

Role of TNF- α -308G/A gene polymorphism in gastric cancer risk: A case control study and meta-analysis

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Cite this article as: Du LC, Gao R. Role of TNF-α -308G/A gene polymorphism in gastric cancer risk: a case control study and metaanalysis. Turk J Gastroenterol 2017; 28: 272-82.

ABSTRACT

Background/Aims: In the Chinese population, gastric cancer (GC) is ranked as the third most common type of cancer. Although the exact etiology of GC development is unclear, several factors, including genetic and environmental, have been identified as risk factors. Variations in cytokine genes and their receptors have been related to a higher risk of GC. A single nucleotide polymorphism in the promoter region of tumor necrosis factor- α (TNF- α) (-308G>A) has been associated with a higher risk of GC and in the present study we evaluated its possible association with GC in a Chinese cohort. In addition, we performed a meta-analysis to draw a firm conclusion about the association between TNF- α gene polymorphisms and GC.

Materials and Methods: We enrolled 400 Chinese GC patients and matched healthy controls hailing from similar geographical areas. The TNF-a -308G/A polymorphism was genotyped by allele-specific polymerase chain reaction (AS-PCR). For the meta-analysis, earlier published articles were searched and eligible studies were included.

Results: Prevalence of the heterozygous mutant (GA) and minor allele (A) were significantly higher in GC cases compared to healthy controls (GA: p<0.0001, odds ratio (OR)=4.90; A: p<0.0001, OR=2.84). A total of 36 eligible studies including the present report, encompassing of 8353 GC patients and 12099 controls, were analyzed for the meta-analysis. A significant association of the TNF- α polymorphism (-308G>A) with susceptibility to GC was only found in the Caucasian population (A vs G: p=0.001; AA vs GG: p=0.01; AG vs GG: p<0.0001; AA vs AG+GG: p=0.01; AA+AG vs p=0.003).

Conclusion: The results of the present case control study and meta-analysis showed that associations between TNF-a variants with susceptibility to GC development is population and ethnic specific.

Keywords: Gene polymorphism, TNF-a, gastric cancer, meta-analysis, association, Chinese

INTRODUCTION

In China, gastric cancer (GC) ranks third as the most common form of cancer. In the year 2005, 400,000 new cases and 300,000 deaths due to GC in China have been reported (1). The age standardized incidence for men and women was 37.1 and 17.4, respectively, and the mortality rate was 32.7 for men and 15 for women in 2005 (1). The incidence of GC varies among different populations and ethnicity. Although the exact etiology of GC development is unclear, several factors such as host genetics and the environment are believed to play a major role in pathogenesis. The importance of diet including consuming fruit and vegetables, smoking habits, and alcohol consumption have been shown to modulate disease severity (2,3). Infection with *Helicobacter pylori* is also a major cause of non-cardia and chronic GC. Although a limited number of infected humans (<1%) develops GC, the contribution of *H. pylori* infection to GC cannot be ruled out because it enhances the development of chronic gastritis to GC through various clinical phenotypes (atrophic gastritis, intestinal metaplasia, and dysplasia) in a sequential manner.

Immune responses to *H. pylori* has been well investigated. Various cytokines produced in response to *H. pylori* infection are intended to clear the microbes. However,

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 Received: January 15, 2017
 Accepted: March 24, 2017

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a dual function of certain pro-inflammatory molecules, including tumor necrosis factor- α (TNF- α) have been demonstrated; optimum levels help in clearance of microbes and in contrast an excessive level is associated with chronic inflammation. A role of TNF- α in GC has been well characterized. Elevated TNF- α induces inflammation in gastric mucosa, one of the important steps toward GC development (4). Several *in vitro* studies have demonstrated the induction of TNF- α production by *H. pylori* and inhibition of gastric acid secretion reveling the importance of TNF- α in GC pathogenesis (5,6).

TNF- α is located on the small arm of chromosome 6. So far, 106 single nucleotide polymorphisms (SNPs) in TNF- α have been reported (https://www.ncbi.nlm.nih.gov/SNP/snp_ref. cgi?locusId=7124). However, certain gene polymorphisms in the regulatory region of TNF-a, which correlate with the plasma level of TNF- α , is point of interest for most researchers. Although several polymorphisms in the promoter region of TNF-asuch as -238G>A, -308G>A, -857C>T, -863C>A, and -1031T>C have been shown to regulate TNF- α levels, the results are not consistent. An association of TNF- α -308G>A (rs1800629) with susceptibility/resistance to GC development has been widely investigated and yielded conflicting results. Studies including GC patients and controls from China (7-14), Brazil (15,16), Portugal (17,18), United States (19), Poland (20), South Korea (21-23), Honduras (24), Italy (25), Colombia (26), and Japan (27) have been associated with susceptibility to GC development. However, other studies including those from India (28), Brazilian (29,30), Romania (31), Spain (32,33), South Korea (34,35), China (36), Mexico (37), Germany (38) and Finland (39) failed to show a possible link between the TNF- α (-308G>A) polymorphism and GC. These observations highlight the necessity for a population-based investigation into the possible link between the TNF- α polymorphism (-308G>A) and GC. In the present study, we conducted a case control study followed by a meta-analysis to draw a firm conclusion on the role of this TNF-a polymorphism in GC.

MATERIALS AND METHODS

Patients and Controls

We enrolled 400 GC patients that were reported/referred to the Department Of Gastroenterology, Beijing Chaoyang Hospital, from 2012 to 2016. This study was approved by the ethics committee of Beijing Chaoyang Hospital, China (Approval No: TCX13461). All patients' diagnosis was confirmed endoscopically and histopathologically. A total of 400 healthy individuals from similar geographical areas without any history of gastric or any other form of cancer, gastritis, or gastric ulcers, were included as controls. Information about age, sex, smoking habits, and drinking habits were also collected from each participant. Approximately 5 mL of intravenous blood was collected from patients and controls. *H. pylori* infection status was screened by Enzyme Linked Immunosorbent Assay (ELISA) as instructed by the manufacturer. The protocol was approved by the Institutional Ethical Committee and written informed consent was obtained from all participants.

DNA Extraction and Genotyping of TNF- α (-308G>A) Polymorphism

DNA was extracted by using a QIAamp DNA Blood Mini Kit (QIAGEN, USA) according to the manufacturer's protocol. Extracted DNA was stored at -70 degree Celsius until used for genotyping. *TNF-a* -308G>A polymorphism was typed by AS-PCR as described previously (28,40). Around 20% of samples were chosen randomly and subjected to direct sequencing and those were found to be absolute concordant with the AS-PCR method.

Literature Search for Meta-Analysis

Two authors, LD and RG, independently searched various databases such as PubMed (Medline), EMBASE and Google Scholar with the following key words: 'Tumor Necrosis Factor' or *TNF-a* or TNF gene polymorphism and Gastric Cancer or GC (last updated on October 2016). Any discrepancy or disagreement about inclusion was resolved by group discussion. All extracted studies were investigated by their titles, abstracts, and we screened appropriate publications based on predetermined inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

The following inclusion-exclusion criteria were selected for the present study: a) all studies must be case-controls that investigated the relationship between TNF- α -308G>A polymorphism and GC; b) should include confirmed GC patients and appropriate controls; and d) must have reported genotype and allele frequency. Reports were excluded based upon the following crite-

Table 1. Distribution of TNF- α (-308G>A) polymorphism in gastric cancer patients and healthy controls

TNF-α -308G> A genotype and allele	HC (n=400)	GC (n=400)	р	OR (95% CI)
Genotype			ref	1
GG	326 (81.5)	204 (51)		
GA	60 (15)	184 (46)	< 0.0001	4.90 (3.48 to 6.88)
AA	14 (3.5)	12 (3)	0.53	1.37 (0.62 to 3.02)
Allele				
G	712 (89)	592 (74)	ref	1
A	88 (11)	208 (26)	<0.0001	2.84 (2.16 to 3.73)

HC: healthy controls; GC: gastric cancer patients; OR: odds ratio; CI: confidence interval; TNF- α : tumor necrosis factor- α

First authors and year	Country	Ethnicity	Control	Cases	Туре	Association
Present study	China	Asian	400	400	ASP	Yes
3hayal et al. 2013 (28)	India	Asian	229	114	ARMS-PCR	No
Xu et al. 2016 (13)	China	Asian	319	296	RFLP-PCR	Yes
de Oliveira et al. 2015 (29)	Brazil	American	240	204	RFLP-PCR	No
Zabaglia et al. 2015 (16)	Brazil	American	40	24	RFLP-PCR	Yes
/u et al. 2014 (14)	China	Asian	300	360	PCR	Yes
Hong et al. (test) 2013 (8)	China	Asian	750	834	TaqMan	Yes
Hong et al. (validation) 2013 (8)	China	Asian	936	1060	TaqMan	Yes
Burada et al. 2012 (31)	Romania	Caucassian	242	105	TaqMan	No
Canedo et al. 2008 (17)	Portugal	Caucassian	713	508	TaqMan	Yes
Trusius et al. 2008 (32)	Spain	Caucassian	1125	236	Real-time PCR	No
El-Omar et al. 2003 (19)	United States	Caucassian	210	314	TaqMan	Yes
Guo et al. 2005 (7)	China	Asian	437	264	RFLP-PCR	Yes
ang et al. 2001 (34)	South Korea	Asian	92	52	RFLP-PCR	No
ei et al. 2004 (36)	China	Asian	164	56	PCR	No
Garcia-Gonzalez et al. 2007 (33)	Spain	Caucassian	404	404	TaqMan	No
Garza-Gonzalez et al. 2005 (37)	Mexico	Caucassian	215	63	RFLP-PCR	No
Glas et al. 2004 (38)	Germany	Caucassian	145	88	RFLP-PCR	No
łou et al. 2007 (20)	Poland	Caucassian	428	305	TaqMan	Yes
(amangar et al. 2006 (39)	Finland	Caucassian	208	112	TaqMan	No
(im et al. 2006 (21)	South Korea	Asian	461	237	RFLP-PCR	Yes
.ee et al. 2004 (22)	South Korea	Asian	261	341	PCR	Yes
ee et al. 2005 (35).	South Korea	Asian	120	122	RFLP-PCR	No
i et al. 2005 (9)	China	Asian	264	59	RFLP-PCR	Yes
u et al. 2005 (10)	China	Asian	300	250	DHPLC-PCR	Yes
Machado et al. 2003 (18)	Portugal	Caucassian	304	287	SSCP-PCR	Yes
Nelo et al. 2009 (15)	Brazil	Caucassian	100	30	RFLP-PCR	Yes
Norgan et al. 2006 (24)	Honduras	Caucassian	161	168	TaqMan	Yes
Perri et al. 2005 (25)	Italy	Caucassian	362	184	RFLP-PCR	Yes
Rocha et al. 2005 (30)	Brazil	Caucassian	535	161	RFLP-PCR	No
ugimoto et al. 2007 (27)	Japan	Asian	172	105	RFLP-PCR	Yes
orres et al. 2004 (26)	Colombia	Caucassian	66	44	PCR	Yes
Vu et al. 2002 (12)	China	Asian	220	150	Direct Sequencing	Yes
Vu et al. 2004 (11)	China	Asian	210	204	Direct Sequencing	Yes
′ang et al. 2009 (23)	South Korea	Asian	322	83	SNaPshot	Yes
Zambon et al. 2005 (52)	Italy	Caucassian	644	129	TaqMan	Yes

PCR: polymerase chain reaction; ASP: allele specific PCR; RFLP: restriction fragment length polymorphism

ria: a) duplicated or overlapping publication, b) study involving only GC cases and devoid of controls, c) without genotype or allele frequency data, d) a review, abstract, or case report.

Data Extraction

Data from each eligible study were extracted such as publication year, first author name, sampling area, ethnicity, source of

Table 3. Genotypic distribution of the TNF-308G/A gene polymorphism included in the meta-analysis

		Cont	rols			Ca	ses		HWE
Authors and year (ref)	GG	GA	AA	MAF	GG	GA	AA	MAF	р
Present Study	326	60	14	0.22	204	184	12	0.26	0.000
3hayal et al. 2013 (28)	76	128	25	0.388	32	76	6	0.385	0.007
de Oliveira et al. 2015 (29)	167	69	4	0.160	138	63	3	0.169	0.296
/u et al. 2014 (14)	251	38	11	0.1	325	6	29	0.088	0.000
Hong et al. (test) 2013 (8)	589	154	7	0.112	690	139	5	0.089	0.376
Hong et al. (validation) 2013 2013 (8)	746	179	11	0.107	895	156	9	0.082	0.943
Ku et al. 2016 (13)	237	50	32	0.178	142	66	88	0.408	0.000
Zabaglia et al. 2015 (16)	33	4	3	0.125	17	4	3	0.208	0.000
Burada et al. 2012 (31)	196	44	2	0.099	78	26	1	0.133	0.784
Canedo et al. 2008 (17)	544	169	0	0.118	330	178	0	0.175	0.000
Crusius et al. 2008 (32)	820	274	31	0.149	170	64	2	0.144	0.165
El-Omar et al. 2003 (19)	152	52	6	0.152	201	87	26	0.221	0.548
Gou et al. 2005 (7)	391	40	6	0.059	240	20	4	0.053	0.000
ang et al. 2001 (34)	85	7	0	0.038	46	4	2	0.076	0.704
ei et al. 2004 (36)	143	20	1	0.067	53	3	0	0.026	0.743
Garcia-Gonzalez et al. 2007 (33)	320	77	7	0.112	309	84	11	0.131	0.350
Garza-Gonzalez et al. 2005 (37)	1	35	179	0.913	0	8	55	0.936	0.607
Glas et al. 2004 (38)	105	36	4	0.151	66	19	3	0.142	0.669
Hou et al. 2007 (20)	304	109	15	0.162	186	98	21	0.229	0.186
Kamangar et al. 2006 (39)	154	52	2	0.134	86	23	3	0.129	0.292
Kim et al. 2006 (21)	400	59	2	0.068	199	34	4	0.088	0.911
.ee et al. 2004 (22)	218	42	1	0.084	297	43	1	0.065	0.493
.ee et al. 2005 (35)	103	17	0	0.070	112	10	0	0.040	0.403
i et al. 2005 (9)	228	34	2	0.071	55	4	0	0.033	0.559
u et al. 2005 (10)	274	24	2	0.046	214	36	0	0.072	0.080
Machado et al. 2003 (18)	231	69	4	0.126	179	105	3	0.193	0.649
Melo et al. 2009 (15)	86	13	1	0.075	24	5	1	0.116	0.528
Morgan et al. 2006 (24)	149	12	0	0.037	151	17	0	0.050	0.623
Perri et al. 2005 (25)	290	65	7	0.109	152	30	2	0.092	0.145
Rocha et al. 2005 (30)	399	123	13	0.139	120	37	4	0.139	0.343
Sugimoto et al. 2007 (27)	169	3	0	0.008	101	4	0	0.019	0.908
orres et al. 2004 (26)	56	10	0	0.075	41	3	0	0.034	0.505
Nu et al. 2002 (12)	180	27	13	0.120	114	27	9	0.15	0.000
Vu et al. 2004 (11)	171	26	13	0.123	163	29	12	0.129	0.000
Yang et al. 2009 (23)	288	34	0	0.052	75	8	0	0.048	0.317
Zambon et al. 2005 (52)	496	138	10	0.122	95	31	3	0.143	0.909

HWE: Hardy Weinberg Equilibrium; MAF: minor allele frequency

samples, number of cases and controls, genotype frequencies, and reported associations. Disagreements or discrepancies were resolved by discussion.

Statistical Analysis

The genotype and allele frequency was calculated by direct counting and their distributions among cases and controls were

analyzed by Fisher's exact test. P<0.05 was defined as statistically significant. For meta-analysis, Comprehensive meta-analysis (CMA) V.2 was employed for calculation of pooled odds ratios (ORs) and 95% confidence interval (CIs). Heterogeneity among included studies for meta-analysis was analyzed by the Q-test and I² statistics. I² values range from 0% to 100%, where a value of 0% indicates no significant observed heterogeneity and larger values indicate an increasing degree of heterogeneity. Based on the heterogeneity results, a random or fixed-effects model was employed for derivation of pooled odds ratio, p value, and 95% CI. Publication bias was investigated by Egger's regression analysis and construction of funnel plots.

RESULTS

Baseline Characteristics of Patients and Controls

Out of 400 GC patients, 70% (n=284) were men and 30% (n=116) were women. Since the present study was a matched case-control study, we enrolled a similar number of health men and women as controls. The mean age of GC patients and healthy controls were 56.3 and 54.5 years, respectively. Smoking and drinking alcohol habits of both patients and controls were comparable (data not shown). *H. pylori* infection was more prevalent in GC cases compared to controls.

Association of -308G>A Polymorphism with Gastric Cancer

TNF-a -308G>A polymorphism was genotyped by AS-PCR. To explore any relationship between the promoter -308G>A polymorphism and GC, allele and genotype distributions were compared among patients and healthy controls. As shown in Table 1, heterozygous mutant (GA) and minor alleles (A) were more prevalent in GC cases compared to healthy subjects (GA: p<0.0001, OR= 4.90, 95% CI= 3.48 to 6.88; A: p<0.0001, OR=2.84, 95% CI=2.16 to 3.73) indicating a possible association between the *TNF-a* -308G>A variant and GC susceptibility.

Studies Included in the Meta-Analysis

A meta-analysis is a powerful tool that pools similar studies to draw a firm conclusion. In the primary search with various online tools, we obtained 238 articles and after detailed evaluation of the titles, abstracts, removal of duplicates, and careful reading of the full text of the articles, 35 eligible articles were screened for the meta-analysis. Furthermore, data from the present study was also included leading to a total of 36 research publications, including 8353 confirmed GC patients and 12099 control subjects. The major characteristics of the selected studies are shown in Table 2. Other relevant extracted data such as genotype and minor allele frequency and Hardy-Weinberg equilibrium (HWE) probability values of control genotypes are shown Table 3. Out of 36 studies included for the present meta-analysis, the genotype distribution in eight studies deviated from HWE.

Sensitivity Analysis

Sensitivity analysis was performed by eliminating each individual study to investigate their effect on the pooled result. The results of the sensitivity analysis revealed that none of the included studies disproportionately influenced the results of the meta-analysis (data not shown).

Results of the Meta-Analysis

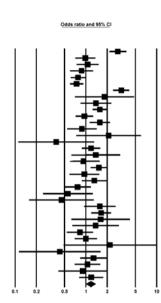
A total of 36 case-control studies including 12099 controls and 8353 confirmed GC cases were included in this meta-analysis. The Q test and I² statistics revealed heterogeneity among the included studies and thus a random-effects model was employed for allele and genotype comparison (Table 4). As shown in Figure 1, the allele (A vs G) and genotype comparison (AA vs GG) model showed a statistical significant role of the *TNF-a* -308G>A polymorphism in susceptibility to GC (A vs. G: p=0.04; AA vs. GG: p=0.04). However, other genetic comparison models failed to show a possible association (AG vs. GG: p=0.24; AA+AG vs. GG: p=0.09; AA vs. GG+AG: p=0.08).

Analysis based on ethnic group has been advised for metaanalysis; thus, in the present study we grouped all published literature including the present report into two broad groups based on ethnicity. a) Asian and b) Caucasian. A total of 18 casecontrol studies were from Asian ethnic backgrounds comprising 5957 controls and 4987 GC cases. Egger's regression analysis showed an absence of publication bias and all comparison models revealed heterogeneity among the included studies; thus, we employed a random-effects model for construction of a forest plot (Table 5). As shown in Figure 2, meta-analysis failed to show any possible association of the *TNF-a* -308G>A polymorphism with GC development in Asian ethnic groups (A

Table 4. Statistics to test publication bias and heterogeneity in the meta-analysis

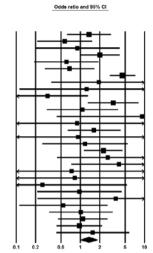
		Egger's regression analysis		He	eterogeneity analys	sis	
Comparisons	Intercept	95% Confidence Interval	р	Q	P _{heterogeneity}	I² (%)	Model used for meta-analysis
A vs G	-0.75	-2.54 to 1.04	0.40	176.88	0.000	80.21	Random
AA vs GG	-1.17	-2.14 to -0.20	0.01	51.21	0.007	43.37	Random
AG vs GG	-0.77	-2.47 to 0.92	0.35	176.07	0.000	80.12	Random
AA+AG vs GG	-0.59	-2.38 to 1.19	0.50	180.95	0.000	80.65	Random
AA vs AG+GG	-1.05	-2.06 to -0.04	0.04	50.21	0.009	42.25	Random

Study name		Statist	ics for e	ach study	1
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Present study	2.843	2.166	3.732	7.527	0.000
Bhayal et al. 2014	0.989	0.714	1.370	-0.068	0.946
Xu et al.2016	1.065	0.747	1.520	0.349	0.727
de Oliveira et al. 2015	0.878	0.606	1.271	-0.689	0.491
Zabaglia et al. 2015	0.778	0.616	0.981	-2.119	0.034
Yu et al 2014	0.743	0.601	0.920	-2.726	0.006
Hong et al. (test) 2013	3.178	2.449	4.124	8.699	0.000
Hong et al. (validation) 2	013842	0.704	4.818	1.245	0.213
Burada et al.2012	1.397	0.850	2.297	1.319	0.187
Canedo et al. 2008	1.580	1.258	1.984	3.933	0.000
Crusius et al. 2008	0.959	0.723	1.271	-0.293	0.770
El-Omar et al. 2003	1.581	1.141	2.191	2.754	0.006
Gou et al. 2005	0.885	0.552	1.420	-0.505	0.613
Jang et al. 2001	2.107	0.742	5.988	1.399	0.162
Fei et al. 2004	0.383	0.112	1.304	-1.535	0.125
Gracia-Gonzalez et al. 2	007190	0.882	1.604	1.140	0.254
Garza-Gonzalez et al. 21	005.389	0.629	3.064	0.813	0.416
Glas et al. 2004	0.926	0.544	1.574	-0.285	0.776
Hou et al. 2007	1.537	1.182	1.997	3.214	0.001
Kamangar et al. 2006	0.956	0.591	1.547	-0.183	0.855
Kim et al. 2006	1.326	0.882	1.992	1.357	0.175
Lee et al. 2004	0.767	0.498	1.182	-1.200	0.230
Lee et al. 2005	0.561	0.251	1.251	-1.112	0,151
Li et al. 2005	0.452	0.158	1.281	-1.428	0.139
Lu et al. 2005	1.585	0.953	2.638	1.774	0.076
Machado et al. 2003	1.653	1.205	27268	3.116	0.002
Melo et al. 2009	1.629	0.631	4 202	1.009	0.313
Morgan et al. 2006	1.377	0.647	2.930	0.830	0.407
Perri et al. 2005	0.831	0.544	1.269	-0.857	0.392
Rocha et al. 2005	1.004	0.701	1.438	0.023	0.982
Sugimoto et al. 2007	2.207	0.489	9.960	1.030	0.303
Torres et al. 2004	0.431	0.115	1.611	-1.252	0.211
Wu et al. 2002	1,289	0.840	1.976	1.162	0.24
Wu et al. 2002	1.057	0.702	1.591	0.263	0.79
Yang et al. 2009	0.908	0.412	2.001	-0.238	0.812
Zambon et al. 2005	1,197	0.814	1.761	0.915	0.360
	1.170	1.001	1.369	1.968	0.049



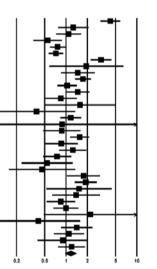
Odds ratio and 95% CI

	Statist	tics for ea	ch study	
Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
1.370	0.621	3.020	0.780	0.435
0.570	0.213	1.522	-1.122	0.262
0.908	0.200	4.124	-0.126	0.900
2.036	0.998	4.155	1.954	0.051
0.610	0.193	1.931	-0.841	0.400
0.682	0.281	1.655	-0.846	0.397
4.590	2.912	7.234	6.565	0.000
1.941	0.353	10.668	0.763	0.445
1.256	0.112	14.055	0.185	0.853
0.311	0.074	1.313	-1.589	0.112
3.277	1.316	8.160	2.550	0.011
1.086	0.303	3.888	0.127	0.899
9.194	0.432	195.546	1.422	0.155
0.894	0.036	22 287	-0.063	0.946
1.627	0.623	4.252	0.994	0.320
0.928	0.037	23.094	-0.046	0.963
1.193	0.259	5.501	0.227	0.001
2.288	1.151	4.549	2.361	0.039
2.686	0.440	16.389	1.072	0.284
4.020	0.730	22.135	1.599	0.110
0.734	0.046	11.800	-0.218	0.827
0.823	0.039	17.396	-0.125	0.901
0.256	0.012	5.359	-0.878	0.380
0.968	0.214	4.380	-0.042	0.966
3.583	0.216	59.429	0.891	0.373
0.545	0.112	2.656	-0.751	0.453
1.023	0.328	3.196	0.039	0.969
1.093	0.453	2.640	0.198	0.843
0.968	0.429	2.184	-0.077	0.938
1.566	0.423	5.798	0.672	0.502
1.362	1.007	1.842	2.003	0.045
	ratio 1.370 0.570 2.036 0.610 2.036 0.610 0.682 4.590 1.941 1.241 1.241 1.247 0.2928 1.943 1.993 2.288 2.288 2.288 2.288 2.288 2.288 2.288 3.583 3.553 3.553 3.553 1.024 1.023 1.023 1.023 1.024 1.023 1.024 1.023 1.024 1.023 1.025 1.023 1.023 1.025 1.023 1	Odd Lower rate 1370 0.621 0.570 0.213 0.570 0.213 0.570 0.213 0.570 0.203 0.662 0.203 0.670 1.030 0.682 0.201 0.570 0.213 1.296 0.213 0.203 0.213 0.404 0.513 1.296 0.112 0.207 0.023 1.190 0.432 0.298 0.229 1.151 1.616 1.627 0.623 0.734 0.623 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734 0.640 0.734<	Odds Lower Imit Upper Imit 13/0 0:21 3:02 0.570 0:213 1:52 0.570 0:213 1:52 0.590 0:200 1:31 0.590 0:200 1:91 0.682 0:530 1:91 0.682 0:231 1:622 0.500 0:122 7:214 0.501 0:127 1:068 0.311 0:727 1:313 0.211 0:162 0:388 9:194 0:432 1:052 0.684 0:032 2:287 1.667 0:622 2:211 0.672 5:201 1:736 0.734 0:640 0:32 2:315 0.734 0:640 1:310 2:041 1.103 0:270 5:201 1:292 0.680 0:422 2:041 1:030 0.734 0:640 1:202 5:01 0.734 0:626 1:130	ratio limit L.Value 1.370 0.621 3.020 0.781 5.70 0.221 3.020 0.781 5.70 0.221 3.020 0.782 0.500 0.224 3.020 1.782 0.500 0.220 4.124 -0.125 0.601 0.903 1.931 -0.841 0.602 0.211 1.655 -0.842 0.612 0.211 1.655 -0.853 1.226 0.112 1.005 0.153 1.236 0.112 1.005 0.152 3.11 0.741 3.13 -1.599 3.277 1.316 0.100 2.523 0.684 0.302 2.2287 -0.646 1.030 0.282 2.504 -1.422 0.684 0.327 2.534 -0.614 1.692 5.551 0.227 2.248 1.559 0.734 0.744 1.339 1.072 0.623



Study name		Statist	tics for e	ach study	1
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Present study	4.233	3.075	5.826	8.849	0.000
Bhayal et al. 2014	1.273	0.778	2.083	0.960	0.337
Xu et al 2016	1.094	0.732	1.636	0.438	0.661
de Oliveira et al. 2015	0.552	0.347	0.877	-2.513	0.012
Zabaglia et al. 2015	0.763	0.594	0.981	-2.114	0.035
Yu et al 2014	0.724	0.575	0.911	-2.753	0.006
Hong et al. (test) 2013	3.134	2.233	4.400	6.602	0.000
Hong et al. (validation) 2	013941	0.585	6.445	1.083	0.279
Burada et al 2012	1.475	0.857	2.538	1.403	0.161
Canedo et al. 2008	1.736	1.351	2.232	4.308	0.000
Crusius et al. 2008	1.044	0.763	1.428	0.268	0.789
El-Omar et al. 2003	1.473	1.007	2.155	1.997	0.046
Gou et al. 2005	0.850	0.506	1.428	-0.614	0.539
Jang et al. 2001	1.584	0.503	4.992	0.785	0.432
Fei et al. 2004	0.385	0.110	1.345	-1.495	0.135
Gracia-Gonzalez et al. 2	007171	0.840	1.633	0.931	0.352
Garza-Gonzalez et al. 20	888.00	0.036	22.069	-0.072	0.942
Glas et al. 2004	0.875	0.478	1.602	-0.433	0.665
Hou et al. 2007	1.569	1.150	2.140	2.839	0.005
Kamangar et al. 2006	0.862	0.504	1.475	-0.541	0.588
Kim et al. 2006	1.252	0.807	1.943	1.003	0.316
Lee et al. 2004	0.751	0.476	1.184	-1.233	0.218
Lee et al. 2005	0.541	0.237	1.235	-1.152	0.145
Li et al. 2005	0.461	0.157	1.348	-1.415	0.157
Lu et al. 2005	1.773	1.038	3.028	2.097	0.036
Machado et al. 2003	1.909	1.338	2724	3.567	0.000
Melo et al. 2009	1.536	0.533	4.424	0.795	0.427
Morgan et al. 2006	1.398	0.645	3.028	0.849	0.396
Perri et al. 2005	0.848	0.535	1.344	-0.702	0.483
Rocha et al. 2005	1.002	0.669	1.502	0.012	0.991
Sugimoto et al. 2007	2.231	0.489	10.171	1.037	0.300
Torres et al. 2004	0.410	0.106	1.583	-1.294	0.196
Wu et al. 2002	1.421	0.855	2.361	1.357	0.175
Wu et al. 2004	1.103	0.677	1.797	0.393	0.694
Yang et al. 2009	0.904	0.402	2 0 3 3	-0.245	0.806
Zambon et al. 2005	1.199	0.778	1.849	0.824	0.410
	1.169	0.976	1.401	1.695	0.090

Odds ratio and 95% CI



Odds ratio Lower Upper limit limit Z-Value p-Value 4.901 1.410 1.105 0.122 3.489 0.854 0.734 6.884 9.165 0.000 2.328 1.344 0.179 1.664 0.478 0.633 Present study Bhayal et al. 2014 Xu et al.2016 de Oliveira et al. 2015 de Oliveira et al. 2015 Zabaglia et al. 2015 Yu et al. 2014 Hong et al. (test) 2013 Hong et al. (validation) 20 Burada et al.2012 Canedo et al. 2008 0.770 2.203 013941 1.485 1.736 1.127 1.265 0.815 1.056 0.405 007130 Canedo et al. 2008 Crusius et al. 2008 El-Omar et al. 2003 Gou et al. 2005 Jang et al. 2001 Fei et al. 2004 Gracia-Gonzalez et al. 20
 Gracia-Gonzalez et al. 2007/130

 Garza-Gonzalez et al. 2006.718

 Glas et al. 2004
 0.840

 Hou et al. 2007
 1.469

 Kim et al. 2006
 1.158

 Lee et al. 2004
 0.751

 Lee et al. 2005
 0.448
 Lee et al. 2005 Li et al. 2005 Lu et al. 2005 Machado et al. 2003 Melo et al. 2009 Morgan et al. 2006 Perri et al. 2005 Dacha et al. 2005 0.488 1.921 1.964 1.378 1.398 0.881 1.000 2.231 0.410 1.579 1.170 0.904 1.173 1.118 Pern et al. 2005 Rocha et al. 2005 Sugimoto et al. 20 Torres et al. 2004 Wu et al. 2004 Wu et al. 2004

Statistics for each study

0.734	1.004	0.478	0.633		L		
0.051	0.293	-4.705	0.000			+	
0.597	0.994	-2.010	0.044			1	
0.574	0.919	-2.659	0.008			1	
1.444	3.361	3.666	0.000			1	
0.431	8.738	0.864	0.387			1	
0.856	2.577	1.405	0.160			1	
1.351	2.232	4.308	0.000			1	
0.820	1.549	0.734	0.463			1	
0.846	1.893	1.144	0.253			1	
0.465	1.427	-0.717	0.473			1	
0.294	3.797	0.083	0.934			1 .	_
0.116	1.418	-1.414	0.157		I —	+	_
0.799	1.598	0.690	0.490			1	
0.027	19.223	-0.197	0.844		<u>ا</u>	+	_
0.445	1.585	-0.539	0.590			1	
1.058	2.040	2.298	0.022			1	
0.454	1.383	-0.820	0.412			1	
0.735	1.826	0.633	0.527			1	
0.475	1.190	-1.218	0.228			1	
0.237	1.235	-1.153	0.145			1-	_
0.166		-1.397	0.191			+	_
1.112	3.317	2.340	0.019			1	
1.369		3.664	0.000			1	
0.447	4.251	0.558	0.577			1	
0.645	3.028	0.849	0.396			1	
0.548	1.416	-0.525	0.600			1	
0.657	1.523	0.001	0.999			1	
0.489	10.171	1.037	0.300			1	_
0.106	1.583	-1.294	0.196		——	+	_
0.882	2.828	1.536	0.124			1	
0.661	2.072	0.539	0.590			1	
0.402	2.033	-0.245	0.806			1	
0.750	1.834	0.699	0.485			1	
0.925	1.350	1.155	0.248			1	
				0	.1	0.2	

Statistics for each study

p-Value 0.690 0.092 0.869 0.022

0.448 0.467

0.467 0.000 0.511 0.907 0.102 0.015 0.878

0.155 0.982 0.344 0.441 0.178 0.040 0.258

0.115 0.850 0.936 0.355 0.762 0.391 0.469 0.969 0.971 0.895 0.536 0.083

AA vs AG+GG Study name

Yang et al. 2009 Zambon et al. 2005

AG vs GG

Study name

	Odds ratio	Lower limit	Upper limit	Z-Value
Present study	0.853	0.389	1.867	-0.398
3hayal et al. 2014	0.453	0.180	1.139	-1.684
Ku et al.2016	0.881	0.195	3.981	-0.165
de Oliveira et al. 2015	2.302	1.130	4.690	2.296
abaglia et al. 2015	0.640	0.202	2.026	-0.759
ru et al 2014	0.720	0.297	1.745	-0.727
long et al. (test) 2013	3.794	2.438	5.905	5.911
long et al. (validation) 2013	1.762	0.326	9.525	0.658
Burada et al.2012	1.154	0.103	12.866	0.116
Crusius et al. 2008	0.302	0.072	1.269	-1.635
El-Omar et al. 2003	3.069	1.241	7.592	2.427
Gou et al. 2005	1.105	0.309	3.953	0.154
Jang et al. 2001	9.158	0.431	194.482	1.421
Fei et al. 2004	0.965	0.039	24.019	-0.022
Gracia-Gonzalez et al. 2007	1.587	0.609	4.137	0.946
Garza-Gonzalez et al. 2005	1.383	0.607	3.150	0.771
3las et al. 2004	1.244	0.272	5.694	0.281
lou et al. 2007	2.036	1.032	4.017	2.050
Kamangar et al. 2006	2.835	0.467	17.222	1.134
Kim et al. 2006	3.940	0.716	21.668	1.576
.ee et al. 2004	0.765	0.048	12.386	-0.189
.i et al. 2005	0.882	0.042	18.620	-0.080
u et al. 2005.	0.238	0.011	4.987	-0.924
/lachado et al. 2003	0.792	0.176	3.571	-0.303
Aelo et al. 2009	3.414	0.207	56.281	0.859
Perri et al. 2005	0.557	0.115	2.710	-0.725
Rocha et al. 2005	1.023	0.329	3.182	0.039
Nu et al. 2002	1.016	0.423	2.442	0.036
Nu et al. 2004	0.947	0.422	2.128	-0.132
ambon et al. 2005	1.510	0.410	5.563	0.619
	1.287	0.968	1.713	1.734

0,1 0.2 0.5 2

Odds ratio and 95% CI

Figure 1. Forest plots of GC risk associated with the TNF- α –308G>A polymorphism (Overall). A total of 36 studies were included in the present meta-analysis. A random-effects model was used for calculation of a combined effect for all studies. The square and horizontal line represent the odds ratio and 95% confidence interval of each study. The square height denotes the weight of the study. The filled diamond represents the combined odds ratio and 95% confidence interval GC: gastric cancer

Du and Gao. TNF- α and gastric cancer

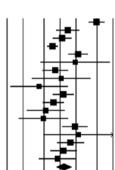
0.1

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Study name		Statisti	ics for ea	ach study				Odds	s rati	o and 95	5% CI			Study name		Statist	ics for ea	ch study			00	ids rat	io and	95% CI		
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value										Odds ratio	Lower limit	Upper limit	Z-Value	p-Value							
Present study	2.843	2.166	3.732	7.527	0.000	1	1		L	1 1		1	1	Present study	1.370	0.621	3.020	0.780	0.435	1	1	1-		+	1	
Bhayal et al. 2014	0.989	0.714	1.370	-0.068	0.946				Ι-	🔹 - I				Bhayal et al. 2014	0.570	0.213	1.522	-1.122	0.262			╼	—			
Xu et al.2016	1.065	0.747	1.520	0.349	0.727				۱.	Ŧ-				Xu et al.2016	0.908	0.200	4.124	-0.126	0.900		\vdash	+	-	+	· I –	
Yu et al 2014	0.743	0.601	0.920	-2.726	0.006				l 🖷	FL I				Yu et al 2014	0.682	0.281	1.655	-0.846	0.397		1 -		⊢–			
Hong et al. (test) 2013	3.178	2.449	4.124	8.699	0.000				I –	1	-	- I -		Hong et al. (test) 2013	4.590	2.912	7.234	6.565	0.000					1 -	-	
Hong et al. (validation) 2013	1.842	0.704	4.818	1.245	0.213				Ι-	┼╺╡		-		Hong et al. (validation) 2013	1.941	0.353	10.668	0.763	0.445		1	+		•—	+	-1
Gou et al. 2005	0.885	0.552	1.420	-0.505	0.613				I–I					Gou et al. 2005	1.086	0.303	3.888	0.127	0.899		1 -	+	-	+		
Jang et al. 2001	2.107	0.742	5.988	1.399	0.162				I -	- •	-	+		Jang et al. 2001	9.194	0.432	195.546	1.422	0.155			+	-	+	+	•
Fei et al. 2004	0.383	0.112	1.304	-1.535	0.125	I-	-	-		+ 1				Fei et al. 2004	0.894	0.036	22.287	-0.068	0.946	- H	+	+	-	+	+-	-
Kim et al. 2006	1.326	0.882	1.992	1.357	0.175	- T			1	┼═┥				Kim et al. 2006	4.020	0.730	22.135	1.599	0.110				+	┿╼╸	-+-	-
Lee et al. 2004	0.767	0.498	1.182		0.230				H	┡┼				Lee et al. 2004	0.734	0.046	11.800	-0.218	0.827	⊢ (⊢	+	+•	•	+	+-	-
Lee et al. 2005	0.561	0.251	1.251	-1.414	0.157			_		+ 1				Li et al. 2005	0.823	0.039	17.396	-0.125	0.901	F	+	+		+	+-	-
Li et al. 2005	0.452	0.158	1.203	-1.480	0.139		+	-	-	+ 1				Lu et al. 2005	0.256	0.012	5.359	-0.878	0.380	- ⊬	┿╾	+	+	+	+	
Lu et al. 2005	1.585	0.953	2.636	1.774	0.076				1	┼╼┽	-			Wu et al. 2002	1.093	0.453	2.640	0.198	0.843			+	-	+		
Sugimoto et al. 2007	2.207	0.489	9.960	1.030	0.303				⊢	+	_	+-	-	Wu et al. 2004	0.968	0.429	2.184	-0.077	0.938			+		+		
Wu et al. 2002	1.289	0.840	1.976	1.162	0.245				1	┿═╾┥					1.297	0.773	2.174	0.985	0.325				-	<u>ام</u>		
Wu et al. 2004	1.057	0.702	1.591	0.263	0.792				I -											0.1	0.2	0.5	1	2	5	1
Yang et al. 2009	0.908	0.412	2.001	-0.238	0.812			-	-											•			•	-	•	
	1.170	0.868	1.578	1.031	0.303				1	ا خ																
						0.1	0.2	2 0	.5	1 2	2	5	10													

Study name		Statist	ics for ea	ich study	_
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Present study	4.901	3.489	6.884	9.165	0.000
Bhayal et al. 2014	1.410	0.854	2.328	1.344	0.179
Xu et al.2016	1.105	0.734	1.664	0.478	0.633
Yu et al 2014	0.726	0.574	0.919	-2.659	0.008
Hong et al. (test) 2013	2.203	1.444	3.361	3.666	0.000
Hong et al. (validation) 2013	1.941	0.431	8,738	0.864	0.387
Gou et al. 2005	0.815	0.465	1.427	-0.717	0.473
Jang et al. 2001	1.056	0.294	3.797	0.083	0.934
Fei et al. 2004	0.405	0.116	1.418	-1.414	0.157
Kim et al. 2006	1.158	0.735	1.826	0.633	0.527
Lee et al. 2004	0.751	0.475	1.190	-1.218	0.223
Lee et al. 2005	0.541	0.237	1.235	-1.438	0.145
Li et al. 2005	0.488	0.186	1.482	-1.307	0.191
Lu et al. 2005	1.921	1.112	3.317	2.340	0.019
Sugimoto et al. 2007	2.231	0.489	10.171	1.037	0.300
Wu et al. 2002	1.579	0.882	2.828	1.536	0.124
Wu et al. 2004	1.170	0.661	2.072	0.539	0.590
Yang et al. 2009	0.904	0.402	2.033	-0.245	0.806
	1.187	0.846	1.663	0.993	0.321

Odds ratio and 95% CI



0.1

Study name		Statist	ics for ea	hch study	_	Odds ratio and 95% CI
	Odds ratio	Lower	Upper limit	Z-Value	p-Value	
Present study	4.233	3.075	5.826	8.849	0.000	
Bhayal et al. 2014	1.273	0.778	2.083	0.960	0.337	
Xu et al.2016	1.094	0.732	1.636	0.438	0.661	-===-
Yu et al 2014	0.724	0.575	0.911	-2.753	0.008	-∎-∏
Hong et al. (test) 2013	3.134	2.233	4.400	6.602	0.000	-■
long et al. (validation) 2013	1.941	0.585	6.445	1.083	0.279	
Gou et al. 2005	0.850	0.506	1.428	-0.614	0.539	│ ┝╼╪── │
Jang et al. 2001	1.584	0.503	4.992	0.785	0.432	
ei et al. 2004	0.385	0.110	1.345	-1.495	0.135 -	→ ∎↓→↓
Kim et al. 2006	1.252	0.807	1.943	1.003	0.316	
ee et al. 2004	0.751	0.476	1.184	-1.238	0.218	│ ┼╋┼ │
_ee et al. 2005	0.541	0.237	1.235	-1.438	0.145	
Li et al. 2005	0.461	0.157	1.318	-1.415	0.157	+
u et al. 2005	1.773	1.308	3.028	2.097	0.036	
Sugimoto et al. 2007	2.231	0.489	10.171	1.037	0.300	
Wu et al. 2002	1.421	0.855	2.361	1.357	0.175	+∎+
Wu et al. 2004	1.103	0.677	1.797	0.393	0.694	-+=-
Yang et al. 2009	0.904	0.402	2.033	-0.245	0.806	│ ∔∎⊑┤
-	1.206	0.861	1.689	1.088	0.277	

Study name		Statis	tics for ea	ch study		Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Present study	0.853	0.389	1.867	-0.398	0.690	
Bhayal et al. 2014	0.453	0.180	1.139	-1.684	0.092	
Xu et al.2016	0.881	0.195	3.981	-0.165	0.869	
Yu et al 2014	0.720	0.297	1.745	-0.727	0.467	
Hong et al. (test) 2013	3.794	2.438	5.905	5.911	0.000	
Hong et al. (validation) 2013	1.762	0.326	9.525	0.658	0.511	
Gou et al. 2005	1.105	0.309	3.953	0.154	0.878	
Jang et al. 2001	9.158	0.431	194.482	1.421	0.155	
Fei et al. 2004	0.965	0.039	24.019	-0.022	0.982	
Kim et al. 2006	3.940	0.716	21.668	1.576	0.115	
Lee et al. 2004	0.765	0.048	12.283	-0.189	0.850	
Li et al. 2005	0.882	0.042	18.620	-0.080	0.936	
Lu et al. 2005	0.238	0.011	4.087	-0.924	0.355	
Wu et al. 2002	1.016	0.423	2.442	0.036	0.971	
Wu et al. 2004	0.947	0.422	2.128	-0.132	0.895	
	1.166	0.703	1.935	0.594	0.553	

Figure 2. Forest plots of GC risk associated with TNF- α –308G>A polymorphism (Asian populations). Published studies were grouped ethnicity wise and a total of 18 reports hailing from the Asian continent including the present study were included for this analysis. A random-effects model was used for calculation of a combined effect of all studies. The square and horizontal line represent the odds ratio and 95% confidence interval of each study. The square height denotes the weight of the study. The filled diamond represents the combined odds ratio and 95% confidence interval GC: gastric cancer

0.1 0.2

0.5

Comparisons Intercep		Egger's regression analysis		He	eterogeneity analys		
	Intercept	95% Confidence Interval	р	Q	P _{heterogeneity}	I² (%)	Model used for meta-analysis
A vs G	-1.04	-4.08 to 1.98	0.47	131.65	0.000	87.08	Random
AA vs GG	-1.24	-2.83 to 0.34	0.11	35.73	0.001	60.82	Random
AG vs GG	-0.29	-3.20 to 2.62	0.83	111.60	0.000	84.76	Random
AA+AG vs GG	-0.64	-3.76 to 2.46	0.66	127.23	0.000	86.63	Random
AA vs AG+GG	-1.06	-2.66 to 0.54	0.17	35.16	0.001	60.19	Random

vs. G: p=0.30; AA vs. GG: p=0.32; AG vs. GG: p=0.32; AA+AG vs. GG: p=0.27; AA vs. GG+AG: p=0.55).

Sixteen studies comprising 5862 controls and 3138 GC patients were from a Caucasian background. Egger's regression analysis revealed no publication bias in the studies considered for meta-analysis; however, two genetic models showed (A vs. G and AA+AG vs. GG) heterogeneity among the included studies (Table 6). Based on the Q statistics and I² value, we used a random-effects model for calculation of an OR and 95% CI. As

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A ve 6 Study name Cds name Barudaet al 2012 1.397 Canedoct al 2008 1.580 Crussive al 2008 0.580 Crussive al 2009 0.561 Gracia-Gonzalez et al 2007.190 Garaza-Gonzalez et al 2007.190 Garaza-Gonzalez et al 2005 0.628 Hou et al 2007 1.537 Kamengar et al 2006 0.377 Melo et al 2009 1.629 Molgan et al 2005 0.381 Torres et al 2005 1.041 Zambon et al 2005 1.041	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Odds ratio and 95% Cl	Relative weight 4 90 9 50 8 34 9 00 2 37 4 51 5 19 8 00 1 72 2 57 8 17 7 51 0 93 8 91	Ar vs AC+CG Study name Barudaet al.2012 1.154 Crusiuset al.2003 3.099 Er-Omar et al.2003 3.099 Eracia-Gonzalez et al.2007.887 Garza-Gonzalez et al.2005.1837 Garza-Gonzalez et al.2005.1837 Garza-Gonzalez et al.2005.835 Machado et al.2009 3.4214 Perri et al.2005 0.557 Machado et al.2005 1.023 Zambon et al.2005 1.510 1.485	Statistics for each study Lower Upper limit X-Value p-Value 0.103 12.866 0.116 0.907 0.102 1.269 1.635 0.102 1.241 7.592 2.427 0.015 0.609 4.137 0.946 0.344 0.607 3.150 0.771 0.441 0.272 5.640 0.281 0.778 1.022 1.12 1.035 0.771 0.441 0.67 1.722 1.132 0.258 0.161 0.207 50.261 0.890 0.391 0.781 0.216 0.571 0.303 0.762 0.329 0.329 0.329 0.329 0.329 0.329 0.329 0.329 0.329 0.329 0.328 0.329 0.869 0.410 0.016	Odds ratio and 95% Cl	Relative weight 1.76 5.01 11.280 15.24 4.47 22.37 3.17 4.56 4.53 8.02 6.07
Aves GG Study name Barudaet al 2012 1.26 Crussives et al 2008 0.31 El-Omar et al 2003 0.37 Garca-Gonzalet et al 2005, 020 Garca-Gonzalet et al 2005, 020 Gasza-Gonzalet et al 2005, 020 2.08 Manangar et al 2007 2.28 Kamangar et al 2009 3.58 Perif et al 2005 0.69 Melo et al 2005 0.54 Rocha et al 2005 1.26 Zambon et al 2005 1.56	imit Z-Value P-Value 0 1112 14.056 0.118 0.863 1 0.74 1.313 1.589 0.112 1 3.16 8.160 2.550 0.011 7 1.318 8.160 2.550 0.011 7 1.318 8.160 2.550 0.011 7 0.523 6.250 0.501 0.250 8 0.37 3.094 -0.046 0.863 0.256 5.501 0.221 0.821 0.771 0.284 8 0.441 18.38 1.071 0.284 3.011 0.256 0.214 4.364 0.481 0.471 0.284 3.011 0.256 0.112 2.656 0.751 0.453 0.373 0.328 3.198 0.672 0.453 0.112 2.656 0.751 0.453 0.502 0.502 0.502 0.502 0.71 1.2238 2.557 0.502 0.502 <td></td> <td>Relative weight 2.09 5.68 14.64 12.21 1.18 5.22 22.60 3.73 5.35 1.54 4.86 9.39 7.11 00</td> <td>Avend vs GO Study name Odds ratio Banudaet al 2012 1.475 Canecodet al.2008 1.044 El-Omar et al.2008 1.044 El-Omar et al.2003 1.473 Gracia-Gonzalez et al.2007 1.589 Kanangaer et al.2006 0.682 Machado et al.2005 0.484 Perrie tal.2006 0.482 Partie tal.2005 0.484 Rocha et al.2005 1.0402 Torres et al.2005 1.490 Zambon et al.2005 1.490</td> <td>Statistics for sub-study Lower Upper International Colspan="2">Upper International Colspan="2">Value P-Value 0.857 0.857 2.538 1.403 0.61 0.857 2.538 1.403 0.600 0.763 1.428 0.268 0.789 0.707 1.165 1.997 0.464 0.840 0.839 0.931 0.852 0.702 2.269 0.072 0.423 0.753 1.475 0.284 0.065 0.554 1.475 0.547 0.542 0.533 4.244 0.705 0.427 0.454 3.057 0.424 0.433 0.544 0.704 0.424 0.424 0.545 1.244 0.705 0.427 0.551 1.542 0.702 0.433 0.753 1.424 0.702 0.433 0.754 0.224 0.410 0.102 0.755 1.424 0.702 0.431 0.755 0.224</td> <td>Odds ratio and B5% Cl</td> <td>Relative weight 5.29 9.78 8.14 9.28 0.22 4.54 9.84 5.37 8.72 1.81 3.10 6.58 7.62 1.18 7.06</td>		Relative weight 2.09 5.68 14.64 12.21 1.18 5.22 22.60 3.73 5.35 1.54 4.86 9.39 7.11 00	Avend vs GO Study name Odds ratio Banudaet al 2012 1.475 Canecodet al.2008 1.044 El-Omar et al.2008 1.044 El-Omar et al.2003 1.473 Gracia-Gonzalez et al.2007 1.589 Kanangaer et al.2006 0.682 Machado et al.2005 0.484 Perrie tal.2006 0.482 Partie tal.2005 0.484 Rocha et al.2005 1.0402 Torres et al.2005 1.490 Zambon et al.2005 1.490	Statistics for sub-study Lower Upper International Colspan="2">Upper International Colspan="2">Value P-Value 0.857 0.857 2.538 1.403 0.61 0.857 2.538 1.403 0.600 0.763 1.428 0.268 0.789 0.707 1.165 1.997 0.464 0.840 0.839 0.931 0.852 0.702 2.269 0.072 0.423 0.753 1.475 0.284 0.065 0.554 1.475 0.547 0.542 0.533 4.244 0.705 0.427 0.454 3.057 0.424 0.433 0.544 0.704 0.424 0.424 0.545 1.244 0.705 0.427 0.551 1.542 0.702 0.433 0.753 1.424 0.702 0.433 0.754 0.224 0.410 0.102 0.755 1.424 0.702 0.431 0.755 0.224	Odds ratio and B5% Cl	Relative weight 5.29 9.78 8.14 9.28 0.22 4.54 9.84 5.37 8.72 1.81 3.10 6.58 7.62 1.18 7.06
AG vs GC <u>Study name</u> Ddds Barudaet al 2012 1.48 Canedoct al. 2008 1.173 Crusiuset al.2008 1.173 Crusiuset al.2008 1.173 Crusiuset al.2008 1.173 Graza-Gonzalez et al.2005.071 Glaset al.2004 1.024 Hou et al.2007 1.468 Kamangar et al.2006 0.175 Mechade al.2007 1.468 Kamangar et al.2006 0.175 Mechade al.2005 1.1588 Perri et al.2005 0.688 Rocha et al.2005 1.067 Torres et al.2005 0.648 Rocha et al.2005 1.075	Imit ZValue p-Value 0 Imit ZValue p-Value 0 0.866 257 1.405 0.460 1 1.541 2.232 4.508 0.000 0 0.201 1.548 0.144 0.465 0 0.864 1.588 0.144 0.253 0 0.964 1.586 0.660 0.460 0 0.451 1.565 0.560 0.564 0 0.441 1.565 0.560 0.424 0 0.441 1.565 0.560 0.412 1.168 2.040 2.288 0.022 0.412 0 0.447 1.368 -0.820 0.412 1.168 2.040 2.288 0.022 0.424 0.445 1.388 -0.820 0.577 0.445 0.425 0.600 0.437 0.445 0.425 0.600 0.499 0.445 0.455 0.600 </td <td>Odds ratio and 95% CI</td> <td>Relative weight 3.90 18.81 11.70 7.30 9.87 0.11 2.94 11.00 3.82 9.09 9.03 1.98 5.25 6.71 0.65 5.93</td> <td>phism (Caucasian sian populations w el was used for ca and horizontal line each study. The sc</td> <td>populations). A tota ere included in the r lculation of a combi represent the odds juare height denote</td> <td>iated with TNF-α -308G>A p of 16 publications including neta-analysis. A random-effe ned effect for all studies. Th ratio and 95% confidence ir s the weight of the study. T ds ratio and 95% confidence</td> <td>cauca- cts mod- e square terval of he filled</td>	Odds ratio and 95% CI	Relative weight 3.90 18.81 11.70 7.30 9.87 0.11 2.94 11.00 3.82 9.09 9.03 1.98 5.25 6.71 0.65 5.93	phism (Caucasian sian populations w el was used for ca and horizontal line each study. The sc	populations). A tota ere included in the r lculation of a combi represent the odds juare height denote	iated with TNF-α -308G>A p of 16 publications including neta-analysis. A random-effe ned effect for all studies. Th ratio and 95% confidence ir s the weight of the study. T ds ratio and 95% confidence	cauca- cts mod- e square terval of he filled

ublications including Caucalysis. A random-effects modct for all studies. The square d 95% confidence interval of each study. The square height denotes the weight of the study. The filled diamond represents the combined odds ratio and 95% confidence interval GC: gastric cancer

Table 6. Statistics to test publication bias and heterogeneity in the meta-analysis (Caucasians)

		Egger's regression analysis		Heterogeneity analysis			
Comparisons	Intercept	95% Confidence interval	р	Q	P _{heterogeneity}	I² (%)	Model used for meta-analysis
A vs G	-1.19	-2.94 to 0.54	0.16	25.31	0.04	40.74	Random
AA vs GG	-0.97	-2.48 to 0.53	0.18	12.09	0.43	0.78	Fixed
AG vs GG	-1.43	-2.93 to 0.05	0.05	24.40	0.06	38.74	Fixed
AA+AG vs GG	-1.30	-2.90 to 0.29	0.10	25.77	0.04	41.80	Random
AA vs AG+GG	-0.89	-2.52 to 0.72	0.24	11.55	0.48	0.00	Fixed

shown in Figure 3, the *TNF-a* -308G>A polymorphism was significantly associated with GC in all genetic comparison models (A vs. G: p=0.001; AA vs. GG: p=0.01; AG vs. GG: p=0.00; AA+AG vs. GG: p=0.003; AA vs. GG+AG: p=0.01).

DISCUSSION

In the present investigation, a common polymorphism (-308G>A) in TNF- α was genotyped in a Chinese cohort and its association with development of GC was investigated. In addition, we searched the previous published literature on for the association of this polymorphism with GC susceptibility and performed a meta-analysis, including data from the present study. The results of the hospital-based case-control study revealed an association between heterozygous mutants and minor allele with a susceptibility to GC. Furthermore, the metaanalysis showed a link between TNF- α (-308G>A) variants with GC predisposition.

Several reports on the distribution of the TNF- α (-308G>A) genotype in healthy controls have been reported for Chinese populations. In the present study, controls were recruited from Beijing and genotyping data found 15% had heterozygous mutations and 3.5% had homozygous mutations. This observation is comparable with previous reports including healthy

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controls from Hubei province (9,36), Henan province (13), Taiwan (11,12) and Nanjing (8). However, other reports from Beijing (10) and Hubei province (7) showed a lower prevalence of heterozygous mutations (8-9%). Interestingly, the distribution of *TNF-a* (-308G>A) genotypes deviated from HWE in all earlier reports including the present study in a Chinese population (7-13,36). Deviation of a genotype distribution from HWE has been attributed to genotyping error, population stratification, or selection pressure. The present study and earlier reports enrolled controls from an ethnic group and employed robust genotyping methods (7-13,36). Deviation from HWE is possibly due to prevalence of various infectious diseases in Chinese populations, which applies selection pressure on the human genome (41).

Various studies have been conducted in different populations of China to identify a possible association of *TNF-a* -308G>A with the development of GC (7-13,36). Most of the studies showed an association of variants with susceptibility to GC. However, a study including patients and controls from Hubei province failed to demonstrate such an association. Consistent with earlier observations, we observed a significant association of heterozygotes and minor allele with GC susceptibility.

The exact mechanism whereby *TNF-a*-308G>A variants are predisposed to GC is unclear. The minor allele for *TNF-a* (-308G>A) polymorphism increases binding of transcription factors and elevated mRNA production compared to the major allele (G) (42,43). *In vitro* stimulation of peripheral blood mononuclear cells (PBMC) derived from heterozygous subjects (GA) with lipopolysaccharide displayed higher levels of TNF- α than those of wild type individuals (GG) (44). This minor allele is possibly linked with a higher transcription rate and that may induce a higher rate of inflammation in subjects harboring the minor allele (45). Furthermore, higher levels of TNF- α inhibit secretion of gastric acid and that may lead to spreading of *H. pylori* to the corpus and subsequently development of GC (6).

Meta-analysis is a powerful investigative method that combines similar studies to draw a firm conclusion. Since the association of the *TNF-a* (-308G>A) polymorphism with a predisposition to GC is unclear, a meta-analysis was performed combining earlier reports with the data of the present study. Results of the meta-analysis revealed a significant association of the *TNF-a* (-308G>A) polymorphism with GC susceptibility. Overall, the analysis showed subjects with the minor allele (A) or homozygous mutation (AA) had a 1.17 and 1.36 fold higher chance of development of GC, respectively. These observations are consistent with earlier meta-analyses (46,47). In addition, we observed an association between *TNF-a* polymorphisms with GC susceptibility in Caucasians but not in Asian ethnic groups, indicating a race-specific link between *TNF-a* -308G>A and GC susceptibility. Several reports have shown ethnic-specific genetic associations of variants with diseases and it has been advised to investigate genetic associations being aware of ethnicity.

Consistent with this, a recent study showed an association for a RAD51 135G>C substitution with susceptibility to breast cancer in Caucasians but not in East-Asians (48). Earlier meta-analyses by two different group also reported similar observations in the year 2014 (46,49). In addition, several reports including only Caucasian ethnic group for analysis demonstrated a possible association with GC susceptibility, further strengthening our observations (50-52). However, the very first meta-analysis including only 15 studies had shown an opposite association, i.e., TNF- α -308G>A variants were linked with GC susceptibility in Asians but not in Caucasians (47). Our present meta-analysis has several advantages over previous reports. The most recent meta-analyses were reported in the year 2014 (46,49,51). In the present study, five recent case-control studies investigating the role of TNF- α -308G>A in GC susceptibility were included, leading to an analysis including a much larger number of cases (n=8353) and controls (n=12099) (13,14,16,28,29).

There are several discrepancies between the results of the present case-control study and the results of the meta-analysis. First, the present case-control study revealed a significant association of heterozygous mutants (GA) with susceptibility to GC but the combined meta-analysis in the Caucasian population showed susceptibility of homozygous mutants to GC development. One possible explanation could be a lower prevalence of homozygous mutants in the studied population (3-3.5%). Because the meta-analysis combined several similar studies from different populations, the total number of studied subjects increased and possibly attained significant power to show an association, if any. Second, heterozygous mutants were associated with susceptibility to GC in the Chinese population but the meta-analysis failed to show any such link between the TNF- α genotype and GC in the Asian population. Because the Asian population included in the meta-analysis consist of various studies reported from China (n=11), India (n=1), North Korea (n=3), South Korea (n=1), and Japan (n=1), these diverse sample origins may be the reason for the discordant observations between the case-control study and the meta-analysis. Interestingly, out of 11 Chinese studies enrolled in the present meta-analysis, only one report failed to demonstrate an association between the *TNF-a* -308G>A polymorphism and GC.

In conclusion, *TNF-a* heterozygous and minor alleles are associated with susceptibility to GC in the studied Chinese population. However, a combined meta-analysis and studies on Asian subjects failed to demonstrate a possible association of the *TNF-a* allele with GC development. Interestingly, meta-analysis

of the *TNF-a* (-08G>A) polymorphism in Caucasians revealed a significant association with GC. We conclude that the *TNF-a* (-308G>A) polymorphism is linked to a GC predisposition in a population-specific manner. In future, studies from different populations including larger samples size are essential to establish a role of TNF- α in GC.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Beijing Chaoyang Hospital, China (Decision No: TCX13461).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - L.D., R.G.; Design - L.D., R.G.; Supervision - R.G.; Resource - L.D., R.G.; Materials - L.D., R.D.; Data Collection and/or Processing - L.D., R.G.; Literature Search - L.D., R.G.; Writing - L.D., R.G.; Critical Reviews - L.D., R.G.

Acknowledgements: Authors would like to thank patients and controls participated in the present study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by Beijing Chaoyang Hospital (Project No: YX132267).

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