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ORIGINAL RESEARCH

Association between CD14 SNP -159 C/T and gastric cancer: an independent case–control study and an updated meta-analysis

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Purpose: The association between CD14 -159C/T polymorphism and the susceptibility to gastric cancer (GC) has been reported. However, the results were inconclusive. In the present study, a case–control study and a meta-analysis were performed to assess the possible association between -159C/T in the CD14 gene and GC risk.

Patients and methods: Relevant studies were searched in several databases including PubMed, Web of Science, EMBASE, Chinese National Knowledge Infrastructure database, and Wanfang database (last search was performed on December 30, 2015). In addition, a case–control study involving 164 GC cases and 169 controls was also performed in the analysis. Statistical analysis was performed by the software Revman5.3.

Results: A total of ten published studies and the present case–control study involving 2,844 GC and 3,983 controls were included for the meta-analysis. The analysis result indicated that the T allele of CD14 -159C/T polymorphism did not confer risk for GC (in our study: [*P*=0.93]; in the meta-analysis: T vs 2N odds ratio =1.28 and 95% confidence interval (CI) =0.95–1.24, [*P*=0.24]). However, we found a significant association in the recessive model (in our study: TT vs TC+CC [*P*=0.04]; in the meta-analysis: TT vs TC+CC odds ratio =1.12 and 95% CI =1.01–1.26, [*P*=0.04]). Furthermore, a subgroup analysis by ethnicity showed that TT genotype was significantly associated with GC in Asian (odds ratio =1.17 and 95% CI =1.02–1.34, [*P*=0.02]) but not in Caucasian.

Conclusion: Our results highlight the TT genotype of CD14 -159C/T as a genetic susceptibility factor for gastric cancer, particularly, in Asians and population-based controls.

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

Introduction

Gastric cancer (GC) is one of the most common gastrointestinal cancers, with a high cancer-related mortality worldwide.[1,2] The progression and development of GC is a multifactorial and multistep process, such as geographic location, life style, genetic background, and *Helicobacter pylori* infection, which is a Gram-negative bacterium and has been causally associated with gastric premalignant and malignant conditions.[3] Host genetic variants are associated with the susceptibility and pathophysiology of multiple cancers.[4] It is well known that chronic inflammation has been implicated in the development of cancer. Variants of some genes involved in innate immunity have been studied and identified as candidates for cancer effectors, especially polymorphisms of TLR4 pathway,[5,6] including the CD14 gene.

Antigenic molecules on the surface of both Gram-positive (peptidoglycans and lipoteichoic acid) and Gram-negative (lipopolysaccharide, LPS) bacteria can be detected by

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many pattern recognition receptors that include Toll-like and CD14 receptors.[7] It is well known that CD14 is expressed and generated as a surface protein by monocytes/macrophages, and CD14 binds LPS-binding protein and apoptotic cells.[7] Within CD14 promoter, T allele of the polymorphism -159 C/T [dbSNP: rs2569190] has the capability to increase the transcriptional activity by lowering the affinity of the GC box for Sp3, which is a factor that inhibits the activity of the promoter. This enhanced transcriptional activity induced to enhance CD14 expression and associated with higher concentrations of soluble CD14.[8] Recently, CD14 -159C/T polymorphism has been identified to be associated with progression and risk of multiple cancers, such as gastric cancer,[9–12] colorectal cancer,[13–15] and pancreatic cancer.[16]

TLR4/CDl4 plays pivotal roles in LPS recognition and downstream signal transduction pathways and LPS of intestinal bacteria is involved in the progression and development of GC. In addition, CD14 expression promoted GC cell invasion and EMT.[17] CDl4 gene polymorphism, especially functional polymorphism, may be susceptible to GC and has a certain influence in early prediction of disease outcome.

Although several studies have tried to elucidate the potential association of CD14 -159 C/T and the susceptibility to GC, the results were conflicting and inconclusive.[18–20] In this study, we performed a case–control study to evaluate the association between CD14 -159 C/T and the risk of GC in a Chinese population. Based on the data from all published studies and our study, a systemic meta-analysis was conducted.

Participants and methods

Study participants

Since 2005, blood samples were prospectively collected from individuals participating in a study looking at the risk factors for GC. The CD14 -159C/T was genotyped following a previously described case–control study.[11] The individuals of 164 GC patients and 169 controls were derived from a Han population in Harbin, People's Republic of China. DNA samples were extracted and kept at −20°C. The study was approved by the Ethnic Committee of Harbin Medical University. Written informed consent was obtained from each participant according to instituted guidelines.

Search strategy and study selection

A systematic literature search strategy was performed for articles published up until May 12, 2015, which shows the association between CD14 -159C/T and the risk of GC. The PubMed, Web of Science, EMBASE, Chinese National Knowledge Infrastructure, and Wanfang databases were searched with the combination of terms "gastric" and "CD14" and "tumor" in combination with "polymorphism or variant or mutation". All articles published in English and Chinese were included in the literature search, and a Japanese study was excluded.[10]

Studies focusing on the association of CD14 -159C/T with the risk of GC, which met the following conditions, were included: 1) the association of CD14 -159C/T with GC was described in the study; 2) the individual number of controls and GC cases were reported in the study; 3) the results of genotype and allele were described by odds ratio (OR) and 95% confidence interval (CI) in the study; and 4) case–control or nested case–control were included in the study.

Statistical analyses

In the case–control study, the χ^2-test was performed to assess the Hardy–Weinberg equilibrium in both controls and GC cases. Comparison of genotype and allele frequencies for CD14 -159C/T was carried out by χ^2-test. Odds ratios[21] and their 95% confidence intervals (95% CI) were calculated by SPSS13.0 (SPSS Inc., Chicago, IL, USA). For each analysis, the results were considered statistically significant when two-tailed *P*-values were <0.05.

In the meta-analysis, the association between GC risk and CD14 -159C/T genotype was estimated under allele model, dominant model, and recessive model.

OR with 95% CI was calculated to measure the strengths of the associations between the risk of GC and CD14 -159C/T. Considering the low statistical power, the significant heterogeneity was determined when *P*-values were <0.10. Furthermore, heterogeneity was quantified by the inconsistency index I^2 calculation, which documented for the variation within studies. Referring to Higgins's study, I^2-values $<25\%$ correspond to mild heterogeneity and I^2-values $>50\%$ were considered as large heterogeneity.[22] Since the test of heterogeneity was not significant, eleven studies were pooled according to fixed effects model (Mantel–Haenszel), otherwise, the random effect (RE) model was be performed.[23,24]

Results

CD14 -159C/T polymorphism in the case–control

The allele and genotype frequencies of the CD14 -159C/T are described in Table 1. The statistical significance of deviation from the Hardy–Weinberg equilibrium was not seen. Moreover, the statistical significance was not shown in the association between allele frequency of CD14 -159 C/T and GC. But, when the genotype frequency was compared, the TT genotype was more frequent in GC cases than that

Table 1 Genotype and allele frequencies for CD14 -159C/T site in case–control of gastric cancer

-159C/T	Gastric cancer	Controls	*P*-value
	n=164	n=169	
Dominant model			
C/C	34	47	0.13
C/T+T/T	130	122	
Recessive model			
C/T+C/C	107	128	0.04
TT	57	41	
Allelic frequencies			
C	141	142	0.93
T	187	186	

Notes: Dominant model is (TT/CT) vs CC; recessive model is TT vs (CC/CT); n is the total number of subjects with each particular genotype.
Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; T, thymine.

in controls (34.8% vs 24.3%). This effect was significantly evident in the recessive model (*P*=0.04). In the Chinese population, a statistically significant association between GC and the CD14 -159C/T polymorphism was confirmed.

Quantitative data synthesis

Furthermore, we did the meta-analysis that included eleven case–control studies with 2,844 cases and 3,983 controls concerning the association of CD14 -159C/T polymorphism and GC. Based on heterogeneity among the eleven eligible studies, a RE model was performed to pool the data of all studies for considering CD14 -159T allele contrasts (Figure 1), a fixed effects model for CD14 -159 TT vs TC+CC (Figure 2) and a RE model for CD14 -159 TC+TT vs CC (Figure 3). No significant association was found between CD14 -159T allele and GC risk in the meta-analysis (OR =1.08; CI =0.86–1.35, *P*=0.24). Nevertheless, the frequency of genotype TT showed a significant increase in GC patients (OR =1.12; 95% CI =1.01–1.26, *P*=0.04). The allele frequencies of CD14 -159 in the control populations were similar to other documented Chinese studies. TT genotype frequency was associated with the risk of GC in the Chinese study (Table 1 and Figure 2).

Subgroup analysis

In the subgroup analysis by ethnicity, based on the dominant model (TT+TC vs CC), the OR was 1.20 (95% CI =0.87–1.66, *P*=0.26) among Asians and was 0.87 (95% CI =0.73–1.05, *P*=0.14) among Caucasians. Thus, both showed no association between the -159C/T polymorphisms of the CD14 gene and GC risk. When analyzed by the recessive model (TT vs TC+CC), the OR was 1.17 (95% CI =0.1.02–134, *P*=0.02) among Asians and was 1.04 (95% CI =0.85–1.26, *P*=0.71) among Caucasians. These results suggested that TT genotype has a 17% decreased risk of GC compared to those individuals with the TC+CC carries in Asians.

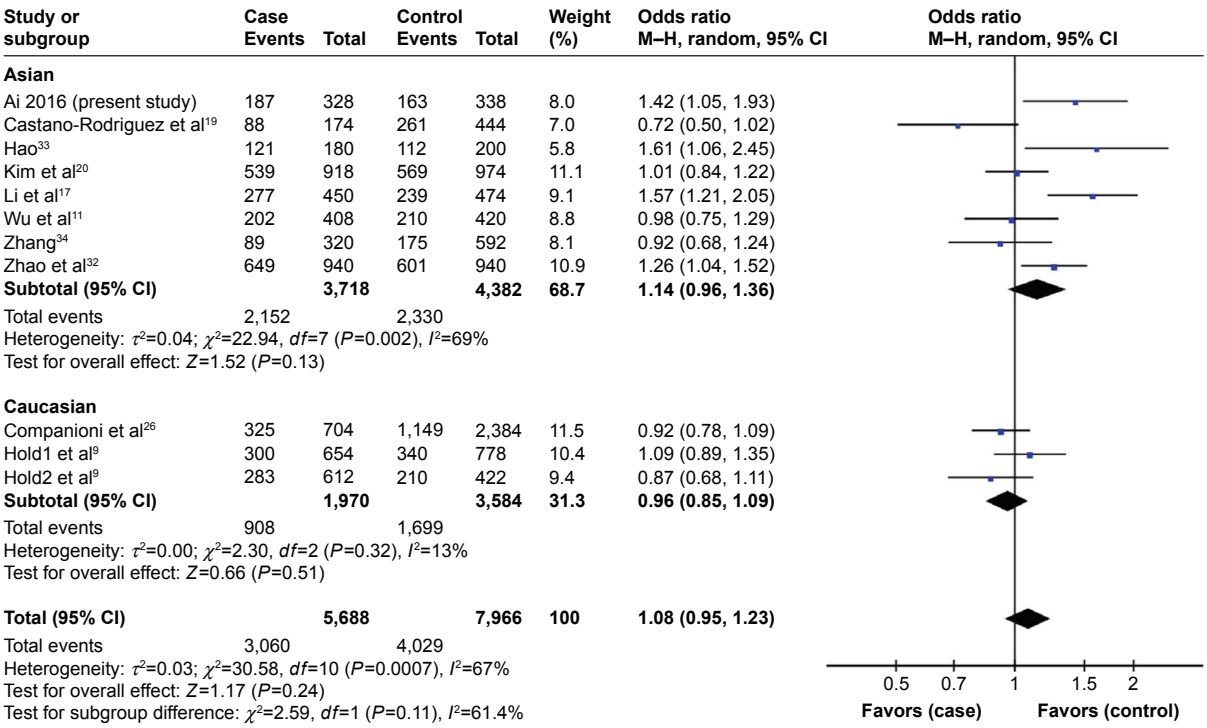

Figure 1 Association of CD14 -159C/T (allele T vs 2N) and risk of gastric cancer.
Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; T, thymine.

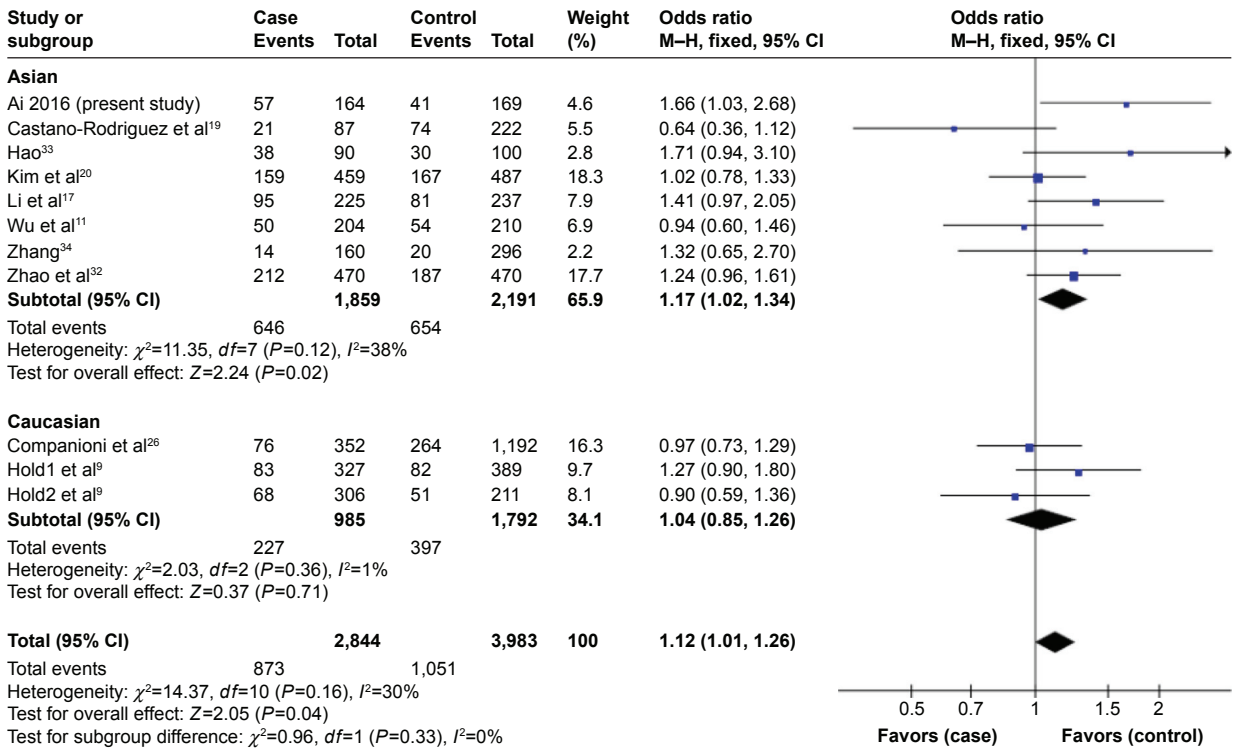

Figure 2 Meta-analysis of association between CD14 -159C/T polymorphism and susceptibility to gastric cancer under dominant model.
Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; T, thymine.

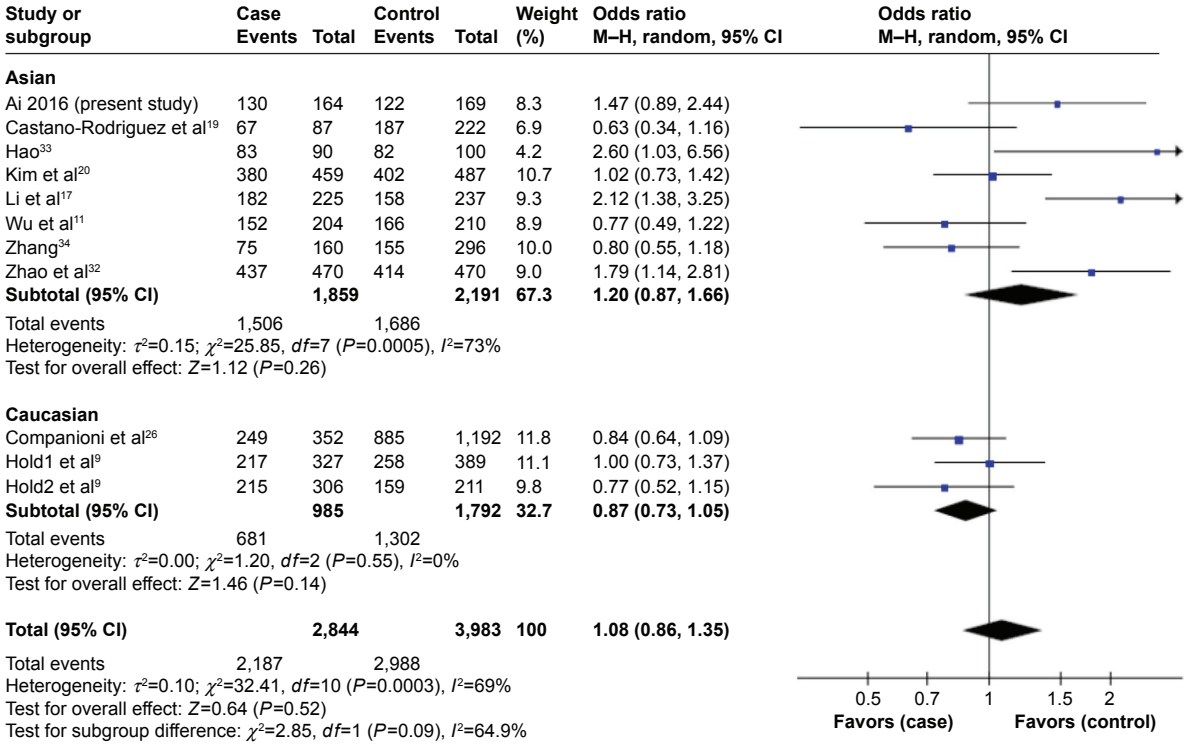

Figure 3 Meta-analysis of association between CD14 -159C/T polymorphism and susceptibility to gastric cancer under recessive model.
Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; T, thymine.

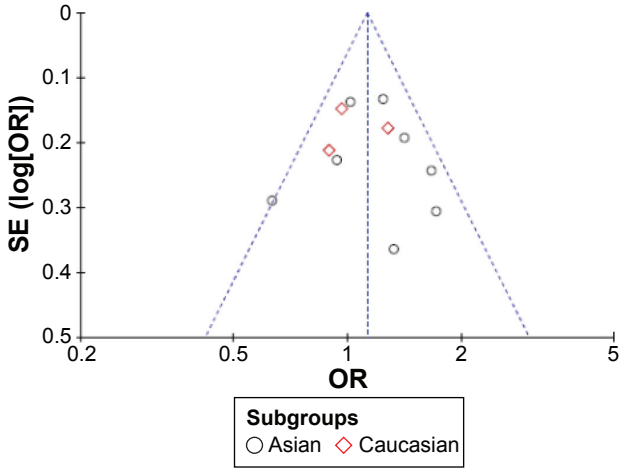

Figure 4 Funnel plot for publication bias in selection of studies on the CD14 -159C/T polymorphism (recessive model).
Abbreviations: -159C/T, CD14 gene polymorphism; CD14, cluster of differentiation 14; C, cytosine; T, thymine; SE, standard error; OR, odds ratio.

Publication bias

Publication bias was performed by using the funnel plot (Figure 4). The result showed that there was no publication bias by Begg's test of STATA (P=0.761).

Discussion

Recently, accumulating evidence suggested that CD14 plays a pivotal role in GC, especially associated with LPS-induced immune activation. Based on the well-known function of the CD14 -159C/T polymorphism, researchers found that the polymorphism was associated with the development of *H. pylori*-induced premalignant gastric changes, which play a key role in assessing their relevance to GC.[25] Therefore, CD14 -159C/T polymorphism as a functional one in the CD14 promoter may be associated with GC susceptibility.

Several studies[9,26,27] have tried to elucidate the potential association of CD14 -159 C/T, but the result of association between CD14 -159 C/T and the risk of GC was conflicting and inconclusive. In the current case–control study and the meta-analysis, we examined the association between a functional polymorphism, CD14 -159 C/T, and the risk of GC because of inconsistent reports in individual studies. Until now, this is the most updated meta-analysis including all data related to the association between the CD14 -159 C/T polymorphism and the risk of GC. In the current case–control study and meta-analysis, comparisons of alleles and genotypes were analyzed between GC patients and controls. The combined results revealed a significant association between TT genotype of CD14 -159C/T and GC risk.

The ethnicity could influence the association between CD14 -159 C/T and GC because of different genetic backgrounds. In the meta-analysis, the data were stratified by ethnicity. For Asians, the result displays that TT carriers have 17% increased risk of GC compared with those individuals carrying CC and CT (P=0.02). But for Caucasians, the association between the CD14 -159 C/T polymorphism and GC risk was not identified in any models.

In all acquired risk factors for GC pathogenesis, *H. pylori* is the most important one. LPS of *H. pylori* could bind CD14 and mediate cross-talking with Toll-like receptors to active innate immunity.[28] According to a number of studies, the CD14 -159C/T T allele is observed to increase sCD14 production.[29] Furthermore, *H. pylori* enhances gastric mucosal inflammation in individuals carrying the -159 C/T T allele, and the level of sCD14 may be an indicator for the inflammation induced by *H. pylori*.[30,31] Consistent with the above results, a multiplicative joint effect between TT genotype of -159 C/T and *H. pylori* infection induced significantly higher sCD14 in GC than controls.[32] Those pooled results indicated that the -159 C/T may be a risk factor for GC in *H. pylori* individuals and may play a role in the outcome of *H. pylori* infection, especially in the development of GC. In a meta-analysis, Wang et al found that the CD14 -159 T/C SNP may increase the risk of GC in individuals with *H. pylori* infection.[6] We did not stratify the data by *H. pylori* infection because only two studies were included. More studies were needed for *H. pylori* factorial analysis.

Limitations

There are some limitations in our meta-analysis. First, the evaluation of potential interactions was not conducted due to the lack of original data. Second, control samples were selected from patients in hospital, who might have a digestive tract disease and correspond to a potentially incremental risk. Third, many environmental and other genetic factors may affect the risk of gastric tumor, for example, *H. pylori*. We did not however analyze the subgroup based on *H. pylori* factor because of the sample scale. Next, large sample scale should be studied for *H. pylori* subgroup analysis.

In conclusion, the above evidence suggests that CD14 -159C/T polymorphism may be associated with the risk of GC, and this genetic variant may increase the risk of GC. More unbiased and well-designed studies with larger sample size should be performed to further evaluate the associations.

Author contributions

This paper is approved by all authors for publication. All authors contributed to design, data analysis, drafting, and

revising the paper. All authors agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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