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Original Article

Association of CD14 -159C/T polymorphism with susceptibility to gastric cancer: a meta-analysis

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Abstract: The CD14 gene has been suggested to play a key role in the pathogenesis of gastric cancer. However, the research conclusions have been inconsistent. In this study, we performed a meta-analysis to clarify the connection of CD14 -159C/T polymorphism with gastric cancer. Relevant articles published up to January 2016 were obtained from Pubmed and Embase electronic databases. A total of 5 case-control studies were enrolled into this meta-analysis, and our results showed no association between CD14 -159C/T polymorphism and gastric cancer risk (TT *vs*. CC: OR=0.95, 95% CI=0.59-1.52; CT *vs*. CC: OR=1.00, 95% CI=0.73-1.38; Dominant model: OR=0.98, 95% CI=0.69-1.40; Recessive model: OR=0.99, 95% CI=0.75-1.30). No publication bias was found in the meta-analysis. In summary, the present meta-analysis suggests that the CD14 -159C/T polymorphism may not be associated with gastric cancer risk.

Keywords: Genetic predisposition to disease, meta-analysis, polymorphism, genetic

Introduction

Gastric cancer is one of the most common malignancies worldwide [1]. The mechanism of gastric carcinogenesis remains elusive. Previous studies have revealed that alcohol consumption, obesity and high sodium intake are significantly associated with gastric cancer [2]. However, these risk factors above cannot fully explain the occurrence and development of gastric cancer, since only a minority of exposed population finally developed gastric cancer, indicating possible interplay between risk factors and personal genetic susceptibility [3]. Recently, many studies demonstrated that gene polymorphisms related to gastric cancer, such as the ACE gene insertion/deletion polymorphism, and the hOGG1 gene Ser326Cys polymorphism [4, 5].

CD14 encodes a protein that binds to lipopolysaccharide, and interacts with co-receptors toll-like receptor 4 and lymphocyte antigen 96 [6]. CD14 is expressed on the surface of monocytes and macrophages as membrane CD14, and its expression may be partly regulated at the genetic level [7]. Previous study showed that *CD14* gene is localized on chromosome 5q31.1. A polymorphism C/T has been identified on the -159 position of promoter region of CD14 gene named -159C/T (rs2569190), which was found to be closely related to increased transcriptional activity that affects expression level of CD14 [8].

Recently, the CD14 -159C/T polymorphism is widely investigated for the susceptibility of gastric cancer. However, the results remain disputable. Meta-analysis is a helpful method for analyzing complicated data from case-control studies were somewhat limited by small sample sizes and represent lower statistical power [9]. To help clarify the findings, we conduct this meta-analysis to evaluate the association between the CD14 -159C/T polymorphism and gastric cancer risk.

Materials and methods

Publication search

PubMed and EMBASE databases were searched for the relevant reports (the last search update was January 1, 2016), using the search

Table 1. Scale for quality assessment

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathological archives, but without a description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens obtained from patients to determine genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
≥ 1000	3
≥ 500 but < 1000	2
≥ 200 but < 500	1
> 0 but < 200	0

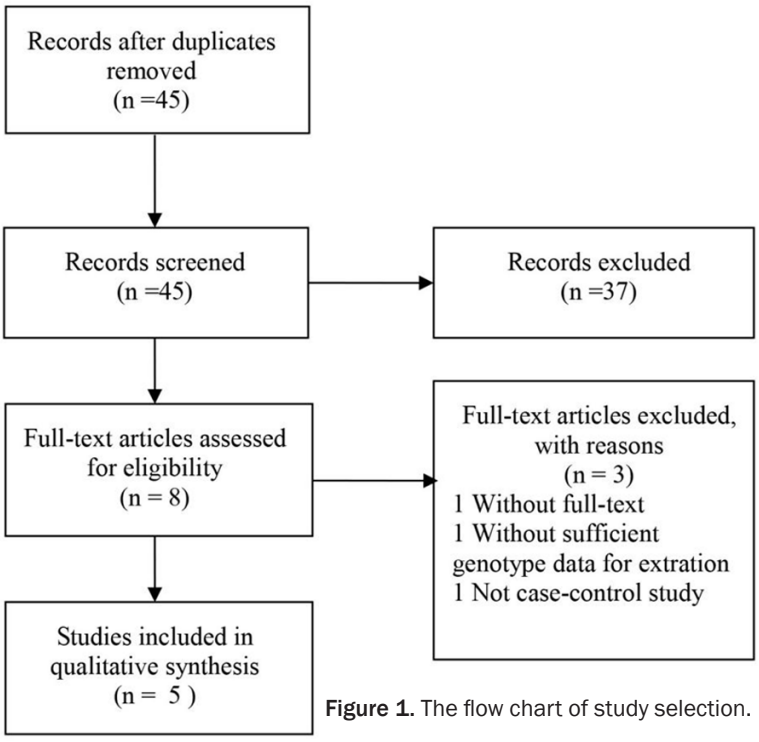

Figure 1. The flow chart of study selection.

terms "CD14" or "-159C/T" or "rs2569190" and "gastric cancer". The retrieval was limited to English language papers. We evaluated the relevant literatures to search all the eligible studies. Their reference checklists were hand-searched to find possible literatures. Of the articles with the repeated data, we merely selected the study with the most extensive information.

Selection criteria

To identify relevant studies for this analysis, we considered the following parameters: (i) the association between the CD14 -159C/T polymorphism and gastric cancer risk, (ii) case-control design, (iii) with sufficient information for calculation of odds ratio (OR) with 95% confidence interval (CI). Criteria for exclusion were as follows: (i) not for gastric cancer research, (ii) review articles or meta analysis, and (iii) reports without usable information.

Data extraction

For each publication, the characteristics were considered as follows: first author, year of publication, country, ethnicity; number of subjects in each category, and the counts of persons with different genotypes in cases and controls. Data on the Hardy-Weinberg equilibrium test (HWE) was also calculated.

Quality evaluation

The quality of these publications was evaluated independently by two investigators according to the predefined quality assessment rules in **Table 1** [10]. The criteria cover the representativeness of cases, source of controls, ascertainment of gastric cancer, total sample size, quality control

Table 2. Characteristics of the included studies for meta-analysis

Study included	Area	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test	Quality scores
			CC	CT	TT	CC	CT	TT		
Zhao 2007	China	470/470	33	225	212	56	227	187	0.30	12
Tahara 2007	Japan	149/94	37	80	32	14	53	27	0.15	11
Hold 2009	Polish	327/389	110	134	83	131	176	82	0.11	12
Companioni 2013	Mixed	1192/352	307	621	264	103	173	76	0.83	13
Castano 2013	Mixed	70/214	18	38	14	34	108	72	0.54	11

of genotyping methods, and HWE in the control population. Different opinions were resolved by consensus. Papers scoring < 10 were classified as "low quality", and those scoring ≥ 10 as "high quality".

Statistical analysis

The strength of association between the CD14 -159C/T polymorphism and risk of gastric cancer was assessed by calculating OR with 95% CI. Four different ORs were calculated: homozygote comparison (TT *vs*. CC), heterozygote comparison (CT *vs*. CC), dominant model (CT+TT *vs*. CC) and recessive model (TT *vs*. CT+CC). Heterogeneity was investigated and measured using the I^2 statistic, I^2 > 50% indicated evidence of heterogeneity. When the heterogeneity was present, the random effects model was used to calculate the pooled OR, whereas the fixed effects model was used [11]. A chi-square test was applied to determine whether genotype distribution of the control population reported conformed to HWE (P < 0.05 was considered significant). A sensitivity analysis was conducted by switching the effects models. Available data were entered into Cochrane Review Manager (version 4.2) and analysed. Publication bias was investigated by Begger and Egger's linear regression tests using Stata software (version 12.0).

Results

Study characteristics

As a result of the search and screening, 45 papers were retrieved by the literature search, of which 5 papers with full-text were included in this meta-analysis and 30 studies were excluded] [12-16]. **Figure 1** displayed the selection process of this study. The countries of these studies contained China, Japan, Polish, and so on. The publishing year of the included literatures ranged from 2007 to 2013. All the studies were written in English. The source of controls was primary based on healthy populations. The genotype distributions among the controls of all studies were in agreement with HWE test (P > 0.05). All included studies were of high quality as the quality score assessment of each one was higher than 10 points. The study characteristics are presented in **Table 2**.

Meta-analysis

The combined results of the CD14 -159C/T polymorphism and gastric cancer risk are summarized in **Figures 2**-**5** and **Table 3**. When all eligible studies were pooled into one dataset, we found no statistical association between the CD14 -159C/T polymorphism and gastric cancer risk (TT vs. CC: OR=0.95, 95% CI=0.59-1.52; CT vs. CC: OR=1.00, 95% CI=0.73-1.38; Dominant model: OR=0.98, 95% CI=0.69-1.40; Recessive model: OR=0.99, 95% CI=0.75-1.30). Sensitivity analyses were calculated via altering the statistic models. No material alteration was found, indicating that our data were statistically robust.

Publication bias

Publication bias of the literature was assessed by Begger and Egger's linear regression tests. No obvious visual asymmetry was observed (**Figure 6**). Results showed that the publication bias was low in this meta-analysis.

Discussion

Gastric cancer is one of the most common malignant tumors of the gastrointestinal tract worldwide. Although the pathogenesis of gastric cancer are still not clear, recent evidence demonstrated that Helicobacter pylori infection, alcohol, smoking and diet have been implicated in the carcinogenesis and development of gastric cancer. Nonetheless, the expo-

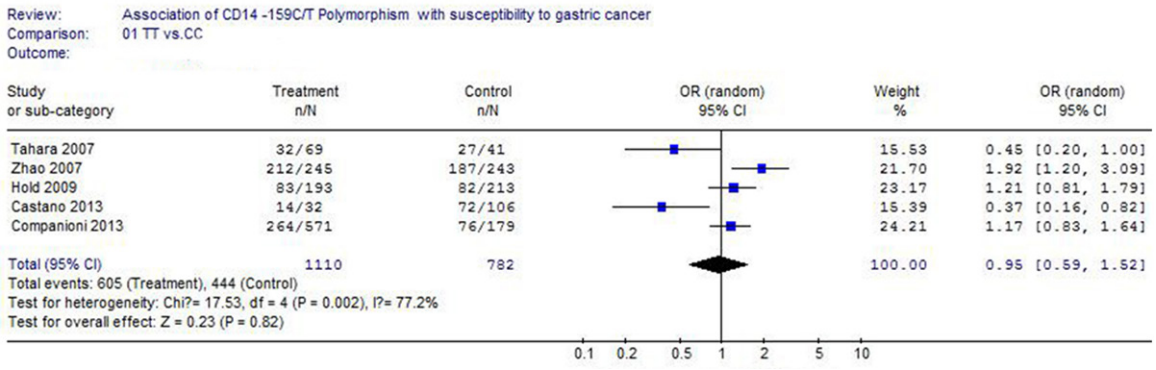

Figure 2. Forest plot of gastric cancer associated with the CD14 -159C/T polymorphism (TT vs.CC).

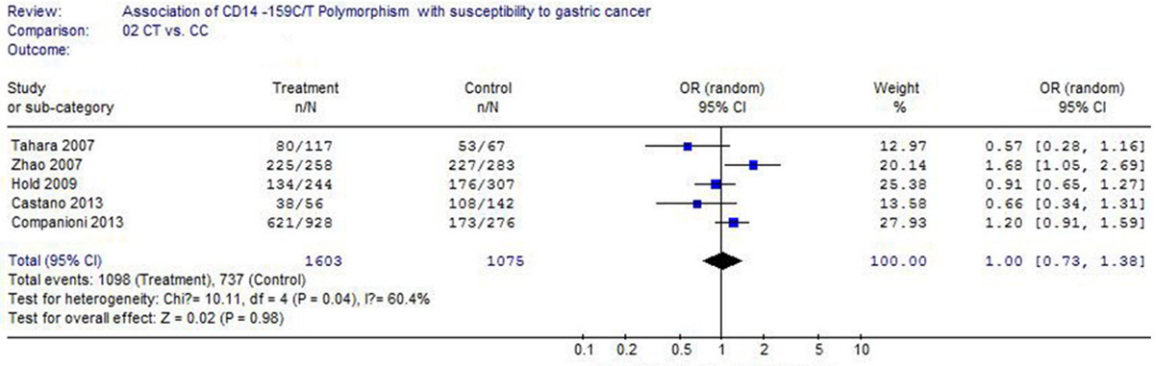

Figure 3. Forest plot of gastric cancer associated with the CD14 -159C/T polymorphism (CT vs.CC).

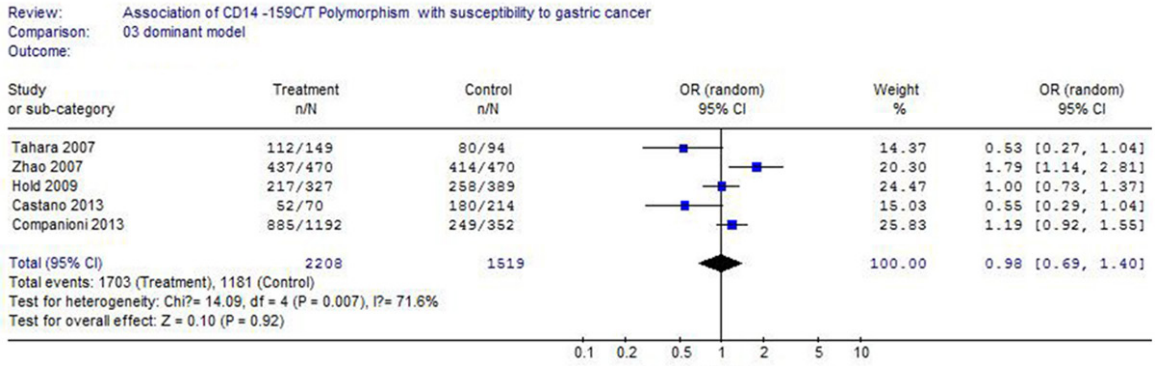

Figure 4. Forest plot of gastric cancer associated with the CD14 -159C/T polymorphism (dominant model).

sure of these factors only results in the development and progression of gastric cancer in a small population of individuals, manifesting that genetic susceptibility may also contribute to the etiology of gastric cancer. CD14 is a key inflammation mediator, and repeated studies have reported that CD14 may be involved in the etiology and pathogenesis of cancer, and many publications have investigated the possible correlation between the CD14 -159C/T gene polymorphism and gastric cancer risk. In this study, we perform a meta-analysis to evaluate the association between the CD14 -159C/T variant and risk of gastric cancer.

Our study quantitatively assessed the association between CD14 -159C/T polymorphism and gastric cancer risk. Among the genetic models examined in this analysis, none of the models provided statistical evidence for a significant

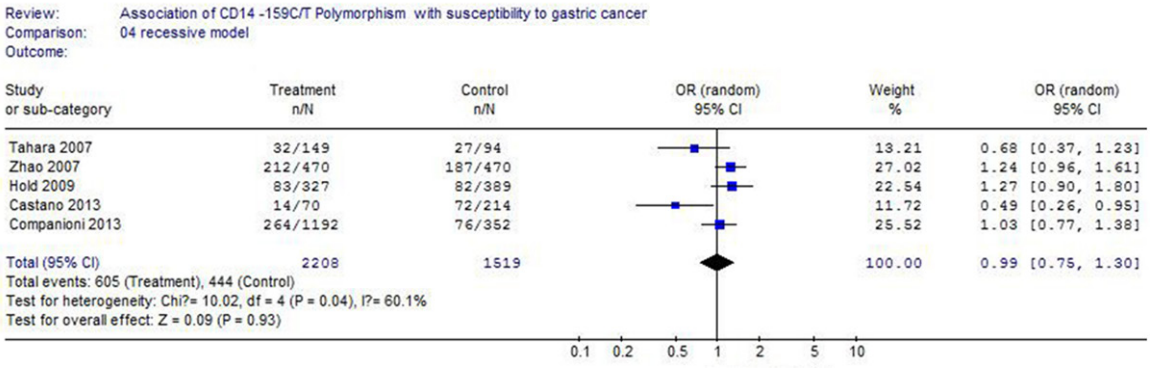

Figure 5. Forest plot of gastric cancer associated with the CD14 -159C/T polymorphism (recessive model).

Table 3. Summary ORs and 95% CI of CD14 -159C/T Polymorphism and gastric cancer risk

Genetic model	Type of model	Test of association	
		OR	95% CI
TT vs. CC	Random	0.95	0.59-1.52
CT vs. CC	Random	1.00	0.73-1.38
the dominant model	Random	0.98	0.69-1.40
the recessive model	Random	0.99	0.751.30

CI: confidence interval; OR: odds ratio.

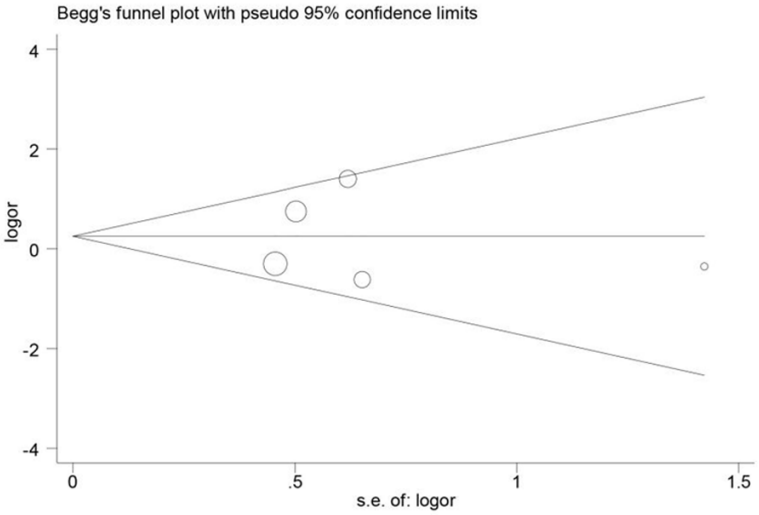

Figure 6. Begg's funnel plot for evaluation of publication bias.

association between gastric cancer risk and the CD14 -159C/T polymorphism. However, growing studies suggest a complicated interaction between gene polymorphism and cancer. The potential influence of this polymorphism may be affected via gene-gene interaction. Previous study demonstrated that the -159C/T and -651C/T polymorphism of the CD14 gene may synergistically increase the risk of gastric cancer [12].

This meta-analysis has some limitations. First, lack of original information of the included publications limited further evaluation of gene-gene and gene-environment relationships. Second, all included studies are retrospective study, which may result in subject selection bias and thereby affecting the reliability of the final results. Third, the inclusion criteria of the cases and controls were not well clearly defined in all the included literatures, which may have influenced the final results.

In summary, our study suggests that the CD14 -159C/T polymorphism might not be associated with gastric cancer risk. Large-scale case-control studies are warranted to investigate the possible gene-gene and gene-environment interrelationships on gastric cancer risk.

Disclosure of conflict of interest

None.

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