Original Article
Association between *IL-10* polymorphisms (-1082A/G, -592A/C and -819T/C) and oral cancer risk

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Abstract: Interleukin-10 (IL-10) is likely to be closely correlated with the outbreak and progression of cancers though aiding tumors to free from the immune response. In previous studies, several polymorphisms sites including -1082A/G, -592A/C and -819T/C in the promoter region of *IL-10* gene were proved to be involved in oral cancer. The purpose of this study was to further explore this association via a meta-analysis. There were four publications with 3783 cases and 4245 controls retrieved though electronic databases. The association among three *IL-10* polymorphisms sites was estimated by summary odds ratios (ORs) and 95% confidence intervals (95% CIs) which were calculated using fixed-effect model. Subgroup analysis by ethnicity (Asian or Caucasian) was also performed for the analysis of *IL-10*-1082A/G polymorphism (three studies in Asians and one study in Caucasian). As a result, we found a moderately increased risk which was related to *IL-10*-1082A/G polymorphism in oral cancer under all the five contrasts [GG vs. AA: OR (95% CI)=2.95 (1.94-4.48); GG+AG vs. AA: OR (95% CI)=1.59 (1.35-1.86); GG vs. AG+AA: OR (95% CI)=2.59 (1.71-3.94); Allele G vs. Allele A: OR (95% CI)=1.68 (1.46-1.94); AG vs. AA: OR (95% CI)=1.53 (1.29-1.81)]. Additionally, the increased risk of oral cancer was also observed in Asians and Caucasians. However, the pooled data indicated that *IL-10*-592A/C and -819T/C polymorphisms sites had no relationship with oral cancer risk. Taken together, the *IL-10*-1082A/G polymorphism site may act as a risk factor in oral cancer, and this issue still needs to be further verified.

Keywords: Interleukin-10, polymorphism, oral cancer, susceptibility

Introduction

Oral cancer, a subtype of head and neck cancer, can occur in any location, though it is commonly observed in some certain tissues, such as the floor of the mouth and the tongue which totally account for about 90% of all the malignancies appearing in the oral cavity [1-3]. As a malignant tumor easy to metastasize to surrounding tissues, oral cancer has an incidence rate of 75% in male patients of more than 60 years old, and about 95% of these cases suffer from squamous cell carcinomas [4, 5]. Oral squamous cell carcinomas are aggressive lesions involving the perineural growth, which has a high recurrence rate and a frequent metastasis to cervical lymph nodes [6]. Remarkable advances have been achieved in surgery and chemotherapy in recent years, however, patients developing oral cancer still have a poor outcome and a low survival rate [7, 8]. Epidemiological studies in Indians have demonstrated tobacco chewing and smoking are primarily responsible for the high morbidity of oral cancer [9, 10]. In addition, among various environmental factors, betel chewing is identified as an independent risk factor for oral cancer in Taiwan population [11-13]. However, the definite molecular pathogenesis of oral cancer is not yet well known.

Recently, cytokines have been confirmed their critical roles in the etiology of oral cancer, including transforming growth factor-β (TGF-β) [14, 15], interleukin-6 (IL-6) [16], interleukin-8 (IL-8) [17] and interleukin-10 (IL-10) [18-21]. Derived from monocytes, macrophages and lymphoid cells, IL-10 is an immunosuppressive cytokine with multiple functions, such as inhibition of cytokine production and T-cells proliferation, and regulation of inflammatory responses [22, 23]. IL-10, with the capacity of both tumor-promotion and tumor-inhibition, plays an important role in assisting tumors to escape from the
immune response, and the elevated levels of IL-10 production have been uncovered in various malignant tumors [24-26].

IL-10 gene located on chromosome 1 has a promoter spanning a range of at least 5 kb upstream of the transcription starting point and comprising at least 27 polymorphisms known so far, including -1082A/G, -592A/C and -819T/C [27, 28]. Polymorphisms in the IL-10 gene promoter may have a close relation with changes in IL-10 expression, thus leading to the occurrence of cancers [29]. To date, there are few studies comprehensively exploring the three IL-10 polymorphisms (-1082A/G, -592A/C and -819T/C) in the oral cancer, therefore, we conducted a meta-analysis so as to give a more authentic cognition concerning this association though data synthesis and analysis.

Materials and methods

Data sources

With the aid of electronic databases of PubMed, all the relevant publications were initially searched according to their titles and abstracts with the following keywords as “interleukin-10”, “polymorphism”, and “oral cancer”. We made no efforts to seek those unpublished studies. All the eligible studies were retrieved their reference lists manually for other additional articles.

All the available publications were limited on English language, but not on sample size, population, and publication year. When there appeared any duplicated studies, only the one with the largest sample size was included in the meta-analysis.

Inclusion and exclusion criteria

All the eligible studies were selected on the basis of inclusion and exclusion criteria. The inclusion criteria incorporated: (i) case-control studies exploring the correlation between IL-10 polymorphisms and oral cancer risk; (ii) having available genotype frequencies in cases and controls; and (iii) presenting necessary data and outcomes for the calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs). We precluded the studies which overlapped with other studies or with information provided by the same authors.

Included studies and collection of useful information

Using a standard reporting stable, two investigators extracting the useful information did not interfere with each other. The information extracted from included studies was as follows: first author, year of study publication, country of origin, ethnicity, source of control populations, genotyping methods, polymorphisms, genotype frequencies, number of oral cancer cases and healthy controls, and \( P \) values of Hardy-Weinberg equilibrium (HWE). When a study reported on not only one polymorphism, the data would be extracted separately. Disagreements, if any, were resolved via discussion between the two investigators.

Statistical analyses for meta-analysis

The whole data procession was fulfilled by using STATA software (version 12, Stata Corp LP, College Station, TX, USA). \( Z \) test was used to determine whether the pooled ORs were significant, and \( P<0.05 \) was set at the significant level. The Q-statistic method was utilized to
check the heterogeneity among studies, and when $P<0.1$, the random-effect model was used to estimate the ORs. And when the $P$ value presented conversely, the fixed-effect model would be applied. The ORs with 95% CIs were calculated for each genetic polymorphism of IL-10 gene under five genetic contrasts to estimate the degree of association of each polymorphism with risk of oral cancer. Subgroup analysis stratified by ethnicity was only conducted for IL-10-1082A/G polymorphism in Asian and Caucasian populations. HWE was examined in control populations by the $\chi^2$ test. As for the publication bias, if Begg's funnel plot revealed an asymmetrical shape and the $P$ value of Egger regression test was less than 0.05, then there existed a marked publication bias in the meta-analysis.

## Results

### Features of published studies

Detailed selection process is shown in Figure 1. In total, 96 articles were firstly found though database of PubMed, among which 83 articles were excluded after title screening, and 13 papers were relevant to IL-10 polymorphisms and oral cancer. Through further selection, 6 studies not adopting case-control design and 3 studies with no detailed genotype data were precluded, and finally 4 publications were considered available and included into the meta-analysis [18-21]. The main features of the four eligible studies are displayed in Table 1. Among the four studies, three aimed at Asians [18, 19, 21] and only one at Caucasians [20]. There were four studies on IL-10-1082A/G polymorphism [18-21], three on IL-10-592A/C polymorphism [18, 19, 21], and three on IL-10-819T/C polymorphism [18, 19, 21].

### Data synthesis and analysis

Table 2 presents the overall results of the relation of IL-10 polymorphisms with oral cancer risk. IL-10-1082A/G polymorphism contributed to an increased risk of oral cancer under all the five models [GG vs. AA: OR (95% CI)=2.95 (1.94-4.48); GG+AG vs. AA: OR (95% CI)=1.59 (1.35-1.86); GG vs. AG+AA: OR (95% CI)=2.59 (1.71-3.94); Allele G vs. Allele A: OR (95% CI)=1.68 (1.46-1.94); AG vs. AA: OR (95% CI)=1.53 (1.29-1.81)]. And similar results could be observed in subgroup analysis by ethnicity in Asians [GG vs. AA: OR (95% CI)=2.87 (1.88-4.39); GG+AG vs. AA: OR (95% CI)=1.59 (1.33-1.89); GG vs. AG+AA: OR (95% CI)=2.55 (1.67-3.89); Allele G vs. Allele A: OR (95% CI)=1.69 (1.45-1.98); AG vs. AA: OR (95% CI)=1.52 (1.26-1.83)] and Caucasians [GG+AG vs. AA: OR (95% CI)=1.60 (1.08-2.38); Allele G vs. Allele A: OR (95% CI)=1.63 (1.14-2.34); AG vs. AA: OR (95% CI)=1.59 (1.07-2.37) (Figure 2). In contrast, this significant correlation was not found between oral cancer risk and IL-10-592A/C or -819T/C polymorphism.

### Test of heterogeneity, sensitivity and publication bias

As described in the total results in Table 2, the $P$ value of heterogeneity test for each polymorphism within IL-10 gene under every genetic model was larger than 0.05, which indicated a

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**Table 1. Main information extracted from studies eligible for the meta-analysis**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Sample size (cases/controls)</th>
<th>Control source</th>
<th>Genotyping method</th>
<th>Polymorphism</th>
<th>$P$ (HWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>145/112</td>
<td>Population-based</td>
<td>PCR-SSP</td>
<td>-1082A/G</td>
<td>0.416</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-819T/C</td>
<td>0.363</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-592A/C</td>
<td>0.363</td>
<td></td>
</tr>
<tr>
<td>Tsai</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>788/956</td>
<td>Population-based</td>
<td>PCR-RFLP</td>
<td>-1082A/G</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-819T/C</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-592A/C</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Vairaktaris</td>
<td>2008</td>
<td>Greece/Germany</td>
<td>Caucasian</td>
<td>144/141</td>
<td>Population-based</td>
<td>PCR-RFLP</td>
<td>-1082A/G</td>
<td>0.001</td>
</tr>
<tr>
<td>Yao</td>
<td>2007</td>
<td>China</td>
<td>Asian</td>
<td>280/300</td>
<td>Population-based</td>
<td>PCR-RFLP</td>
<td>-1082A/G</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-819T/C</td>
<td>0.809</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-592A/C</td>
<td>0.809</td>
<td></td>
</tr>
</tbody>
</table>

PCR-SSP: polymerase chain reaction sequence-specific primer; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; $P$ (HWE): $P$ value for Hardy-Weinberg equilibrium test.
Table 2. Overall results about IL-10 polymorphisms and oral cancer risk

<table>
<thead>
<tr>
<th>Genetic contrast</th>
<th>Subgroup</th>
<th>Model for analysis</th>
<th>OR (95% CI)</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1082A/G</td>
<td>GG vs. AA</td>
<td>FEM</td>
<td>2.95 (1.94, 4.48)</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>FEM</td>
<td>2.87 (1.88, 4.39)</td>
<td>0.897</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>FEM</td>
<td>8.40 (0.40, 178.68)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>GG+AG vs. AA</td>
<td>FEM</td>
<td>1.59 (1.35, 1.86)</td>
<td>0.198</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>FEM</td>
<td>1.59 (1.33, 1.89)</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>FEM</td>
<td>1.60 (1.08, 2.38)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>GG vs. AA+AG</td>
<td>FEM</td>
<td>2.59 (1.71, 3.94)</td>
<td>0.955</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>FEM</td>
<td>2.55 (1.67, 3.89)</td>
<td>0.926</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>FEM</td>
<td>4.90 (0.23, 102.89)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>G vs. A</td>
<td>FEM</td>
<td>1.68 (1.46, 1.94)</td>
<td>0.163</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>FEM</td>
<td>1.69 (1.45, 1.98)</td>
<td>0.078</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>FEM</td>
<td>1.63 (1.14, 2.34)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>AG vs. AA</td>
<td>FEM</td>
<td>1.53 (1.29, 1.81)</td>
<td>0.191</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>FEM</td>
<td>1.52 (1.26, 1.83)</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>FEM</td>
<td>1.59 (1.07, 2.37)</td>
<td>0.000</td>
</tr>
<tr>
<td>-592A/C</td>
<td>CC vs. AA</td>
<td>FEM</td>
<td>1.10 (0.85, 1.43)</td>
<td>0.304</td>
</tr>
<tr>
<td></td>
<td>CC+AC vs. AA</td>
<td>FEM</td>
<td>1.04 (0.91, 1.19)</td>
<td>0.184</td>
</tr>
<tr>
<td></td>
<td>CC vs. AA+AC</td>
<td>FEM</td>
<td>1.08 (0.85, 1.39)</td>
<td>0.506</td>
</tr>
<tr>
<td></td>
<td>C vs. A</td>
<td>FEM</td>
<td>1.05 (0.94, 1.17)</td>
<td>0.128</td>
</tr>
<tr>
<td></td>
<td>AC vs. AA</td>
<td>FEM</td>
<td>1.04 (0.90, 1.20)</td>
<td>0.149</td>
</tr>
<tr>
<td>-819T/C</td>
<td>CC vs. TT</td>
<td>FEM</td>
<td>1.20 (0.93, 1.55)</td>
<td>0.522</td>
</tr>
<tr>
<td></td>
<td>CC+TC vs. TT</td>
<td>FEM</td>
<td>1.09 (0.95, 1.25)</td>
<td>0.301</td>
</tr>
<tr>
<td></td>
<td>CC vs. TT+TC</td>
<td>FEM</td>
<td>1.15 (0.90, 1.47)</td>
<td>0.688</td>
</tr>
<tr>
<td></td>
<td>C vs. T</td>
<td>FEM</td>
<td>1.10 (0.98, 1.23)</td>
<td>0.294</td>
</tr>
<tr>
<td></td>
<td>TC vs. TT</td>
<td>FEM</td>
<td>1.09 (0.94, 1.27)</td>
<td>0.232</td>
</tr>
</tbody>
</table>

Note: FEM, fixed-effects model.

less obvious heterogeneity and allowed the use of fixed-effect model to pool the data. Evaluation of sensitivity was performed to measure the impact of each individual study on the overall results. After deleting each study at a time, we did not observe any substantial alterations (data not given), which verified the reliability of the total results. There was no remarkable publication bias, which could be revealed in the visual symmetry of Begg’s funnel plot (Figure 3) and the P value larger than 0.05 (P=0.780) in Egger regression test.

Discussion

It has been acknowledged that the expression levels of IL-10 may play an important part in the formation of new blood vessels, intrusion and final metastasis [35].

Association studies have provided accumulating evidence for the linkage between inflammation and cancers, verifying the critical role of chronic inflammation in the generation and development of cancers [37, 38], such as hepatocarcinoma [39], gastric cancer [40] and colon cancer [38]. IL-10, an anti-inflammatory and immune stimulatory cytokine identified in 1989 [41], has been reported to cause the regression of tumors and an increase in tumor-specific immunogenicity [22]. However, there are also contradictory findings reporting that the block of IL-10 signaling pathway could facilitate the anti-tumor immunity [42]. Therefore, the under-
IL-10 polymorphisms in oral cancer

Polymorphisms within the promoter region of IL-10 gene are likely to affect IL10 mRNA transcription and IL-10 expression levels [39, 43, 44]. Among numerous IL-10 polymorphisms, -1082A/G, -592A/C and -819T/C at upstream positions have been studied most frequently. IL-10-1082A/G polymorphism that results in decreased expression levels of IL-10 has been reported to correlate with several cancers, such as breast cancer [27], cervical cancer [45], and prostate cancer [46]. In addition, several studies have analyzed IL-10 -1082A/G involved in the etiology of oral cancer. Yao et al. found the G allele of IL-10 -1082A/G was related to increased risk of oral cancer in a Chinese population, firstly demonstrating the significant role of IL-10 gene in the progression of oral cancer [21], which was verified later by the study of Vairaktaris et al. [20]. In a case-control study taking Taiwanese as study subjects, Tsai et al. reported the synergistic effects of IL-10 -1082A/G AG
and GG genotype with smoking and areca chewing habits could mediate the susceptibility to oral cancer, emphasizing the great significance of gene-environment interactions in the development of cancer [19]. There also exist contradictory findings later put forward, in which Hsu et al. did not detect any significant association of oral cancer with IL10-1082A/G, but found an elevated oral cancer risk involving IL10-592A/C and -819T/C polymorphisms [18]. A small sample size with only 145 cases and 112 controls for IL10-1082A/G polymorphism in this study may contribute to its inconsistency with other association studies described above. Other than a single polymorphism, the haplotypes constituted by IL10-1082A/G, -592A/C and -819T/C polymorphisms have been revealed to have relation with oral cancer, and may put individuals at a high risk of developing oral cancer [21].

In this meta-analysis, although we simultaneously discussed the three IL-10 polymorphisms in oral cancer, the limited number of included studies and corresponding sample sizes in a large degree restricted the comprehensiveness of data synthesis and meta-analysis. Besides, the unbalanced number of studies on Asians (three studies) and Caucasians (one study) was disadvantageous, though the subgroup analysis by ethnicity for IL10-1082A/G polymorphism was conducted.

In conclusion, this meta-analysis uncovered a significantly increased risk of oral cancer caused by IL10-1082A/G polymorphism. However, due to its own disadvantages, the precise association between IL-10 polymorphisms and oral cancer requires to get further verification in later large-sized studies.

Disclosure of conflict of interest

None.

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[27] Giordani L, Bruzzi P, Lasalandra C, Quaranta M, Schittulli F, Dell’Agostino G, Delisio M and Iolascon A. Association of breast cancer and polymor-
**IL-10 polymorphisms in oral cancer**


