A meta-analysis of tumor necrosis factor-α-308 G>A polymorphism in gastric cancer

Xin Jiang¹, Niyaz Ahmad Naikoo²*, Shuowei Gao³

Abstract

Background: Gastric cancer (GC) is the common cause of cancer-related deaths worldwide and inflammation represents the early phases in the GC.

Objective: To review the tumor necrosis factor (TNF-α)-308 G>A (GG, GA, and AA) in GC by meta-analysis studies for any differences in TNF-α-308 G>A gene polymorphisms.

Methods: Case–control studies published from 2003 to 2017 were identified by searching PubMed, EMASE, and the Internet with the English language. The analysis published on TNF-α-308 G>A polymorphism was analyzed and a limited number of articles were included in the present study. TNF-α-308 G>A from 4,157 patients and 5,185 healthy controls was evaluated. Studies were evaluated using Cochrane Q-test and publication bias was evaluated by constructing funnel plots.

Results: Overall, TNF-α-308 GA genotype showed significant association \[ P < 0.0001, \text{ odds ratio (OR), 95\% confidence interval (CI)} = 0.82 (0.74–0.91) \]. However, meta-analysis of TNF-α-308 genotypes (GG, GA, AA, and GA + AA) between GC patients and controls showed nonsignificant association with GC \[ P > 0.05, \text{ recessive model: OR} = 1.38, 95\% CI: 1.15–1.66; \text{ dominant model: OR} = 1.23, 95\% CI: 1.09–1.39; (G/A) vs. (G/G): OR = 1.15, 95\% CI: 1.02–1.28; (A/A) vs. (G/G): OR = 1.44, 95\% CI: 1.19–1.73 \]. Analysis stratified by ethnicity showed same results in Asian and Caucasian populations.

Conclusions: Results revealed nonsignificant association of TNF-α-308 genotypes (GG, GA, AA, and GA + AA) and GC. TNF-α-308GA genotype showed significant association whereas homozygous genotype AA did not show association with GC risk.

Keywords: gastric cancer; meta-analysis; TNF-α-308

Gastric cancer (GC) is commonly diagnosed with malignancies and remained a considerable health problem [1]. Tumor necrosis factor-alpha (TNF-α) produced by macrophages is a cytokine playing a pivotal role in the pathogenesis of malignant diseases [2]. TNF-α is a pro-inflammatory cytokine involved in the growth, differentiation, and survival of many cells. TNF-α is also playing an important role in the pathogenesis of cancer [3]. Studies have shown that TNF-α promoter polymorphism-308 (rs1800629) may regulate TNF-α production [4]. TNF-α-308 has been confirmed as a risk factor...
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Figure 1. Flow chart of studies identification and inclusion. A. Forest plot of gastric cancer (GC) risk with the TNF-α-308 G>A genotype (overall). A random-effects model was used for calculation. B. Forest plot of GC risk with the TNF-α-308 GA genotype (overal). A fixed-effects model was used for calculation. C. Forest plot of GC risk with the TNF-α-308 AA genotype (overal). A random-effects model was used for calculation.
Results

Study characteristics

Twelve studies were analyzed in which 12 sets of data were compared with distributions of TNF-\(\alpha\)-308 genotypes in patients and healthy controls.

Analysis using Fischer’s exact test revealed that TNF-\(\alpha\)-308 GA genotype was significantly prevalent in GC cases compared with healthy controls \([P < 0.0001, \text{OR (95\% CI)} = 0.82 (0.74–0.91)]\), and homozygous genotype AA did not show association with GC risk \([P = 0.49, \text{OR (95\% CI)} = 0.62 (0.44–0.86)]\), as shown in Table 1, thus indicating possible association of TNF-\(\alpha\)-308 GA with the GC susceptibility. However, a meta-analysis of TNF-\(\alpha\)-308 genotypes in GC cases and healthy controls revealed nonsignificant association, hence we evaluated 54 articles; after the screening of titles, abstracts and analysis of articles, 12 eligible studies were screened for meta-analysis, including 4,852 GC patients and 5,197 controls. Characteristics of studies and other relevant data, such as genotype frequency in cases and controls, are shown in Table 2. Q-test and I\(^2\) statistics showed heterogeneity in the included studies, and therefore a random-effects model was employed for genotype comparison; however, nonsignificant heterogeneity was observed in TNF-\(\alpha\)-308 AA genotype and therefore fixed-effects model was employed for genotype comparison among cases and controls (Table 3).

### Table 1. Distribution of TNF-\(\alpha\)-308 G>A (rs1800629) genotypes in GC patients and healthy controls

| TNF-\(\alpha\)-308 G>A (rs1800629) Genotypes | GC   | Healthy controls | OR (95\% CI) | \(P\) |
|------------------------------------------|------|-----------------|--------------|------|
| GG                                      | 3,200| 4,300           | Reference    | –    |
| GA                                      | 891  | 806             | 0.82 (0.74–0.91) | <0.0001 |
| AA                                      | 66   | 79              | 0.62 (0.44–0.86) | 0.49 |

GG, homozygous wild; GA, heterozygous; AA, homozygous variant; TNF-\(\alpha\), tumor necrosis factor-alpha; GC, gastric cancer; OR, odds ratio; CI, confidence interval.

### Table 2. Main characteristics of studies selected for meta-analysis and distribution of TNF-\(\alpha\)-308 G>A (rs1800629) polymorphism in cases and healthy controls

| First author (year)       | Ethnicity/country | Case | Healthy control |
|---------------------------|-------------------|------|-----------------|
| Li-Chuan Du et al. (2017) | China             | 204  | 326             |
| Paulo Canedo et al. (2008)| Portugal          | 330  | 544             |
| Wu et al. (2002)          | USA               | 144  | 214             |
| Liping Jiang et al. (2017)| China             | 207  | 411             |
| Yan Hong et al. (2013)    | China             | 1335 | 1585            |
| David Stubljar et al. (2014)| Slovenia     | 63   | 83              |
| Amar C Bhayal et al. (2013)| India           | 32   | 76              |
| Garcia-Gonzalez et al. (2007)| Spain     | 309  | 320             |
| Sugimoto et al. (2007)    | Japan             | 101  | 169             |
| Wanli Lu et al. (2005)    | China             | 214  | 274             |
| Carlos Machado et al. (2003)| Portugal   | 179  | 231             |
| Seilanian Toosi M et al. (2007)| Iran     | 82   | 67              |

*(GA + AA).*

### TNF-\(\alpha\)-308 GG distribution

The TNF-\(\alpha\)-308 GG genotype distribution in patients and controls was 3,200/4,300. Significant heterogeneity among studies with \(Q = 222.03, I^2 = 95.04\%\), and \(P = 0.00\) is indicated...
in Table 3. Meta-analysis by random-effects model indicated nonsignificant results with pooled OR = 1.65 (0.98–2.76), $Z = 1.9$, and $P = 0.056$ as shown in Figure 1A.

**TNF-α-308 GA distribution**

TNF-α-308 GA genotype distribution in patients and controls was 891/806 and significant heterogeneity with $Q = 109.14$, $I^2 = 90.83\%$, and $P = 0.00$ (Table 3). Meta-analysis of the TNF-α-308 GA genotype did not show significant results with pooled OR = 0.74 (0.48–1.15), $Z = –1.30$, and $P = 0.19$ using random-effects model as indicated in the forest plot in Figure 1B.

**TNF-α-308 AA distribution**

TNF-α-308 AA genotype distribution in patients and controls was 66/79. Nonsignificant heterogeneity with $Q = 9.39$, $I^2 = 4.23\%$, and $P = 0.40$ is shown in Table 3. The meta-analysis overall showed nonsignificant results with pooled OR = 1.01 (0.71–1.43), $Z = 0.57$, and $P = 0.95$ by fixed-effects model.

**TNF-α-308 GA + AA distribution**

TNF-α-308 GA + AA genotype distribution in patients and controls was 1,135/1,054. Significant heterogeneity with $Q = 100.59$, $I^2 = 89.06\%$, and $P = 0.00$ is shown in Table 3. Meta-analysis showed nonsignificant results with pooled OR = 0.73 (0.51–1.04), $Z = –1.73$, and $P = 0.082$ by random-effects model.

**Publication bias**

Begg’s funnel plot and Egger’s test were used to assess publication bias and results did not indicate evidence of publication bias for TNF-α-308 polymorphisms in cases and controls [(TNF-α-308 GG Begg’s test, $P = 0.84$; Egger’s test, $P = 0.39$), (TNF-α-308 GA Begg’s test, $P = 1.0$; Egger’s test, $P = 0.95$), (TNF-α-308 AA Begg’s test, $P = 0.60$; Egger’s test, $P = 0.56$), and (TNF-α-308 GA Begg’s test, $P = 1.0$; Egger’s test, $P = 0.95$)] as shown in Figure 2.

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### Table 3. Statistics to test publication bias and heterogeneity in the meta-analysis

| No. of studies | Genotype (case/control) | Egger’s regression analysis | Effect size and 95% CI | Heterogeneity analysis |
|----------------|-------------------------|-----------------------------|------------------------|-------------------------|
|                |                         | Intercept | $P$  | RE-OR | 95% CI | $Z$  | $P$  | $Q$-Statistic | $P$ (heterogeneity) | $I^2$ (%) |
| 12             | GG (3,200/4,300)        | 0.508     | 0.39 | 1.65  | (0.98–2.76) | 1.90  | 0.056 | 222.03        | 0.00                     | 95.04     |
| 11             | GA (891/806)            | -0.291    | 0.95 | 0.74  | (0.48–1.15) | -1.30 | 0.19  | 109.14        | 0.00                     | 90.83     |
| 10             | AA* (66/79)             | 0.009     | 0.56 | 1.01  | (0.71–1.43) | 0.57  | 0.95  | 9.39          | 0.40                     | 4.23      |
| 12             | GG + GA (1,135/1,054)   | -0.308    | 0.95 | 0.73  | (0.51–1.04) | -1.73 | 0.082 | 100.59        | 0.00                     | 89.06     |

Chi-square Q-statistic for homogeneity in random-effects model.
*Fixed-effects model.
† $P$ for the Q-statistic in random-effects model.
‡ Higgins $I^2$ statistic for heterogeneity in random-effects model.
CI, confidence interval; RE, random effect; OR, odds ratio.
Discussion

Inflammation is considered as one of the key factors involving in the pathogenesis of cancer, and TNF-α is believed to be one of the most crucial inflammatory cytokines. TNF-α G>A is produced by macrophages, neutrophils, fibroblasts, T-cells, B-cells, and tumor cells, and it has been reported to play an important role in the pathogenesis of cancer [3, 15]. The transcription of TNF-α is regulated under genetic control. Studies have indicated that promoter polymorphisms at rs361525, rs1800629, rs1799724, and rs1799964 may regulate TNF-α production and it was reported that expression level of TNF-α was proved to be affected by polymorphisms in the promoter region of TNF [4, 16, 17]. Results of meta-analysis showed an overall nonsignificant association of TNF-α-308 GG, GA, AA, and GA + AA genotypes with GC. The discrepancy in results could be identified in sample size, ethnicity, or etiological factors that contribute to the heterogeneity.

Several meta-analyses on TNF-α-308 G>A polymorphism showed an association of TNF-α-308 G>A genotypes with GC risk [18, 19]. Overall results on TNF-α-308 G>A genotypes did not show the association between AA genotype and GC risk using GG as the reference genotype yielded statistically significant risk of GC with TNF-α-308 GA genotype. However, the meta-analysis was conducted using fixed- and random-effects models; none of the TNF-α-308 G>A genotypes showed significant association with GC. Earlier studies suggested that frequencies of genetic markers often show high variations among various ethnic and racial groups whereas differences in genetic effects in terms of ORs are much less common [20]. Heterogeneity between studies was high for TNF-α-308 genotypes and low for TNF-α-308 AA genotype, as indicated by the $I^2$ value of >80. Studies were subjected to publication bias using funnel plots and Egger’s weighted regression and rank correlation method [21], and no publication bias was detected in studies. The summary ORs for GG, GA, AA, and GA + AA genotypes remained close to null and were nonsignificant. However, the hypothesis that TNF-α genotypes may be associated with GC is still unclear and the results of earlier association studies have largely been inconsistent. The present study supports the fact that TNF-α-308 G>A genotypes have no role in early diagnosis and treatment of gastric inflammation. Since TNF-α-308 genotypes do not have a role in GC predisposition, TNF-α-308 G>A genotypes make nonsignificant contribution to prevent the occurrence of GC.

To understand the carcinogenesis of GC, prospective studies in combination with the analysis of other cytokines are required. Earlier identification of TNF-α polymorphisms yielded some suggestions on understanding the genetic predisposition of gastric and colorectal cancers [22].

Taken together, meta-analysis data do not support the association between TNF-α-308 genotypes (GG, GA, AA, and GA + AA) and GC predisposition. However, additional case–control studies in different populations are still needed.

Author contributions. All the authors contributed substantially to the study conception and design, acquisition of data, and its analysis. XJ and NN drafted the manuscript. SG contributed substantially to its critical revision. All the authors approved the final version submitted for publication and take responsibility for the statements made in the published article.

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Conflict of interest statement. The authors have completed and submitted the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

Data sharing statement. No data sets were generated or analyzed during the present study. The present review is based on the references cited.

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