Annals of Gastroenterology (2014) **27,** 139-148

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

Theodoros Rokkas, Panos Sechopoulos, Dimitrios Pistiolas, Fotis Kothonas, Georgios Margantinis, Georgios Koukoulis

Henry Dunant Hospital, Athens, Greece

Abstract

Background Recent meta-analyses have studied population differences concerning *interleukin* (*IL*)*-1* gene 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. The aim of the study was to systematically review the role of *TNF-α-238* and *TNF-α-308* gene polymorphisms (genotypes G/G, G/A, A/A) in gastric carcinogenesis by meta-analyzing all relevant studies to look for any differences concerning TNF-α gene polymorphisms in gastric carcinogenesis.

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

Ann Gastroenterol 2014; 27 (2): 139-148

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

Gastroenterology Clinic, Henry Dunant Hospital, Athens, Greece

Conflict of Interest: None

Correspondence to: Theodore Rokkas MD, PhD, FACG, AGAF, FEBGH, Gastroenterology Clinic, Henry Dunant Hospital, 192B Alexandras Ave., Athens 11521, Greece, e-mail: sakkor@otenet.gr

Received 25 July 2013; accepted 9 October 2013

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» OR «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.

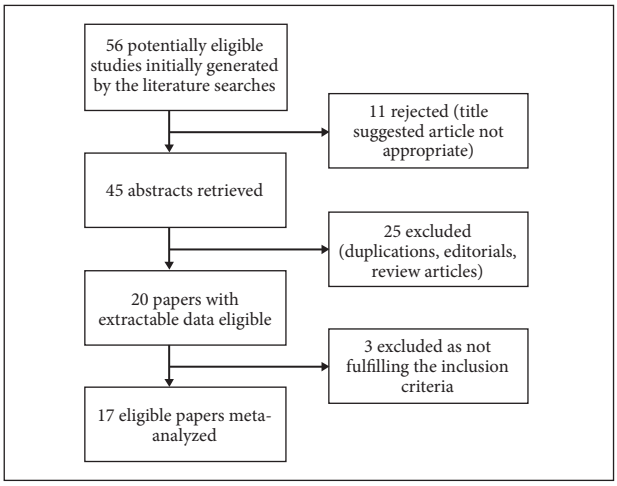

Figure 1 Flow diagram of the studies identified in this meta-analysis

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

	Genotype frequency						
	GG		GA		AA		
Author/Country	Patients	Controls	Patients	Controls	Patients	Controls	Type of study
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	No data	No data	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)	

CCS, 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

	Genotype frequency						
	GG		GA		AA		
Author/Country	Patients	Controls	Patients	Controls	Patients	Controls	Type of study
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
Lee JY 2005 [25], Korea	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)	3,854/4,964 (77.64)	672/3,452 (19.46)	844/4,964 (17)	151/3,452 (4.3)	266/4,964 (5.3)	

CS, control study; CCS, case-control study

TNF-α-308

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, I^2= 40.3%, P=0.04) but no publication bias (P=0.13) (Fig. 2). The meta-analysis overall (random effects model) showed pooled OR=0.837 (0.712-1.021), test for overall effect Z= -2.177, P=0.029 by random effects model] (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), 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 (Q=28.08, df(Q)=17 , I^2=39.45%, P=0.044) but no publication bias (P=0.45) (Fig. 4). The meta-analysis showed no significant results [pooled OR=0.874 (0.717-1.065), Z=-1.338, P=0.181 (random effects model)] (Fig. 4). The subgroup analyses showed no significant results for Caucasians, Asians or Hispanics.

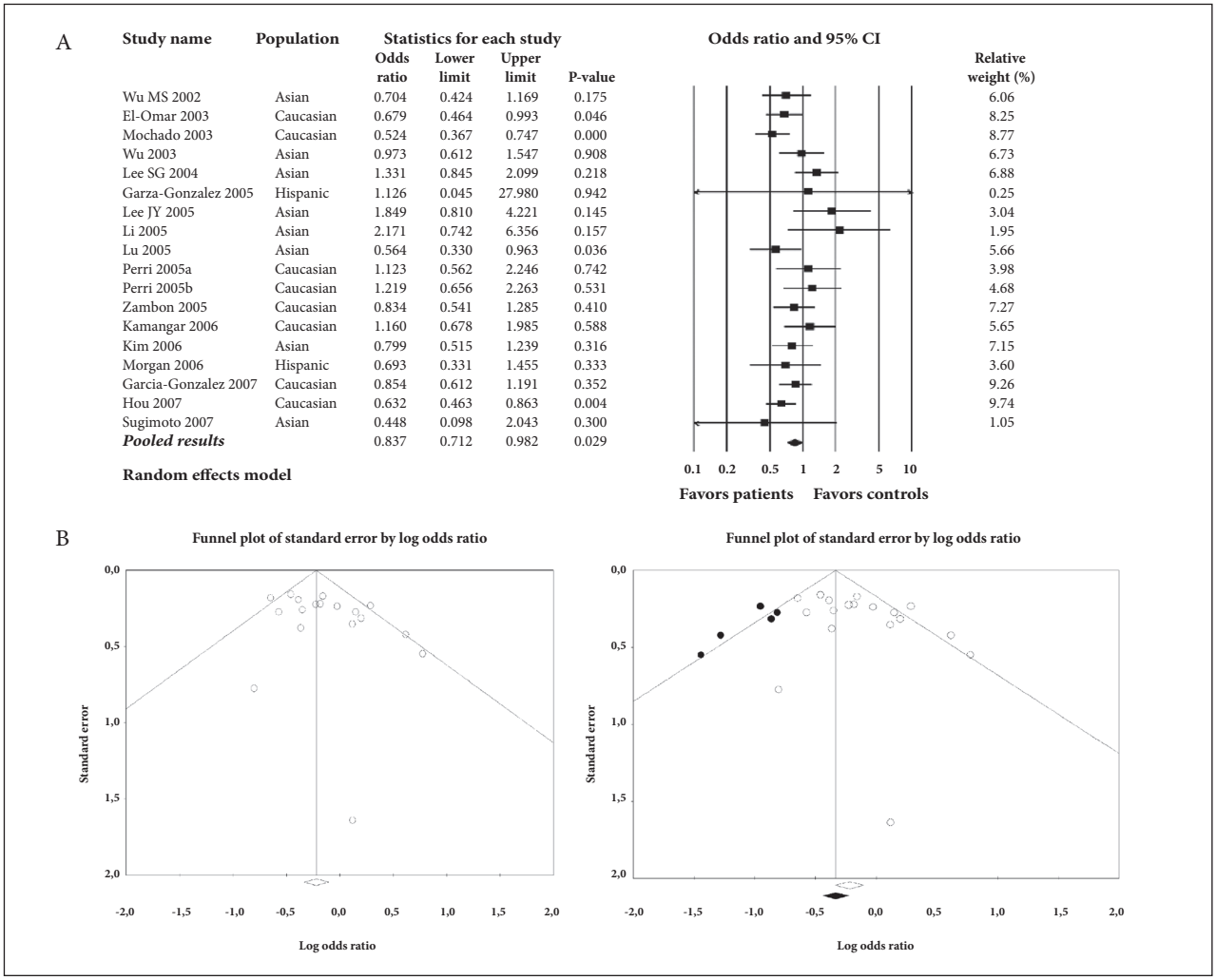

Figure 2 (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing *TNF-α-308* polymorphism (genotype G/G), in patients and controls. (B) Funnel plot of the above studies including the hypothetically missed studies using the "trim-and-fill" method. Funnel plot of the above studies.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

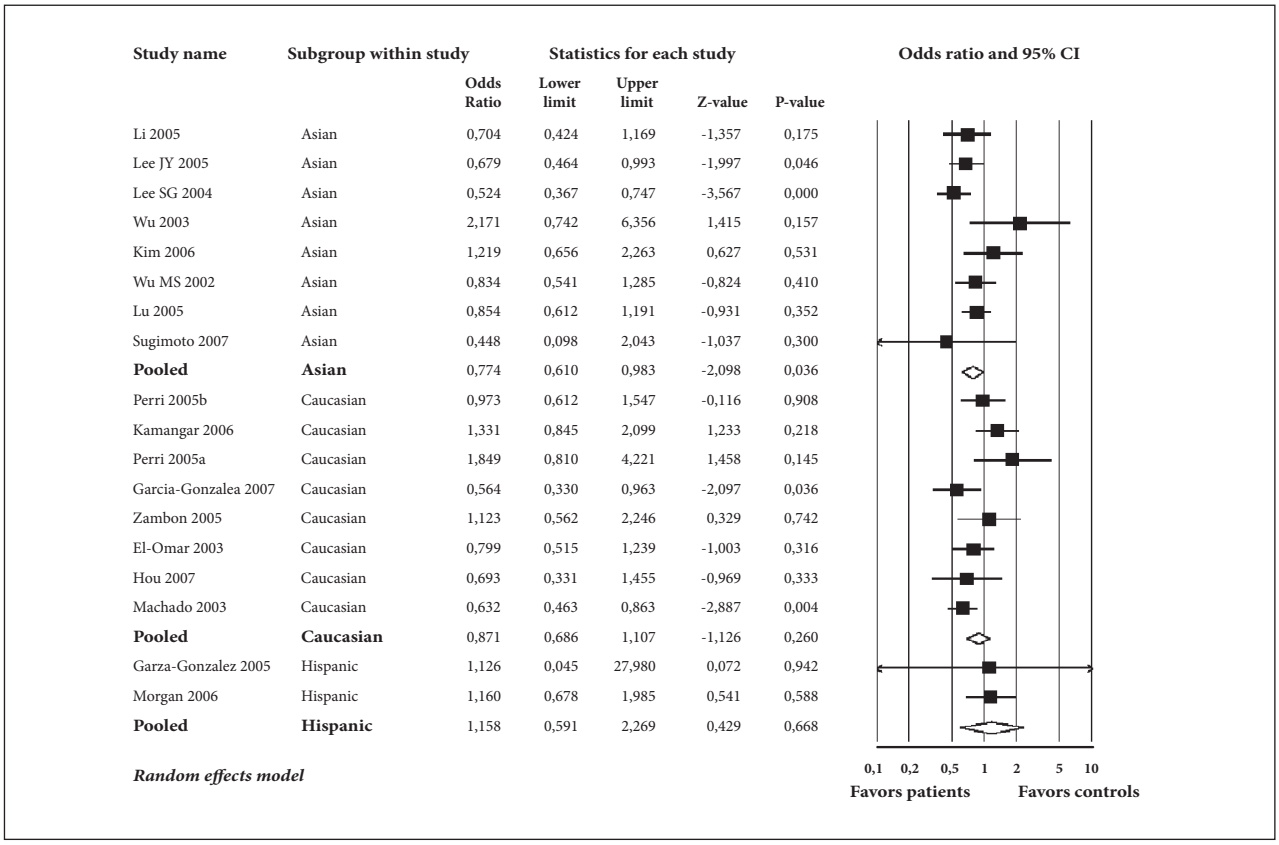

Figure 3 Funnel plot (subgroup analysis) of studies examining the *TNF-α-308* gene polymorphism (genotype G/G), grouped by geographical location and population composition

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.

TNF-a-238

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.

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=0.621) nor publication bias (P=0.36) (Fig. 6). Subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.

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

The G/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=0.332, P=0.740 (by random effects model)]. There was significant heterogeneity (Q=10.766, df(Q)=4, I^2=62.845%, P=0.029) but no publication bias (P=0.32) (Fig. 6). Subgroup analyses showed no significant results for Caucasians, Asians and Hispanics.

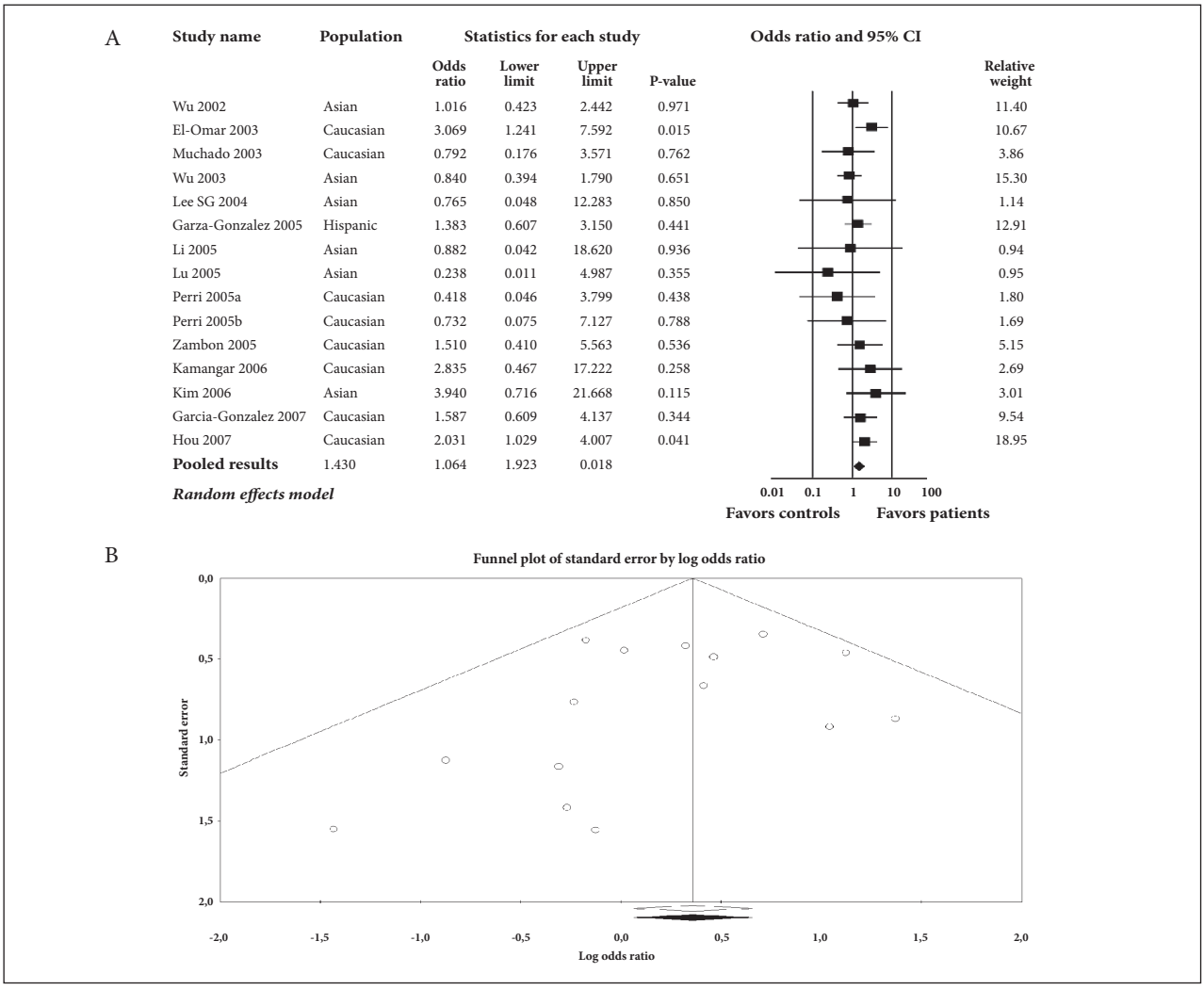

Figure 4 (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing *TNF-α-308* gene polymorphism (genotype G/A), in patients and controls. (B) Funnel plot of the above studies. No evidence of publication bias (P=0.45, by Begg and Mazumdar adjusted rank correlation test)

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 promotor 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

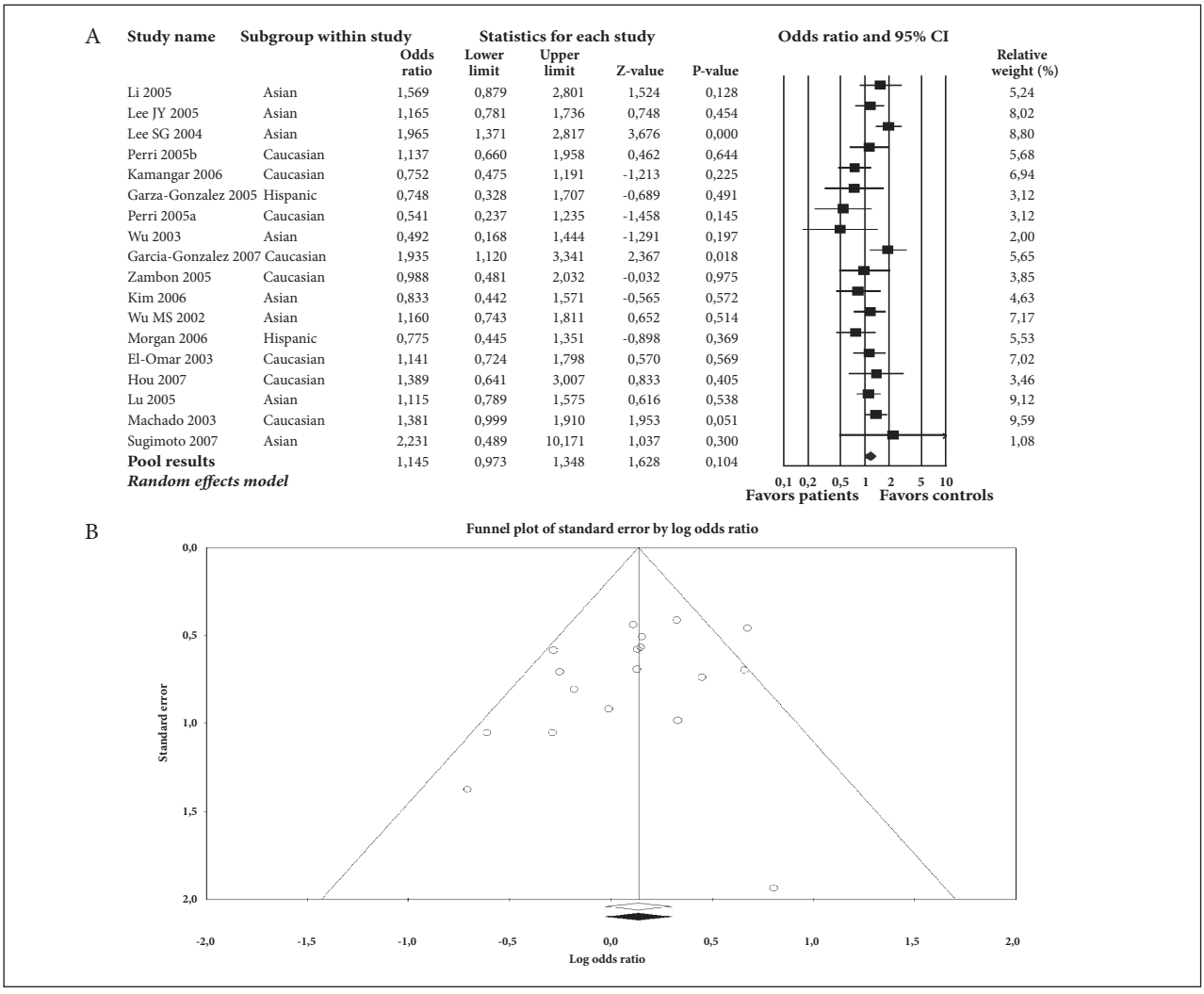

Figure 5 (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing *TNF-α-308* gene polymorphism (genotype A/A), in patients and controls. (B) Funnel plot plot of the above studies. No evidence of publication bias (P=0.12, by Begg and Mazumdar adjusted rank correlation test)

stretch that includes position -238, this polymorphism has been associated with decreased susceptibility to cancers [44].

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 *TNA-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,

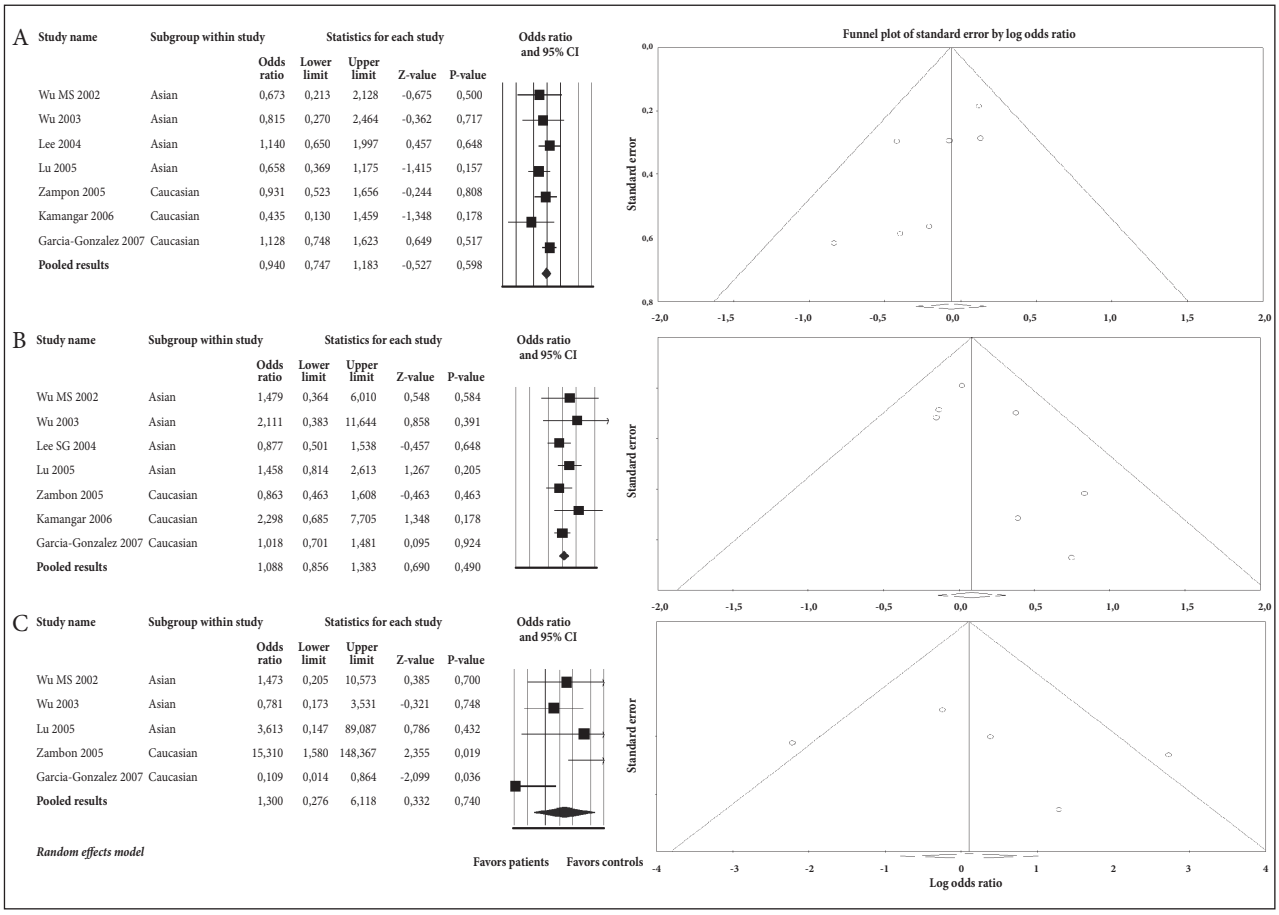

Figure 6 (A) Forest plot showing individual and pooled ORs (95% CIs) in studies comparing *TNF-α-238* gene polymorphism (genotypes G/G, G/A, A/A), in patients and controls. (B) Funnel plots of the above studies. No evidence of publication bias [(P=0.29, 0.36, 0.32 respectively for studies examining genotypes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

References

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;**80**:827-841.
2. Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991;**325**:1127-1131.
3. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;**345**:784-789.
4. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process-first American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992;**52**:6735-6740.
5. Sipponen P. Gastric cancer-a long-term consequence of *Helicobacter pylori* infection? *Scand J Gastroenterol* (Suppl) 1994;**201**:24-27.
6. Kuipers EJ, Uyterlinde AM, Pena AS, et al. Long-term sequelae of *Helicobacter pylori* gastritis. *Lancet* 1995;**345**:1525-1528.
7. Ponder BA. Cancer genetics. *Nature* 2001;**411**:336-341.
8. Peto J, Houlston RS. Genetics and the common cancers. *Eur J Cancer* 2001;**37**(Suppl 8):S88-S96.
9. Camargo MC, Mera R, Correa P, et al. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1674-1687.
10. Kamangar F, Cheng C, Abnet CC, Rabkin CS. Interleukin-1B polymorphisms and gastric cancer risk--a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:1920-1928.
11. Gorouhi F, Islami F, Bahrami H, Kamangar F. Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. *British Journal of Cancer* 2008;**98**:1443-1451.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Nat Cancer Inst* 1959;**22**:719-748.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
14. Cochran WG. The compination of estimates from different experiments. *Biometrics* 1954;**8**:101-129.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539-1558.
16. Copas JB, Shi JQ. A sensitivity analysis for publication bias in systematic reviews. *Stat Methods Med Res* 2001;**10**:251-265.
17. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**:1088-1101.
18. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;**56**:455-463.
19. Wu MS, Huang SP, Chang YT, et al. Tumor necrosis factor-alpha and interleukin-10 promoter polymorphisms in Epstein-Barr virus-associated gastric carcinoma. *J Infect Dis* 2002;**185**:106-109.
20. El-Omar EM, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003;**124**:1193-1201.
21. Machado JC, Figueiredo C, Canedo P, et al. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003;**125**:364-371.
22. Wu MS, Wu CY, Chen CJ, et al. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. *Int J Cancer* 2003;**104**:617-623.
23. Lee SG, Kim B, Yook JH, et al. TNF/LTA polymorphisms and risk for gastric cancer/duodenal ulcer in the Korean population. *Cytokine* 2004;**28**:75-82.
24. Garza-González E, Bosques-Padilla FJ, El-Omar E, et al. Role of the polymorphic IL-1B, IL-1RN and TNF-A genes in distal gastric cancer in Mexico. *Int J Cancer* 2005;**114**:237-241.
25. Lee JY, Kim HY, Kim KH, et al. Association of polymorphism of IL-10 and TNF-A genes with gastric cancer in Korea. *Cancer Lett* 2005;**225**:207-714.
26. Li C, Xia B, Yang Y, Li J, Xia HH. TNF gene polymorphisms and *Helicobacter pylori* infection in gastric carcinogenesis in Chinese population. *Am J Gastroenterol* 2005;**100**:290-294.
27. Lu W, Pan K, Zhang L, Lin D, Miao X, You W. Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor {alpha} and risk of gastric cancer in a Chinese population. *Carcinogenesis* 2005;**26**:631-636.
28. Perri F, Piepoli A, Bonvicini C, et al. Cytokine gene polymorphisms in gastric cancer patients from two Italian areas at high and low cancer prevalence. *Cytokine* 2005;**30**:293-302.

29. Zambon CF, Basso D, Navaglia F, et al. Pro-and anti-inflammatory cytokines gene polymorphisms and Helicobacter pylori infection: interactions influence outcome. *Cytokine* 2005;**29**:141-152.
30. Kamangar F, Abnet CC, Hutchinson AA, et al. Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). *Cancer Causes Control* 2006;**17**:117-125.
31. Kim N, Cho SI, Yim JY, et al. The effects of genetic polymorphisms of IL-1 and TNF-A on Helicobacter pylori-induced gastroduodenal diseases in Korea. *Helicobacter* 2006;**11**:105-112.
32. Morgan DR, Dominguez RL, Keku TO, et al. Gastric cancer and the high combination prevalence of host cytokine genotypes and *Helicobacter pylori* in Honduras. *Clin Gastroenterol Hepatol* 2006;**4**:1103-1111.
33. García-González MA, Lanas A, Quintero E, et al.; Spanish Gastroenterological Association AEG. Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain. *Am J Gastroenterol* 2007;**102**:1878-1892.
34. Hou L, El-Omar EM, Chen J, et al. Polymorphisms in Th1-type cell-mediated response genes and risk of gastric cancer. *Carcinogenesis* 2007;**28**:118-123.
35. Sugimoto M, Furuta T, Shirai N, et al. Different effects of polymorphisms of tumor necrosis factor-alpha and interleukin-1 beta on development of peptic ulcer and gastric cancer. *J Gastroenterol Hepatol* 2007;**22**:51-59.
36. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000;**404**:398-402.
37. Anderson GM, Nakada MT, DeWitte M. Tumor necrosis factor-alpha in the pathogenesis and treatment of cancer. *Curr Opin Pharmacol* 2004;**4**:314-320.
38. Wang SS, Purdue MP, Cerhan JR, et al. Common gene variants in the tumor necrosis factor (TNF) and TNF receptor superfamilies and NF-kB transcription factors and non-Hodgkin lymphoma risk. *PLoS One* 2009;**4**:e5360.
39. Huizinga TW, Westendorp RG, Bollen EL, et al. TNF-alpha promoter polymorphisms, production and susceptibility to multiple sclerosis in different groups of patients. *J Neuroimmunol* 1997;**72**:149-153.
40. Hellmig S, Fischbach W, Goebeler-Kolve ME, et al. A functional promotor polymorphism of TNF-alpha is associated with primary gastric B-Cell lymphoma. *Am J Gastroenterol* 2005;**100**:2644-2649.
41. Lindholm E, Bakhtadze E, Cilio C, et al. Association between LTA, TNF and AGER polymorphisms and late diabetic complications. *PLoS One* 2008;**3**:e2546.
42. Shen C, Sun H, Sun D, et al. Polymorphisms of tumor necrosis factor-alpha and breast cancer risk: a meta-analysis. *Breast Cancer Res Treat* 2011;126:763-770.
43. Yang Y, Luo C, Feng R, Bi S. The TNF-alpha, IL-1B and IL-10 polymorphisms and risk for hepatocellular carcinoma: a meta-analysis. *J Cancer Res Clin Oncol* 2011;**137**:947-952.
44. Jang WH, Yang YI, Yea SS, et al. The -238 tumor necrosis factor-alpha promoter polymorphism is associated with decreased susceptibility to cancers. *Cancer Lett* 2001;**166**:41-46.
45. Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:1239-1248.
46. Ioannidis JP, Ntzani EE, Trikalinos TA. 'Racial' differences in genetic effects for complex diseases. *Nat Genet* 2004;**36**:1312-1318.
47. Zhou P, Lv GQ, Wang JZ, et al. The TNF-Alpha-238 polymorphism and cancer risk: a meta-analysis. *PLoS One* 2011;**6**:e22092.
48. Uedo N, Takeuchi Y, Ishihara R. Endoscopic management of early gastric cancer: endoscopic mucosal resection or endoscopic submucosal dissection: data from a Japanese high-volume center and literature review. *Ann Gastroenterol* 2012;**25**:281-290.
49. Yao K. The endoscopic diagnosis of early gastric cancer. *Ann Gastroenterol* 2013;**26**:11-22.
50. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;**127**:2893-2917.