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Association of Interleukin-16 rs4778889 T>C Gene Polymorphism with Cancer Risk: a Meta-analysis

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IL-16, polymorphisms, cancer, meta-analysis
Abstract
BACKGROUND: Rs4778889 T>C is one of the single nucleotide polymorphisms (SNPs) in interleukin-16 (IL-16). As a growth factor, IL-16 might play a significant impact on cancer formation. Several studies have investigated the relationship between IL-16 rs4778889 T>C gene polymorphisms and cancer risk, but the results are contradictory. We conducted a meta-analysis on the association between IL-16 rs4778889 T>C gene polymorphism and cancer risk.

METHODS: Twelve case–control studies with 3066 cases and 4433 controls from Web of Science, PubMed, and Embase databases were included. The data was analyzed using the STATA software and the combined odds ratio (ORs) and the corresponding 95% confidence interval (CIs) were used to identify the correlation strength.

RESULTS: Our results show that no significant associations were observed between the IL-16 rs4778889 T>C gene polymorphisms and cancer risk in all genetic models (C vs. T: OR=1.06, 95% CI: 0.90–1.26, Ph<0.001; CC vs. TT: OR=1.07, 95% CI: 0.71–1.62, Ph<0.001; CT vs. TT: OR=1.07, 95% CI: 0.91–1.26, Ph=0.002; CC+CT vs. TT: OR=1.08, 95% CI: 0.90–1.30, Ph<0.001; CC vs. CT+TT: OR=1.04, 95% CI: 0.73–1.50, Ph=0.001). Subgroup and sensitivity analyses also were performed.

CONCLUSIONS: The results of this meta-analysis indicate that there are no significant associations between IL-16 rs4778889 T>C gene polymorphisms and cancer risk. To verify these results, further studies with larger sample size and multiracial populations are needful.

Keywords: IL-16, polymorphisms, cancer, meta-analysis

Background
According to the global cancer statistics, an estimated 18.1 million new cancer cases and 9.6 million cancer deaths were recorded in 2018. Lung cancer, prostate cancer, colorectal cancer, liver cancer, and stomach cancer had the highest incidence and mortality among males, whereas breast cancer, colorectal cancer, lung cancer, and cervical cancer among females[1]. Cancer has become a global health problem affecting human beings. At present, the pathogenesis of cancer is still unclear; however, continuous cellular proliferation is central to the carcinogenic process[2]. Therefore, solving the problem of cell proliferation is the key in treating cancer.
Genetic studies on cancer are popular at present. In cancer tissues, most DNA replication genes are expressed at high levels, which may reflect the high proliferation property of cancer\textsuperscript{[3]}. The abnormal replication of DNA can lead to genetic mutations that cause cells to proliferate indefinitely. In human cells, E2F transcription families are involved in the expression control of DNA replication genes\textsuperscript{[4]}. Different levels of human DNA replication genes are expressed at different stages of human development in different organs, tissues, and cells, leading to a variety of cancers.

The interleukin (IL)-16 gene is a single copy gene located at chromosome 15q26.1-3 in humans. IL-16 is synthesized by various immune (T cells, eosinophils, and dendritic cells) and non-immune (fibroblasts, epithelial, and neuronal) cells\textsuperscript{[5]} CD4 expresses the biological activity of IL-16 by inducing the signaling of second messengers and cell migration\textsuperscript{[6]}. For lymphocytes, IL-16 demonstrates chemotactic and chemokinetic activities. Besides inducing cell migration, IL-16 is a growth factor that plays an important role in cell cycle progression in CD4\textsuperscript{+} T lymphocytes\textsuperscript{[7]}.

Previous meta-analyses have reported that IL-16 gene polymorphisms (including IL-16 rs1131445, IL-16 rs11556218, and IL-16 rs11556218) are associated with cancer development \textsuperscript{[8-10]} However, Xu et al.\textsuperscript{[11]} did not find any association between IL-16 rs4778889 T > C polymorphism and cancer. Since then, several new literatures about IL-16 rs4778889 T > C polymorphism and cancer risk have been published. Therefore, the present meta-analysis, including previous and some recently published studies\textsuperscript{[12-23]}, was conducted to provide a more accurate estimation of the association of IL-16 rs4778889 T > C polymorphisms with cancer. At the same time, we also conducted subgroup analysis to analyze different cancers, including digestive cancer, renal cell carcinoma, and nasopharyngeal carcinoma.

**Methods**

**Publication search**

The PubMed, Embase, and Web of Science databases were used for the comprehensive retrieval of related articles (up to October 27, 2019) with the following keywords “IL-16 or Interleukin 16,” “genetic variant or polymorphism or SNPs,” and “cancer or carcinoma or tumour.” The publications
that met the above preset eligibility criteria were considered for further examination. In addition, references from the retrieved studies were searched for other related reports.

**Inclusion And Exclusion Criteria**

**Inclusion criteria:**

1. Investigates the relationship between IL-16 rs4778889 T > C polymorphisms and cancer risk
2. Case–control or cohort study design
3. Published in English
4. Includes detailed genotype data to estimate the odds ratio (OR) and 95% confidence interval (CI)

**Exclusion criteria:**

1. Lack of case–control or cohort study design
2. Meta-analyses, letters, single-case reports, duplicate studies, animal model studies, and studies without available data
3. Case reports, reviews, comments, or animal studies
4. Inadequate genotype data

**Data Extraction And Quality Assessment**

The data from the eligible studies were independently screened by two authors. The extracted data included the first author, publication year, country, source of controls, genotyping method, ethnicity, and number of cases and controls. Any differences shall be resolved by consensus with a third author. Two reviewers independently evaluated the research quality according to the quality rating scale (see Supplementary Table 1). Any disagreement was solved by discussion between the two reviewers.

Total scores ranged from 0 (worst) to 15 (best)\(^2\).4\(^1\).

**Statistical analysis**

We utilized Stata 12.0 software (Stata Corporation, College Station, TX, USA) to conduct the meta-analysis and evaluate heterogeneity among the included studies. The ORs and 95% CIs were used to assess any associations between IL-16 polymorphisms and cancer risk in five genetic models: the allele, homozygote, heterozygote, dominant, and recessive models. Heterogeneity was assessed using the chi-square-based Q-test and was considered significant if the P-value was less than 0.05\(^2\).25\(^1\). Cochran's Q test and Higgins I-squared statistics were used for heterogeneity test. An I\(^2\)
value greater than 50% manifested heterogeneity between studies, and the random-effects model was used to observe heterogeneity ($I^2 > 50\%, P < 0.05$). Or else, the fixed-effects model was used$^{[26, 27]}$. A chi-square test was used to reckon HWE in the controls. Sensitivity analyses were conducted to assess the stability of the results by deleting a single study at a time. Begg’s and Egger’s tests were performed to evaluate the publication bias of the eligible literature$^{[28, 29]}$. Furthermore, subgroup analyses were proceeded on the basis of types of cancers (renal cell carcinoma, digestive cancer, nasopharyngeal carcinoma, and other cancers).

Result

Characteristics of the studies

The flow chart of study selection program is shown in Fig. 1. Initially, a total of 32 articles from Embase, PubMed, and Web of Science databases were reviewed. Twelve were excluded as they were comments and irrelevant studies or meta-analysis, and 20 were selected. After reviewing the studies, eight were removed as they did not focus on the selected single nucleotide polymorphism (SNP) and contained insufficient genotype data. Finally, 12 case–control studies with 3066 cases and 4433 controls were included in the meta-analysis. Three studies focused on renal cell carcinoma, five on digestive cancer, two on nasopharyngeal carcinoma, one on osteosarcoma, and one on glioma. The important features of the included articles are listed in Table 1, whereas the genotype distributions and allele frequencies are presented in Table 2.
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 | Genotypes | PHWE | Quality scores |
|--------------|------|---------|-----------|-------------|-------------------|------------------|------------|------|----------------|
| Zhu[12]      | 2010 | China   | Asian     | renal cell carcinoma | Hospital-based | PCR-RFLP | 335 | 340 | Y | 11 |
| Yang[13]     | 2016 | China   | Asian     | renal cell carcinoma | Hospital-based | PCR-RFLP | 273 | 274 | Y | 11 |
| Wang[14]     | 2015 | China   | Asian     | renal cell carcinoma | Hospital-based | PCR-RFLP | 181 | 278 | Y | 10 |
| Wang[15]     | 2015 | China   | Asian     | gastric cancer    | Hospital-based | Not Shown | 132 | 1195 | Y | 11 |
| Li[16]       | 2011 | China   | Asian     | hepatocellular carcinoma | Hospital-based | PCR-RFLP | 206 | 264 | Y | 10 |
| Azimzadeh[17]| 2011 | Iran    | Asian     | colorectal cancer | Not Shown | PCR-RFLP | 260 | 405 | Y | 10 |
| Gao[18]      | 2009 | China   | Asian     | gastric cancer    | Hospital-based | PCR-RFLP | 220 | 480 | Y | 11 |
| Gao[18]      | 2009 | China   | Asian     | colorectal cancer | Hospital-based | PCR-RFLP | 376 | 480 | Y | 11 |
| Zhang[19]    | 2013 | China   | Asian     | gastric cancer    | Hospital-based | PCR-RFLP | 228 | 347 | N | 8 |
| Gao[20]      | 2009 | China   | Asian     | nasopharyngeal carcinoma | Hospital-based | PCR-RFLP | 206 | 373 | Y | 11 |
| Qin[21]      | 2014 | China   | Asian     | nasopharyngeal carcinoma | Hospital-based | PCR-RFLP | 75 | 75 | Y | 9 |
| Tang[22]     | 2016 | China   | Asian     | osteosarcoma      | Hospital-based | PCR-RFLP | 358 | 402 | Y | 11 |
| Luo[23]      | 2014 | China   | Asian     | glioma           | Hospital-based | PCR-RFLP | 216 | 275 | Y | 10 |

Note: Y, the distribution of genotypes among controls are in Hardy-Weinberg equilibrium

Table 2
Genotype distributions of IL-16 rs4778889 T/C polymorphism of enrolled studies

| Study | Case | Control | Case | Control |
|-------|------|---------|------|---------|
|       | TT   | CT      | CC   | TT      | CT      | CC   | T   | C   | T   | C   |
| Zhu[12]| 199 | 122 | 14 | 171 | 135 | 34 | 520 | 150 | 477 | 203 |
| Yang[13]| 132 | 113 | 28 | 176 | 84 | 14 | 377 | 169 | 436 | 112 |
| Wang[14]| 82  | 77  | 22 | 160 | 106 | 12 | 241 | 121 | 426 | 130 |
| Wang[15]| 65  | 61  | 6  | 640 | 477 | 78 | 191 | 73  | 1757 | 633 |
| Li[16] | 158 | 178 | 117 | 246 | 119 | 77 | 65 | 36 | 127 | 68 |
| Azimzadeh[17]| 158 | 178 | 117 | 246 | 119 | 77 | 65 | 36 | 127 | 68 |
| Gao[18] | 131 | 139 | 215 | 142 | 42  | 73  | 119 | 77  | 65  | 36  |
| Gao[18] | 131 | 139 | 215 | 142 | 42  | 73  | 119 | 77  | 65  | 36  |
| Zhang[19] | 131 | 139 | 215 | 142 | 42  | 73  | 119 | 77  | 65  | 36  |
| Gao[20] | 158 | 178 | 117 | 246 | 119 | 77 | 65 | 36 | 127 | 68 |
| Qin[21] | 158 | 178 | 117 | 246 | 119 | 77 | 65 | 36 | 127 | 68 |
| Tang[22] | 131 | 131 | 215 | 142 | 42  | 73  | 119 | 77  | 65  | 36  |
| Luo[23] | 131 | 139 | 215 | 142 | 42  | 73  | 119 | 77  | 65  | 36  |
Results Of Meta-analysis

The chi-squared-based Q-test and $I^2$ statistics showed the substantial amount of heterogeneity in all genetic models, leading to the use of random-effects model to process the data. The results of the meta-analysis are shown in Table 3 and Fig. 2. The overall ORs showed no statistically significant association with high or low risk between IL-16 rs4778889 T > C polymorphism and cancer in neither genetic models (C vs. T: OR = 1.06, 95% CI: 0.90–1.26, Ph < 0.001; CC vs. TT: OR = 1.07, 95% CI: 0.71–1.62, Ph < 0.001; CT vs. TT: OR = 1.07, 95% CI: 0.91–1.26, Ph = 0.002; CC + CT vs. TT: OR = 1.08, 95% CI: 0.90–1.30, Ph < 0.001; CC vs. CT + TT: OR = 1.04, 95% CI: 0.73–1.50, Ph = 0.001). In addition, we also performed a subgroup analysis on the basis of the type of cancer. The results suggested no association between IL-16 rs4778889 T > C gene polymorphism and renal cell carcinoma, digestive cancer, and nasopharyngeal carcinoma.

Table 3
Meta-analysis of the association between Interleukin-16 Gene Polymorphism rs4778889 T/C polymorphisms and cancer risk.

| Subgroup                  | C vs. T | CC vs. TT | CT vs. TT | CC + CT vs. TT | CC vs. CT + TT |
|---------------------------|---------|-----------|-----------|----------------|----------------|
|                           | OR (95% CI) | Ph | OR (95% CI) | Ph | OR (95% CI) | Ph | OR (95% CI) | Ph | OR (95% CI) | Ph |
| Overall                   | 1.06 (0.90–1.26) | .482 < .001 | 1.07 (0.71–1.62) | .592 < .001 | 1.07 (0.91–1.26) | .406 < .001 | 1.08 (0.90–1.30) | .451 < .001 | 1.04 (0.73–1.50) | .636 < .001 |
| Renal cell carcinoma      | 1.24 (0.66–2.33) | .496 < .001 | 1.49 (0.35–6.39) | .781 < .001 | 1.25 (0.74–2.09) | .684 < .001 | 1.29 (0.67–2.49) | .671 < .001 | 1.36 (0.38–4.79) | .876 < .001 |
| Digestive cancer          | 1.04 (0.85–1.27) | .725 < .001 | 1.06 (0.69–1.63) | .955 .101 | 1.05 (0.84–1.30) | .636 .041 | 1.05 (0.84–1.32) | .613 .016 | 1.03 (0.70–1.53) | .871 .158 |
| Nasopharyngeal carcinoma  | 1.11 (0.71–1.74) | .635 .145 | 1.02 (0.46–2.23) | .322 N/A | 1.17 (0.61–2.25) | .512 .078 | 1.18 (0.62–2.22) | .377 .083 | 1.01 (0.48–2.38) | .353 N/A |
| Others                    | 0.90 (0.74–1.09) | .287 .382 | 0.75 (0.43–1.32) | .732 .691 | 0.92 (0.73–1.17) | .407 .338 | 0.90 (0.72–1.13) | .411 .335 | 0.77 (0.44–1.34) | .816 .790 |

OR = odds ratio, 95% CI = 95% confidence interval, $P_{OR} = pool P$ value, $P_h = P$ value of heterogeneity test. Random effects models were used for all genotypes.

Sensitivity Analysis

Sensitivity analysis excludes the influence of a single study on the overall risk estimate. We removed each study in turn from the analysis and then determined the pooled ORs. We found no individual study that significantly affected the pooled OR, indicating that our meta-analysis results are stable and reliable (Fig. 3).

Publication Bias

Begg’s funnel plots and Egger’s test were performed to evaluate the potential publication bias. Begg’s
funnel plot is shown in Fig. 4. Egger’s test results showed no evidence of publication bias (C vs. T: P = 0.68; CC vs. TT: P = 0.44; CT vs. TT: P = 0.45; CC + CT vs. TT: P = 0.43; CC vs. CT + TT: P = 0.46).

Begg’s funnel plot and Egger’s test showed no publication bias among all the comparison models in each genetic model and the allelic comparison.

Discussion
In randomly selected human genomes, approximately 0.1% of the gene sequences are different. The cause of this change is a genetic mutation called polymorphism. There is no doubt that the identification of genes underlying polygenic and complex diseases can be used by clinicians and geneticists for the diagnosis and treatment of disease, evolutionary biology studies, and gene discovery and mapping[30].

SNPs are relatively stable and not affected by disease activity and remain unchanged over time. For analyzing complex diseases such as cancer, biogenetic research is a powerful method of determining low-penetration susceptibility genes that can affect biological processes, which can be used for linkage analysis[31].

Inflammatory response plays an important role in host response against infection and participates in tissue repair, in case of damage. Chronic inflammation causes repeated tissue damage and repair, which alters the immune system and ultimately leads to cancer[32]. In recent years, cytokines are receiving increasing attention due to their function in adjusting and balancing the immune response including inflammation. They can also regulate the pro-inflammatory and anti-inflammatory network and participate in tissue damage and repair to stimulate signaling pathways involved in malignancy development[33]. In 1982, IL-16 was initially identified as a T cell chemoattractant factor produced from mitogen- or antigen-stimulated human peripheral blood mononuclear cells[34]. As a cytokine, IL-16 participates in various cellular biological processes, including the chemotaxis of immune cells, initiation of inflammatory responses, and production of proangiogenic cytokines[35]. Therefore, it may be involved in the occurrence and development of cancer.

Many scientists have reported the association between IL-16 rs4778889 T > C gene polymorphism and
cancer risk. However, the results are contradictory. In addition, the molecular and biological mechanism behind the association between IL-16 rs4778889 T > C gene polymorphism and cancer risk is not completely understood. Therefore, a larger sample size and subgroup analysis are needed to evaluate the potential role of IL-16 rs4778889 T > C polymorphism as a genetic risk factor for cancer. A large sample size with statistical robustness can decrease random errors by combining ORs from many early published researches\(^{[36]}\). Meta-analyses address a wide variety of clinical problems using early published data. The present meta-analysis included 12 case–control studies with 3066 cases and 4433 controls and analyzed the pooled ORs and P-value to determine the precise relationship between IL-16 rs4778889 T > C gene polymorphism and cancer risk. The results showed no association between the IL-16 rs4778889 T > C gene polymorphism and cancer susceptibility by any genetic model. At the same time, the results of subgroup analysis showed that the IL-16 rs4778889 T > C gene polymorphism was not associated with renal cell carcinoma, digestive cancer, and nasopharyngeal carcinoma.

An early meta-analysis by Xu et al.\(^{[11]}\) did not find any association between the IL-16 rs4778889 T > C polymorphism and cancer. Generally, this meta-analysis yielded the same results, making our study redundant. However, the present study has the following advantages: first, this meta-analysis added new published studies that increased the number of included subjects in both cases and controls. A total of 12 studies were analyzed, which was more representative of rs4778889 than the previous meta-analysis. Hence, our results provide strong evidence to draw accurate and robust conclusions that make our results more credible. Second, the subgroup analyses were performed in accordance with the type of cancer (renal cell carcinoma, digestive cancer, nasopharyngeal carcinoma) to explore the possible sources of heterogeneity, measure the stability of studies, and investigate the role of IL-16 in the pathogenesis of different cancers. Therefore, to a certain extent, our meta-analysis provides a more precise result that the IL-16 rs4778889 T > C gene polymorphism is not significantly associated with cancer risk.

Although case-control studies were included, the results of the current meta-analysis should be
interpreted carefully due to the following limitations. First, interstudy heterogeneity was discovered in the overall comparison from each genetic model, which may be due to differences in countries, ethnicities, and sources of controls. Therefore, we minimized the likelihood of this problem by performing data analysis using the random-effects model. Second, the study included only Asian populations. The results may require further verified in multiple ethnic groups. Third, the occurrence of cancer is the result of multiple factors. Gene and environment interactions may play important roles in the pathology of cancer. We did not analyze gene and environment interactions and epigenetic inheritance. Other risk factors, including age, ethnic groups, body mass index, and smoking and drinking status, are also associated with the occurrence of cancer.

Conclusion
The current meta-analysis indicates no significant associations between the IL-16 rs4778889 T > C gene polymorphism and cancer risk. The results of subgroup analysis show that the IL-16 rs4778889 T > C gene polymorphism is not associated with renal cell carcinoma, digestive cancer, and nasopharyngeal carcinoma. To confirm these results, further studies with larger sample size and multiple ethnicities are necessary.

Abbreviations
IL-16(interleukin-16), SNPs(single nucleotide polymorphisms), ORs(odds ratios), CIs(confidence intervals).

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Figures
Figure 1

PRISMA flow chart of studies inclusion and exclusion. PRISMA=preferred reporting items for systematic reviews and meta-analyses.
Figure 2

Forest plot of ORs with 95% CI of cancer risk associated with IL-16 rs4778889 T/C polymorphism (A: C vs. T; B: CC vs. TT; C: CT vs. TT; D: CC+CT vs. TT; E: CC vs. CT+TT).
Sensitivity analyses between IL-16 rs4778889 T/C polymorphism cancer risk (A: C vs. T; B: CC vs. TT; C: CT vs. TT; D: CC+CT vs. TT; E: CC vs. CT+TT).
Figure 4

Funnel plots in the meta-analysis of the association between the IL-16 rs4778889 T/C polymorphism and cancer risk (A: C vs. T; B: CC vs. TT; C: CT vs. TT; D: CC+CT vs. TT; E: CC vs. CT+TT).