Population differences concerning TNF-α gene polymorphisms in gastric carcinogenesis based on meta-analysis

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Introduction

Gastric cancer (GC) is one of the most common gastrointestinal malignancies worldwide and the second most common cause of cancer related death with over 600,000 deaths per year [1]. Helicobacter pylori (H. pylori) plays an important role in gastric carcinogenesis through physiological and histological changes that H. pylori infection induces in the stomach [2,3]. However, a striking difference exists between the number of infected individuals and the number that go on to develop GC [4-6]. Therefore a multifactorial etiology is possible, with H. pylori infection, dietary factors and host genetic susceptibility all playing a role in its development. Host genetic factors are emerging as key determinants of disease for many cancers [7,8], as genetic variations in pro-inflammatory and anti-inflammatory cytokine genes influence individual response to carcinogenic exposures. Various studies have evaluated the role of pro-inflammatory gene polymorphisms in GC and two recent meta-analyses have examined the role of interleukin (IL)-1 gene cluster polymorphisms in gastric carcinogenesis [9,10]. In addition to the IL-1 gene cluster, candidate genes include those encoding the pro-inflammatory cytokine tumor necrosis factor (TNF)-α.

Methods

Extensive English language medical literature searches for human studies were performed up to the end of May 2013, using suitable keywords. Pooled estimates [odds ratio (OR) with 95% confidence intervals (CI)] were obtained using the random-effects model. Heterogeneity between studies was evaluated with the Cochran Q test whereas the likelihood of publication bias was assessed by constructing funnel plots. Their symmetry was estimated by the adjusted rank correlation test.

Results

In seventeen studies, from various countries, the TNF-α-308 and TNF-α-238 frequencies of genotypes G/G, G/A, A/A were examined in gastric cancer patients and controls. For TNF-α-308 frequency overall, the pooled ORs with 95%CI for genotype G/G, A/A and G/A were 0.837 (0.712-0.982), 1.430 (1.064-1.923) and 1.145 (0.973-1.348) with respective P values 0.029, 0.018 and 0.104. Subgroup analyses showed significant results for genotype G/G only in Asians [OR=0.774 (0.610-0.983), P=0.036].

Conclusion

In this meta-analysis there was an overall statistically significant increased cancer risk associated with TNF-α-308 G/G and A/A genotypes. Subgroup analyses showed significant results for genotype G/G in Asians, whereas no such significant results were found for Caucasians and Hispanics.

Keywords TNF-α-308 gene, TNF-α-238 gene, polymorphism, gastric cancer, meta-analysis

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necrosis factor (TNF)-α and indeed studies on the association between TNF-α gene polymorphisms and gastric carcinoma have been published with discrepant results. A meta-analysis on this subject has been published some years ago [11]. However, in this meta-analysis population differences concerning TNF-α gene polymorphisms in gastric carcinogenesis have not been adequately addressed. The aim of this study therefore was to systematically review the role of TNF-α-308 and TNF-α-238 gene polymorphisms (genotypes G/G, G/A, A/A) in gastric carcinogenesis and in particular to look for population differences by meta-analyzing all relevant studies.

Material and methods

Data identification and extraction

We searched the PubMed, Medline and Embase databases through May 2013 to identify all relevant English language medical literature for human studies under the search text terms; (“stomach neoplasms” OR “stomach” AND “neoplasms” OR “stomach neoplasms” OR “gastric” AND “cancer” OR “gastric cancer”) AND (TNF-α AND «polymorphism, genetic» OR «polymorphism» AND «genetic polymorphism» OR «polymorphism»). We also performed a full manual search of all review articles, recently published editorials and of retrieved original studies. Data were extracted independently from each study by two of the authors (T.R. and D.P.) by using a predefined form, and disagreements were resolved by discussion with a third investigator and consensus.

Selection criteria

Inclusion and exclusion criteria were delineated before the commencement of the literature search. Thus, eligible studies were included in this meta-analysis if they met all the following criteria: 1) published as full articles; 2) written in English; 3) to be cohort or case control studies. Studies not meeting the aforementioned criteria and in addition studies without data for retrieval and duplicate publications were excluded. When two papers reported the same study, the publication that was more informative was selected.

Statistical analysis

Agreement on the selection of studies between the two reviewers was evaluated by the κ coefficient. We calculated the pooled odds ratios (ORs) and 95% confidence intervals (CIs) and compared outcomes of individual studies by using the fixed effects model [12] (Mantel and Haenszel method), unless significant heterogeneity was present, where the random effects model [13] was used (DerSimonian and Laird method). Forest plots were constructed for visual display of ORs of individual studies. Heterogeneity between studies was evaluated with the Cochran Q test [14] and it was considered to be present if the Q test provided a P value of less than 0.10 [15]. In the presence of significant statistical heterogeneity, sensitivity analyses were performed to exclude any possible influence of a single study. These analyses were achieved by repeating the meta-analyses with exclusion of each individual study one at a time, in order to assess the overall effect of each study on the pooled ORs [15]. This indicates which particular studies are most influential and might help in the evaluation of the possibility that the conclusions result from the influence of a particular study. The likelihood of publication bias was assessed by constructing funnel plots which were obtained by plotting the log ORs vs. precision (1/SE) of individual studies [16]. Their symmetry was estimated by the Begg and Mazumdar adjusted rank correlation test [17], whereas the number of studies missing from a meta-analysis was estimated using Duval and Tweedie’s nonparametric trim and fill rank-based method [18]. All analyses were performed by using Comprehensive Meta-analysis software (Version 2, BIOSTAT INC., Englewood, NJ, USA).

Results

Descriptive assessment and study characteristics

A flow chart describing the process of study selection is shown in Fig. 1. Out of 56 titles initially generated by the literature searches, 17 case control studies from various countries remained eligible for meta-analysis [19-35]. Initial agreement between the reviewers for the selection of relevant articles was high [κ = 0.94, 95% CI (0.86-1)].

One of the studies [28] contained separate data from two areas of Italy and therefore in the 17 meta-analyzed studies, conducted in different parts of the world, there were totally 18 sets of data comparing the TNF-α-308 and TNF-α-238 frequencies of genotypes G/G, G/A, A/A in GC patients and controls. The main characteristics of the papers eligible for meta-analysis are shown in Tables 1 and 2.

![Flow diagram of the studies identified in this meta-analysis](10)
Table 1 The main characteristics of studies, selected for meta-analysis, examining TNF-α-308 gene polymorphisms (genotypes G/G, G/A, A/A) in patients and controls

| Author/Country | Genotype frequency | Type of study |
|----------------|--------------------|---------------|
|                | GG                 | GA            | AA            | Patients | Controls | Patients | Controls | Patients | Controls |                |
| Wu 2002 [19], Taiwan | 144/150 | 214220 | 4/150 | 4/220 | 2/150 | 2/220 | Population based CCS |
| El-Omar 2003 [20], USA | No data | No data | No data | No data | No data | No data | Population based CCS |
| Machado 2003 [21], Portugal | No data | No data | No data | No data | 3/287 | 4/304 | Population based CCS |
| Wu 2003 [22], Taiwan | 213/220 | 224/230 | 4/220 | 2/230 | 3/220 | 4/230 | Population based CCS |
| Lee SG 2004 [23], Korea | 312/341 | 236/261 | 29/341 | 25/261 | 0/341 | 0/261 | Population based CCS |
| Garza-González 2005 [24], Mexico | No data | No data | No data | No data | No data | No data | Population based CCS |
| Lee JY 2005 [25], Korea | No data | No data | No data | No data | No data | No data | Population based CCS |
| Li 2005 [26], China | No data | No data | No data | No data | No data | No data | Population based CCS |
| Lu 2005 [27], China | 222/250 | 277/300 | 27/250 | 23/300 | 1/250 | 0/300 | Population based CCS |
| Perri 2005 [28], North Italy | No data | No data | No data | No data | No data | No data | Population based CCS |
| Perri 2005 [28], South Italy | No data | No data | No data | No data | No data | No data | Population based CCS |
| Zambon 2005 [29], Italy | 113/129 | 569/644 | 13/129 | 74/644 | 3/129 | 1/644 | Population based CCS |
| Kamangar 2006 [30], Finland | 106/112 | 203/208 | 6/112 | 5/208 | 0/112 | 0/208 | Nested CCS |
| Kim 2006 [31], Korea | No data | No data | No data | No data | 203/208 | 13/208 | Population based CCS |
| Morgan 2006 [32], Honduras | No data | No data | No data | No data | No data | No data | Population based CCS |
| García-González 2007 [33], Spain | 337/404 | 330/404 | 66/404 | 65/404 | 1/404 | 9/404 | Population based CCS |
| Hou 2007 [34], Poland | No data | No data | No data | No data | No data | No data | Population based CCS |
| Sugimoto 2007 [35], Japan | No data | No data | No data | No data | No data | No data | Population based CCS |
| Σ (+ve) / Σ (total) | 1,447/1,606 (90) | 2,053/2,267 (90.5) | 149/1,606 (9.2) | 198/2,267 (17) | 10/1,606 (0.6) | 16/2,267 (0.7) |

CS, case-control study.

Table 2 The main characteristics of studies, selected for meta-analysis, examining TNF-α-238 gene polymorphisms (genotypes G/G, G/A, A/A) in patients and controls

| Author/Country | Genotype frequency | Type of study |
|----------------|--------------------|---------------|
|                | GG                 | GA            | AA            | Patients | Controls | Patients | Controls | Patients | Controls |                |
| Wu 2002 [19], Taiwan | 114/150 | 180/220 | 27/150 | 27/220 | 9/150 | 13/220 | Hospital based CS |
| El-Omar 2003 [20], USA | 201/314 | 152/210 | 87/314 | 52/210 | 26/314 | 6/210 | Multicenter population based CCS |
| Machado 2003 [21], Portugal | 179/287 | 231/304 | 105/287 | 69/304 | 3/287 | 4/304 | Population based CCS |
| Wu 2003 [22], Taiwan | 176/220 | 185/230 | 31/220 | 29/230 | 13/220 | 16/230 | Population based CCS |
| Lee SG 2004 [23], Korea | 297/341 | 218/261 | 43/341 | 42/261 | 1/341 | 1/261 | Population based CCS |
| Garza-González 2005 [24], Mexico | 0/63 | 1/215 | 8/63 | 35/215 | 55/63 | 179/215 | Population based CCS |
| Kamangar 2006 [30], Finland | 112/122 | 103/120 | 10/122 | 17/120 | 0/122 | 0/120 | Population based CCS |
| Li 2005 [26], China | 55/59 | 228/264 | 4/59 | 34/264 | 0/59 | 2/264 | Population based CCS |
| Lu 2005 [27], China | 214/250 | 274/300 | 36/250 | 24/300 | 0/250 | 2/300 | Population based CCS |
| Perri 2005 [28], North Italy | 71/86 | 118/146 | 14/86 | 24/146 | 1/86 | 4/146 | Population based CCS |
| Perri 2005 [28], South Italy | 81/98 | 172/216 | 16/98 | 41/216 | 1/98 | 3/216 | Population based CCS |
| Zambon 2005 [29], Italy | 95/129 | 496/644 | 31/129 | 138/644 | 3/129 | 10/644 | Population based CCS |
| Kamangar 2006 [30], Finland | 86/112 | 154/208 | 23/112 | 52/208 | 3/112 | 2/208 | Nested CCS |
| Kim 2006 [31], Korea | 199/237 | 400/461 | 34/237 | 59/461 | 4/237 | 2/461 | CCS |
| Morgan 2006 [32], Honduras | 151/170 | 149/162 | 17/170 | 12/162 | 0/170 | 0/162 | Population based CCS |
| García-González 2007 [33], Spain | 309/404 | 320/404 | 84/404 | 77/404 | 11/404 | 7/404 | Population based CCS |
| Hou 2007 [34], Poland | 186/305 | 304/427 | 98/305 | 109/427 | 21/305 | 15/427 | Population based CCS |
| Sugimoto 2007 [35], Japan | 101/105 | 169/172 | 4/105 | 3/172 | 0/105 | 0/172 | Population based CCS |
| Σ (+ve) / Σ (total) | 2,627/3,452 (76.1) | 4,523/5,946 (77.6) | 672/3,452 (19.4) | 844/5,946 (17) | 151/3,452 (4.3) | 266/5,946 (5.3) |

CS, control study; CCS, case-control study.
whereas no significant results were found for Caucasians and Hispanics [OR=0.871, 95% CI (0.686-1.107), Z=-1.126, P=0.260] and OR=1.158, 95% CI (0.591-2.269), Z=0.429, P=0.668 respectively].

G/A genotype frequency (18 complete sets of data)

The G/A genotype frequencies, in patients and controls, were 672/3,452 (19.46%) vs. 844/4,964 (17%). There was significant heterogeneity among studies (Q=28.479, df(Q)=17, I²= 40.3%, P=0.04) but no publication bias (P=0.13) (Fig. 2). The subgroup analyses were made, grouping studies by geographical location and population composition (Asians, Caucasians and Hispanics) (Fig. 3). These analyses showed significant results for Asians [OR=0.774, 95% CI (0.61-0.983), Z=-2.098, P=0.036].

G/G genotype frequency (18 complete sets of data)

The G/G genotype frequencies, in patients and controls, were 2,627/3,452 (76.1%) vs. 3,854/4,964 (77.64%). There was significant heterogeneity among studies (Q =28.479, df(Q)=17, I²= 40.3%, P=0.04) but no publication bias (P=0.13) (Fig. 2). Due to significant heterogeneity, except for using the random effects model, sensitivity analyses were performed. Thus subgroup analyses were made, grouping studies by geographical location and population composition (Asians, Caucasians and Hispanics) (Fig. 3). These analyses showed significant results for Asians [OR=0.774, 95% CI (0.61-0.983), Z=-2.098, P=0.036].

### Study name  Population  Odds ratio and 95% CI

| Study name | Population | Odds ratio | Lower limit | Upper limit | P-value |
|------------|------------|------------|-------------|-------------|---------|
| Wu MS 2002 | Asian      | 0.704      | 0.424       | 1.169       | 0.175   |
| El-Omar 2003 | Caucasian | 0.679      | 0.464       | 0.993       | 0.046   |
| Mochado 2003 | Caucasian | 0.524      | 0.367       | 0.747       | 0.000   |
| Wu 2003 | Asian      | 0.973      | 0.612       | 1.547       | 0.908   |
| Lee SG 2004 | Asian      | 1.331      | 0.845       | 2.099       | 0.218   |
| Garza-Gonzalez 2005 | Hispanic | 1.126      | 0.045       | 27.980      | 0.942   |
| Lee TF 2005 | Asian      | 1.849      | 0.810       | 4.221       | 0.145   |
| Li 2005 | Asian      | 2.171      | 0.742       | 6.356       | 0.157   |
| Lu 2005 | Asian      | 0.564      | 0.330       | 0.963       | 0.036   |
| Perri 2005a | Caucasian | 1.123      | 0.562       | 2.246       | 0.742   |
| Perri 2005b | Caucasian | 1.219      | 0.656       | 2.263       | 0.531   |
| Zambon 2005 | Caucasian | 0.834      | 0.541       | 1.285       | 0.410   |
| Kamangar 2006 | Caucasian | 1.160      | 0.678       | 1.985       | 0.588   |
| Kim 2006 | Asian      | 0.799      | 0.515       | 1.339       | 0.316   |
| Morgan 2006 | Hispanic | 0.693      | 0.331       | 1.455       | 0.333   |
| Garcia-Gonzalez 2007 | Caucasian | 0.854      | 0.612       | 1.191       | 0.352   |
| Sugimoto 2007 | Asian | 0.448      | 0.098       | 2.043       | 0.300   |

Pooled results 0.837 0.712 0.982 0.029

Figure 2 (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing TNF-α-308 polymorphism (genotype G/G), in patients and controls. (B) Funnel plot of the above studies including the hypothetically missed studies using the "trim-and-fill" method. Funnel plot of the above studies. No evidence of publication bias (P=0.13, by Begg and Mazumdar adjusted rank correlation test).
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### A/A genotype frequency (18 complete sets of data)

The A/A genotype frequencies, in patients and controls, were 151/3,452 (4.3%) vs. 266/4,964 (5.3%). There was neither significant heterogeneity ($Q=11.952$, $df(Q)=14$, $I^2=0\%$, $P=0.021$) nor publication bias ($P=0.12$) (Fig. 5). The meta-analysis overall showed significant results [pooled OR=1.430 (1.064-1.923), $Z=2.371$, $P=0.018$ by both fixed and random effects model] (Fig. 5). Subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.

### G/A genotype frequency (7 complete sets of data)

The G/A genotype frequencies in patients and controls were 149/1,606 (9.2%) vs. 198/2,267 (17%) [pooled OR with 95% CI=1.088 (0.856-1.383), test for overall effect $Z=0.690$, $P=0.490$ by both fixed model and random effects model]. There was neither significant heterogeneity ($Q=4.415$, $df(Q)=6$, $I^2=0\%$, $P=0.36$) nor publication bias ($P=0.36$) (Fig. 6). Subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.

### G/G genotype frequency (7 complete sets of data)

The G/G genotype frequencies in patients and controls were 1,447/1,606 (90%) vs. 2,053/2,267 (90.5%) [pooled OR with 95% CI=0.940 (0.747-1.183), test for overall effect $Z=-0.527$, $P=0.598$ by both fixed and random effects model]. There was neither significant heterogeneity ($Q=4.816$, $df(Q)=6$, $I^2=0\%$, $P=0.568$) nor publication bias ($P=0.29$) (Fig. 6). The subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.

### A/A genotype frequency (5 complete sets of data)

The A/A genotype frequencies in patients and controls were 10/1,606 (0.6%) vs. 16/2,267 (0.7%) [pooled OR with 95% CI=1.3 (0.276-6.118), test for overall effect $Z=0.32$, $P=0.740$ (by random effects model)]. There was significant heterogeneity ($Q=10.766$, $df(Q)=4$, $I^2=62.84\%$, $P=0.029$) but no publication bias ($P=0.32$) (Fig. 6). Subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.
Discussion

Besides environmental factors, cytokine gene polymorphisms have been linked to inter-individual differences in GC susceptibility. Indeed, host genetic factors are emerging as key determinants of disease for many cancers [7,8] as genetic variations in pro-inflammatory and anti-inflammatory cytokine genes influence individual response to carcinogenic exposures. Since El-Omar et al first reported an association between IL-1B and IL-1RN gene polymorphisms and an increased risk of gastric atrophy, as well as GC [36], many investigators have explored the association of these gene polymorphisms with the risk of GC. Two recent meta-analyses have explored the role of IL-1 gene cluster polymorphisms in gastric carcinogenesis [9,10].

In addition to polymorphisms in IL genes, the polymorphisms in the promoter region of TNF-α gene have been studied in relation to cancer. TNF-α is the most important proinflammatory cytokine involved in the growth, differentiation, cellular function and survival of many cells. It is produced by diverse kinds of cells, such as macrophages, neutrophils, fibroblasts, keratinocytes, NK cells, T and B cells, and tumor cells [37]. TNF-α has been reported to play an important role in the pathogenesis of cancer [38]. As transcription of TNF-α is regulated under genetic control, recent studies [39-41] have shown that its promoter polymorphisms at 2238 (rs361525), 2308 (rs1800629), 2857 (rs1799724), and 21031 (rs1799964) positions could regulate TNF-α production. Two polymorphisms in TNF-α gene have been studied in greater detail than others, i.e. TNF-α-308 and TNF-α-238; in fact TNF-α-308 polymorphism has been confirmed as a risk factor for a range of cancers, such as breast and hepatocellular cancers [42,43]. However, the significance of TNF-α-238 polymorphism is less clear, but because a putative repressor site is located in a 25-base
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The results of our meta-analysis showed that overall there was no association between TNF-α-308 G/A genotype and GC risk, but there was an overall statistically significant increased risk associated with TNF-α-308 G/G and A/A genotypes. However, as shown by sensitivity (subgroup) analysis, this association was limited to studies in Asians and no association was found in studies concerning Caucasians and Hispanics. The reason for these discrepant results is unclear and differences in sample size, methodologies, ethnicities and dominance of different etiologic factors in different populations could contribute to this heterogeneity of results. However, studies have suggested that the frequency of genetic markers often shows high variation among various ethnic and racial groups [45,46]. No significant results were found concerning TNF-α-238 frequency for genotypes G/G, A/A, G/A and these results are similar to those found by others [47]. According to these results it seems likely that in Asians, TNF-α-308 gene polymorphism plays an important role as host genetic factor predisposing to gastric carcinogenesis and it could be used as a screening marker. Indeed, in countries like Japan this could be of particular importance since in this country many efforts have been made in screening and accurate early detection of GC [48,49], considering that half of the global total of GC occurs in Eastern Asia where the highest mortality rates are expected (28.1 per 100,000 in men, 13.0 per 100,000 in women) [50].

Among the strengths of this meta-analysis are the relatively large number of cases and controls, the methods we used to examine the robustness of our results and the fact that the statistically significant positive relationship we found was consistent over the years as judged by the results of the cumulative meta-analysis of studies, ordered by the year of publication. However,

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### Table

| Study name | Subgroup within study | Statistics for each study | Odds ratio and 95% CI | Relative weight (%) |
|------------|-----------------------|---------------------------|-----------------------|---------------------|
| Li 2005    | Asian                 | 1.569 (0.879, 2.601)      | 1.524 (0.128)         | 5.24                |
| Lee JY 2005| Asian                 | 1.165 (0.781, 1.736)      | 0.748 (0.454)         | 8.02                |
| Lee SG 2004| Asian                 | 1.965 (1.371, 2.817)      | 3.676 (0.000)         | 8.80                |
| Perri 2005b| Caucasian             | 1.137 (0.660, 1.958)      | 0.462 (0.644)         | 5.68                |
| Kamangar 2006| Caucasian           | 0.752 (0.475, 1.191)      | 0.225                 | 6.94                |
| Garcia-Gonzalez 2005| Hispanic | 0.748 (0.328, 1.707)      | 0.491                 | 3.12                |
| Perri 2005a| Caucasian             | 0.541 (0.237, 1.235)      | 0.145                 | 3.12                |
| Wu 2003    | Asian                 | 0.492 (0.168, 1.444)      | 0.197                 | 2.00                |
| Garcia-Gonzalez 2007| Caucasian | 1.935 (1.120, 3.341)      | 0.018                 | 5.65                |
| Zambon 2005| Caucasian             | 0.888 (0.481, 2.032)      | 0.973                 | 3.85                |
| Kim 2006   | Asian                 | 0.833 (0.442, 1.571)      | 0.572                 | 4.63                |
| Wu MS 2002| Asian                 | 1.160 (0.743, 1.811)      | 0.652                 | 7.17                |
| Morgan 2006| Hispanic             | 0.775 (0.445, 1.351)      | 0.369                 | 5.53                |
| El-Omar 2003| Caucasian           | 1.141 (0.724, 1.798)      | 0.570                 | 7.02                |
| Hou 2007   | Caucasian             | 1.389 (0.641, 3.007)      | 0.405                 | 3.46                |
| Lu 2005    | Asian                 | 1.115 (0.789, 1.575)      | 0.616                 | 9.12                |
| Machado 2003| Caucasian           | 1.381 (0.999, 1.910)      | 0.051                 | 9.59                |
| Sugimoto 2007| Asian             | 2.231 (0.489, 10.171)     | 1.037                 | 1.08                |

**Random effects model**

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**Figure 5** (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing TNF-α-308 gene polymorphism (genotype A/A), in patients and controls. (B) Funnel plot plot of the above studies. No evidence of publication bias (P=0.12, by Begg and Mazumdar adjusted rank correlation test)
| Study name       | Subgroup within study | Statistics for each study | Odds ratio and 95% CI     |
|------------------|-----------------------|---------------------------|---------------------------|
| Wu MS 2002       | Asian                 | 0.673                     | 0.213                     |
| Wu 2003          | Asian                 | 0.815                     | 0.270                     |
| Lee 2004         | Asian                 | 1.140                     | 0.650                     |
| Lu 2005          | Asian                 | 0.858                     | 0.369                     |
| Zampon 2005      | Caucasian             | 0.910                     | 0.525                     |
| Kamangar 2006    | Caucasian             | 0.450                     | 0.130                     |
| Garcia-Gonzalez 2007 | Caucasian           | 1.328                     | 0.748                     |
| Pooled results   |                       | 0.940                     | 0.747                     |

| Study name       | Subgroup within study | Statistics for each study | Odds ratio and 95% CI     |
|------------------|-----------------------|---------------------------|---------------------------|
| Wu MS 2002       | Asian                 | 1.479                     | 0.364                     |
| Wu 2003          | Asian                 | 2.111                     | 0.385                     |
| Lee 2005         | Asian                 | 0.877                     | 0.501                     |
| Lu 2005          | Asian                 | 1.408                     | 0.814                     |
| Zambon 2005      | Caucasian             | 2.298                     | 0.685                     |
| Kamangar 2006    | Caucasian             | 1.018                     | 0.701                     |
| Garcia-Gonzalez 2007 | Caucasian           | 1.808                     | 0.856                     |
| Pooled results   |                       | 1.088                     | 0.856                     |

Random effects model

**Figure 6** (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing TNF-α-238 gene polymorphism (genotypes G/G, G/A, A/A), in patients and controls. (B) Funnel plots of the above studies. No evidence of publication bias [(P=0.29, 0.36, 0.32 respectively for studies examining genotypes G/G, G/A, A/A) by Begg and Mazumdar adjusted rank correlation test]

we acknowledge that this meta-analysis also has limitations, such as the significant heterogeneity found in some of the analyses. We tackled this problem by assessing the homogeneity of the effects across studies using suitable heterogeneity tests, sensitivity, meta-regression and publication bias analyses as outlined in detail in the statistical analysis section.

In conclusion, in this meta-analysis the comparison of genotype frequencies between the control group and individuals with GC showed that there was a statistically significant increased risk associated with G/G and A/A genotype which was limited to studies from Asian countries, whereas no association was found in studies concerning Caucasians and Hispanics. According to these results it seems likely that in Asians, TNF-α-308 gene polymorphism plays an important host genetic factor predisposing to gastric carcinogenesis. However, since the magnitude of each etiologic factor might differ among populations, large studies examining the interaction between host genetic factors and environmental factors, in association with anatomical or histological subtypes of GC and *H. pylori* positivity, in different geographic areas and ethnic groups, are required to elucidate the real significance of host genetic factors in gastric carcinogenesis.
Summary Box

What is already known:

- Gastric cancer (GC) is one of the most common gastrointestinal malignancies worldwide and the second most common cause of cancer related death
- A multifactorial etiology is possible, with Helicobacter pylori infection, dietary factors and host genetic susceptibility all playing a role in its development. Host genetic factors are emerging as key determinants of disease, as genetic variations in pro-inflammatory and anti-inflammatory cytokine genes influence individual response to carcinogenic exposures
- Recent meta-analyses have examined the role of interleukin (IL)-1 gene cluster polymorphisms in gastric carcinogenesis. In addition to the IL-1 gene cluster, candidate genes include those encoding the pro-inflammatory cytokine tumor necrosis factor (TNF)-α and studies on the association between TNF-α gene polymorphisms and GC have been published with discrepant results

What the new findings are:

- In this meta-analysis the comparison of genotype frequencies between the control group and individuals with GC showed that there was a statistically significant increased risk associated with TNF-α-308 G/G and A/A genotype which was limited to studies from Asian countries, whereas no association was found in studies concerning Caucasians
- No significant results were found concerning TNF-α-238 frequencies for genotypes G/G, A/A, G/A
- It seems likely that in Asians, TNF-α-308 gene polymorphism plays an important as host genetic factor predisposing to gastric carcinogenesis. This could be of particular importance in countries like Japan since in this country many efforts have been made in screening for GC

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