Non-Association of IL-16 rs4778889 T/C Polymorphism with Cancer Risk in Asians: a Meta-analysis

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Abstract

The IL-16 rs4778889 T/C polymorphism is associated with cancer risk. However, the results are conflicting. We performed this meta-analysis to derive a more precise estimation of the relationship. A comprehensive literature search was performed using PubMed, Embase and Web of Science databases. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the strength of association. A total of 6 studies including 1,603 cases and 2,342 controls were identified. With all studies involved, results showed no statistically significant association between IL-16 rs4778889 T/C polymorphism and cancer risk (CC vs. CT+TT: OR=0.74, 95% CI: 0.55-1.02, \( P_{\text{het}}=0.15 \); CC+CT vs. TT: OR=0.89, 95% CI: 0.72-1.00, \( P_{\text{het}}=0.03 \); CC vs. TT: OR=0.73, 95% CI: 0.53-1.00, \( P_{\text{het}}=0.08 \); CT vs. TT: OR=0.91, 95% CI: 0.79-1.05, \( P_{\text{het}}=0.08 \); C vs. T: OR=0.89, 95% CI: 0.74-1.07, \( P_{\text{het}}=0.02 \). In addition, the results were not changed when studies were stratified by cancer type. However, to verify our findings, it is essential to perform more well-designed studies with larger sample sizes in the future.

Keywords: IL-16 - rs4778889 - polymorphism - cancer - meta-analysis

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Introduction

Cancer is a major worldwide public health problem. It has been reported to give rise to approximately 12.7 million new cases and 7.6 million deaths in 2008 (Ferlay et al., 2008). The pathogenesis of cancer is a multistep and multifactorial process resulting from complex interactions between environmental and genetic factors (Pharoah et al., 2004). There is obvious evidence that inflammation is a risk factor for tumor development (Chow et al., 2012; Kundu et al., 2012).

IL-16 is considered a pro-inflammatory cytokine and plays an important role in inflammatory diseases as well as in carcinogenesis. IL-16 can activate CD4+ T cells, monocytes, macrophages and dendritic cells by binding to the CD4 molecule (Cruikshank et al., 1994; Center et al., 1996). Furthermore, IL16 can stimulate the secretion of different inflammatory cytokines, such as tumor necrosis factor-a (TNF-a), IL1b, IL6 and IL15, which are associated with carcinogenesis (Mathy et al., 2000). The gene encoding IL-16 cytokine is located on chromosome 15q26.3 in the human genome (Kim et al., 1999).

Numerous studies have investigated the potential association of IL-16 rs4778889 T/C polymorphism and cancer risk (Gao et al., 2009; Gao et al., 2009; Zhu et al., 2010; Azimzadeh et al., 2011; Li et al., 2011). However, a single study might have been underpowered to detect the overall effects, and the genetic epidemiological studies into cancer risk are conflicting. Therefore, we performed a comprehensive meta-analysis to derive a more precise estimation of the relationship between IL-16 rs4778889 T/C polymorphism and the risk of cancer.

Materials and Methods

Publication search

A comprehensive literature search was performed using PubMed, Embase and Web of Science databases for relevant articles (up to November 20, 2013) with the following key words “IL-16”, “polymorphism” and “cancer”. In addition, references of retrieved articles were also screened.

Inclusion criteria

Studies included in this meta-analysis had to meet the following criteria: (1) an evaluation of the associations between IL-16 rs4778889 T/C polymorphism and cancer risk; (2) case-control studies; (3) detailed genotype data for estimating of odds ratio (OR) and 95% confidence interval (CI); and (4) the distribution of genotypes among controls are in Hardy–Weinberg equilibrium (\( P>0.05 \)). If multiple studies had overlapping or duplicate data, only those with complete data were included.

Data extraction

Data were independently evaluated and extracted from the relevant papers by two of the authors (XLL and SZC). Any disagreement was resolved by discussion with a third

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Statistical analysis
HWE was evaluated for controls in each study by the Chi-square test and \( p < 0.05 \) was considered as departure from HWE. A \( \chi^2 \)-based Q-test examined the heterogeneity between each study. If \( p < 0.05 \) for Q-test suggested significant heterogeneity, and the random-effects model was conducted to calculate the pooled OR; Otherwise, the fixed-effects model was used. Odds ratio (OR) and 95% confidence interval (CI) were used to assess the strength of association between IL-16 rs4778889 T/C polymorphism and cancer risk. Sensitivity analysis was performed to identify the effect of data from each study on the pooled OR. Finally, Begg’s funnel plots and Egger’s test were carried out to evaluate publication bias of literatures (Begg et al., 1994; Egger et al., 1997). All analyses were done with RevMan 5.0 and STATA12.0 software.

Results

Study characteristics
A flow chart of the study selection procedure is shown in Figure 1. A total of 31 publications from PubMed, Embase and Web of Science databases were reviewed. After a review of titles, abstracts and articles, 6 studies with 1,603 cases and 2,342 controls were included in this meta-analysis.

Table 1. Characteristics of Studies Included in IL-16 rs4778889 Polymorphism and Cancer Risk

| First author     | Year | Country | Ethnicity         | Cancer type                      | Source of controls | Genotyping method | Cases  | Controls | \( P_{HWE} \) |
|------------------|------|---------|-------------------|----------------------------------|--------------------|-------------------|--------|----------|-------------|
| Jian Zhu         | 2010 | China   | Asian             | renal cell carcinoma             | Hospital-based     | PCR–RFLP          | 335    | 340      | Y           |
| Lin-Bo Gao 1     | 2009 | China   | Asian             | nasopharyngeal carcinoma         | Hospital-based     | PCR-RFLP          | 206    | 373      | Y           |
| Lin-Bo Gao 2     | 2009 | China   | Asian             | colorectal cancer                | Hospital-based     | PCR-RFLP          | 376    | 480      | Y           |
| Pedram Azimzadeh | 2011 | Iran    | Asian             | colorectal cancer                | Not Shown           | PCR-RFLP          | 260    | 405      | Y           |
| Shan Li          | 2011 | China   | Asian             | hepatocellular carcinoma         | Hospital-based     | PCR-RFLP          | 206    | 264      | Y           |

Note: \( P_{HWE} \), \( P \)-value of heterogeneity test

Table 2. Results of the Meta-analysis on IL-16 rs4778889 T/C Polymorphism and Cancer Risk

| Variables            | CC vs. CT+TT OR (95% CI) \( P \) | CC+CT vs. TT OR (95% CI) \( P \) | CC vs. TT OR (95% CI) \( P \) | CT vs. TT OR (95% CI) \( P \) | C vs. T OR (95% CI) \( P \) |
|----------------------|---------------------------------|---------------------------------|-------------------------------|--------------------------|-------------------------|
| Total                | 0.74 (0.55-1.02) \( 0.15 \)      | 0.89 (0.72-1.10) \( 0.03 \)      | 0.73 (0.53-1.00) \( 0.08 \)    | 0.91 (0.79-1.05) \( 0.08 \) | 0.89 (0.74-1.07) \( 0.02 \) |
| Cancer type          |                                 |                                 |                               |                          |                          |
| Digestive cancer     | 0.89 (0.60-1.34) \( 0.45 \)      | 0.94 (0.71-1.26) \( 0.03 \)      | 0.90 (0.60-1.35) \( 0.33 \)    | 0.95 (0.71-1.27) \( 0.04 \) | 0.95 (0.83-1.10) \( 0.05 \) |
| Colorectal cancer    | 0.67 (0.39-1.16) \( 0.79 \)      | 0.89 (0.71-1.10) \( 0.52 \)      | 0.65 (0.38-1.13) \( 0.72 \)    | 0.92 (0.74-1.15) \( 0.53 \) | 0.87 (0.73-1.05) \( 0.56 \) |

Note: \( P \), \( P \)-value of heterogeneity test
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Firstly, our results were based on unadjusted estimates, while a more precise analysis could be conducted if individual data were available. Secondly, a relatively small number of studies and subjects were included, which may reduce the statistical power of the analysis. Thirdly, although the statistical data did not reflect publication bias, potentially publication bias will be existed in our results because studies reporting positive findings are more likely to be published than those reporting negative results.

In conclusion, this meta-analysis suggested that IL-16 rs4778889 T/C polymorphism was not associated with the risk of cancer. In addition, our results also demonstrated IL-16 rs4778889 T/C polymorphism was not associated with the risk of digestive cancer including colorectal cancer. However, large and well-designed studies are warranted to validate our findings.

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