

The -159C/T polymorphism in the CD14 gene and cancer risk: a meta-analysis

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Purpose: The -159C/T polymorphism in the cluster of differentiation (CD)14 gene has been extensively studied for an association with cancer; however, results from replication studies have been inconclusive. The aim of this study was to perform a comprehensive assessment of the possible association between the -159C/T polymorphism in the CD14 gene and cancer risk, by meta-analysis.

Methods: We searched in PubMed, Embase, and other databases, covering all case-control studies on the possible association between CD14 -159C/T gene polymorphism and cancer risk. Data were extracted and statistical analyses were performed using RevMan 5.0 and STATA 12.0 software.

Results: A total of 12 case-control studies met our inclusion criteria, including 2,498 cases and 2,696 controls. The combined analysis indicated that the CD14 -159C/T gene polymorphism didn't confer risk for cancer – the recessive model (TT versus (vs) CT + CC), showed odds ratio (OR) = 1.01, 95% confidence interval (CI) = 0.82–1.23 ($P=0.94$), while the dominant model (TT + TC vs CC) showed OR = 0.81, 95% CI = 0.66–1.00 ($P=0.05$). A subgroup analysis by ethnicity showed that the cancer risk associated with CD14 -159C/T gene polymorphism was significantly decreased among Caucasians for the TC + TT vs CC comparison (OR = 0.83, 95% CI = 0.70–0.98 [$P=0.03$]). The subgroup analysis by cancer type suggested that the CD14 -159C/T gene polymorphism was not associated with gastric cancer risk.

Conclusion: The evidence from the present meta-analysis did not support the CD14 -159C/T gene polymorphism as a genetic risk factor for cancer. Further studies on different cancer types and ethnicities are needed to validate our findings.

Keywords: CD14, cancer, gene, polymorphism, meta-analysis

Introduction

Cancer remains a major public health problem around the world. It is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.¹ Although the etiology of cancer is complicated and has not been fully elucidated, recent studies have suggested an association between chronic inflammation and the increased risk of developing several types of cancers, and a hypothesized sequence of pathogenesis beginning with inflammation and progressing to atrophy, metaplasia, dysplasia, carcinoma in situ, and finally, to cancer.² A growing number of studies have suggested that genetic variations in the inflammatory factor genes, which play an important role in the regulation of inflammation, are correlated with increased risk in several malignant tumors and may play critical roles in the pathogenesis of cancer.³ Repeated studies have investigated the association

of genetic variants of the inflammatory factor genes with cancer susceptibility,^{3,4} and among them, the -159 cytosine/thymine (C/T) polymorphism in the cluster of differentiation 14 (CD14) gene has been highlighted.

CD14 is encoded by a single-copy gene that is located at bands 5q23q31, with about 3,900 bp harbored in two exons.⁵ CD14 is a pattern-recognition receptor that plays a central role in immune regulation; CD14 acts by transferring lipopolysaccharide to the Toll-like receptor 4, which results in the activation of inflammatory genes, production of proinflammatory cytokines, the generation of oxygen free radicals, and the beginning of the inflammation process.^{6,7} Thus, the regulation of CD14 expression is important in determining whether growth-arrested cells are induced to undergo differentiation or apoptosis, which are the critical process of carcinogenesis.^{7,8} Studies have proposed CD14 gene polymorphism to increase CD14 production, leading to increased expression levels of CD14,^{9,10} thus, a growing number of studies have studied the relationship between CD14 gene polymorphism and cancer susceptibility.

Recent studies suggest that the gene variant within the CD14 -159C/T (rs2569190) polymorphism, also called CD14 -260C/T, is critical for CD14 expression and has been suggested as a genetic factor for cancer susceptibility.⁶⁻⁸ Several studies⁶⁻⁸ have investigated whether the -159C/T polymorphism in the CD14 gene is associated with cancer risk, and the results were inconclusive. Since pooled estimates based on meta-analysis have proven useful in determining the overall risk of certain cancer polymorphisms when results of individual studies were inconsistent,¹¹ we decided to perform a meta-analysis to investigate the potential association between the CD14 -159C/T gene polymorphism and cancer risk.

Methods

Literature search

Two authors (W Zhou and L Jia) independently performed systematic searches of the PubMed, Embase, China National Knowledge Infrastructure (CNKI), Weipu, and Wanfang databases to identify studies examining the possible association between the -159C/T polymorphism in the CD14 gene and cancer risk. The search terms were as follows: “cancer or carcinoma or neoplasm” in combination with “CD14 or cluster of differentiation 14” in combination with “polymorphism or variant or mutation.” The search was conducted for all terms updated until July 10, 2013. The reference lists of the identified original studies and review articles were also manually searched to find additional relevant publications.

Study selection

A study was included in this meta-analysis if it satisfied the following inclusion criteria: (1) it evaluated the potential association between the CD14 -159C/T gene polymorphism and cancer risk; (2) it was a case-control study; (3) genotype distributions in the cases and controls were available for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) the distribution of genotypes in the control group was consistent with Hardy–Weinberg equilibrium (HWE);¹² and (5) it was published in the English language. In studies of several types of cancer, each type of cancer was treated as a single study in this meta-analysis. Reviews, conference abstracts, and studies in which the genotype frequencies were not reported were excluded. When studies involved the same or overlapping data sets, only the study with the largest number of participants was included.

Data extraction

Two reviewers (W Zhou and L Jia) independently extracted data from the final set of included studies. The following data were extracted: the name of the first author, year of publication, country of origin, ethnicity, sample size, cancer type, genotyping method, and the genotype frequencies in the cancer cases and controls. Disagreements between authors were resolved by consensus.

Statistical analysis

Crude ORs and 95% CIs were used to determine the strength of the association between the CD14 gene -159C/T polymorphism and the risk of cancer. The significance of the pooled OR was determined using the Z-test, and $P < 0.05$ was considered statistically significant. First, we evaluated the recessive model (TT versus (vs) TC + CC) and the dominant model (TT + TC vs CC), followed by the additive model (TT vs CC). The allelic model (T vs C) was also used to estimate the potential association. To evaluate whether the association showed any ethnicity- or cancer type-specific effects, we analyzed the data for subgroups defined by ethnicity and cancer type.

Heterogeneity was evaluated using a χ^2 -based Q statistic and I^2 statistic, with $P < 0.10$ and $I^2 > 50\%$ as considered statistically significant. When $P \geq 0.10$ and $I^2 < 50\%$, the pooled OR of each study was calculated using a fixed effects model; otherwise, a random effects model was used.¹³

Begg's funnel plots and Egger's test were used to detect the potential publication bias among the included studies.¹³ All statistical tests were performed using RevMan 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark) and

STATA 12.0 (StataCorp LP, College Station, TX, USA) software.

Results

Study inclusion and characteristics

A total of 243 articles were identified after an initial search from the PubMed, Embase, CNKI, Weipu, and Wanfang databases. After removing duplications, 127 publications were identified. Then, 103 articles were excluded that were abstracts or reviews, or that were irrelevant to CD14 polymorphisms and cancer risk. After reading the full texts of the remaining 24 articles, 12 of these were excluded: eight studies that were not concerned with the -159C/T polymorphism, two prognostic studies, and two studies for which there was insufficient data. After the HWE test, three more articles were excluded. Finally, a total of nine articles reporting on 12 case-control studies that evaluated the possible association between the CD14 -159C/T gene polymorphism and cancer risk were included in the meta-analysis (Figure 1).^{14–22}

A total of nine publications met our inclusion criteria and involved 5,194 subjects: 2,498 cases and 2,696 controls. There were seven case-control studies of Asians and five of Caucasians. The cancer types included gastric cancer (n=6), colorectal cancer (n=2), acute lymphoblastic leukemia (n=1), lymphoma (n=1), esophageal cancer (n=1), and mucosal-associated lymphoid tissue lymphoma (n=1). The characteristics of each study, including author information, ethnicity, sample size, cancer type, genotyping method, country of origin, and other data in this meta-analysis are presented in Table 1. The genotype frequencies and HWE examination results are listed in Table 2.

Quantitative data synthesis

A total of 2,498 cancer cases and 2,696 controls in 12 case-control studies were included. First, we analyzed the heterogeneity of the recessive model (TT vs TC + CC) in order to identify the best risk model. The value of χ^2 was 26.85, with eleven degrees of freedom and $P=0.005$, suggesting significant

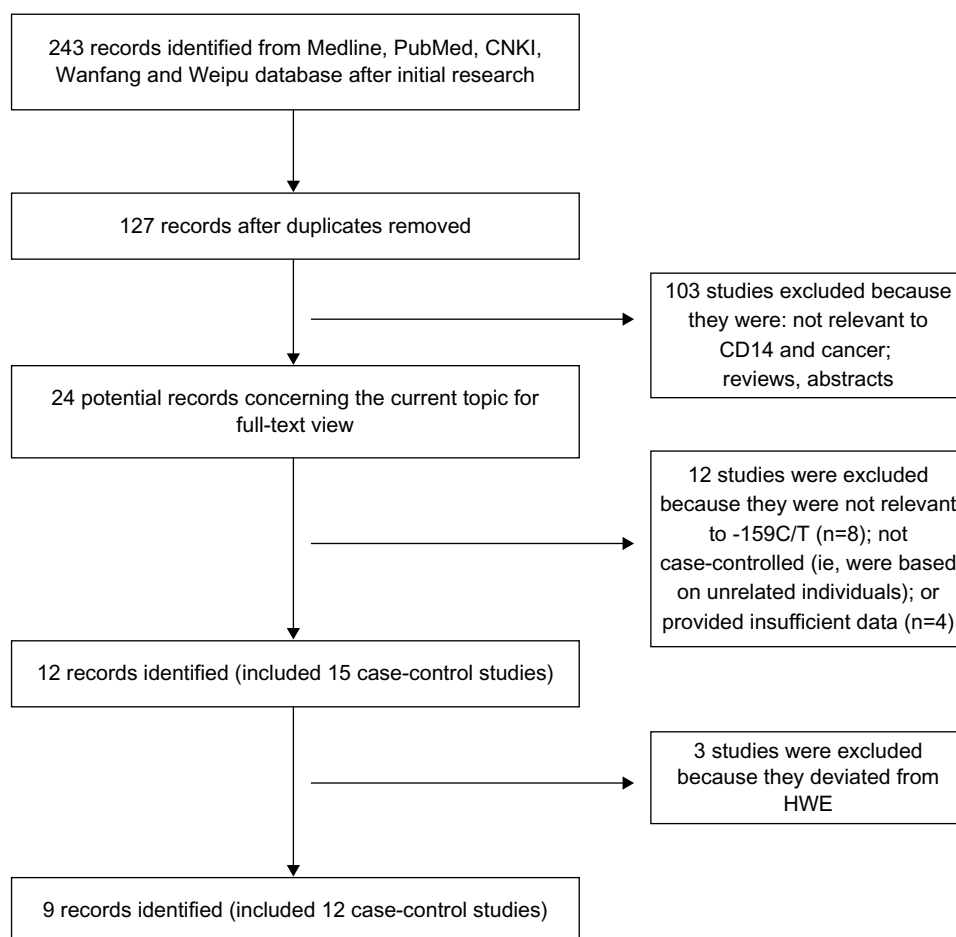


Figure 1 The flow diagram of included and excluded studies.

Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; CNKI, China National Knowledge Infrastructure (database); HWE, Hardy–Weinberg equilibrium.

Table 1 Characteristics of studies included in the present meta-analysis

Author	Year	Country	Ethnicity	Cancer	Cases/controls	Genotyping method
Andrie et al ¹⁴	2009	Greece	Caucasian	Lymphoma	83/83	PCR
Castaño-Rodríguez et al ¹⁵	2013	Singapore	Asian	Gastric cancer	70/214	PCR
Guo et al ¹⁶	2006	Malaysia	Asian	Colorectal cancer	110/160	PCR-RFLP
Hold et al ¹⁷	2009	China	Asian	Gastric cancer	327/389	TaqMan® (Life Technologies Corp, Carlsbad, CA, USA)
Hold et al ^{17,*}	2009	Poland	Caucasian	Gastric cancer	306/211	TaqMan
Hold et al ^{17,*}	2009	USA	Caucasian	Gastric cancer	158/211	TaqMan
Landi et al ¹⁸	2006	USA	Caucasian	Esophageal cancer	377/326	TaqMan
Tahara et al ¹⁹	2006	Spain	Caucasian	Colorectal cancer	149/94	PCR-RFLP
Wu et al ²⁰	2007	Japan	Asian	Gastric cancer	70/210	PCR
Wu et al ^{20,*}	2006	China	Asian	MALT	204/210	PCR
Yu et al ²¹	2006	China	Asian	Gastric cancer	174/539	PCR-RFLP
Zhao et al ²²	2011	China	Asian	Acute lymphoblastic leukemia	470/470	PCR-RFLP

Note: *Different cancers were studied in one publication and each was treated to a separate analysis.

Abbreviations: MALT, mucosal-associated lymphoid tissue lymphoma; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

heterogeneity among the included studies. Thus, we chose the random effects model to analyze the data. For the recessive model, the pooled OR was 1.01 (95% CI =0.82–1.23), and the Z-value, for overall effect, was 0.08 ($P=0.94$) (Figure 2). For the dominant model (TT + TC vs CC), the OR was 0.81 (95% CI =0.66–1.00) and the test for overall effect Z-value was 1.94 ($P=0.05$) (Figure 2). These results suggested that the TT homozygote and TC heterozygote carriers did not have an increased risk of cancer compared with those individuals with the CC homozygote. For the additive model (TT vs CC), the OR was 0.94 (95% CI =0.81–1.08), and the test for overall effect Z-value was 0.90 ($P=0.37$). These results showed no association between the -159C/T polymorphisms of the CD14 gene and cancer risk. A summary of results from other comparisons is listed in Table 3.

Subgroup analysis

In the subgroup analysis by ethnicity, the OR was 1.07 (95% CI =0.80–1.44) ($P=0.65$) among Asians and was 0.96 (95% CI =0.79–1.16) ($P=0.66$) among Caucasians, based on the recessive model (TT vs TC + CC), thus both showed on association between the -159C/T polymorphisms of the CD14 gene and cancer risk. When analyzed by the dominant model (TT + TC vs CC), the OR was 0.82 (95% CI =0.55–1.21) ($P=0.31$) among Asians and was 0.83 (95% CI =0.70–0.98) ($P=0.03$) among Caucasians. These results suggested that TT and TC carriers have a 17% decreased risk of cancer compared with those individuals with the CC homozygote in Caucasians. The other models didn't show any association between this polymorphism and cancer risk in Caucasians.

Table 2 Distributions of CD14 -159C/T polymorphism genotypes and alleles among cancer patients and controls

Author	Case			Control			Case		Control		
	TT	CT	CC	TT	CT	CC	T	C	T	C	HWE P-value
Andrie et al ¹⁴	13	39	31	23	42	18	65	101	88	78	0.89
Castaño-Rodríguez et al ¹⁵	14	38	18	72	108	34	66	74	252	176	0.54
Guo et al ¹⁶	41	34	35	58	77	25	116	104	193	127	0.95
Hold et al ¹⁷	83	134	110	82	176	131	300	354	340	438	0.11
Hold et al ^{17,*}	68	147	91	51	108	52	283	329	210	212	0.73
Hold et al ^{17,*}	34	74	50	51	108	52	142	174	210	212	0.73
Landi et al ¹⁸	68	151	62	63	137	65	287	275	263	267	0.58
Tahara et al ¹⁹	32	80	37	27	53	14	144	154	107	81	0.15
Wu et al ²⁰	24	29	17	54	102	54	77	63	210	210	0.68
Wu et al ^{20,*}	50	102	52	54	102	54	202	206	210	210	0.68
Yu et al ²¹	90	55	29	200	259	80	235	113	659	419	0.80
Zhao et al ²²	212	225	33	187	227	56	649	291	601	339	0.30

Note: *Different cancers were studied in one publication and each was treated to a separate analysis.

Abbreviations: C, cytosine; CD, cluster of differentiation; T, thymine; HWE, Hardy–Weinberg equilibrium.

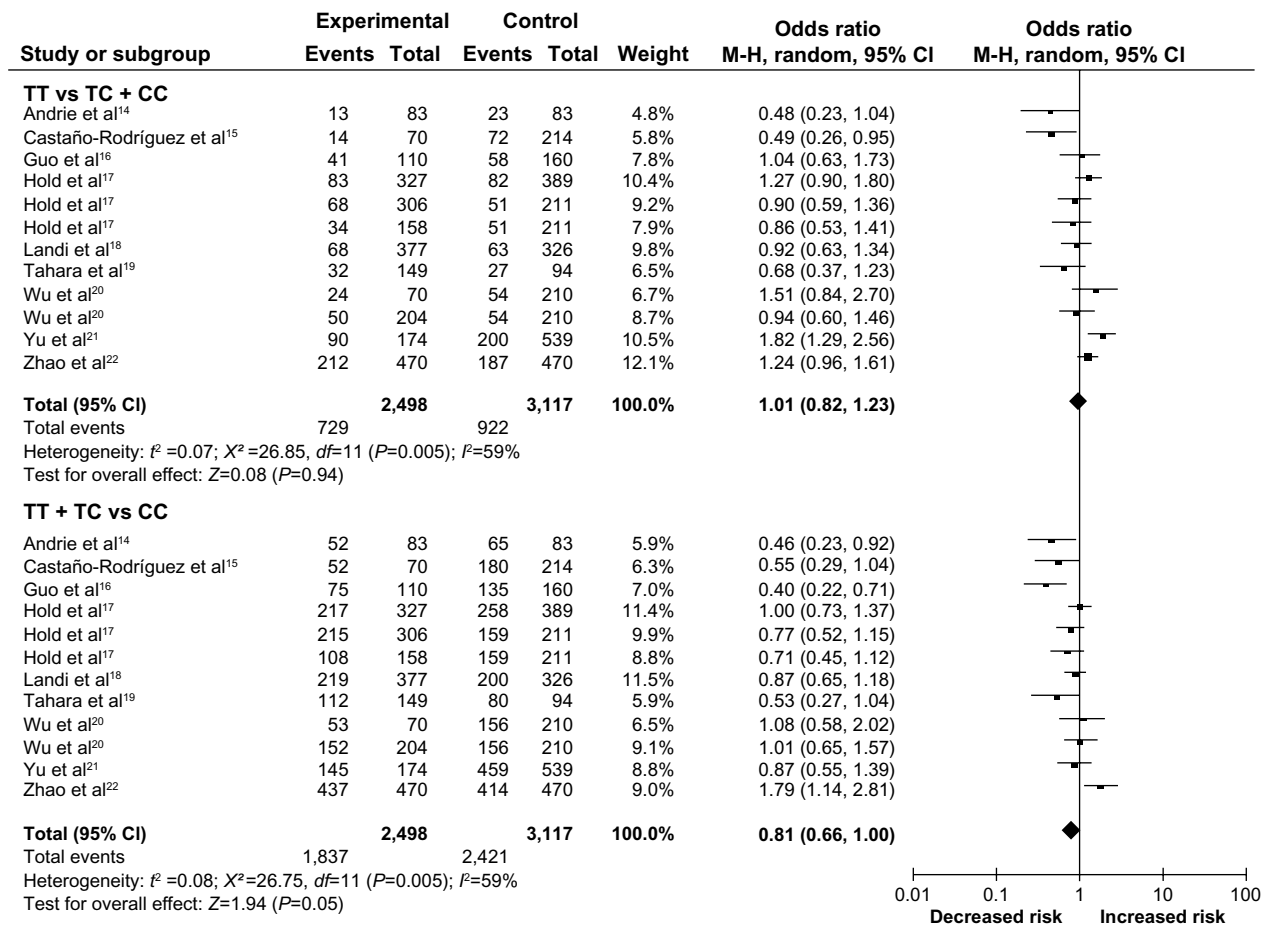


Figure 2 Meta-analysis with a random-effects model, for the association between cancer risk and the CD14 -159C/T polymorphism (TT vs TC + CC) and (TT + TC vs CC). **Abbreviations:** -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; T, thymine; vs, versus.

In the subgroup analysis by cancer type, gastric cancer was investigated in six studies,^{15,17,19,20,22} involving 1,526 gastric cancer cases and 1,588 controls. The pooled OR was 0.96 (95% CI=0.74–1.23) ($P=0.72$) for the recessive TT vs TC + CC model (Figure 3), and was 0.91 (95% CI=0.66–1.25) ($P=0.55$) for the TT + TC vs CC model and therefore, showed no association. Due the limited number of included studies, we didn't perform a subgroup analysis of the other cancer types.

Publication bias

Publication bias was analyzed by using the Begg's funnel plots and Egger's test. The shape of the funnel plots seemed asymmetrical in the TT vs TC + CC comparator genetic model, suggesting the presence of a publication bias (Figure 4). The Egger's test was performed to provide statistical evidence of funnel plot asymmetry. The result indicated a significant publication bias ($P=0.008$).

Table 3 Summary of results from different comparative genetic models

	N*	Case/control	TT vs TC + CC		TT + TC vs CC		T vs C		TT vs CC	
			OR (95% CI)	P**	OR (95% CI)	P**	OR (95% CI)	P**	OR (95% CI)	P**
Total	12	2,498/2,696	1.01 (0.82, 1.23)	0.94	0.81 (0.66, 1.00)	0.05	0.94 (0.81, 1.08)	0.37	0.86 (0.64, 1.14)	0.29
By ethnicity										
Asian	7	1,247/1,687	1.07 (0.80, 1.44)	0.65	0.82 (0.55, 1.21)	0.31	0.96 (0.77, 1.20)	0.73	0.87 (0.55, 1.38)	0.56
Caucasian	5	1,251/1,009	0.96 (0.79, 1.16)	0.66	0.83 (0.70, 0.98)	0.03	0.91 (0.75, 1.09)	0.29	0.84 (0.58, 1.20)	0.33
By cancer type										
Gastric cancer	6	1,526/1,588	0.96 (0.74, 1.23)	0.72	0.91 (0.66, 1.25)	0.55	0.93 (0.76, 1.13)	0.48	0.87 (0.56, 1.36)	0.55

Notes: *Number of included studies; **P-value for the Z-test.

Abbreviations: C, cytosine; CD, cluster of differentiation; CI, confidence interval; T, thymine; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; vs, versus.

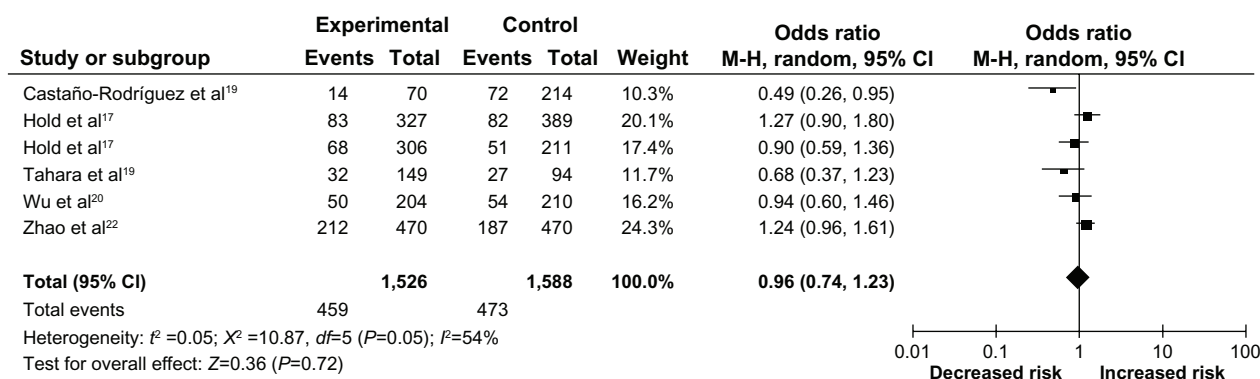


Figure 3 Meta-analysis with a random-effects model for the association between gastric cancer risk and the CD14 -159C/T polymorphism (TT vs TC + CC).
Abbreviations: CD14, cluster of differentiation 14; C, cytosine; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; T, thymine; vs, versus.

Discussion

Chronic inflammation is associated with the development and progression of several types of cancer.² CD14 is an important inflammation mediator, and repeated studies have confirmed that the genetic variations of CD14 are associated with classical inflammatory diseases, such as asthma and inflammatory bowel disease.^{23,24} Studies have reported that CD14 may be involved in cancer development and progression, and a growing number of studies have investigated the potential relationship between the CD14 -159C/T gene polymorphism and cancer risk. However, the results from different published studies have been inconsistent. Thus, we performed this meta-analysis to comprehensively analyze their associations.

In present study, the effect of dominant/recessive models and the effect of allele frequency were all assessed to

investigate the precise role of the CD14 -159C/T gene polymorphism in cancer. What's more, the consistency of the genetic effects across populations of different ethnicities and cancer types was also investigated. The findings from present study indicated that -159C/T polymorphism in the CD14 gene showed no association with cancer risk. In addition, the dominant allele model showed a potential decreased risk of cancer for this polymorphism (OR = 0.81, 95% CI = 0.66–1.00). Since the genetic–protein interaction is complicated, it is not surprising that there was no association found between the CD14 -159C/T gene polymorphism and cancer risk. Growing studies suggest a complex interaction between gene polymorphism and cancer. The contributions of genetic factors to cancer are quite complicated, except for the current known gene polymorphisms, and uncommon

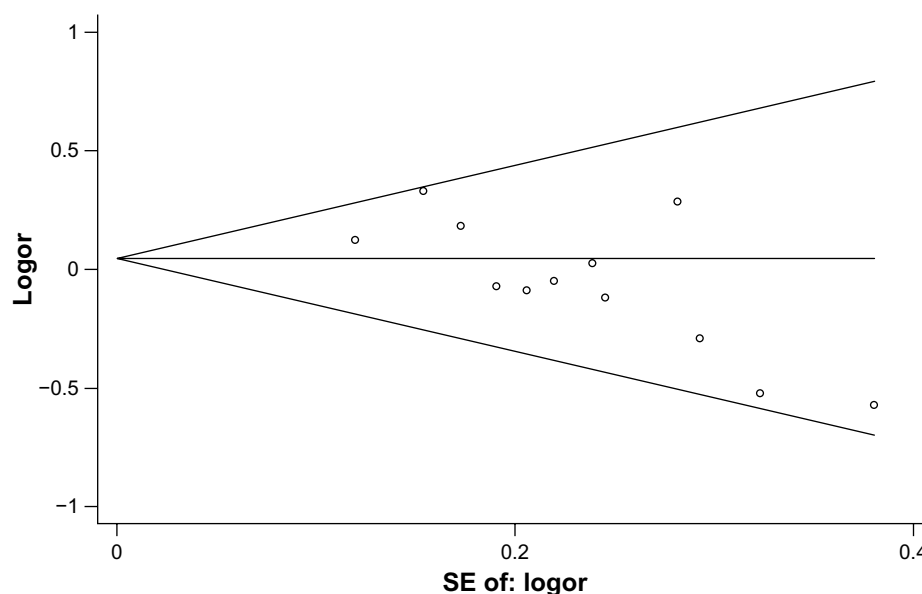


Figure 4 Begg's funnel plot for publication bias in selection of studies on the CD14 -159C/T polymorphism (TT vs TC + CC).

Note: Pseudo 95% confidence limits.

Abbreviations: CD14, cluster of differentiation 14; C, cytosine; T, thymine; SE, standard error; v, versus.

polymorphisms may also contribute to cancer.²⁵ In addition, the effects of gene–gene and gene–environment interactions remain questions.²⁶ For a deeper understanding of the precise role of the CD14 -159C/T gene polymorphism in cancer risk, more studies are needed.

Our study included several types of cancer, and we did a subgroup analysis on gastric cancer to investigate whether the relationship between CD14 -159C/T gene polymorphism and cancer risk is tumor origin–specific. A total of six studies on gastric cancer were included. However, the results failed to show any association (OR =0.91, 95% CI =0.66–1.25) ($P=0.55$) for dominant model. Since *Helicobacter pylori* (*H. pylori*) infection plays an important role in the pathogenic process of gastric cancer, Zhao et al investigated this. The researchers reported that the CD14 -159C/T gene polymorphism is associated with a greater risk of *H. pylori*–related gastric cancer and postulated that this polymorphism might play a role in the outcome of *H. pylori* infection, further suggesting that the effect of CD14 -159C/T gene polymorphism on gastric cancer is quite complex and that other pathogenic factors should be taken into consideration.²² In addition, we also have noticed that the association between the CD14 -159C/T gene polymorphism and cancer risk may also be cancer subtype-specific – in a study by Andrie et al, a significantly increased risk for Hodgkin lymphoma was found with presence of the CD14 -159C/T polymorphism, while not for non-Hodgkin lymphoma.¹⁴ These results indicated that the effect of CD14 -159C/T gene polymorphism on cancer risk may be tumor origin-specific and subtype-specific.

Different ethnicities have different genetic backgrounds, which may influence the association between polymorphism and cancer susceptibility in those groups. In this meta-analysis, data were also stratified by ethnicity. For Asians, no potential association between the CD14 -159C/T gene polymorphism and cancer risk was identified in any of the models, and for Caucasians, the results suggested that TT and TC carriers have a 17% decreased risk of cancer compared with those individuals with the CC homozygote ($P=0.03$). However, it should be pointed out that there may be differences in the genes involved, in different populations; different polymorphisms within a specific locus; and different loci within the same gene and that environmental factors may even play a role in the expression of these changes.²⁷ The identification of susceptibility genes in cancer patients of different ethnicities provides an opportunity to explore new mechanisms of disease that are specific in different populations.²⁸

The objective of our meta-analysis was to integrate the results from comparable studies on the potential association

between CD14 -159C/T gene polymorphism and cancer risk, in order to increase their sample size and statistical power and to draw more valid conclusions. However, the present meta-analysis also has several limitations that should be addressed. First, strict inclusion and exclusion criteria were used in order to reduce selection bias, and the resulting limited number of studies and subjects may not have enough power to explore the association between CD14 -159C/T gene polymorphism and cancer susceptibility. Second, the included studies were based on Asian and Caucasian population, and additional studies are warranted to evaluate the effect of this functional polymorphism on cancer risk among different populations, eg, in Latinos. Third, only published studies in the selected databases were included in this meta-analysis, and our meta-analysis identified significant publication bias among included studies. It is possible that some studies that were not included in these databases or some unpublished studies with null results were not identified, and this may have biased our results.

Conclusion

Taken together, the findings from the current meta-analysis don't support the CD14 -159C/T gene polymorphism as a risk factor for cancer. To further investigate gene–gene and gene–environment interactions between this polymorphism and cancer risk, additional case-control studies of different cancer types and ethnicities should be performed.

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Disclosure

The authors report no conflicts of interest in this work.

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