

# The relationship between tumor necrosis factor- $\alpha$ polymorphisms and gastric cancer risk: An updated meta-analysis

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**Abstract.** The aim of the present study was to evaluate the relationship between tumor necrosis factor- $\alpha$  (*TNF- $\alpha$* ) and the development of gastric cancer, and to investigate whether it can be used as a biological marker for gastric cancer. In the current study, a new meta-analysis was performed to assess the association between *TNF- $\alpha$*  gene polymorphisms and gastric cancer susceptibility. Subgroup analyses based on ethnicity, control population source and non-cardia cancers were also conducted. Summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. *TNF- $\alpha$*  308 polymorphisms indicated a significant relationship with gastric cancer risk among a normal population [GA/AA vs. GG; 1.17 (1.10-1.23)]. In analysis stratified by ethnicity, *TNF- $\alpha$*  238 displayed an association with gastric cancer risk in eastern populations [GA/AA vs. GG: 1.24 (1.02-1.50)], but not in western populations [GA/AA vs. GG: 0.96 (0.79-1.18)]. The overall ORs (95% CIs) for *TNF- $\alpha$*  857, *TNF- $\alpha$*  1031 and *TNF- $\alpha$*  863 were 1.13 (1.04-1.24), 0.94 (0.85-1.05) and 0.89 (0.78-1.02), respectively, under dominant genetic model comparison. Among the above three SNPs, only *TNF- $\alpha$*  857 was robustly associated with gastric cancer inclination, and

this association remained consistently robust when limited to non-cardia gastric cancers [GA/AA vs. GG: 1.16 (1.03-1.31)]. *TNF- $\alpha$*  308 and *TNF- $\alpha$*  857 genotypes were potential risk factors of statistical significance in gastric cancer, and *TNF- $\alpha$*  238 indicated to be significantly associated with gastric cancer risk only in eastern populations. *TNF- $\alpha$*  1031 and *TNF- $\alpha$*  863 were not significantly associated with gastric cancer risk.

## Introduction

Although the incidence and mortality of gastric cancer have both declined in most areas of the world, gastric cancer is still the fourth most frequent cancer occurred and the second leading cause of cancer related death worldwide, and is especially higher among East Asian countries (1). Thus, identification of possible risk factors is especially essential for the prevention of gastric cancer. It is suggested that gastric cancer is relevance to many factors, including gastric precursor lesions, *Helicobacter pylori* infection and genetic polymorphisms. Among all polymorphisms, the variants of pro- and anti-inflammatory cytokines such as interleukin (2) and tumor necrosis factors (TNFs) (3) were most extensively investigated. *TNF- $\alpha$*  is a cytokine initially taken as a serum factor causing necrosis of transplanted tumors and it serves an important role in host defense against infectious diseases, whereas excessive expression product may lead to organ failure and a strong inflammatory response which may modify gastric cancer risk (4).

Previously, identification of polymorphisms of *TNF- $\alpha$*  gave some suggestions on understanding the genetic predisposition of gastric and colorectal cancers (5). The expression level of *TNF- $\alpha$*  was proved to be obviously affected by polymorphisms in its promoter region, and previous studies have identified that such polymorphisms at 238 (rs361525), 308 (rs1800629), 857 (rs1799724) and 1031 (rs1799964) positions may influence

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production of *TNF- $\alpha$*  (6-9). However, the hypotheses that *TNF- $\alpha$*  polymorphisms may be associated with gastric cancers are still in controversial and the results of previous association studies have been largely inconclusive.

Most of the published studies about *TNF- $\alpha$*  polymorphisms just refer to a small or modest sample size, and none of them were able to get a reliable conclusion. Therefore, the authors conducted a new meta-analysis to review studies that have examined those polymorphisms, to further investigate the relevance between polymorphisms of *TNF- $\alpha$*  and the risk of gastric cancer.

## Materials and methods

**Data sources.** The authors searched for all articles that had been published about the relevance between *TNF- $\alpha$*  polymorphisms and the inclination of gastric cancer, applying the following topics in the MEDLINE, PubMed, EMBASE and the Cochrane library: ['Tumor Necrosis Factor-alpha' (MeSH) OR (Tumor Necrosis) OR TNF] AND ['Polymorphism, Genetic' (MeSH) OR polymorphism OR polymorphisms OR risk] AND (gastric cancer). All articles were updated on July 15, 2013. References of all primary studies and review articles were reviewed for additional references. The search was carried out by two individual researchers to confirm that no published papers were missed.

**Criteria for inclusion and exclusion.** Subjects enrolled in the study must meet the following criteria: i) Case-control studies about the relevance between *TNF- $\alpha$*  polymorphisms and gastric cancer; ii) available genotype frequencies in cases and controls provided; and iii) self-reported results and risk assessment and/or displayed data necessary for evaluating OR with 95% CI. The authors eliminated studies that crossing with other studies or reported with data from the same authors.

**The process of data extraction.** The data was picked up independently by two scientists. Related information of the author's last name, publication year, country of origin, study population origin, genotypes and the number of cases and controls were recorded. The number of studies on *TNF- $\alpha$*  308, *TNF- $\alpha$*  238, *TNF- $\alpha$*  857, *TNF- $\alpha$*  1031, *TNF- $\alpha$*  863 and gastric cancer were 33, 16, 8, 6, 5, respectively. More than half of the studies took frequency-matched controls to cases by age and sex.

**Statistical data analysis.** The authors used the Hardy-Weinberg equilibrium to compare the observed genotype frequencies with expected genotype frequencies in controls of all studies. ORs and 95% CIs were adopted to evaluate the robust relationship between *TNF- $\alpha$*  polymorphisms and inclination of gastric cancer under homozygote comparison and dominant genetic model comparison. Random-effects models were taken to compute overall summary ORs and 95% CIs. Study populations were divided into western (Europe and America) or eastern (China, Korea, India and Iran).

The importance of the overall ORs was assessed by the Z-test, in which two-sided  $P < 0.05$  was considered to indicate a statistically significant difference. The Q-statistic was adopted to evaluate the heterogeneity among studies, and  $P < 0.1$  was considered as a significant gap. The  $I^2$ -statistic

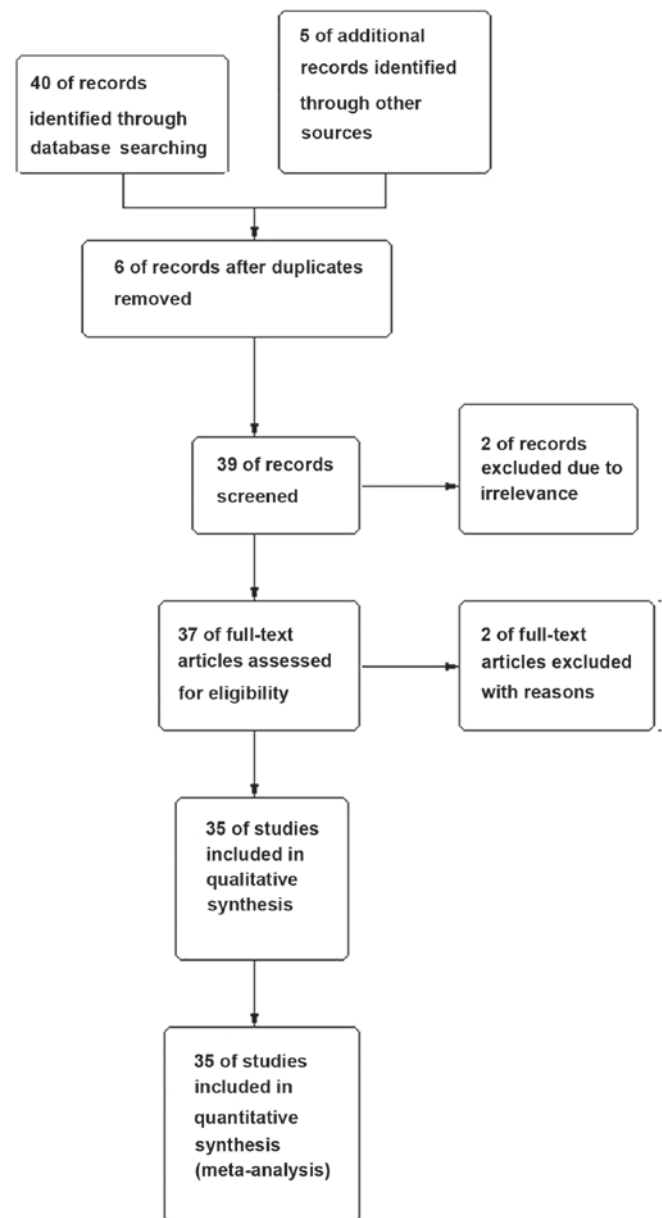


Figure 1. The process of the study selection.

can also be taken to check test heterogeneity efficiently, with  $I^2 < 25%$ , 25-75% and  $> 75%$  considered to display low, moderate and high degree of inconsistency, respectively. Begg's funnel plot was taken to gauging the underlying publication bias (10). As for the sensitivity analysis, relatively smaller studies were rejected and the overall ORs (95% CIs) were checked again. All data analyses were carried out by STATA software (version 12.0; STATA Corporation, College Station, TX, USA).

## Results

**Characteristics of studies.** The authors searched 355 records. Following elimination of duplicated and irrelevant records by checking the titles and abstracts, 35 full-text articles were picked up for intensive study. The process of selection process was shown in (Fig. 1). Each risk of bias item for each included study was shown in (Figs. 2 and 3).

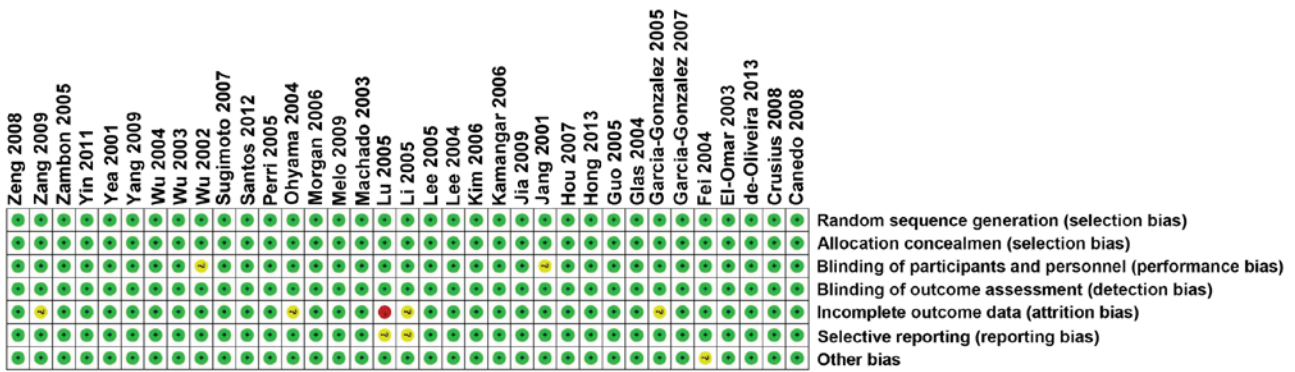


Figure 2. Risk of bias summary. Authors' judgments concerning each risk of bias item for each included study.

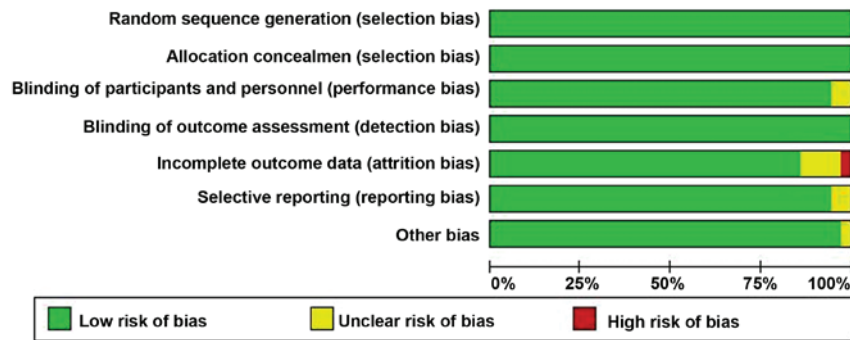


Figure 3. Risk of bias graph. Authors' judgments concerning each risk of bias item presented as percentages across all included studies.

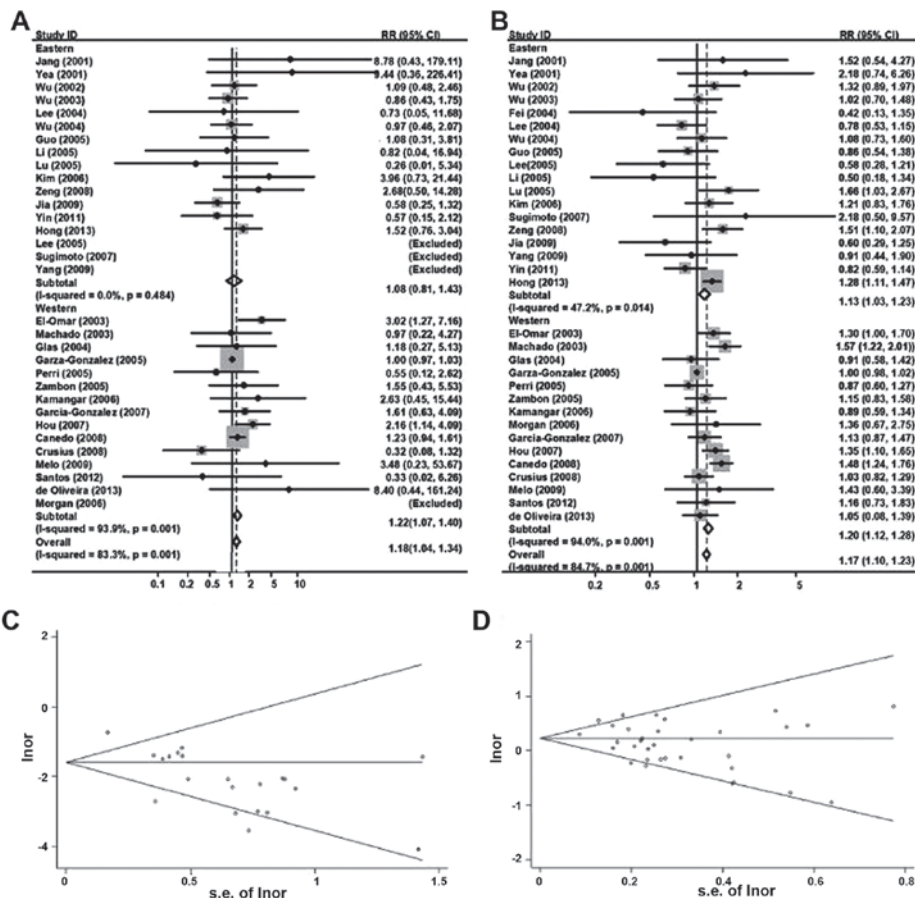


Figure 4. The association between tumor necrosis factor- $\alpha$  308 and gastric cancer. (A) AA vs. GG, Forest plot; (B) AA/GA vs. GG, Forest plot; (C) AA vs. GG, Begg's funnel plots; (D) AA/GA vs. GG, Begg's funnel plots.



Table I. Continued.

First author	Year	Loc.	Control source	Case	Control	308-A (%)	P <sub>HWE</sub>	238-A (%)	P <sub>HWE</sub>	857-T (%)	P <sub>HWE</sub>	1031-C (%)	P <sub>HWE</sub>	863-A (%)	P <sub>HWE</sub>	Refs.
Oliveira	2012	W	PB	200	240	15.21	0.01	-	-	21.04	0.01	-	-	-	-	(34)
Hong	2013	E	HB	1,686	1,894	8.53	0.95	-	-	-	-	-	-	-	-	(21)

Loc., location of the population; E, Eastern country; W, Western country; P<sub>HWE</sub>, P-value of Hardy-Weinberg equilibrium, Chi-square test; 308-A%, percentage of 308-A allele frequency among controls; 238-A%, percentage of 238-A allele frequency among controls; 857-T%, percentage of 857-T allele frequency among controls; 1031-C%, percentage of 1031-C allele frequency among controls; 863-A%, percentage of 863A allele frequency among controls.

A total of 35 studies with 8,147 cases and 12,182 controls were included in this analysis (Fig. 4). The most popular investigated genotypes were *TNF-α 308*, *TNF-α 238*, which were presented in 33 and 16 studies, respectively (11-44). Other genotypes, such as *TNF-α 857*, *TNF-α 863*, and *TNF-α 1031* were also included in this meta-analysis. Genotype and allele distributions of *TNF-α 308* are presented in Table I. Median frequencies of *TNF-α 308A* allele were 13.46% in western populations and 7.20% in eastern populations. Corresponding frequencies for the *TNF-α 238A* allele were 5.52 and 3.92%, respectively. While the frequencies for *TNF-α 857*, *TNF-α 1031*, *TNF-α 863* were 19.64, 20.28, 14.98%, respectively in western populations and 15.90, 20.30, 15.87%, respectively in eastern populations.

*TNF-α 308*. Fig. 4A displayed the random-effect overall OR (95% CIs) of *TNF-α 308* polymorphisms under homozygous genotype comparison [AA vs. GG: 1.18 (1.04-1.34)]. Since the frequencies of AA were too low, AA and AG groups were summed up as 'A carriers' groups for subsequent comparison with GG groups, which did not change the previous conclusion much [GA/AA vs. GG: 1.17 (1.10-1.23); Fig. 4B].

Classified by ethnicity, it reported an obvious relevance between *TNF-α 308* and gastric cancer inclination in eastern populations [AA vs. GG: 1.08 (0.80-1.42); GA/AA vs. GG: 1.13 (1.03-1.23), random-effects model]. A similar association was also identified in western populations (AA vs. GG: 1.22 (1.07-1.40); GA/AA vs. GG: 1.20 (1.12-1.28), random-effects model).

Analysis stratified by control population source (hospital-based, HB or population-based, PB) was also conducted (Table II). There was an obvious association between *TNF-α 308* and gastric cancer inclination in both HB subgroup [GA/AA vs. GG: 1.13 (1.04-1.23)] and PB subgroup [GA/AA vs. GG: 1.19 (1.10-1.28), AA vs. GG: 1.35 (1.11-1.64)]. For non-cardia cancers only, the summary ORs (95% CIs) for GA/AA vs. GG and AA vs. GG were 0.98 (0.86-1.12) and 1.01(0.67-1.54), respectively, which were not statistically significant (Table II). When the analysis was limited to *H. pylori*-positive cases, these ORs (95% CIs) for AA vs. GG and GA/AA vs. GG were 2.07 (0.74-5.79) and 1.27 (1.04-1.55), respectively.

For publication bias investigation, Fig. 4C and D used Begg's funnel plot for the association between *TNF-α 308* and the cancer risk under homozygous and dominant genetic model comparison, and no evidence for bias was identified using Egger's weighted regression method (AA vs. GG, P for bias=0.43; GA/AA vs. GG, P for bias=0.20). To further confirm these reports, the authors carried out the sensitivity analysis. It indicated that there was little modification of the assessment following rejection of any single studies.

*TNF-α 238*. Analyzed by the same procedure as *TNF-α 308* above, Fig. 5A and B summarized the ORs and 95% CIs for the associations between *TNF-α 238* polymorphisms and overall risk of the gastric cancer [AA vs. GG: 1.29 (0.75-2.20); GA/AA vs. GG: 1.10(0.98-1.26), random-effects model].

In the analyses stratified by ethnicity, the ORs (95% CIs) of *TNF-α 238* and gastric cancer risk in eastern populations were 1.96 (0.94-4.07) for AA vs. GG and 1.24 (1.02-1.50) for

Table II. Overall and group-specific summary statistics for *TNF- $\alpha$  308*, *TNF- $\alpha$  238*, *TNF- $\alpha$  857*, *TNF- $\alpha$  1031* and *TNF- $\alpha$  863* in gastric cancer.

Variables	No. of studies	Comparison	Test of association		Test of heterogeneity	
			OR (95% CI)	P-value (Z test)	I <sup>2</sup> (%)	P-value
<i>TNF-<math>\alpha</math> 308</i>						
Hospital based	12	AA vs. GG	1.00 (0.86-1.15)	0.96	22	0.24
	12	GA + AA vs. GG	1.13 (1.04-1.23)	0.01	90	<0.001
Population based	21	AA vs. GG	1.35 (1.11-1.64)	0.02	0	0.50
	21	GA + AA vs. GG	1.19 (1.10-1.28)	<0.001	46	0.10
Non-cardia cancers	9	AA vs. GG	1.14 (0.75-1.72)	0.53	0	0.45
	12	GA + AA vs. GG	0.98 (0.86-1.12)	0.76	8	0.36
<i>H. pylori</i> -positive	4	AA vs. GG	2.07 (0.74-5.79)	0.17	15	0.31
	6	GA + AA vs. GG	1.27 (1.04-1.55)	0.02	28	0.23
<i>TNF-<math>\alpha</math> 238</i>						
Hospital based	6	AA vs. GG	3.35 (1.46-7.67)	0.01	46	0.10
	16	GA + AA vs. GG	0.84 (0.65-1.11)	0.12	3	0.40
Population based	4	AA vs. GG	0.51 (0.22-1.20)	0.12	32	0.22
	11	GA + AA vs. GG	1.22 (1.04-1.43)	0.02	17	0.28
Non-cardia cancers	2	AA vs. GG	3.04 (0.90-10.20)	0.07	67	0.08
	5	GA + AA vs. GG	1.08 (0.80-1.47)	0.61	0	0.68
<i>TNF-<math>\alpha</math> 857</i>						
Hospital based	2	TT vs. CC	1.92 (0.93-3.97)	0.08	58	0.12
	2	TT + TC vs. CC	1.08 (0.88-1.33)	0.46	61	0.11
Population based	6	TT vs. CC	1.71 (1.20-2.43)	<0.001	0	0.45
	6	TT + TC vs. CC	1.15 (1.04-1.27)	0.01	40	0.14
Non-cardia cancers	5	TT vs. CC	2.13 (1.46-3.09)	<0.001	0	0.57
	5	TT + TC vs. CC	1.16 (1.03-1.31)	0.01	51	0.09
<i>TNF-<math>\alpha</math> 1031</i>						
Hospital based	4	CC vs. TT	1.45 (0.92-2.28)	0.11	0	0.73
	4	CC + CT vs. TT	0.85 (0.75-0.97)	0.01	0	0.85
Population based	2	CC vs. TT	1.59 (0.85-2.97)	0.15	73	0.05
	2	CC + CT vs. TT	1.19 (0.99-1.43)	0.06	83	0.85
Non-cardia cancers	4	CC vs. TT	1.39 (0.88-2.19)	0.15	26.50	0.64
	4	CC + CT vs. TT	1.00 (0.88-1.14)	0.99	75	0.01
<i>TNF-<math>\alpha</math> 863</i>						
Hospital based	1	AA vs. CC	2.62 (0.60-11.38)	0.17	0	0.96
	1	AC + AA vs. CC	1.54 (1.10-2.13)	0.14	76	0.04
Population based	4	AA vs. CC	1.35 (0.86-2.13)	0.19	0	0.96
	4	AC + AA vs. CC	0.81 (0.70-0.95)	0.01	0	0.86
Non-cardia cancers	3	AA vs. CC	1.03 (0.55-1.95)	0.93	0	0.79
	3	AC + AA vs. CC	0.97 (0.82-1.15)	0.76	79	0.01

CI, confidence interval; OR, odds ratio; TNF- $\alpha$ , tumor-necrosis factor- $\alpha$ ; *H. pylori*, *Helicobacter pylori*.

GA/AA vs. GG. Corresponding ORs (95% CIs) were 0.69 (0.30-1.60) and 0.98 (0.79-1.18) in western populations.

For GA/AA vs. GG, the overall ORs (95% CIs) of *TNF- $\alpha$  238* and gastric cancer risk was 0.84 (0.65-1.11) in the HB subgroup and 1.22 (1.04-1.43) in the PB subgroup. For AA vs. GG, the HB subgroup demonstrated a more significant association, with a OR (95% CI) of 3.35 (1.46-7.67). For non-cardia cancers, the OR (95% CI) for GA/AA vs. GG genotypes was

1.08 (0.80-1.47). However, AA vs. GG genotypes were rejected for the null values to AA genotype frequency.

To rule out any possible publication bias, Begg's funnel plot were indicated in Fig. 5C and D, and no evidence for bias was detected (AA vs. GG, P for bias=0.93; AA vs. GG, p for bias=0.31). In the subgroup analyses of populations, the results did not alter obviously when the authors rejected the relatively small studies.

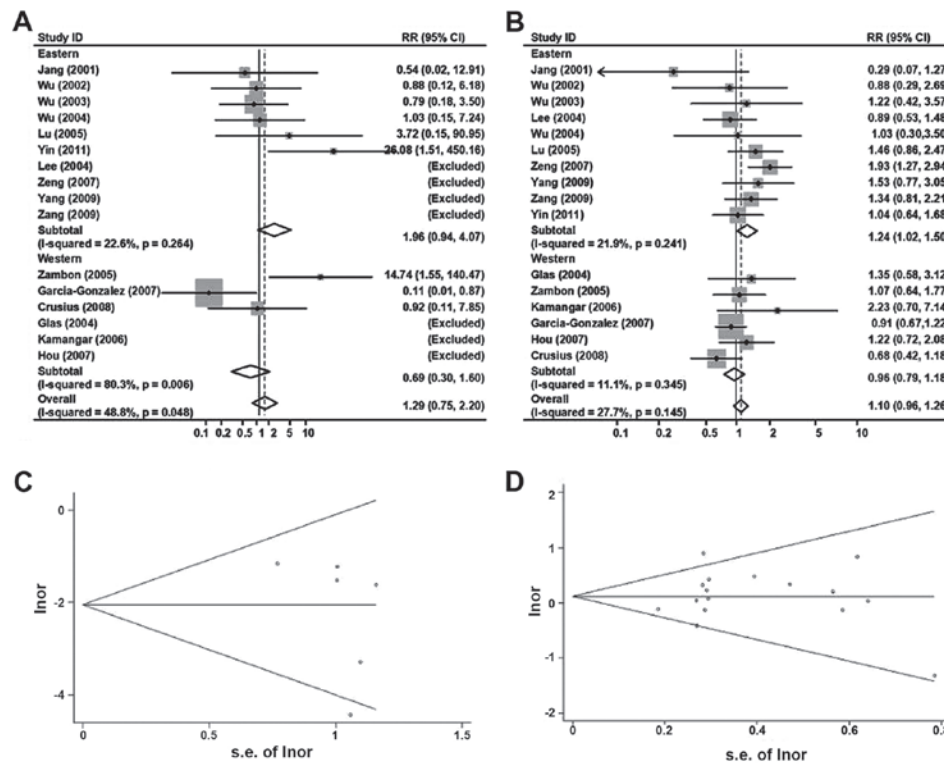


Figure 5. The association between tumor necrosis factor- $\alpha$  238 and gastric cancer. (A) AA vs. GG, Forest plot; (B) AA/GA vs. GG, Forest plot; (C) AA vs. GG, Begg's funnel plots; (D) AA/GA vs. GG, Begg's funnel plots.

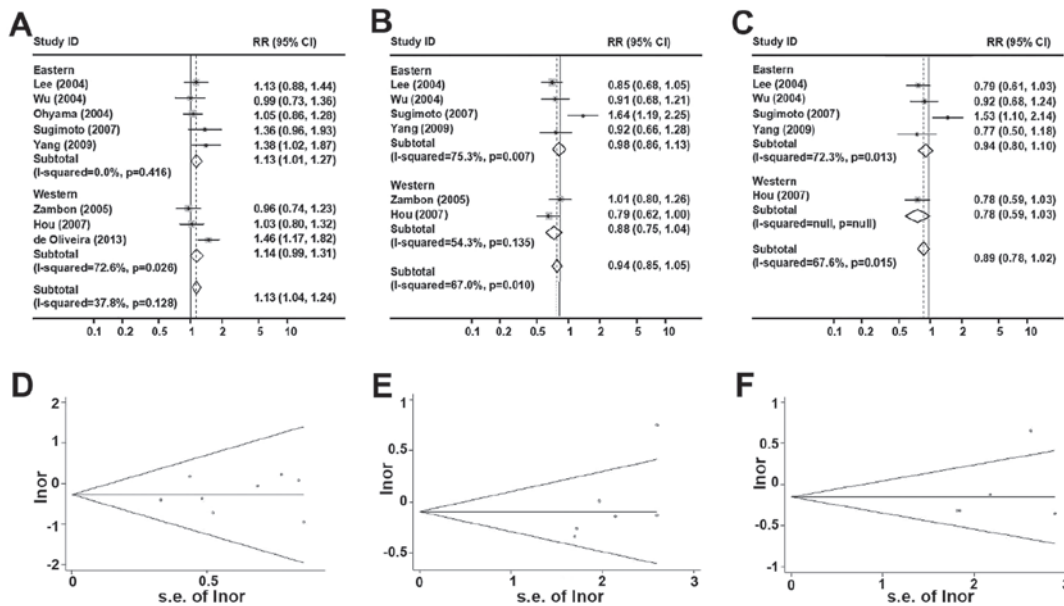


Figure 6. The association between (A and D) tumor necrosis factor- $\alpha$  857, (B and E) 1031, (C and F) 863 and gastric cancer under dominant genetic model comparison. (A-C), Forest plot; (D-F), Begg's funnel plots.

*TNF- $\alpha$  857*, *TNF- $\alpha$  1031* and *TNF- $\alpha$  863*. Fig. 6 summarized the ORs and 95% CIs for the relationships between the genotypes of *TNF- $\alpha$  857* (TC/TT vs. CC; Fig. 3A), *TNF- $\alpha$  1031* (CT/CC vs. TT; Fig. 6B), *TNF- $\alpha$  863* (AC/AA vs. CC; Fig. 6C) and gastric cancer risk. Since the case populations of the included studies were small, especially the homozygous subgroups, only dominant genetic model of these three *TNF- $\alpha$*  polymorphisms was investigated. For overall analysis, the random-effect OR

(95% CI) for *TNF- $\alpha$  857* was 1.13 (1.04-1.24), indicating *TNF- $\alpha$  857* is a potential risk factor of gastric cancer. Similar ORs (95% CIs) were obtained in the analyses stratified by ethnicity and control population source, and also subgroup of non-cardia cancers (Table II).

*TNF- $\alpha$  1031* [CT/CC vs. TT: 0.94 (0.85-1.05)] and *TNF- $\alpha$  863* [AC/AA vs. CC: 0.89 (0.78-1.02)] both seemed to be associated with a reduced risk of gastric cancer, but

neither of them was statistically significant probably due to a small population size. Analyses stratified by ethnicity and control population source were also performed; no inconsistency between different populations was identified in Fig. 6. However, in a population-based subgroup, the OR (95% CI) was 0.81 (0.70-0.95) for the association between *TNF- $\alpha$  863* (AC/AA vs. CC) and gastric cancer risk. (Table II; P=0.007).

Begg's funnel plot for the relationship among these three *TNF- $\alpha$*  polymorphisms and gastric cancer was presented in Figs. 6D-F. For *TNF- $\alpha$  857*, *TNF- $\alpha$  1031*, *TNF- $\alpha$  863*, there were no evidence for bias using the method of Begg (P for bias=0.80, 0.11, 0.42, respectively).

## Discussion

Inflammation is usually considered as a significant factor involving in the pathogenesis of cancer, and the polymorphisms of inflammation related genes have been extensively studied for many years (2). *TNF- $\alpha$*  is the most well-studied inflammatory factor gene in gastric cancers, and it was proved that *TNF- $\alpha$*  related cell functions were greatly affected by the polymorphisms in the promoter region of *TNF- $\alpha$*  gene (3). So far, polymorphisms at 238 (rs361525), 308 (rs1800629), 857 (rs1799724), and 1031 (rs1799964) positions were all reported to be related with risk of cancer (3,45), but all the conclusions are still in controversial and the results of previous relevant studies were ambiguous. Up to now, at least five meta-analyses about the relationships between *TNF- $\alpha$*  polymorphisms and gastric cancer risks have been published, and even those meta-analyses held inconsistent opinions (3,46-48). Furthermore, to the best of the authors' knowledge, no systematic review about all the above five SNPs has been published yet. Thus, this review and a bran-new meta-analysis can display a further proof about the relationship between those polymorphisms and the risk of gastric cancer comprehensively and systematically.

For *TNF- $\alpha$  308*, a total of 33 studies, more than those included in previous meta-analysis (3,49), were included in the present study. Analysis on *TNF- $\alpha$  308* reported a significant relationship between certain genotypes and gastric cancer risk in worldwide populations. A previous meta-analysis summarizing data on *TNF- $\alpha$ -308* variants have suggested some race-specific associations, with increased gastric cancer risk in different ethnic populations (3). The presented results indicated that the median prevalence of *TNF- $\alpha$  308A* allele in western populations was almost twice as high as in eastern populations (13.46 vs. 7.20%) and the OR was also slightly higher in western populations. The PB subgroup demonstrated a much more significant association probably perhaps HB controls may not be representative of the universal population and such studies usually had biases. Together, the results proved that *TNF- $\alpha$  308* 'A carrier' genotypes were potential risk factors of statistical significance in gastric cancers.

For *TNF- $\alpha$  238*, a total of 18 studies was identified to be associated with gastric cancer risks, nearly doubled those of the previous meta-analyses (23,41,45). Consistent with the previous results, *TNF- $\alpha$  238* polymorphisms were not significantly associated with the risk of gastric cancer when pulled all the ORs together. As a relatively large population size was used in current data, stratified analyses could be carried out. Interestingly, *TNF- $\alpha$  238* presented a totally variable effect in

different populations, therefore displaying an obvious relationship with gastric cancer risks in eastern populations, but not western populations. This difference could be explained by the high incidence of *H. pylori* infection among the Asian populations, so that the inflammation related genes such as *TNF- $\alpha$*  may serve a much more important role there. Furthermore, a significant association between *TNF- $\alpha$  238* polymorphisms and gastric cancer risks was just observed in the PB subgroup but not in the HB subgroup, probably because HB controls may not be representative of the general. In addition, the incidence of *H. pylori* infection of the PB and HB subgroups may also be distinctive, which may potentially contribute to the conclusion above. In conclusion, a more detailed investigation with larger numbers of universal participants is required to confirm the relevance between the *TNF- $\alpha$  238* polymorphisms and gastric cancer risks, and confirm the difference between subgroups.

The present study also stated clearly that the T allele of the *TNF- $\alpha$  857* polymorphisms be associated with a higher risk of gastric cancer. The random-effect OR (95% CI) for *TNF- $\alpha$  857* was 1.13 (1.04-1.24) for overall analysis, implying *TNF- $\alpha$  857* T allele is a potential risk factor of gastric cancers. The relevance was also endorsed by a report about increased transcriptional activity of the *TNF- $\alpha$*  gene with the 857 T allele and the pathological role of excessive expressed *TNF- $\alpha$*  (9). Additionally, it is the first time that the relationship between *TNF- $\alpha$  857* polymorphisms and gastric cancer risks was reviewed by a meta-analysis.

In the present meta-analysis, not enough evidence was promulgated to authenticate the existing association between *TNF- $\alpha$  1031*, *TNF- $\alpha$  863* polymorphisms and gastric cancer risks. However, both of the SNPs were suggested to be related with a reduced risk of gastric cancer, according to the ORs and 95% CIs. The association between *TNF- $\alpha$  1031*, *TNF- $\alpha$  863* and gastric cancers was of approximate significance, so more studies are required. Additionally, it is to be remarked that in population-based subgroup, the OR (95% CI) for *TNF- $\alpha$  863* becomes statistically significant, which supports the above suggestions from another side.

*H. pylori* infection is a key risk factor of gastric cancer. *H. pylori* strains and host genotypes possibly affected the host inflammatory response and epithelial-cell physiology, thus aggravated the risk of gastric cancer (50). Zambon *et al* (43) reported that *H. pylori* infection was associated with the *TNF- $\alpha$  308* genotype. The current study demonstrated that the *TNF- $\alpha$  308* polymorphisms had much more effect on the risk of catching gastric cancer in the populations with *H. pylori* infection, which indicated the existence of interaction between *H. pylori* infection and *TNF- $\alpha$*  pathway in gastric carcinogenesis. However, for *TNF- $\alpha$  238* and other SNPs, studies with detailed *H. pylori* infection status information were so limited that data could not be stratified according to *H. pylori* infection status.

Some limitations of this meta-analysis should also be taken into account. Firstly, the sample size was too small to conduct stratified analyses, which weakened the conclusions, especially in the analyses of *TNF- $\alpha$  857*, *TNF- $\alpha$  1031* and *TNF- $\alpha$  863*. More studies need to be picked up to achieve a much more credible conclusion. Secondly, detailed information was lacking in this meta-analysis, for which many analyses, for example analyses stratified by histology and sex, could not be carried

out. Also, gene-gene, gene-phenotype and gene-environment interactions should also be checked in further studies provided that individual raw data were available.

Based on these analyses collectively, this systematic review had collected all the available data related with the TNF- $\alpha$  polymorphisms and gastric cancer, and this meta-analysis indicated that *TNF- $\alpha$  308*, *TNF- $\alpha$  238* and *TNF- $\alpha$  857* were moderately associated with an increased risk of gastric cancer. However, the association between *TNF- $\alpha$  1031*, *TNF- $\alpha$  863* polymorphisms and gastric cancer risk was of similar significance. To understand the molecular carcinogenesis panorama of gastric cancer, further prospective studies in combination with analysis of other cytokines and environmental factors are required.

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