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

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Research article

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

Posted Date: March 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-19338/v1>

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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^[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^[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^[5]. CD4 expresses the biological activity of IL-16 by inducing the signaling of second messengers and cell migration^[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 CD41 T lymphocytes^[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^[8–10]. However, Xu et al.^[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^[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)^[24].

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^[25]. 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	Cases	Controls	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	Asina	nasopharyngeal carcinoma	Hospital-based	PCR-RFLP	75	75	Y	9
Tang ^[22]	2016	China	Asina	osteosarcoma	Hospital-based	PCR-RFLP	358	402	Y	11
Luo ^[23]	2014	China	Asina	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	42	6	182	76	6	358	54	440	88
Azimzadeh ^[17]	178	73	9	274	112	19	429	91	660	150
	117	90	13	294	164	22	324	116	752	208
Gao ^[18]	246	119	11	294	164	22	611	141	752	208
Gao ^[18]	119	77	32	212	106	29	315	141	530	164
Zhang ^[19]	131	65	10	228	128	17	327	85	584	162
	39	36	0	49	26	0	114	36	124	26
Gao ^[20]	215	127	16	240	140	22	557	159	420	184
Qin ^[21]	142	68	6	165	99	11	352	80	429	121
Tang ^[22]										
Luo ^[23]										

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)	P _{OR} P _h	OR (95% CI)	P _{OR}	P _h	OR (95% CI)	P _{OR}	P _h	OR (95% CI)	P _{OR} P _h
Overall	1.06 (0.90–1.26)	.482 < .001	1.07 (0.71–1.62)	.592 < .001	1.07 (0.91–1.26)	.406 .002	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 .002	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 .009	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	1.07 (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-penetrance 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).

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication All authors agree to publish.

Availability of data and material: This article is a meta-analysis, and all data are available in the references.

Competing interests: The author has no conflict of interest to disclose.

Funding: Project supported by the National Natural Science Foundation of China (81660125), The corresponding author is the main person in charge of the project.

Authors' contributions - please include contributions for all authors:

Conceptualization: QL, ZJW

Data curation: ZYT, MCJ

Methodology: LCY

Software: MCJ

Writing – original draft:QL, ZJW

Writing – review and editing: CJW, LCY

All authors have read and approved the manuscript

Acknowledgements: Not applicable.

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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).

Figure 3

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).