NPC who smoked than in the smoking controls. Moreover, another study (Wei et al., 2007) has shown that the NPC patients with detectable EBV DNA viremia carry the genotype A/A, when compared with EBV DNA-positive patients or healthy controls, and the frequency of the IL-10-A1082G allele, which is associated with high IL-10 expression, showed an almost statistically significant increase in NPC EBV DNA-negative patients compared with healthy controls.

IL-10 polymorphisms are of particular interest in relation to cancer because IL-10 is a multifunctional cytokine with immunosuppressive functions, which may promote tumors. Convincing evidence has been obtained that a large number of polymorphisms (primarily SNPs) have been identified in the IL-10 gene promoter, and these polymorphisms are associated with differential expression of IL-10 *in vitro* and in some cases *in vivo*. Many studies suggest that NPCs are characterized by a high level of leukocyte infiltration among tumor cells. IL-10 is produced mainly by macrophages and T lymphocytes. It is an important anti-inflammatory and immunosuppressive

cytokine that works by downregulating the expression of T helper 1 (Th1) cytokines and costimulatory molecules, and may regulate angiogenesis in various cancers. Overall, it has been hypothesized that IL-10 may contribute to the escape of tumor cells from immune surveillance and may favor tumor growth. Multiple epidemiologic studies have provided evidence that the IL10-A1082G genotype plays an important role in renal cell carcinoma (Uwatoko et al., 2002), hepatocellular carcinoma (Tseng et al., 2006), lung cancer (De Vita et al., 2000), leukemia (Guzowski et al., 2005; de Deus et al., 2012; Yao et al., 2013), and gastroduodenal disease (Kang et al., 2009). However, there have also been several results reporting no association of this SNP with various types of cancers (Barbisan et al., 2012).

Moreover, in NPC, some studies have found that the IL-10 gene polymorphisms are positively associated with tumor growth; however, opposite findings have also been reported. Previous studies have shown increased IL-10 expression in epithelial NPC cells and IL-10 serum level associations with undifferentiated and clinical late-stage NPC (Farhat et al., 2008). In contrast, other reports detected no NPC cell expression of IL-10 and no association with serum levels (Beck et al., 2001). There is no denying that these currently published studies have a small sample size, which needs to be enlarged, and the evidence might not produce a reliable conclusion. Moreover, the evidence from the literature concerning IL-10 gene polymorphisms and NPC association is still poor. Therefore, IL-10 polymorphism cannot be excluded as a risk factor for NPC. A small number of studies on IL-10 polymorphisms have been reported and more evidence is needed to confirm the association with NPC.

Several limitations might be acknowledged in this meta-analysis. First, although an increased risk of NPC was observed to be associated with the variant allele and genotypes of IL-10, the sample sizes of all eligible studies carried out were too limited to determine a convictive gene association, which might have resulted in a reduced statistical power. Second, we failed to assess the combination of established environmental factors involving smoking, alcohol consumption, and EBV exposure, with the IL-10 polymorphism in NPC pathogenesis, because relevant studies included in the current meta-analysis were insufficient. Third, despite performing sensitivity analyses, we could not further stratify the results by other potential confounding factors to detect the major source of heterogeneity, because of the lack of data in the original publications, although it is worth noting that the pooled results still turned out to be significant. In addition, residual and unmeasured confounding factors, such as source of controls, family history of cancer, diet changes, and environmental factors, are of concern and might confound the interpretation of the IL-10 polymorphisms and NPC risk association, and potentially produce biases. Another limitation of this analysis is the association of gene-gene and gene-environment interactions, which might modify the risk estimates and should be established and analyzed in future studies of the association between IL-10 polymorphisms and NPC risk. Therefore, the facticity of the results might be influenced by this.

In conclusion, despite these limitations, our meta-analysis firstly provided a more accurate estimate of the association between IL-10 polymorphisms and NPC risk. Our results showed that the 1082 A/G polymorphism of the IL-10 gene was significantly associated with an elevated cancer risk in the cohort studies when the subgroup analyses were stratified according to study design. Nevertheless, IL-10 may be a promising gene for predicting NPC patients, and more high quality cohort studies concerning the role of IL-10 polymorphism in NPC pathogenesis are warranted for further elucidation. In addition, the potential effect of gene-environment interaction on NPC risk needs to be investigated in subsequent studies.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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