Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis

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Inflammation is one of the early phases in the development of gastric cancer. Therefore, several studies have examined the association of polymorphisms in tumour-necrosis factor-A gene (TNF-A) with gastric cancer risk. This meta-analysis reviews and summarises published evidence for these associations. Searching several databases yielded 24 independent studies that reported on the associations between TNF-A polymorphisms and gastric cancer risk. We analysed available data for the most commonly investigated polymorphisms: TNF-A –308G>A (23 studies), TNF-A –238G>A (9 studies), and TNF-A –857C>T (5 studies). Summary odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated in the random-effects model using the DerSimonian–Laird method. Q-statistic and I2-statistic were calculated to examine heterogeneity, and funnel plots were plotted to examine small study effects. The overall ORs (95% CIs) for AG and AA genotypes vs GG genotype for TNF-A –308 were 1.09 (0.94–1.27) and 1.49 (1.11–1.99), respectively. For TNF-A –238, the corresponding ORs (95% CIs) were 1.05 (0.84–1.33) and 1.25 (0.30–5.26), respectively. The overall ORs (95% CIs) for CT and TT genotypes vs CC for TNF-A –857 were 1.06 (0.89–1.27) and 1.57 (0.91–2.70), respectively. The statistically significant association between TNF-A –308GG and gastric cancer was limited to western populations. This association showed little heterogeneity (I2 = 0) and remained consistently strong when analyses were limited to anatomie and histologic subtypes of gastric cancer; or limited to studies in which genotype frequencies were in Hardy–Weinberg equilibrium, or limited to larger studies. These same subgroup analyses did not change results associated with other polymorphisms. In conclusion, TNF-A –308AA genotype was associated with a statistically significant increased risk of gastric cancer, whereas other studied polymorphisms were not. The association between TNF-A –857TT genotype and gastric cancer was near significant, and may become significant if more studies are published.

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the purpose of this meta-analysis is to review studies that have examined these polymorphisms. Where possible, we examine these associations by anatomical or histological subtypes of gastric cancer, and by Helicobacter pylori positivity.

METHODS
Selection of studies
We conducted a comprehensive search by examining several databases for all papers that had been published on the association between TNF-A polymorphisms and gastric cancer risk. All results were updated on 15 October 2007. The following terms were used in PubMed Databases search: ('Interleukins' [MeSH] OR 'Tumor Necrosis Factor-alpha' [MeSH] OR 'Tumor Necrosis') OR TNF AND ('Stomach Neoplasms' [MeSH] OR (gastric cancer) OR (stomach cancer)) AND ('Polymorphism, Generic' [MeSH] OR polymorphism OR polymorphisms). The following terms were used in ISI Database search: (TS = (Interleukins) OR TS = (Tumor Necrosis Factor-alpha) OR TS = (Tumor Necrosis) OR TS = (TNF)) AND (TS = (Stomach Neoplasms) OR TS = (gastric cancer) OR TS = (stomach cancer)) AND (TS = (Polymorphism, Generic) OR TS = (polymorphisms)). Other databases and search terms were MedCarib, LILACS, IMEMR, IndMed, and PAHO databases, searched for (gastric OR stomach) AND (cancer OR carcinoma OR neoplasms); IMSEAR database, searched for combinations of gastric or stomach with cancer or carcinoma or neoplasms; and J- EAST database, searched for combinations of gastric or stomach with cancer or carcinoma or neoplasms plus polymorphism. In addition, references of cited articles were reviewed. Two of the authors reviewed results of each of the database searches to make sure that published papers are not missed. In addition, where overall data were missing, we contacted the authors for further information.

Using these approaches, reports on TNF-A polymorphisms in relation to gastric cancer was found in a total of 29 articles (Jang et al., 2001; Wu et al., 2002, 2003, 2004; El Omar et al., 2003; Garza-Gonzalez et al., 2003, 2005; Machado et al., 2003; Fei et al., 2004; Glas et al., 2004; Lee et al., 2004, 2005; Ohyama et al., 2004; Torres et al., 2004; Guo et al., 2005; Li et al., 2005; Lu et al., 2005; Perri et al., 2005; Rocha et al., 2005; Zambon et al., 2005; Kamangar et al., 2006a; Kim et al., 2006; Morgan et al., 2006; Shirai et al., 2006; Deans et al., 2007; Garcia-Gonzalez et al., 2007; Hou et al., 2007; Seno et al., 2007; Sugimoto et al., 2007). Three studies (Garza-Gonzalez et al., 2003; Wu et al., 2003; Shirai et al., 2006) were excluded from the analyses because their results were reported in other studies (Ohyama et al., 2004; Wu et al., 2004; Garza-Gonzalez et al., 2005). One more study was excluded because the results had been reported for a combination of oesophageal and gastric cancers (Deans et al., 2007). Another study (Seno et al., 2007) was excluded because genotype frequencies were not reported. Therefore, a total of 24 studies were used for calculating summary statistics.

Data extraction and statistical analysis
For TNF-A –308 (rs1800629) and TNF-A –238 (rs361525), numbers and percentages of GG, GA, and AA genotypes, and for TNF-A –857 (rs1799724), numbers and frequencies of CC, CT, and TT genotypes were extracted by case status. For GG and GA vs GG genotypes (TNF-A –308 and –238) and for TT and TC vs CC genotypes (TNF-A –857), odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. We performed similar calculations for AA vs a combination of GA and GG genotypes (TNF-A –308 and –238), and for TT vs a combination of TC and CC genotypes (TNF-A –857) to examine the applicability of recessive models. Likewise, we did similar analyses for a combination of AA and GA vs GG genotypes (TNF-A –308 and –238) and for combination of TT and TC vs CC genotypes (TNF-A –857) to examine whether dominant models apply. We used both random-effects models (DerSimonian – Laird method) and fixed-effects models (Mantel – Haenszel method) to calculate overall summary ORs and 95% CIs. Because these two methods yielded similar results, we chose only random-effects models (Moayyedi, 2004) to present forest plots, and all other analyses described from here onwards.

Some of the published studies found associations only with certain anatomical subtypes (ie, noncardia) or histological subtypes (ie, intestinal type) of gastric cancer. Therefore, we calculated summary ORs and 95% CIs for noncardia cancer, where data were presented by anatomical location, and for intestinal-type cancer, where data on histology were available. We examined the association between TNF-A –308 and gastric cancer in studies that reported this association among H. pylori-positive subjects. It has been suggested that proinflammatory polymorphisms in interleukins may be associated with higher risk of gastric cancer in western countries, but not in East Asian countries. Therefore, study populations were classified as western (Europe and Americas) vs East Asian (China, Korea, Taiwan, and Japan), and subgroup analyses were performed for each group. In all, 12 studies were from western and 12 studies were from East Asian countries.

We examined the effect of Hardy–Weinberg equilibrium (HWE) on the results of our meta-analysis by calculating summary ORs and 95% CIs for studies in which these alleles were in HWE among controls. The strategy was to exclude studies in which genotypes violated HWE at at .05. We plotted Begg’s funnel plot to examine small study effects (Sterne et al., 2001). We also used the method of Begg and Mazumdar (1994) to calculate P for rank correlation and Egger’s weighted regression method (Egger et al., 1997) to calculate P for bias. For sensitivity analysis, we excluded smaller studies and recalculated the summary ORs (95% CIs) using only larger studies.

To examine result heterogeneity among studies, the I2-statistic for homogeneity (using Mantel–Haenszel weights) and the P2-statistic (Higgins et al., 2003) were calculated. All analyses were done using STATA software, version 9.2 (STATA Corporation, College Station, TX, USA). Throughout the paper, two-sided P-values <0.05 were considered as statistically significant.

RESULTS
Twenty-four studies with a total number of 4399 cases and 6855 controls were included in this analysis (Table 1). The most commonly investigated genotypes were TNF-A –308, –238, and –857, which were reported in 23, 9, and 5 studies, respectively. Since other genotypes, such as TNF-A –1031, were investigated in a very small number of studies, only data on the above mentioned three genotypes were analysed. Most studies used healthy volunteers or blood donors as control subjects. The frequency of TNF-A –308A and TNF-A –238A alleles ranged from 0.9 to 16.2% and from 1.2 to 10.3%, respectively. The frequency of TNF-A –857T allele ranged from 14.3 to 19.6%. Median frequencies of TNF-A –857T allele were 15.0% in western populations and from 1.2 to 10.3%, respectively. The frequency of TNF-A –857T allele was 19.6 and 15.0%, respectively.

TNF-A –308
Study-specific and summary ORs (95% CIs) are shown in Figure 1A. For all gastric cancers, the random-effect overall ORs (95% CIs) associated with heterozygous (GA vs GG) and homozygous (AA vs GG) proinflammatory genotypes were 1.09
Table 1  Study characteristics

| First author | Study location | Year | Number of cases/controls | Source of control selection | % 308A allele frequency | % 238A allele frequency | % 857T allele frequency | P, HWE – 308 | P, HWE – 238 | P, HWE – 857 |
|--------------|----------------|------|--------------------------|-----------------------------|-------------------------|-------------------------|-------------------------|-------------|-------------|-------------|
| Jang         | Korea (E)      | 2001 | 52/92                    | Healthy volunteers          | 3.8                     | 7.1                     | —                       | 0.70        | 0.39        | —           |
| Wu           | Taiwan (E)     | 2002 | 150/220                  | Healthy volunteers          | 12.0                    | 1.8                     | —                       | <0.01       | <0.01       | —           |
| El-Omar      | USA (W)        | 2003 | 314/210                  | Population based            | 15.2                    | —                       | —                       | 0.55        | —           | —           |
| Machado      | Portugal (W)   | 2003 | 287/304                  | Healthy volunteers          | 12.7                    | —                       | —                       | 0.65        | —           | —           |
| Fei          | China (E)      | 2004 | 56/164                   | Healthy volunteers          | 6.7                     | —                       | —                       | 0.12        | —           | —           |
| Glas         | Germany (W)    | 2004 | 88/145                   | Healthy volunteers          | 15.2                    | 3.8                     | —                       | 0.67        | 0.63        | —           |
| Lee SG       | Korea (E)      | 2004 | 341/261                  | Healthy volunteers          | 8.4                     | 4.8                     | 15.9                    | 0.49        | 0.42        | 0.85        |
| Torres       | Colombia (W)   | 2004 | 44/66                    | Clinic based                | 7.6                     | —                       | —                       | 0.51        | —           | —           |
| Wu           | Taiwan (E)     | 2004 | 204/210                  | Healthy volunteers          | 12.4                    | 1.7                     | 14.3                    | <0.01       | <0.01       | 0.20        |
| Ohayama      | Japan (E)      | 2004 | 300/472                  | Clinic based                | —                       | —                       | 18.6                    | —           | —           | 0.90        |
| Garza-Gonzalez | Mexico (W)    | 2005 | 63/215                   | Clinic based                | 8.6                     | —                       | —                       | 0.61        | —           | —           |
| Guo          | China (E)      | 2005 | 264/437                  | Healthy volunteers          | 5.9                     | —                       | —                       | <0.01       | —           | —           |
| Lee JY       | Korea (E)      | 2005 | 122/120                  | Healthy volunteers          | 7.1                     | —                       | —                       | 0.40        | —           | —           |
| Li           | China (E)      | 2005 | 59/264                   | Healthy volunteers          | 7.2                     | —                       | —                       | 0.56        | —           | —           |
| Lu           | China (E)      | 2005 | 250/300                  | Population based            | 4.7                     | 3.8                     | —                       | 0.08        | 0.49        | —           |
| Perri        | Italy (W)      | 2005 | 184/362                  | Healthy volunteers          | 10.9                    | —                       | —                       | 0.15        | —           | —           |
| Rocha        | Brazil (W)     | 2005 | 161/535                  | Healthy volunteers          | 13.9                    | —                       | —                       | 0.34        | —           | —           |
| Zambon       | Italy (W)      | 2005 | 129/644                  | Clinic based                | 12.3                    | 5.9                     | 19.6                    | 0.90        | 0.38        | <0.01       |
| Kamangar     | Finland (W)    | 2006 | 112/208                  | Healthy cohort subjects    | 13.5                    | 1.2                     | —                       | 0.29        | 0.86        | —           |
| Kim          | Korea (E)      | 2006 | 237/461                  | Healthy volunteers          | 6.8                     | —                       | —                       | 0.91        | —           | —           |
| Morgan       | Honduras (W)   | 2006 | 168/161                  | Population based            | 3.7                     | —                       | —                       | 0.62        | —           | —           |
| Hou          | Poland (W)     | 2007 | 305/427                  | Population based            | 16.2                    | —                       | —                       | 0.19        | —           | —           |
| Sugimoto     | Japan (E)      | 2007 | 105/172                  | Clinic based                | 0.9                     | —                       | 15.7                    | 0.91        | —           | 0.11        |
| Garcia-Gonzalez | Spain (W)    | 2007 | 404/404                  | Healthy volunteers          | 11.3                    | 10.3                    | —                       | 0.35        | 0.01        | —           |

E = East Asian country; HWE = Hardy–Weinberg equilibrium; TNF-A = tumour-necrosis factor-A; W = western country. Year: Publication year. % 308A allele frequency among controls. % 238A allele frequency among controls. % 857T allele frequency among controls. P-value for HWE for TNF-A – 308 polymorphism among controls. P-value for HWE for TNF-A – 238 polymorphism among controls. P-value for HWE for TNF-A – 857 polymorphism among controls.
 associations. For example, only 6 out of the 23 studies reported their ORs and 95% CIs. Only a fraction of studies presented data on GA vs GG on the test power. Therefore, the results are reported separately for genotype was much more frequent than GA and AA genotypes, \(P = 0.02\) and \(I^2 = 34\%) showed a moderate variation for GA vs GG genotypes. For AA vs GG genotypes, the Q-statistic was not significant \((P = 0.74) and \(I^2 = 0.74\) was equal to zero. Subgroup analyses showed similar patterns as overall analyses. While for most subgroup analyses, the \(P\)-value for GA vs GG genotypes was significant or remained close to significance level and \(I^2 = 0.74\) showed moderate heterogeneity among studies, \(P\) for heterogeneity was not significant for AA vs GG genotypes (Table 2).

**TNF-A –238**

Figure 2A summarises the ORs and 95% CIs for the associations between TNF-A –238A carrying genotypes and gastric cancer risk. For all gastric cancers, the random-effect overall ORs (95% CIs) were 1.05 (0.84 – 1.33) for GA vs GG genotypes and 1.25 (0.30 – 5.26)
Table 2  Overall and group-specific summary statistics for TNF-A –308, TNF-A –238, and TNF-A –857 and gastric cancer

| Number of studies | Polymorphisms | Q-statistic | P-value | I² (%) | Random-effect OR (95% CI) | Fixed-effect OR (95% CI) |
|-------------------|---------------|-------------|---------|--------|--------------------------|-------------------------|
| **TNF-A –308 (4099/6383)**<sup>a</sup> |               |             |         |        |                          |                         |
| All gastric cancers | 23            | GA vs GG    | 36.43   | 0.03   | 40           | 1.09 (0.94–1.27)         | 1.14 (1.02–1.27)        |
| 19**              | AA vs GG      | 13.77       | 0.04   | 58     | 1.17 (0.85–1.59)        | 1.23 (1.02–1.49)        |
| Noncardia cancers  | 6             | GA vs GG    | 11.80   | 0.04   | 57           | 0.98 (0.68–1.40)         | 1.03 (0.83–1.29)        |
| Intestinal-type cancers | 6     | AA vs GG    | 4.08    | 0.44   | 0           | 2.17 (1.17–4.03)         | 2.00 (1.11–3.61)        |
| Helicobacter pylori-positive subjects | 3     | GA vs GG    | 4.03    | 0.13   | 50           | 0.66 (0.33–1.30)         | 0.77 (0.51–1.15)        |
| Western populations | 12            | GA vs GG    | 18.37   | 0.07   | 44           | 1.14 (0.95–1.37)         | 1.19 (1.04–1.36)        |
| East Asian population | 10            | AA vs GG    | 6.53    | 0.06   | 0           | 1.74 (1.21–2.51)         | 1.76 (1.24–2.50)        |
| Studies in HWE    | 20            | GA vs GG    | 33.83   | 0.02   | 48           | 1.08 (0.91–1.28)         | 1.14 (1.01–1.28)        |
| **TNF-A –238 (1730/2484)**<sup>a</sup> |               |             |         |        |                          |                         |
| All gastric cancers | 9             | GA vs GG    | 6.87    | 0.55   | 0           | 1.05 (0.84–1.33)         | 1.04 (0.83–1.31)        |
| 6**              | AA vs GG      | 11.12       | 0.06   | 55     | 1.25 (0.30–5.26)        | 0.87 (0.41–1.87)        |
| Noncardia cancers  | 3             | GA vs GG    | 2.39    | 0.30   | 16           | 1.04 (0.71–1.52)         | 1.01 (0.74–1.40)        |
| Intestinal-type cancers | 3     | AA vs GG    | 9.49    | <0.01  | 89           | 1.38 (0.01–157.00)       | 0.72 (0.24–2.09)        |
| H. pylori-positive subjects | 0     | GA vs GG    | 1.80    | 0.41   | 0           | 1.40 (0.93–2.10)         | 1.39 (0.93–2.08)        |
| Western populations | 4             | GA vs GG    | 2.33    | 0.51   | 0           | 1.05 (0.78–1.41)         | 1.05 (0.78–1.41)        |
| East Asian populations | 5     | AA vs GG    | 10.25   | <0.01  | 90           | 1.25 (0.01–171.9)        | 0.64 (0.02–1.85)        |
| Studies in HWE    | 4             | GA vs GG    | 4.54    | 0.34   | 12           | 1.04 (0.69–1.58)         | 1.03 (0.72–1.47)        |
| **TNF-A –857 (1079/1759)**<sup>a</sup> |               |             |         |        |                          |                         |
| All gastric cancers | 5             | CT vs CC    | 1.24    | 0.87   | 0           | 1.06 (0.89–1.27)         | 1.06 (0.89–1.27)        |
| 5**              | TT vs CC      | 5.06        | 0.28   | 21     | 1.57 (0.91–2.70)        | 1.54 (0.98–2.43)        |
| Noncardia cancers  | 1             | CT vs CC    | 1.70    | 0.00   | 0           | 0.94 (0.63–1.41)         | 0.94 (0.63–1.41)        |
| Intestinal-type cancers | 1     | TT vs CC    | 0.00    | 0.00   | 0           | 0.75 (0.17–3.38)         | 0.74 (0.17–3.38)        |
| H. pylori-positive subjects | 0     | CT vs CC    | 0.00    | 0.00   | 0           | —                       | —                       |
| Western populations | 1             | CT vs CC    | 0.00    | 0.00   | 0           | 0.94 (0.63–1.41)         | 0.94 (0.63–1.41)        |
| East Asian populations | 4     | CT vs CC    | 0.81    | 0.85   | 0           | 1.09 (0.90–1.33)         | 1.09 (0.90–1.33)        |
| Studies in HWE    | 4             | CT vs CC    | 0.81    | 0.85   | 0           | 1.09 (0.90–1.33)         | 1.09 (0.90–1.33)        |

CI = confidence interval; HWE = Hardy–Weinberg equilibrium; OR = odds ratio; TNF-A = tumour-necrosis factor-A. *Q*-statistic for homogeneity in random-effect model. **P-value for the *Q*-statistic in random-effect model. *Higgins' *I²*-statistic for heterogeneity in random-effect model. *Number of cases/number of controls. *Some studies were excluded because of the null values for AA genotype frequency among both cases and controls.

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SE was 1.04 (0.82 – 1.33). For AA genotype, all of the studies had an overall association ($P = 0.55$) and subgroup analyses, and $I^2$-statistic showed little heterogeneity among studies (Table 2). For AA genotype, the Q-statistic was significant for the overall association ($P = 0.05$) and also for noncardia, intestinal-type, and western populations subgroups, where $I^2$-statistic showed moderate-to-high heterogeneity.

**TNF-A –857**

Figure 3A summarises the ORs and 95% CIs for the associations between TNF-A –857T carrying genotypes (TC and TT vs CC) and gastric cancer risk. For all gastric cancers, the random-effect overall ORs (95% CIs) for TC vs CC and TT vs CC genotypes were 1.06 (0.89 –1.27) and 1.57 (0.91 –2.70), respectively. The fixed-effect ORs (95% CIs) were 1.06 (0.89 –1.27) and 1.54 (0.98 –2.43), respectively. Like TNF-A –238, TNF-A –857 showed neither recessive nor dominant model. Therefore, the results are reported separately for TC vs CC and TT vs CC genotypes.

Only one study reported the associations between TNF-A –857 and noncardia cancers. This study was also the only study from western countries; the ORs (95% CIs) for TC and TT genotypes in this study were 0.94 (0.63 –1.41) and 0.75 (0.17 –3.38), respectively. For studies from eastern countries, summary ORs (95% CIs) for TC and TT genotypes were 1.09 (0.90 –1.33) and 1.73 (0.95 –3.14), respectively.

In one study, TNF-A –857 genotypes among controls were not in HWE (Table 1). After excluding that study, the summary ORs (95% CIs) for TC and TT genotypes were 1.09 (0.90 –1.33) and 1.73 (0.95 –3.14), respectively.
and also for the subgroup analyses. Furthermore, the OR associated with AA genotype showed a difference between western and East Asian studies. We cannot explain the reasons for this latter observed difference. No SNPs have been consistently associated with gastric cancer risk (Gonzalez et al, 2002). Indeed, because several initially promising gene–disease associations gravitated towards null over time (Ioannidis et al, 2001; Kamangar et al, 2006b), it has been suggested that journals should take a cautious approach in publishing such associations (Ioannidis, 2006). However, as shown in the results and discussed below, within the studies from western countries, the association between TNF-A –308AA genotype and gastric cancer risk seems robust to many tests, including testing for publication bias, heterogeneity, and HWE. Interestingly, a study within the InterLymph Consortium found that this same polymorphism was consistently associated with an increased risk.

Begg’s funnel plot for the association between TNF-A –857 and gastric cancer is shown in Figure 3B. For both TC and CC genotypes, there was no evidence for bias using either the method of Begg and Mazumdar (P for rank correlation = 0.81 and 0.46, respectively) or Egger’s weighted regression method (P for bias = 0.87 and 0.89, respectively). For TC vs CC genotypes, none of the studies had an SE > 0.5. For TT vs CC genotypes, after excluding two studies with SEs > 0.5, the summary OR (95% CI) changed to 1.66 (0.81 – 3.42).

The Q-statistic was nonsignificant for the overall associations and also for the subgroup analyses. Furthermore, I²-statistic showed little to moderate heterogeneity among studies (Table 2).

DISCUSSION

Gastric cancer is the second most common cause of cancer death in the world (Parkin et al, 2005; Kamangar et al, 2006c). Because inflammation is one of the initial phases of gastric carcinogenesis, especially for intestinal-type gastric cancer (Correa, 1992), inflammation-related polymorphisms, including single-nucleotide polymorphisms (SNPs) in TNF-A gene, have been extensively studied in relation to gastric cancer (Camargo et al, 2006). The most extensively studied of these proinflammatory polymorphisms are two linked SNPs in IL-1B (−511C>T and −31T>C) and a penta-allelic variable number tandem-repeat polymorphism and allele 2 (IL-1RN*2). So far, at least three meta-analyses of the associations between these polymorphisms and gastric cancer risk have been published (Camargo et al, 2006; Kamangar et al, 2006b; Wang et al, 2007). However, to our knowledge, no systematic review has been previously published on the association between TNF-A SNPs and gastric cancer. Of the three polymorphisms reviewed in this report, −308G>A is studied more extensively and a biologic role for it has been identified.

An analysis of the 23 studies that presented results on TNF-A –308G>A showed no association between GA genotype (vs GG) and gastric cancer risk. However, there was a statistically significant increased risk associated with AA genotype using both fixed-effects and random-effects models. This association was limited to studies from western countries, and no association was found in studies from East Asian countries. Previous studies have suggested that frequencies of genetic markers often show high variations among various ethnic and racial groups (Garte et al, 2001; Ioannidis et al, 2004), whereas differences in genetic effects (in terms of ORs) are much less common (Ioannidis et al, 2004). This meta-analysis found that the median prevalence of TNF-A –308A carrier genotypes was almost twice as high in western as in East Asian populations (23.5 vs 13.4%). However, unlike what has been shown for most previous associations (Ioannidis et al, 2004), the OR associated with AA genotype showed a difference between western and East Asian studies. We cannot explain the reasons for this latter observed difference.

No SNPs have been consistently associated with gastric cancer risk (Gonzalez et al, 2002). Indeed, because several initially promising gene–disease associations gravitated towards null over time (Ioannidis et al, 2001; Kamangar et al, 2006b), it has been suggested that journals should take a cautious approach in publishing such associations (Ioannidis, 2006). However, as shown in the results and discussed below, within the studies from western countries, the association between TNF-A –308AA genotype and gastric cancer risk seems robust to many tests, including testing for publication bias, heterogeneity, and HWE. Interestingly, a study within the InterLymph Consortium found that this same polymorphism was consistently associated with an increased risk.

Figure 3 The association between TNF-A –857 and gastric cancer (TC and TT genotypes vs CC). (A) Forest plot – studies are sorted in order of publication year. (B) Begg’s funnel plots for the associations.
of diffuse large B-cell lymphoma with a comparable magnitude of association (Rothman et al, 2006); the ORs associated with GA and AA genotypes (vs GG genotype) were 1.29 and 1.65, respectively. The studies that participated in this Consortium were all from western countries.

The forest plots for TNF-A –308AA genotype did not suggest a dominant effect for any single study. We used funnel plots and two formal statistical methods (Egger's weighted regression method and the rank correlation method of Begg and Mazumdar) to detect bias. In general, smaller studies, that is, those with higher SEs, had lower ORs, and there was some evidence for publication bias using both formal methods. However, excluding smaller studies did not materially change the results. In 20 out of 23 studies, distribution of TNF-A –308 among controls was in HWE. Limiting the analyses to these 20 studies, the results remained essentially unchanged. The overall heterogeneity between the studies was very low, as indicated by the I² value of zero.

Since subgroup analyses are often limited by selective reporting of significant subgroup results, such analyses generally need to be interpreted with caution. However, in this report, limiting the results of TNF-A –308 polymorphism to noncardia gastric cancers or intestinal-type cancers made little difference. The summary ORs for the AG genotype remained close to null and were nonsignificant, whereas those for the GG genotype remained statistically significantly above one.

We found nine studies that examined the association between TNF-A –238G > A polymorphism and gastric cancer risk. Unlike that for TNF-A –308AA > A polymorphism, a clear biologic role for this polymorphism has not been found (Jang et al, 2001). There was no association between gastric cancer risk and either the GA or the AA genotypes using either random-effects or fixed-effects models. Examining the data by anatomic and histologic subtypes did not make a difference. No statistically significant association was found when data were limited to East Asian populations, western populations, studies with larger sample sizes, or studies in which genotype frequencies were in HWE.

We found only five studies that had examined the association between TNF-A –857C > T polymorphisms and gastric cancer. No evidence was found for the association between CT (vs CC) genotype and gastric cancer. Almost all studies showed null associations, and there was little evidence for heterogeneity. The overview association with the TT genotype, however, was near significant. The overall pattern and magnitude of association is similar to that found for TNF-A –308G > A polymorphism, but further studies are needed to examine whether gastric cancer is significantly associated with this polymorphism. The studies showed some heterogeneity, with three showing strong positive associations, one showing no association, and one showing an inverse association. We believe that the currently available data do not provide conclusive evidence for the presence of an association, or lack thereof, between TNF-A –857TT genotype and gastric cancer.

Inappropriate selection of controls is a major source of bias in case–control studies. However, control groups for most of the studies used in this meta-analysis were selected from among healthy volunteers or blood donors, and TNF-A polymorphisms are unlikely to be associated with these conditions. Because TNF locus is on chromosome 6 (and not sex chromosomes), the distribution of this polymorphism is not associated with sex. Therefore, in theory, matching for sex should not affect the results.

Strengths of this meta-analysis are including 24 published studies with a large number of cases and controls, presenting data on several relevant methodologic aspects of these studies, subgroup analyses according to predefined criteria, and using other methods to examine the robustness of the summary statistics. We acknowledge that this meta-analysis also has limitations. Combining observational studies conducted in different populations with various qualities of design to obtain summary ORs and 95% CIs can sometimes be misleading (Shapiro, 1994), and summary statistics need to be interpreted with caution (Egger et al, 1998). However, as mentioned above, there is little evidence for improper selection of control groups or for associations within specific subgroups.

In summary, this systematic review found that TNF-A –308AA genotype was moderately associated with an increased risk of gastric cancer. TNF-A –308AG, TNF-A –238AA or AG, and TNF-A –857CT or TT were not statistically significantly associated with gastric cancer risk. It is possible that, with increasing the number of studies, TNF-A –857TT may also be associated with an increased risk of gastric cancer.

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