World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i48.9461

World J Gastroenterol 2013 December 28; 19(48): 9461-9471
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

TNF-α-308 polymorphism and risk of digestive system cancers: A meta-analysis

Xu-Feng Guo, Jun Wang, Shi-Jie Yu, Jia Song, Meng-Yao Ji, Zhuo Cao, Ji-Xiang Zhang, Jing Wang, Wei-Guo Dong

Xu-Feng Guo, Jun Wang, Shi-Jie Yu, Jia Song, Meng-Yao Ji, Zhuo Cao, Ji-Xiang Zhang, Jing Wang, Wei-Guo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Author contributions: Guo XF and Wang J contributed equally to this work. Guo XF wrote the manuscript; Wang J conducted the analysis of pooled data; Yu SJ, Song J, Ji MY, Cao Z, Zhang JX and Wang J collected the literature; Dong WG revised the manuscript.

Correspondence to: Dr. Wei-Guo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, Hubei Province, China. dwg@whu.edu.cn

Telephone: +86-27-88041911 Fax: +86-27-88042292
Received: September 2, 2013 Revised: October 11, 2013
Accepted: November 2, 2013
Published online: December 28, 2013

Abstract

AIM: To evaluate the association between the tumour necrosis factor alpha-308 (*TNF-α-308*) gene polymorphism and the risk of digestive system cancers.

METHODS: All eligible case-control studies published up to December 2012 were identified by searching PubMed, Web of Science, Embase and China National Knowledge Internet without language restrictions. The risk of digestive system cancers associated with the *TNF-α-308* polymorphism was estimated for each study using odds ratio (OR) together with its 95%CI, respectively. Cochrane Collaboration RevMan 5.1 was used to perform the analysis. A χ^2-test-based Q statistic test and an I^2 test were performed to assess the between-study heterogeneity. When the Q test was significant ($P < 0.05$) or $I^2 > 50\%$, the random effects model was used, otherwise the fixed effects model was used.

RESULTS: Fifty-eight studies from fifty-five publications with a total of 9986 cancer patients and 15511 healthy controls were included. Overall, a significant association was found between the *TNF-α-308* polymorphism and the risk of digestive system cancers [dominant model: OR = 1.23, 95%CI: 1.09-1.39, (G/A) *vs* (G/G): OR = 1.15, 95%CI: 1.02-1.28, (A/A) *vs* (G/G): OR = 1.44, 95%CI: 1.19-1.73, recessive model: OR = 1.38, 95%CI: 1.15-1.66]. Furthermore, when the analysis was stratified by ethnicity, similar results were observed in both the Asian and Caucasian populations, except for the dominant model and heterozygote comparisons in the Asian population [dominant model: OR = 1.24, 95%CI: 0.99-1.56, (G/A) *vs* (G/G): OR = 1.09, 95%CI: 0.96-1.24]. When the cancer type subgroups were examined, similar results were detected in gastric and hepatocellular carcinomas; however, no significant association was observed among other digestive system cancers.

CONCLUSION: The *TNF-α-308* gene polymorphism may be significantly associated with the risk of gastric and hepatocellular carcinomas, but not colorectal, pancreatic, or oesophageal cancer, in the Asian population.

Key words: Tumour necrosis factor alpha; rs1800629; Polymorphism; Digestive system cancer; Meta-analysis; Association

Core tip: Genetic polymorphisms contribute to the risk of human malignant tumours. Many studies have reported the relationship between the tumour necrosis factor alpha-308 (*TNF-α-308*) gene polymorphism and risk of digestive system cancers. However, the results of these studies are inconsistent and contradictory. In this meta-analysis, our results suggest that the *TNF-α-308* polymorphism is significantly associated with the risk of gastric and hepatocellular carcinomas in the Asian

population (dominant model: 95%CI: 1.02-1.34, $P < 0.05$ and 95%CI: 1.20-2.54, $P < 0.05$, respectively). This finding indicates that certain polymorphisms and mutations at TNF-α-308 may increase susceptibility to digestive system cancers.

Guo XF, Wang J, Yu SJ, Song J, Ji MY, Cao Z, Zhang JX, Wang J, Dong WG. *TNF-α-308* polymorphism and risk of digestive system cancers: A meta-analysis. *World J Gastroenterol* 2013; 19(48): 9461-9471 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i48/9461.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i48.9461

INTRODUCTION

Digestive system cancers are the most common malignant tumours worldwide, with 3.4 million new cases each year, and their mortality rates have increased gradually over the past decade[1,2]. Molecular epidemiology has confirmed that carcinogenesis is a complex, multifactorial and multistep event, in which the interaction of environmental triggers and genetic susceptibility may play an important role. However, the exact mechanism of carcinogenesis is still not fully understood.

Tumour necrosis factor-alpha (TNF-α), which is mainly produced by macrophages, is a multifunctional cytokine that plays an important role in the pathogenesis of inflammatory, autoimmune, and malignant diseases[3]. The *TNF-α* gene is located in the major histocompatibility complex class Ⅲ region on the short arm of chromosome six. Several polymorphisms in the promoter region of the *TNF-α* gene have been identified and are implicated in the regulation of *TNF-α* transcription[4-5]. The *TNF-α-308* polymorphism (rs1800629) is the most extensively studied polymorphism in digestive system cancers[6-9]. However, the results of the studies on TNF-α-308 have been inconclusive or inconsistent. Therefore, we conducted a meta-analysis to evaluate the association between the *TNF-α-308* polymorphism and susceptibility to digestive system cancers.

MATERIALS AND METHODS

Search strategy

A literature search was conducted using PubMed, Web of Science, Embase and CNKI for studies that were published up to December 2012 without language restrictions. The relevant studies were identified using the following terms: ["tumour necrosis factor alpha or TNF alpha or TNF-α"] AND ["genetic polymorphism or polymorphisms or variant"] AND ["digestive system cancer or gastric cancer or colorectal cancer or hepatocellular carcinoma or pancreatic cancer or oesophageal cancer"]. The search was restricted to humans. Additional studies were identified by a manual search of references of original or review articles on this topic. If more than one cancer type was reported in one study, the data for each type was extracted separately. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) studies that evaluated the association between the *TNF-α-308* polymorphism and digestive system cancer risk; (2) studies with a case-control study design; and (3) studies with detailed genotype frequencies for cases and controls or text that allowed for the calculation of these values. The major exclusion criteria were: (1) case-only studies, case reports, or review articles; (2) studies without raw data for the *TNF-α-308G/A* genotype; and (3) studies that compared the *TNF-α-308G/A* variants in precancerous lesions and other cancers.

Data extraction and quality assessment

Two investigators (Guo XF and Wang J) independently extracted the data and reached a consensus on each item. If the two investigators generated different results, they would check the data again and have a discussion to come to an agreement. If they could not reach an agreement, an expert (Dong WG) was invited to the discussion. The data extracted from the selected articles included the first author's name, year of publication, country of origin, ethnicity, cancer type, genotyping methods, and number of cases and controls. The ethnicities were categorised as Asian or Caucasian. The cancer types were categorised as gastric, colorectal, hepatocellular, pancreatic, or oesophageal.

Statistical analysis

The meta-analysis was performed using the Cochrane Collaboration RevMan 5.1 software (Copenhagen, 2008). The association between the risk of digestive system cancers and the *TNF-α-308* polymorphism was estimated for each study using the odds ratio (OR) and 95%CI. A χ^2 test-based calculation of the Q statistic was performed to assess the between-study heterogeneity[10]. We also quantified the effect of heterogeneity with an I^2 test. When the Q test was significant ($P < 0.05$) or $I^2 > 50\%$, indicating heterogeneity across studies, the random effects model was used[11]; otherwise, the fixed effects model was used[12]. Before estimating the relationship between the *TNF-α-308* polymorphism and digestive system cancer risk, we tested whether the genotype frequencies of the controls were in Hardy-Weinberg equilibrium (HWE) using a χ^2 test. We first estimated this relationship with the dominant model [G/A (GA) + A/A (AA) *vs* G/G (GG)] and the recessive model (AA *vs* GA + GG) and then with the co-dominant model (GA *vs* GG and AA *vs* GG). To evaluate the ethnicity-specific and cancer type-specific effects, we performed stratification analyses with respect to ethnicity and cancer type. Sensitivity analysis was performed to evaluate the stability of the results. Funnel plots were used to evaluate publication bias.

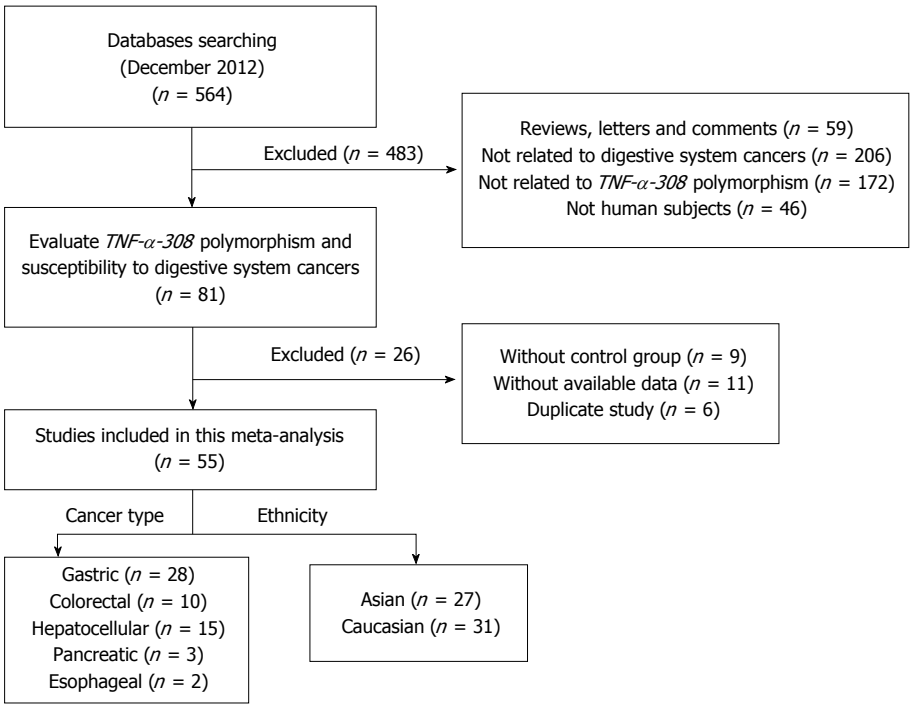

Figure 1 Flow chart showing study selection procedure. TNF-α: Tumour necrosis factor-alpha.

RESULTS

Study characteristics

The search strategy retrieved 564 potentially relevant studies. According to the inclusion criteria, 55 studies with full-text were included in this meta-analysis and 509 studies were excluded. A flow chart of the study selection is shown in Figure 1. Because the studies of El-Omar *et al*[9], Guo *et al*[13] and Jang *et al*[14] each included separate analyses of two cancer types, we treated them separately in this meta-analysis[9,13,14]. Therefore, as shown in Table 1, there were 58 case-control studies from 55 publications on the *TNF-α-308* polymorphism with a total of 9986 cancer cases and 15511 controls. Two ethnicities were addressed: 27 studies focused on Asian populations, and 31 studies focused on Caucasian populations. Five cancer types were addressed: 28 studies focused on gastric cancer[6-9,13-36], 10 studies on colorectal cancer[14,37-45], 15 studies on hepatocellular carcinoma[46-60], 3 studies on pancreatic cancer[61-63], and 2 studies on oesophageal cancer[9,13]. The genotype distribution in the controls was consistent with HWE for all of the selected studies, except for four studies on gastric cancer[7,13,33-34], one study on colorectal cancer[43], six studies on hepatocellular carcinoma[47,49,51-52,55-56], and one study on esophageal cancer[13].

Quantitative data synthesis

Overall, there was a significant difference in the *TNF-α-308G/A* genotype distribution between the digestive system cancer patients and the controls (dominant model: OR = 1.23, 95%CI: 1.09-1.39, $P < 0.00001$; GA *vs* GG: OR = 1.15, 95%CI: 1.02-1.28, $P < 0.0001$; AA *vs* GG: OR = 1.44, 95%CI: 1.19-1.73, $P = 0.23$; recessive model: OR = 1.38, 95%CI: 1.15-1.66, $P = 0.50$) (Table 2, Figure 2). In the analysis of the ethnic subgroups, similar results were observed in the Caucasian population; but in the Asian population, we found that there was no significant association between the *TNF-α-308* polymorphism and the risk of digestive system cancers in the dominant model and heterozygote comparisons (GA + AA *vs* GG: OR = 1.24, 95%CI: 0.99-1.56, GA *vs* GG: OR = 1.09, 95%CI: 0.96-1.24) (Table 2, Figure 2). When stratified by cancer type, similar results were detected for gastric and hepatocellular carcinomas; however, no significant association was observed among the other digestive system cancer types (Table 2, Figure 3). Furthermore, we found that there was significant heterogeneity for the dominant model and heterozygote comparisons both overall and in the stratified analyses: $I^2 = 64\%$ and 52% in the overall population, $I^2 = 66\%$ and 45% ($P = 0.008$) in the Asian population, $I^2 = 64\%$ and 58% in the Caucasian population, $I^2 = 76\%$ and 70% in colorectal cancer, and $I^2 = 73\%$ and 66% in hepatocellular carcinoma. In addition, there was evidence of heterogeneity in gastric cancer (dominant model: $P = 0.009$). Thus, the random effects model was employed in the OR calculations. Then, sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. We examined the influence of these studies on the pooled OR by repeating the meta-analysis while excluding the study that was not in HWE. The estimated pooled OR did not show a significant change (Table 2), indicating that our results are statistically robust. The shapes of the funnel plots did not reveal any evidence of asymmetry, suggesting that there was no publication bias among the studies (Figure 4).

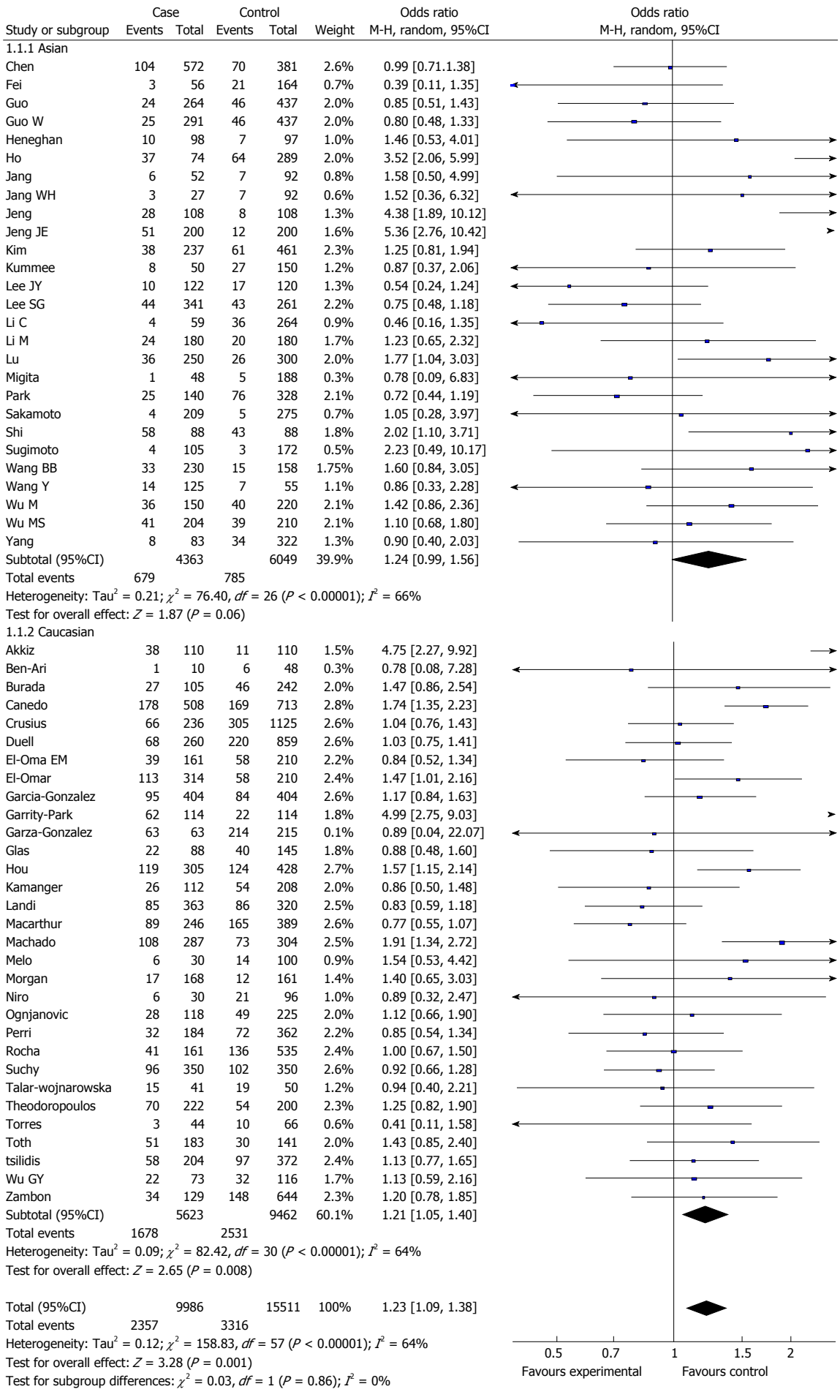

Figure 2 Subgroup analysis of tumour necrosis factor α-308 polymorphism by ethnicity (dominant model).

Study or subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95%CI
1.2.1 Gastric cancer						
Burada	27	105	46	242	2.0%	1.47 [0.86, 2.54]
Canedo	178	508	169	713	2.8%	1.74 [1.35, 2.23]
Crusius	66	236	305	1125	2.6%	1.04 [0.76, 1.43]
El-Omar	113	314	58	210	2.4%	1.47 [1.01, 2.16]
Fei	3	56	21	164	0.7%	0.39 [0.11, 1.35]
Garcia-Gonzalez	95	404	84	404	2.6%	1.17 [0.84, 1.63]
Garza-Gonzalez	63	63	214	215	0.1%	0.89 [0.04, 22.07]
Glas	22	88	40	145	1.8%	0.88 [0.48, 1.60]
Guo	24	264	46	437	2.0%	0.85 [0.51, 1.43]
Hou	119	305	124	428	2.7%	1.57 [1.15, 2.14]
Jang	6	52	7	92	0.8%	1.58 [0.50, 4.99]
Kamanger	26	112	54	208	2.0%	0.86 [0.50, 1.48]
Kim	38	237	61	461	2.3%	1.25 [0.81, 1.94]
Lee JY	10	122	17	120	1.3%	0.54 [0.24, 1.24]
Lee SG	44	341	43	261	2.2%	0.75 [0.48, 1.18]
Li C	4	59	36	264	0.9%	0.46 [0.16, 1.35]
Lu	36	250	26	300	2.0%	1.77 [1.04, 3.03]
Machado	108	287	73	304	2.5%	1.91 [1.34, 2.72]
Melo	6	30	14	100	0.9%	1.54 [0.53, 4.42]
Morgan	17	168	12	161	1.4%	1.40 [0.65, 3.03]
Perri	32	184	72	362	2.2%	0.85 [0.54, 1.34]
Rocha	41	161	136	535	2.4%	1.00 [0.67, 1.50]
Sugimoto	4	105	3	172	0.5%	2.23 [0.49, 10.17]
Torres	3	44	10	66	0.6%	0.41 [0.11, 1.58]
Wu M	36	150	40	220	2.1%	1.42 [0.86, 2.36]
Wu MS	41	204	39	210	2.1%	1.10 [0.68, 1.80]
Yang	8	83	34	322	1.3%	0.90 [0.40, 2.03]
Zambon	34	129	148	644	2.3%	1.20 [0.78, 1.85]
Subtotal (95%CI)		5061		8885	49.6%	1.17 [1.02, 1.34]
Total events	1204		1932			

Heterogeneity: Tau^2 = 0.05; χ^2 = 47.60, *df* = 27 (*P* = 0.009); I^2 = 43%
Test for overall effect: *Z* = 2.32 (*P* = 0.02)

1.2.2 Colorectal cancer						
Garrity-Park	62	114	22	114	1.8%	4.99 [2.75, 9.03]
Jang WH	3	27	7	92	0.6%	1.52 [0.36, 6.32]
Landi	85	363	86	320	2.5%	0.83 [0.59, 1.18]
Li M	24	180	20	180	1.7%	1.23 [0.65, 2.32]
Macarthur	89	246	165	389	2.6%	0.77 [0.55, 1.07]
Park	25	140	76	328	2.1%	0.72 [0.44, 1.19]
Suchy	96	350	102	350	2.6%	0.92 [0.66, 1.28]
Theodoropoulos	70	222	54	200	2.3%	0.25 [0.82, 1.90]
Toth	51	183	30	141	2.0%	1.43 [0.85, 2.40]
Tsilidis	58	204	97	372	2.4%	1.13 [0.77, 1.65]
Subtotal (95%CI)		2029		2486	20.7%	1.17 [0.87, 1.57]
Total events	563		659			

Heterogeneity: Tau^2 = 0.16; χ^2 = 37.06, *df* = 9 (*P* < 0.00001); I^2 = 76%
Test for overall effect: *Z* = 1.02 (*P* = 0.31)

1.2.3 Hepatocellular carcinoma						
Akkiz	38	110	11	110	1.5%	4.75 [2.27, 9.92]
Ben-Ari	1	10	6	48	0.3%	0.78 [0.08, 7.28]
Chen	104	572	70	381	2.6%	0.99 [0.71, 1.38]
Heneghan	10	98	7	97	1.0%	1.46 [0.53, 4.01]
Ho	37	74	64	289	2.0%	3.52 [2.06, 5.99]
Jeng	28	108	8	108	1.3%	4.38 [1.89, 10.12]
Jeng JE	51	200	12	200	1.6%	5.36 [2.76, 10.42]
Kummee	8	50	27	150	1.2%	0.87 [0.37, 2.06]
Migita	1	48	5	188	0.3%	0.78 [0.09, 6.83]
Niro	6	30	21	96	1.0%	0.89 [0.32, 2.47]
Ognjanovic	28	118	49	225	2.0%	1.12 [0.66, 1.90]
Sakamoto	4	209	5	275	0.7%	1.05 [0.28, 3.97]
Shi	58	88	43	88	1.8%	2.02 [1.10, 3.71]
Wang BB	33	230	15	158	1.7%	1.60 [0.84, 3.05]
Wang Y	14	125	7	55	1.1%	0.86 [0.33, 2.28]
Subtotal (95%CI)		2070		2468	19.9%	1.74 [1.20, 2.54]
Total events	421		350			

Heterogeneity: Tau^2 = 0.35; χ^2 = 51.15, *df* = 14 (*P* < 0.00001); I^2 = 73%
Test for overall effect: *Z* = 2.89 (*P* = 0.004)

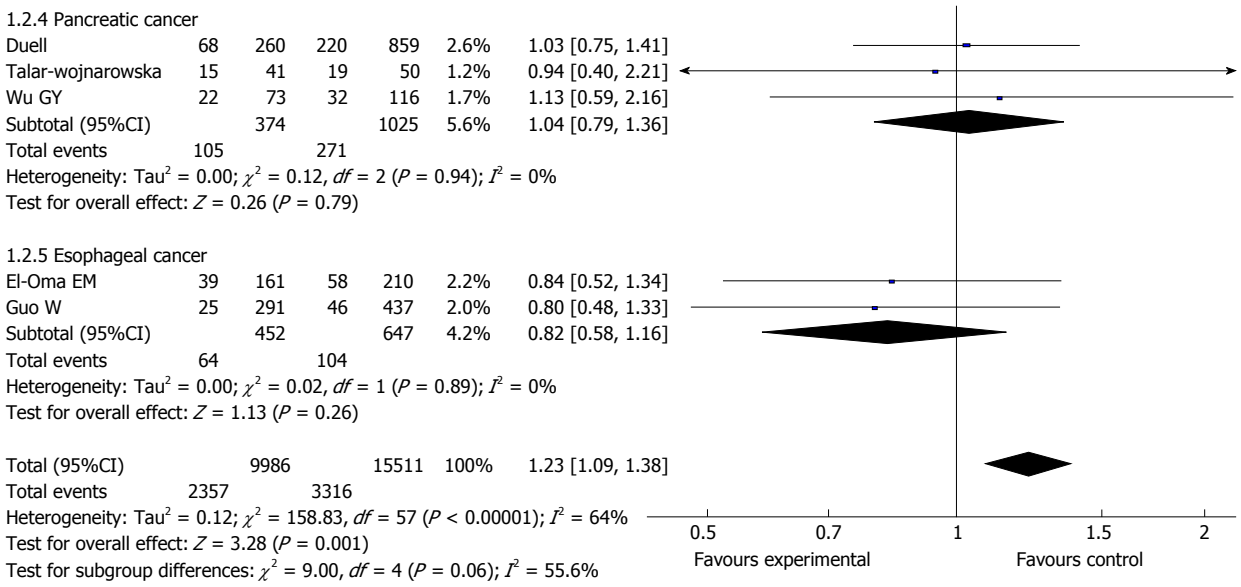

Figure 3 Subgroup analysis of tumor necrosis factor α-308 polymorphism by cancer type (dominant model).

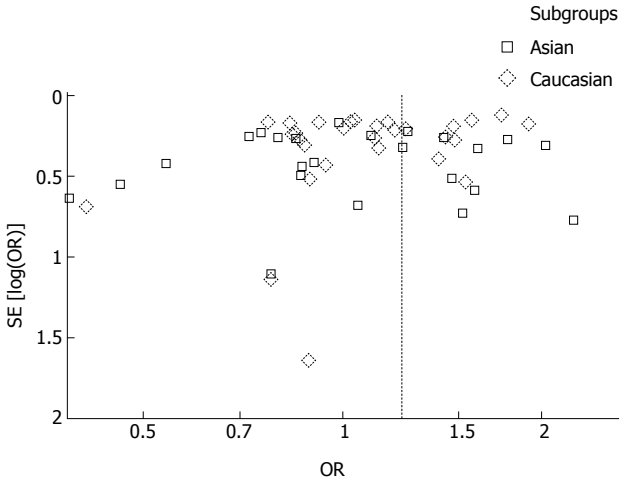

Figure 4 Funnel plots analysis to detect publication bias. Each point represents an independent study for the indicated association.

DISCUSSION

TNF, an important pro-inflammatory cytokine, plays an important role in the regulation of cell differentiation, proliferation and death as well as in inflammation and the innate and adaptive immune response. TNF has also been implicated in a wide variety of human diseases. The presence of DNA sequence variations in the regulatory region might interfere with transcription of the *TNF* gene, influencing the circulating level of TNF and thus increasing susceptibility to human diseases, such as cancer[64]. The TNF enhancer polymorphism has been implicated in several diseases, and the *TNF-α-308* polymorphism has been described as the most important TNF polymorphism in human disease susceptibility. The significance of these polymorphisms reflects their possible influence on the transcription of the *TNF* gene. However, the results of studies in this area are inconsistent. Canedo *et al*[7] found that the *TNF-α-308G/A* polymorphism increases the risk of gastric carcinoma. However, some studies have reported that no statistically significant association exists between the *TNF-α-308G/A* polymorphism and cancer risk[14,20].

The current meta-analysis, which included 58 case-control studies and 25497 subjects, was conducted to explore the association of the *TNF-α-308* polymorphism with digestive system cancer risk. Overall, a significant association was identified between the *TNF-α-308* polymorphism and the risk of digestive system cancers. When the analysis was stratified by ethnicity, we found a statistically significant association between this polymorphism and the risk of these cancers in the Caucasian population. However, no significant association was observed in the dominant model and heterozygote comparisons in the Asian population, which could be due to ethnic differences. When the analysis was stratified by cancer type, we found a significant association between this polymorphism and gastric and hepatocellular carcinoma risk under all four genetic models, but no significant association was observed among colorectal, pancreatic or oesophageal cancer.

Heterogeneity is a potential problem when interpreting the results of meta-analyses. In this meta-analysis, heterogeneity was found in the dominant model and heterozygote comparisons in both the overall and subgroup analyses; thus, the random effects model was used. Sensitivity analyses were also conducted by excluding the study that was not in HWE. With this exclusion, the estimated pooled OR did not change significantly, strengthening our confidence in our results. This finding suggests that the population selection and the study that was not in HWE were not sources of heterogeneity. Alternatively, lifestyle, environment and other unknown factors may be sources of heterogeneity. Moreover, no publication bias was shown, suggesting that our results

Table 1 Characteristics of studies included in the meta-analysis

Ref.	Year	Country	Ethnicity	Cancer type	Genotyping method	Case				Control				*P*
						Total	GG	GA	AA	Total	GG	GA	AA	
Burada *et al*[6]	2012	Romania	Caucasian	Gastric	TaqMan	105	78	26	1	242	196	44	2	0.78
Canedo *et al*[7]	2008	Portugal	Caucasian	Gastric	TaqMan	508	330	178[1]		713	544	169[1]		NA
Crusius *et al*[8]	2008	Spain	Caucasian	Gastric	Real-time PCR	236	170	64	2	1125	820	274	31	0.17
El-Omar *et al*[9]	2003	United States	Caucasian	Gastric	TaqMan	314	201	87	26	210	152	52	6	0.55
Guo *et al*[13]	2005	China	Asian	Gastric	PCR-RFLP	264	240	20	4	437	391	40	6	< 0.01
Jang *et al*[14]	2001	South Korea	Asian	Gastric	PCR-RFLP	52	46	4	2	92	85	7	0	0.70
Fei *et al*[15]	2004	China	Asian	Gastric	PCR	56	53	3	0	164	143	20	1	0.74
Garcia-Gonzalez *et al*[16]	2007	Spain	Caucasian	Gastric	TaqMan	404	309	84	11	404	320	77	7	0.35
Garza-Gonzalez *et al*[17]	2005	Mexico	Caucasian	Gastric	PCR-RFLP	63	0	8	55	215	1	35	179	0.61
Glas *et al*[18]	2004	Germany	Caucasian	Gastric	PCR-RFLP	88	66	19	3	145	105	36	4	0.67
Hou *et al*[19]	2007	Poland	Caucasian	Gastric	TaqMan	305	186	98	21	428	304	109	15	0.19
Kamangar *et al*[20]	2006	Finland	Caucasian	Gastric	TaqMan	112	86	23	3	208	154	52	2	0.29
Kim *et al*[21]	2006	South Korea	Asian	Gastric	PCR-RFLP	237	199	34	4	461	400	59	2	0.91
Lee *et al*[22]	2004	South Korea	Asian	Gastric	PCR	341	297	43	1	261	218	42	1	0.49
Lee *et al*[23]	2005	South Korea	Asian	Gastric	PCR-RFLP	122	112	10	0	120	103	17	0	0.40
Li *et al*[24]	2005	China	Asian	Gastric	PCR-RFLP	59	55	4	0	264	228	34	2	0.56
Lu *et al*[25]	2005	China	Asian	Gastric	PCR-DHPLC	250	214	36	0	300	274	24	2	0.08
Machado *et al*[26]	2003	Portugal	Caucasian	Gastric	PCR-SSCP	287	179	105	3	304	231	69	4	0.65
Melo *et al*[27]	2009	Brazil	Caucasian	Gastric	PCR-RFLP	30	24	5	1	100	86	13	1	0.53
Morgan *et al*[28]	2006	Honduras	Caucasian	Gastric	TaqMan	168	151	17	0	161	149	12	0	0.62
Perri *et al*[29]	2005	Italy	Caucasian	Gastric	PCR-RFLP	184	152	30	2	362	290	65	7	0.15
Rocha *et al*[30]	2005	Brazil	Caucasian	Gastric	PCR-RFLP	161	120	37	4	535	399	123	13	0.34
Sugimoto *et al*[31]	2007	Japan	Asian	Gastric	PCR-RFLP	105	101	4	0	172	169	3	0	0.91
Torres *et al*[32]	2004	Colombia	Caucasian	Gastric	PCR	44	41	3	0	66	56	10	0	0.51
Wu *et al*[33]	2002	China	Asian	Gastric	Direct sequencing	150	114	27	9	220	180	27	13	< 0.01
Wu *et al*[34]	2004	China	Asian	Gastric	Direct sequencing	204	163	29	12	210	171	26	13	< 0.01
Yang *et al*[35]	2009	South Korea	Asian	Gastric	SNaPshot	83	75	8	0	322	288	34	0	0.32
Zambon *et al*[36]	2005	Italy	Caucasian	Gastric	TaqMan	129	95	31	3	644	496	138	10	0.91
Garrity-Park *et al*[37]	2008	Ireland	Caucasian	Colorectal	PCR, sequencing	114	52	49	13	114	92	20	2	0.46
Jang *et al*[14]	2001	South Korea	Asian	Colorectal	PCR-RFLP	27	24	3	0	92	85	7	0	0.70
Landi *et al*[38]	2003	Spain	Caucasian	Colorectal	TaqMan	363	278	80	5	320	234	76	10	0.22
Li M *et al*[39]	2011	China	Asian	Colorectal	PCR-RFLP	180	156	15	9	180	160	19	1	0.60
Macarthur *et al*[40]	2005	Scotland	Caucasian	Colorectal	TaqMan	246	157	74	15	389	224	145	20	0.58
Park *et al*[41]	1998	South Korea	Asian	Colorectal	PCR-RFLP	140	115	24	1	328	252	72	4	0.65
Suchy *et al*[42]	2008	Poland	Caucasian	Colorectal	PCR-RFLP	350	254	87	9	350	248	95	7	0.55
Theodoropoulos *et al*[43]	2006	Greece	Caucasian	Colorectal	PCR-RFLP	222	152	56	14	200	146	44	10	0.01
Toth *et al*[44]	2007	Hungary	Caucasian	Colorectal	PCR-SSP	183	132	48	3	141	111	30	0	0.16
Tsilidis *et al*[45]	2009	United States	Caucasian	Colorectal	TaqMan	204	146	55	3	372	275	90	7	0.91
Akkiz *et al*[46]	2009	Turkey	Caucasian	Hepatocellular	PCR-RFLP	110	72	35	3	110	99	11	0	0.58
Ben-Ari *et al*[47]	2003	United States	Caucasian	Hepatocellular	PCR-SSP	10	9	1[1]		48	42	6[1]		NA
Chen *et al*[48]	2005	China	Asian	Hepatocellular	TaqMan	572	468	95	9	381	311	67	3	0.77
Heneghan *et al*[49]	2003	China	Asian	Hepatocellular	ASO-PCR	98	88	10	0	97	90	6	1	0.03
Ho *et al*[50]	2004	China	Asian	Hepatocellular	PCR-RFLP	74	37	34	3	289	225	62	2	0.30
Jeng *et al*[51]	2007	China	Asian	Hepatocellular	PCR-SSO	108	80	28[1]		108	100	8[1]		NA
Jeng JE *et al*[52]	2009	China	Asian	Hepatocellular	PCR-SSO	200	149	51[1]		200	188	12[1]		NA
Kummee *et al*[53]	2007	Thailand	Asian	Hepatocellular	PCR-RFLP	50	42	8	0	150	123	26	1	0.77
Migita *et al*[54]	2005	Japan	Asian	Hepatocellular	PCR-SSP	48	47	1	0	188	183	5	0	0.85
Niro *et al*[55]	2005	Italy	Caucasian	Hepatocellular	Direct sequencing	30	24	6[1]		96	75	21[1]		NA
Ognjanovic *et al*[56]	2009	United States	Caucasian	Hepatocellular	TaqMan	118	90	28[1]		225	176	49[1]		NA
Sakamoto *et al*[57]	2008	Japan	Asian	Hepatocellular	PCR-RFLP	209	205	4	0	275	270	5	0	0.88
Shi *et al*[58]	2011	China	Asian	Hepatocellular	PCR-RFLP	88	30	43	15	88	45	35	8	0.75
Wang *et al*[59]	2003	Japan	Asian	Hepatocellular	Direct sequencing	125	111	13	1	55	48	6	1	0.16
Wang *et al*[60]	2010	China	Asian	Hepatocellular	PCR-SSO	230	197	30	3	158	143	15	0	0.53
Duell *et al*[61]	2006	United States	Caucasian	Pancreatic	PCR-RFLP	260	192	63	5	859	639	198	22	0.16
Talor-wojnarowska *et al*[62]	2009	Poland	Caucasian	Pancreatic	PCR-RFLP	41	26	12	3	50	31	17	2	0.86
Wu GY *et al*[63]	2010	Germany	Caucasian	Pancreatic	PCR-RFLP	73	51	20	2	116	84	30	2	0.72
El-Omar *et al*[9]	2003	United States	Caucasian	Esophageal	TaqMan	161	122	34	5	210	152	52	6	0.55
Guo *et al*[13]	2005	China	Asian	Esophageal	PCR-RFLP	291	266	21	4	437	391	40	6	< 0.01

[1]Numbers of GA+AA. P_{HWE} was calculated by goodness-of fit χ^2-test, and $P_{HWE} < 0.05$ was considered statistically significant. PCR-DHPLC: Polymerase chain reaction-based denaturing high-performance liquid chromatography; HWE: Hardy-Weinberg equilibrium; NA: Not available; GG: Guanine/Guanine; GA: Guanine/Adenine; AA: Adenine/Adenine; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

are accurate.

Some limitations of this meta-analysis should be addressed. First, the number of published studies, especially for oesophageal and pancreatic cancers, was not suf-

Table 2 Stratified analysis of the tumor necrosis factor alpha polymorphism and digestive system cancers risk

Group	GA + AA *vs* GG			GA *vs* GG			AA *vs* GG			AA *vs* GA + GG		
	n	OR (95%CI)	*P*[1]	*n*	OR (95%CI)	*P*[1]	*n*	OR (95%CI)	*P*[1]	*n*	OR (95%CI)	*P*[1]
Overall	58	1.23 (1.09, 1.38)[2]	< 0.00001	52	1.14 (1.01, 1.28)[2]	< 0.00001	44	1.43 (1.19, 1.73)	0.26	44	1.38 (1.15, 1.66)	0.55
Studies with HWE	46	1.18 (1.03, 1.34)[2]	< 0.00001	46	1.14 (1.00, 1.29)[2]	< 0.00001	38	1.54 (1.25, 1.90)	0.15	38	1.48 (1.20, 1.81)	0.40
Cancer type												
Gastric	28	1.23 (1.12, 1.34)[2]	0.009	27	1.15 (1.04, 1.27)	0.07	22	1.38 (1.06, 1.80)	0.63	22	1.33 (1.03, 1.72)	0.67
Colorectal	10	1.17 (0.87, 1.57)[2]	< 0.0001	10	1.10 (0.83, 1.45)[2]	0.0004	9	1.45 (0.76, 2.75)[2]	0.02	9	1.40 (0.99, 2.00)	0.07
Hepatocellular	15	1.74 (1.20, 2.54)[2]	< 0.00001	10	1.58 (1.05, 2.39)[2]	0.002	8	2.55 (1.38, 4.70)	0.49	8	2.15 (1.19, 3.90)	0.66
Pancreatic	3	1.04 (0.79, 1.36)	0.94	3	1.04 (0.79, 1.38)	0.88	3	0.99 (0.46, 2.14)	0.63	3	0.99 (0.46, 2.13)	0.60
Esophageal	2	0.82 (0.58, 1.16)	0.89	2	0.80 (0.55, 1.15)	0.89	2	1.01 (0.42, 2.43)	0.95	2	1.05 (0.44, 2.51)	0.92
Ethnicity												
Asian	27	1.24 (0.99, 1.56)[2]	< 0.00001	25	1.07 (0.94, 1.22)[2]	0.008	19	1.55 (1.11, 2.17)	0.43	19	1.47 (1.05, 2.06)	0.60
Caucasian	31	1.21 (1.05, 1.40)[2]	< 0.00001	27	1.17 (1.01, 1.35)[2]	< 0.0001	25	1.38 (1.10, 1.74)	0.18	25	1.34 (1.08, 1.67)	0.39

[1]Test for heterogeneity; [2]Random-effects model was used when the *P* for heterogeneity test was < 0.05. GG: Guanine/Guanine; GA: Guanine/Adenine; AA: Adenine/Adenine; HWE: Hardy-Weinberg equilibrium.

ficiently large for a comprehensive analysis, and some studies with small sample sizes may not have enough statistical power to prove authentic associations. Therefore, our analysis should be interpreted with caution, and more studies are needed. Second, our results were based on unadjusted estimates, and lack of information for the data analysis may cause serious confounding bias. Third, significant heterogeneity was found in some models, which may lead to failure to confirm marginal associations. In spite of these limitations, our meta-analysis had several advantages. First, a substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, the quality of the case-control studies included in the current meta-analysis was satisfactory and met our inclusion criteria. Third, we did not detect any publication bias, suggesting that the whole pooled result is unbiased.

In summary, this meta-analysis suggests that the *TNF-α-308* polymorphism increases susceptibility to digestive system cancers in the Caucasian population. The *TNF-α-308 AA* genotype is closely related to the risk of digestive system cancers in people of Asian descent. The *TNF-α-308* polymorphism may be significantly associated with the risk of gastric and hepatocellular carcinomas, but not colorectal, pancreatic, or oesophageal cancer. Future studies should use standardised unbiased genotyping methods, examine homogeneous cancer patients and well-matched controls, and include multiethnic groups.

ACKNOWLEDGMENTS

We are very grateful to Mr. Hong Xia from the Key Laboratory of Hubei Province for Digestive System Disease for assistance in data collection.

COMMENTS

Background

Digestive system cancers are the most common malignant tumors worldwide. Tumor necrosis factor alpha-308 (*TNF-α-308*) polymorphism (rs1800629) is the most extensively studied polymorphism in digestive system cancers. However, the results are different or even inconsistent.

Research frontiers

Molecular epidemiology has confirmed that carcinogenesis is a complex, multifactorial, and multistep event, and genetic mutation play an important role in the process. Many studies have reported the association between the *TNF-α-308* polymorphism and human malignant tumors, but no agreements have been reached till now.

Innovations and breakthroughs

This meta-analysis systemically assessed the association between *TNF-α-308* polymorphism and risk of digestive system cancers. Results show that *TNF-α-308* polymorphism may be significantly associated with the risk of gastric and hepatocellular carcinomas in Asians.

Applications

This study results indicate that *TNF-α-308* polymorphism may be used as a detectable biomarker for gastric and hepatocellular carcinoma patients.

Peer review

The authors present a meta-analysis study over the influence of a polymorphism of TNF-α on digestive system cancers. The manuscript is well written and interesting, especially because it is the first meta-analysis study on the subject.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Jemal A**, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1893-1907 [PMID: 20647400 DOI: 10.1158/1055-9965.EPI-10-0437]

3 **Bazzoni F**, Beutler B. The tumor necrosis factor ligand and receptor families. *N Engl J Med* 1996; **334**: 1717-1725 [PMID: 8637518 DOI: 10.1056/NEJM199606273342607]

4 **Wilson AG**, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci USA* 1997; **94**: 3195-3199 [PMID: 9096369 DOI: 10.1073/pnas.94.7.3195]

5 **Dunham I**, Sargent CA, Trowsdale J, Campbell RD. Molecular mapping of the human major histocompatibility complex by pulsed-field gel electrophoresis. *Proc Natl Acad Sci USA* 1987; **84**: 7237-7241 [PMID: 3118362 DOI: 10.1073/pnas.84.20.7237]

6 **Burada F**, Angelescu C, Mitrut P, Ciurea T, Cruce M, Saftoiu A, Ioana M. Interleukin-4 receptor -3223T& amp; #8594; C polymorphism is associated with increased gastric adenocarcinoma risk. *Can J Gastroenterol* 2012; **26**: 532-536 [PMID: 22891178]

7 **Canedo P**, Durães C, Pereira F, Regalo G, Lunet N, Barros H, Carneiro F, Seruca R, Rocha J, Machado JC. Tumor necrosis fac-

tor alpha extended haplotypes and risk of gastric carcinoma. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2416-2420 [PMID: 18768512 DOI: 10.1158/1055-9965.EPI-08-0413]

8 **Crusius JB**, Canzian F, Capellá G, Peña AS, Pera G, Sala N, Agudo A, Rico F, Del Giudice G, Palli D, Plebani M, Boeing H, Bueno-de-Mesquita HB, Carneiro F, Pala V, Save VE, Vineis P, Tumino R, Panico S, Berglund G, Manjer J, Stenling R, Hallmans G, Martínez C, Dorronsoro M, Barricarte A, Navarro C, Quirós JR, Allen N, Key TJ, Binghan S, Caldas C, Linseisen J, Kaaks R, Overvad K, Tjønneland A, Büchner FC, Peeters PH, Numans ME, Clavel-Chapelon F, Trichopoulou A, Lund E, Jenab M, Rinaldi S, Ferrari P, Riboli E, González CA. Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). *Ann Oncol* 2008; **19**: 1894-1902 [PMID: 18628242 DOI: 10.1093/annonc/mdn400]

9 **El-Omar EM**, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF, Chow WH. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003; **124**: 1193-1201 [PMID: 12730860 DOI: 10.1016/S0016-5085(03)00157-4]

10 **Lau J**, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820-826 [PMID: 9382404 DOI: 10.7326/0003-4819-127-9-199711010-00008]

11 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

12 **MANTEL N**, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719-748 [PMID: 13655060]

13 **Guo W**, Wang N, Li Y, Zhang JH. Polymorphisms in tumor necrosis factor genes and susceptibility to esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma in a population of high incidence region of North China. *Chin Med J* (Engl) 2005; **118**: 1870-1878 [PMID: 16313841]

14 **Jang WH**, Yang YI, Yea SS, Lee YJ, Chun JH, Kim HI, Kim MS, Paik KH. The -238 tumor necrosis factor-alpha promoter polymorphism is associated with decreased susceptibility to cancers. *Cancer Lett* 2001; **166**: 41-46 [PMID: 11295285 DOI: 10.1016/S0304-3835(01)00438-4]

15 **Fei BY**, Xia B, Deng CS, Xia XQ, Xie M, Crusius JB, Pena AS. Association of tumor necrosis factor genetic polymorphism with chronic atrophic gastritis and gastric adenocarcinoma in Chinese Han population. *World J Gastroenterol* 2004; **10**: 1256-1261 [PMID: 15112338]

16 **García-González MA**, Lanas A, Quintero E, Nicolás D, Parra-Blanco A, Strunk M, Benito R, Angel Simón M, Santolaria S, Sopeña F, Piazuelo E, Jiménez P, Pascual C, Mas E, Irún P, Espinel J, Campo R, Manzano M, Geijo F, Pellisé M, González-Huix F, Nieto M, Espinós J, Titó L, Bujanda L, Zaballa M. 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 [PMID: 17640324 DOI: 10.1111/j.1572-0241.2007.01423.x]

17 **Garza-González E**, Bosques-Padilla FJ, El-Omar E, Hold G, Tijerina-Menchaca R, Maldonado-Garza HJ, Pérez-Pérez GI. 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 [PMID: 15540224 DOI: 10.1002/ijc.20718]

18 **Glas J**, Török HP, Schneider A, Brünnler G, Kopp R, Albert ED, Stolte M, Folwaczny C. Allele 2 of the interleukin-1 receptor antagonist gene is associated with early gastric cancer. *J Clin Oncol* 2004; **22**: 4746-4752 [PMID: 15570075 DOI: 10.1200/JCO.2004.03.034]

19 **Hou L**, El-Omar EM, Chen J, Grillo P, Rabkin CS, Baccarelli A, Yeager M, Chanock SJ, Zatonski W, Sobin LH, Lissowska J, Fraumeni JF, Chow WH. Polymorphisms in Th1-type cell-mediated response genes and risk of gastric cancer. *Carcinogenesis* 2007; **28**: 118-123 [PMID: 16885196 DOI: 10.1093/carcin/bgl130]

20 **Kamangar F**, Abnet CC, Hutchinson AA, Newschaffer CJ, Helzlsouer K, Shugart YY, Pietinen P, Dawsey SM, Albanes D, Virtamo J, Taylor PR. Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). *Cancer Causes Control* 2006; **17**: 117-125 [PMID: 16411061 DOI: 10.1007/s10552-005-0439-7]

21 **Kim N**, Cho SI, Yim JY, Kim JM, Lee DH, Park JH, Kim JS, Jung HC, Song IS. The effects of genetic polymorphisms of IL-1 and TNF-A on Helicobacter pylori-induced gastroduodenal diseases in Korea. *Helicobacter* 2006; **11**: 105-112 [PMID: 16579840 DOI: 10.1111/j.1523-5378.2006.00384.x]

22 **Lee SG**, Kim B, Yook JH, Oh ST, Lee I, Song K. TNF/LTA polymorphisms and risk for gastric cancer/duodenal ulcer in the Korean population. *Cytokine* 2004; **28**: 75-82 [PMID: 15381184 DOI: 10.1016/j.cyto.2004.06.009]

23 **Lee JY**, Kim HY, Kim KH, Kim SM, Jang MK, Park JY, Lee JH, Kim JH, Yoo JY. Association of polymorphism of IL-10 and TNF-A genes with gastric cancer in Korea. *Cancer Lett* 2005; **225**: 207-214 [PMID: 15978325 DOI: 10.1016/j.canlet.2004.11.028]

24 **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 [PMID: 15667484 DOI: 10.1111/j.1572-0241.2005.40806.x]

25 **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 [PMID: 15579481 DOI: 10.1093/carcin/bgh349]

26 **Machado JC**, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, Castro Alves C, Campos ML, Van Doorn LJ, Caldas C, Seruca R, Carneiro F, Sobrinho-Simões M. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003; **125**: 364-371 [PMID: 12891537 DOI: 10.1016/S0016-5085(03)00899-0]

27 **Melo Barbosa HP**, Martins LC, Dos Santos SE, Demachki S, Assumpção MB, Aragão CD, de Oliveira Corvelo TC. Interleukin-1 and TNF-alpha polymorphisms and Helicobacter pylori in a Brazilian Amazon population. *World J Gastroenterol* 2009; **15**: 1465-1471 [PMID: 19322919]

28 **Morgan DR**, Dominguez RL, Keku TO, Heidt PE, Martin CF, Galanko JA, Omofoye OA, Sandler RS. Gastric cancer and the high combination prevalence of host cytokine genotypes and Helicobacter pylori in Honduras. *Clin Gastroenterol Hepatol* 2006; **4**: 1103-1111 [PMID: 16820326 DOI: 10.1016/j.cgh.2006.05.025]

29 **Perri F**, Piepoli A, Bonvicini C, Gentile A, Quitadamo M, Di Candia M, Cotugno R, Cattaneo F, Zagari MR, Ricciardiello L, Gennarelli M, Bazzoli F, Ranzani GN, Andriulli A. Cytokine gene polymorphisms in gastric cancer patients from two Italian areas at high and low cancer prevalence. *Cytokine* 2005; **30**: 293-302 [PMID: 15927855 DOI: 10.1016/j.cyto.2005.01.011]

30 **Rocha GA**, Guerra JB, Rocha AM, Saraiva IE, da Silva DA, de Oliveira CA, Queiroz DM. IL1RN polymorphic gene and cagA-positive status independently increase the risk of noncardia gastric carcinoma. *Int J Cancer* 2005; **115**: 678-683 [PMID: 15704154 DOI: 10.1002/ijc.20935]

31 **Sugimoto M**, Furuta T, Shirai N, Nakamura A, Xiao F, Kajimura M, Sugimura H, Hishida A. 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 [PMID: 17201881 DOI: 10.1111/j.1440-1746.2006.04442.x]

32 **Torres MM**, Acosta CP, Sicard DM, Groot de Restrepo H. [Genetic susceptibility and risk of gastric cancer in a human population of Cauca, Colombia]. *Biomedica* 2004; **24**: 153-162 [PMID: 15495595]

33 **Wu MS**, Huang SP, Chang YT, Shun CT, Chang MC, Lin MT, Wang HP, Lin JT. Tumor necrosis factor-alpha and interleukin-10 promoter polymorphisms in Epstein-Barr virus-associated gastric carcinoma. *J Infect Dis* 2002; **185**: 106-109 [PMID: 11756988 DOI: 10.1086/324771]

34 **Wu MS**, Chen LT, Shun CT, Huang SP, Chiu HM, Wang HP, Lin MT, Cheng AL, Lin JT. Promoter polymorphisms of tumor necrosis factor-alpha are associated with risk of gastric mucosa-associated lymphoid tissue lymphoma. *Int J Cancer* 2004; **110**: 695-700 [PMID: 15146559 DOI: 10.1002/ijc.20199]

35 **Yang JJ**, Ko KP, Cho LY, Shin A, Gwack J, Chang SH, Shin HR, Yoo KY, Kang D, Park SK. The role of TNF genetic variants and the interaction with cigarette smoking for gastric cancer risk: a nested case-control study. *BMC Cancer* 2009; **9**: 238 [PMID: 19615068 DOI: 10.1186/1471-2407-9-238]

36 **Zambon CF**, Basso D, Navaglia F, Belluco C, Falda A, Fogar P, Greco E, Gallo N, Rugge M, Di Mario F, Plebani M. Pro- and anti-inflammatory cytokines gene polymorphisms and Helicobacter pylori infection: interactions influence outcome. *Cytokine* 2005; **29**: 141-152 [PMID: 15652446 DOI: 10.1016/j.cyto.2004.10.013]

37 **Garrity-Park MM**, Loftus EV, Bryant SC, Sandborn WJ, Smyrk TC. Tumor necrosis factor-alpha polymorphisms in ulcerative colitis-associated colorectal cancer. *Am J Gastroenterol* 2008; **103**: 407-415 [PMID: 18289203 DOI: 10.1111/j.1572-0241.2007.01572.x]

38 **Landi S**, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, Capella G, Canzian F. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. *Cancer Res* 2003; **63**: 3560-3566 [PMID: 12839942]

39 **Li M**, You Q, Wang X. Association between polymorphism of the tumor necrosis factor alpha-308 gene promoter and colon cancer in the Chinese population. *Genet Test Mol Biomarkers* 2011; **15**: 743-747 [PMID: 21631297 DOI: 10.1089/gtmb.2011.0068]

40 **Macarthur M**, Sharp L, Hold GL, Little J, El-Omar EM. The role of cytokine gene polymorphisms in colorectal cancer and their interaction with aspirin use in the northeast of Scotland. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1613-1618 [PMID: 16030091 DOI: 10.1158/1055-9965.EPI-04-0878]

41 **Park KS**, Mok JW, Rho SA, Kim JC. Analysis of TNFB and TNFA NcoI RFLP in colorectal cancer. *Mol Cells* 1998; **8**: 246-249 [PMID: 9638659]

42 **Suchy J**, Kłujszo-Grabowska E, Kładny J, Cybulski C, Wokołorczyk D, Szymańska-Pasternak J, Kurzawski G, Scott RJ, Lubiński J. Inflammatory response gene polymorphisms and their relationship with colorectal cancer risk. *BMC Cancer* 2008; **8**: 112 [PMID: 18433468 DOI: 10.1186/1471-2407-8-112]

43 **Theodoropoulos G**, Papaconstantinou I, Felekouras E, Nikiteas N, Karakitsos P, Panoussopoulos D, Lazaris ACh, Patsouris E, Bramis J, Gazouli M. Relation between common polymorphisms in genes related to inflammatory response and colorectal cancer. *World J Gastroenterol* 2006; **12**: 5037-5043 [PMID: 16937502 DOI: 1007-9327/12/5037.asp]

44 **Tóth EK**, Kocsis J, Madaras B, Bíró A, Pocsai Z, Fust G, Blaskó B, Karádi I, Adány R, Laki J. The 8.1 ancestral MHC haplotype is strongly associated with colorectal cancer risk. *Int J Cancer* 2007; **121**: 1744-1748 [PMID: 17594690 DOI: 10.1002/ijc.22922]

45 **Tsilidis KK**, Helzlsouer KJ, Smith MW, Grinberg V, Hoffman-Bolton J, Clipp SL, Visvanathan K, Platz EA. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. *Cancer Causes Control* 2009; **20**: 1739-1751 [PMID: 19760027 DOI: 10.1007/s10552-009-9427-7]

46 **Akkiz H**, Bayram S, Bekar A, Ozdil B, Akgöllü E, Sümbül AT, Demiryürek H, Doran F. G-308A TNF-alpha polymorphism is associated with an increased risk of hepatocellular carcinoma in the Turkish population: case-control study. *Cancer Epidemiol* 2009; **33**: 261-264 [PMID: 19683483 DOI: 10.1016/j.canep.2009.06.001]

47 **Ben-Ari Z**, Mor E, Papo O, Kfir B, Sulkes J, Tambur AR, Tur-Kaspa R, Klein T. Cytokine gene polymorphisms in patients infected with hepatitis B virus. *Am J Gastroenterol* 2003; **98**: 144-150 [PMID: 12526950 DOI: 10.1111/j.1572-0241.2003.07179.x]

48 **Chen CC**, Yang SY, Liu CJ, Lin CL, Liaw YF, Lin SM, Lee SD, Chen PJ, Chen CJ, Yu MW. Association of cytokine and DNA repair gene polymorphisms with hepatitis B-related hepatocellular carcinoma. *Int J Epidemiol* 2005; **34**: 1310-1318 [PMID: 16172101 DOI: 10.1093/ije/dyi191]

49 **Heneghan MA**, Johnson PJ, Clare M, Ho S, Harrison PM, Donaldson PT. Frequency and nature of cytokine gene polymorphisms in hepatocellular carcinoma in Hong Kong Chinese. *Int J Gastrointest Cancer* 2003; **34**: 19-26 [PMID: 15235132 DOI: 10.1385/IJGC:34:1:19]

50 **Ho SY**, Wang YJ, Chen HL, Chen CH, Chang CJ, Wang PJ, Chen HH, Guo HR. Increased risk of developing hepatocellular carcinoma associated with carriage of the TNF2 allele of the -308 tumor necrosis factor-alpha promoter gene. *Cancer Causes Control* 2004; **15**: 657-663 [PMID: 15280623 DOI: 10.1023/B:CACO.0000036173.99930.75]

51 **Jeng JE**, Tsai JF, Chuang LY, Ho MS, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY, Chang JG. Tumor necrosis factor-alpha 308.2 polymorphism is associated with advanced hepatic fibrosis and higher risk for hepatocellular carcinoma. *Neoplasia* 2007; **9**: 987-992 [PMID: 18030367 DOI: 10.1593/neo.07781]

52 **Jeng JE**, Tsai HR, Chuang LY, Tsai JF, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY, Chang JG. Independent and additive interactive effects among tumor necrosis factor-alpha polymorphisms, substance use habits, and chronic hepatitis B and hepatitis C virus infection on risk for hepatocellular carcinoma. *Medicine* (Baltimore) 2009; **88**: 349-357 [PMID: 19910749 DOI: 10.1097/MD.0b013e3181c10477]

53 **Kummee P**, Tangkijvanich P, Poovorawan Y, Hirankarn N. Association of HLA-DRB1*13 and TNF-alpha gene polymorphisms with clearance of chronic hepatitis B infection and risk of hepatocellular carcinoma in Thai population. *J Viral Hepat* 2007; **14**: 841-848 [PMID: 18070287 DOI: 10.1111/j.1365-2893.2007]

54 **Migita K**, Miyazoe S, Maeda Y, Daikoku M, Abiru S, Ueki T, Yano K, Nagaoka S, Matsumoto T, Nakao K, Hamasaki K, Yatsuhashi H, Ishibashi H, Eguchi K. Cytokine gene polymorphisms in Japanese patients with hepatitis B virus infection--association between TGF-beta1 polymorphisms and hepatocellular carcinoma. *J Hepatol* 2005; **42**: 505-510 [PMID: 15763337 DOI: 10.1016/j.jhep.2004.11.026]

55 **Niro GA**, Fontana R, Gioffreda D, Valvano MR, Lacobellis A, Facciorusso D, Andriulli A. Tumor necrosis factor gene polymorphisms and clearance or progression of hepatitis B virus infection. *Liver Int* 2005; **25**: 1175-1181 [PMID: 16343069 DOI: 10.1111/j.1478-3231.2005.01166.x]

56 **Ognjanovic S**, Yuan JM, Chaptman AK, Fan Y, Yu MC. Genetic polymorphisms in the cytokine genes and risk of hepatocellular carcinoma in low-risk non-Asians of USA. *Carcinogenesis* 2009; **30**: 758-762 [PMID: 19126646 DOI: 10.1093/carcin/bgn286]

57 **Sakamoto T**, Higaki Y, Hara M, Ichiba M, Horita M, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S, Tanaka K. Interaction between interleukin-1beta -31T/C gene polymorphism and drinking and smoking habits on the risk of hepatocellular carcinoma among Japanese. *Cancer Lett* 2008; **271**: 98-104 [PMID: 18603357 DOI: 10.1016/j.canlet.2008.05.036]

58 **Shi Z**, Du C. Tumor necrosis factor alpha 308 G/A polymorphism and hepatocellular carcinoma risk in a Chinese population. *Genet Test Mol Biomarkers* 2011; **15**: 569-572 [PMID: 21401328 DOI: 10.1089/gtmb.2011.0008]

59 **Wang Y**, Kato N, Hoshida Y, Yoshida H, Taniguchi H, Goto T, Moriyama M, Otsuka M, Shiina S, Shiratori Y, Ito Y, Omata M. Interleukin-1beta gene polymorphisms associated with hepatocellular carcinoma in hepatitis C virus infection. *Hepatology* 2003; **37**: 65-71 [PMID: 12500190 DOI: 10.1053/jhep.2003.50017]

60 **Wang B**, Wang J, Zheng Y, Zhou S, Zheng J, Wang F, Ma X, Zeng Z. A study of TNF-alpha-238 and -308 polymorphisms

with different outcomes of persistent hepatitis B virus infection in China. *Pathology* 2010; **42**: 674-680 [PMID: 21080879 DOI: 10.3109/00313025.2010.523696]

61 **Duell EJ**, Casella DP, Burk RD, Kelsey KT, Holly EA. Inflammation, genetic polymorphisms in proinflammatory genes TNF-A, RANTES, and CCR5, and risk of pancreatic adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 726-731 [PMID: 16614115 DOI: 10.1158/1055-9965.EPI-05-0797]

62 **Talar-Wojnarowska R**, Gasiorowska A, Smolarz B, Romanowicz-Makowska H, Kulig A, Malecka-Panas E. Tumor necrosis factor alpha and interferon gamma genes polymorphisms and serum levels in pancreatic adenocarcinoma. *Neoplasma* 2009; **56**: 56-62 [PMID: 19152246 DOI: 10.4149/neo_2009_01_56]

63 **Wu GY**, Lu Q, Hasenberg T, Niedergethmann M, Post S, Sturm JW, Keese M. Association between EGF, TGF-{beta}1, TNF-{alpha} gene polymorphisms and cancer of the pancreatic head. *Anticancer Res* 2010; **30**: 5257-5261 [PMID: 21187523]

64 **Qidwai T**, Khan F. Tumour necrosis factor gene polymorphism and disease prevalence. *Scand J Immunol* 2011; **74**: 522-547 [PMID: 21790707 DOI: 10.1111/j.1365-3083.2011.02602.x]

P- Reviewers: Marcos R, Nagahara H, Swierczynski J
S- Editor: Ma YJ **L- Editor**: Wang TQ **E- Editor**: Liu XM

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327