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META-ANALYSIS

TNF-\alpha-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

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Abstract

AIM: To evaluate the association between the tumour necrosis factor alpha-308 (*TNF-\alpha-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 betweenstudy 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-\alpha-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.

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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 (*TWF-\alpha-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 *TWF-\alpha-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.

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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-a-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 $TNF \alpha$ -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 $TNF \alpha$ -308G/A genotype; and (3) studies that compared the $TNF \alpha$ -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.



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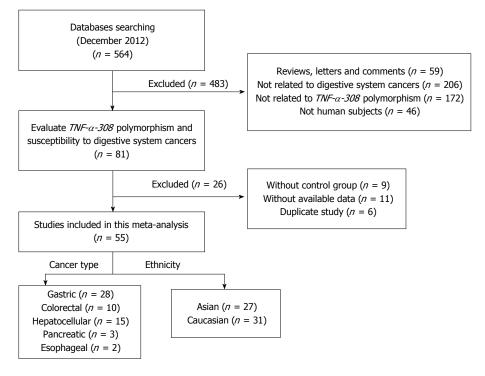


Figure 1 Flow chart showing study selection procedure. TNF- α : Tumour necrosis factor-alpha.

RESULTS

Study characteristics

The search strategy retrieved 564 potentially relevant studies. According to the inclusion criteria, 55 studies with fulltext 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 $at^{[13]}$ and Jang et $at^{[14]}$ 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).

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C 4 59 36 224 0.9% 0.46 [0.16, 1.5] 4 30 M 36 220 26 300 2.0% 1.77 [1.04, 3.03] glaa 1 48 5 188 0.3% 0.78 [0.09, 6.83] Karbo 2 10 76 2.28 2.1% 0.72 [0.44, 1.19] Karbo 4 209 5 275 0.7% 1.05 [0.28, 3.97] i 558 88 43 88 1.8% 2.10 [1.01, 3.71] ang V 14 105 3 172 0.5% 2.23 [0.44, 1.19] ang V 14 125 7 55 1.1% 0.68 [0.33, 2.28] M 36 150 40 220 2.1% 1.47 [0.68, 2.36] M 36 150 40 220 2.1% 1.42 [0.68, 2.36] M 36 150 40 220 2.1% 1.42 [0.99, 1.56] total elements 70 785 terogenenty: Tau ² = 0.540, dr = 26 ($\rho < 0.00001$); $l^2 = 66%$ tf or overall effect: $Z = 1.87 (\rho = 0.06)$ L2 Caucasian elel element 6 220 839 2.1% 1.47 [0.68, 2.26] M 39 161 58 210 2.2% 0.44 [0.62, 7.18] H 39 161 58 210 2.2% 0.44 [0.62, 7.13] L2 Caucasian elel element 6 62 260 230 25% 0.43 [0.52, 1.14] Orar 113 314 58 210 2.2% 0.44 [0.52, 1.34] H 39 161 58 210 2.2% 0.48 [0.52, 1.34] H 30 51 224 428 2.7% 1.57 [1.15, 2.14] H 40 4 2.6% 1.17 [0.55, 1.67] H 41 161 15 353 2.24% 1.00 [0.67, 1.50] H 41 161 15 353 2.24% 1.00 [0.67, 1.50] H 41 161 15 353 2.24% 1.00 [0.67, 1.50] H 41 161 15 353 2.24% 1.00 [0.57, 1.51] H 41 161 15 353 2.24% 1.00 [0.57, 1.51] H 41 161 15 353 2.4% 1.00 [0.56, 1.50] H 41 161 15 353 2.4% 1.00 [0.56, 1.50] H 41 161 15 353 2.4% 1.00 [0.56, 1.50] H 41 161 15 353	e JY	10	122	17	120	1.3%	0.54 [0.24, 1.24]	← • • • • • • • • • • • • • • • • • • •
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	e SG	44	341	43	261	2.2%	0.75 [0.48, 1.18]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	С	4	59	36	264	0.9%	0.46 [0.16, 1.35]	< ▪
pita 1 48 5 188 0.3% 0.78 [0.09, 6.83] kamoto 4 209 5 2.75 0.7% 1.05 [0.28, 3.97] i 58 88 43 68 1.8% 2.02 [1.10, 3.71] ginoto 4 105 17 25 0.5% 2.23 [0.49, 10.71] ang BB 33 2.00 15 158 1.75% 1.60 [0.84, 1.05] ang Y 14 125 7 55 1.1% 0.86 [0.33, 2.28] u M 36 150 40 2.20 2.1% 1.10 [0.68, 1.80] ng 8 83 34 322 1.3% 0.90 [0.40, 2.03] tototal (5% CL) 43 5.21 C (\$P < 0.0001); I ² = 66% st for overall effect: $Z = 2.65 (P = 0.05]$ $L^2 Guessian L 2 = 0.06 (P < 0.00001); I2 = 66% st for overall effect: Z = 1.87 (P = 0.66)L2 Guessian L 2 2.2% 0.44 [1.05, 1.14]Ona EM 39 161 58 210 2.2% 0.47 [1.05, 1.14]Ona EM 39 161 58 210 2.2% 0.47 [1.05, 1.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.47 [1.05, 2.14]Ona EM 39 164 58 210 2.2% 0.48 [0.50, 1.48]nu 119 305 124 428 2.7% 0.37 [1.15, 2.14]Ona EM 39 164 58 210 2.2% 0.48 [0.48, 1.60]u 119 305 124 428 2.7% 0.31 [0.59, 1.18]scarthur 89 246 153 849 2.5% 0.37 [0.55, 1.07]rrs 3 22 88 40 145 1.3% 0.88 [0.49, 1.60]u 119 305 124 428 2.7% 0.31 [0.51, 1.43]rrs 400 108 287 73 304 2.5% 0.17 [1.53, 2.14]or 6 30 21 96 1.0% 0.89 [0.32, 2.47]rrs 3 144 10 66 53 80 [0.52, 1.48]rrs 41 161 136 535 2.2 (2.5% 0.31 [0.59, 1.18]scarthur 89 246 153 389 2.2% 0.38 [0.59, 1.18]rrs 3 144 10 66 6.6% 0.41 [1.158]this 58 204 2.7% 1.37 [1.55, 2.16]rrs 3 44 10 66 0.6% 0.41 [1.158]this 58 224 2.7% 1.37 [1.55, 2.16]rrs 3 44 10 66 0.6% 0.41 [1.158]this 58 204 2.7% 1.37 [1.25, 2.16]rrs 3 44 10 66 0.6% 0.41 [1.158]this 58 204 2.7% 1.37 [1.25, 2.16]rrs 3 44 10 66 0.6% 0.41 [1.158]this 58 204 2.7% 1.37 [1.25, 2.16]rrs 3 44 10 66 0.6% 0.41 [1.158]this 113 30 102 2.5% 0.47 [0.40, 2.21]this 113 30 102 2.5% 0.47 [0.40, 2.21]this 113 30 102 2.5% 0.2% 0.50 [0.54, 1.35]to coveral effect: Z = 2.5\% (P $	М	24	180	20	180	1.7%	1.23 [0.65, 2.32]	
rk 25 140 76 328 2.1% 0.72 [0.48, 1.97] i 58 88 43 88 1.8% 2.02 [1.0, 3.71] imoto 4 105 3 172 0.5% 2.02 [1.0, 3.71] imoto 4 105 3 172 0.5% 2.23 [0.44, 1.07] img B 33 2.30 15 158 1.7% 1.60 (0.84, 2.28] img V 14 125 7 55 1.1% 0.66 (0.34, 2.28] img W 41 120 4 39 210 0.44 0.99 1.56 ing W 41 120 7 55 1.3% 0.50 0.40 0.03 ind GiSWCL) 436 60.49 39.9% 1.24 0.99,1.56 1.24 0.99,1.56 ind events 679 75 46 242 2.0% 1.04 0.08,7.28 0.03 0.75 1.11 inded 39 161 58 210 2.2% <th< td=""><td></td><td>36</td><td>250</td><td>26</td><td>300</td><td>2.0%</td><td>1.77 [1.04, 3.03]</td><td></td></th<>		36	250	26	300	2.0%	1.77 [1.04, 3.03]	
kamoto 4 209 5 275 0.7% 1.05 [0.28, 397] i 58 88 43 88 18% 2.02 [1.10, 3.71] ginoto 4 105 3 172 0.5% 2.23 [0.49, 10.17] ng BB 33 230 15 158 1.75% 1.60 [0.84, 3.05] ng Y 14 125 7 55 1.1% 0.86 [0.33, 2.28] M 36 150 40 220 2.1% 1.10 [0.68, 1.80] ng 8 83 34 322 1.3% 0.90 [0.40, 2.03] total (9%CI) 4363 6049 39.9% 1.24 [0.99, 1.56] Tal events 679 785 terogenety: Tau ² = 0.74, 2½ = 76.40, d ² = 26 (P < 0.00001); J ² = 66% st for veral field = 27 105 46 242 2.0% 1.47 [0.86, 2.83] islus 66 236 305 1125 2.6% 1.04 [0.067, 1.43] nedo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 1125 2.6% 1.04 [0.75, 1.43] nedo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 1125 2.6% 1.04 [0.75, 1.43] nedo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 1125 2.6% 1.04 [0.75, 1.43] nedo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 1.04 [0.75, 1.43] nedo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 0.46 [0.57, 1.43] medo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 0.46 [0.57, 1.43] medo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 0.46 [0.57, 1.43] medo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 0.46 [0.57, 1.43] medo 178 508 169 713 2.8% 1.74 [1.35, 2.23] islus 66 236 305 125 2.6% 0.47 [0.57, 1.43] medo 178 508 169 713 2.8% 1.74 [1.35, 2.43] medo 188 27 73 304 2.2% 0.85 [0.59, 1.14] manger 26 112 54 208 2.0% 0.46 [0.59, 1.48] medo 18 287 73 304 2.2% 0.45 [0.59, 1.14] manger 26 112 54 208 2.0% 0.46 [0.59, 1.48] medo 108 287 73 304 2.2% 0.5% [0.54, 1.34] medo 18 287 73 304 2.2% 0.45 [0.59, 1.14] medo 18 287 73 304 2.2% 0.45 [0.59, 1.14] medo 18 287 73 304 2.2% 0.45 [0.59, 1.14] medo 19 201 22 54 2.0% 0.44 [0.45, 1.59] medo 19 22 54 2.0% 0.44 [0.45, 1.59] medo 19 22 54 2.0% 0.44 [0.45, 2.54] medo 19 22 54 2.0% 0.44 [0.47, 1.50] medo 19 21 90 2.2 54 0.22% 0.45 [0.59, 1.14] medo 19 20 2.2 54 0.2 2.2% 0.45 [0.59, 1.14] medo 19 20 2.2 54 0.2 2.2% 0.45 [0.59, 1.14] medo 10	gita	1	48	5	188	0.3%	0.78 [0.09, 6.83]	•
i 58 88 43 88 18% 202 [110, 271] ginoto 4 105 31 72 0.5% 2.23 [0.49, 10.17] ang W 14 125 7 55 1.7% 1.60 [0.84, 3.05] ang Y 14 125 7 55 1.7% 1.60 [0.84, 3.05] ang Y 14 125 7 55 1.1% 0.86 [0.32, 2.28] \downarrow M 36 150 40 220 2.1% 1.12 [0.86, 2.36] \downarrow M 36 150 40 220 2.1% 1.10 [0.68, 1.80] \downarrow M 36 150 40 220 2.1% 1.24 [0.99, 1.56] tatevents 679 725 terogenety: Tat' = 0.21; χ^2 = 76.40, d' = 26 ($P < 0.00001$); J' = 66% st for overall effect: $Z = 1.37$ ($P = 0.06$) \downarrow L2 Caucasian \downarrow L3 \downarrow L2 \downarrow L3% \downarrow L2 \downarrow L3% \downarrow L2 \downarrow L2 \downarrow L3% \downarrow L2 \downarrow	rk	25	140	76	328	2.1%	0.72 [0.44, 1.19]	
gimoto 4 105 3 172 0.5% 2.23 [0.49]0.7] ang BB 33 230 15 158 1.75% 1.60 [0.84, 3.05] ang Y 14 125 7 55 1.1% 0.66 [0.33, 2.28] M 36 150 40 220 2.1% 1.42 [0.86, 2.36] ang 8 8 33 34 322 1.3% 0.90 [0.40, 2.03] thotal (5% Ct) 436.3 6049 39.9% 1.24 [0.99, 1.56] tal events 679 785 terogeneity: Tau ² = 0.21; $z2 = 76.40, dr = 26 (P < 0.00001); t2 = 66%st for overall effect: Z = 1.87 (P = 0.08)L2 Caucasiankiz and 10 11 11 01 0.5% 4.75 [2.27, 9.22]usius 66 236 305 1125 2.6% 1.04 [0.86, 1.33]usius 66 236 305 1125 2.6% 1.04 [0.75, 1.41]Ornar 11 3145 82 110 2.24% 1.47 [1.15, 2.23]usius 66 236 305 1125 2.6% 1.03 [0.75, 1.41]Ornar 11 3145 82 110 2.24% 1.47 [1.15, 2.13]usius 66 236 305 1125 2.6% 1.04 [0.75, 1.43]eel el 68 260 220 859 2.6% 1.03 [0.75, 1.41]Ornar 11 3145 82 110 2.24% 1.47 [1.15, 2.13]usius 66 236 305 1125 2.6% 1.03 [0.75, 1.41]Ornar 11 3145 82 110 2.24% 1.47 [1.15, 2.13]usius 66 236 305 1125 2.6% 1.03 [0.75, 1.41]Ornar 113 314 58 210 2.24% 1.47 [1.15, 2.13]usius 66 326 316 212 2.4% 0.47 [1.15, 2.14]ornar 2.5% 1.04 84 0.04 2.6% 1.05 [0.42, 0.7]as 2.2 88 40 145 1.8% 0.88 [0.42, 1.6]arwojnarowska 15 41 19 00 0.9% 1.54 [0.53, 3.0]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.21]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.21]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.21]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.13]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.13]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.13]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.21]arwojnarowska 15 41 19 50 1.2% 0.94 [0.40, 2.21]arwojnarowska$	kamoto	4	209	5	275	0.7%	1.05 [0.28, 3.97]	<
ang BB 33 230 15 158 1.75% 1.60 [0.84, 3.05] ang Y 14 125 7 55 1.1% 0.86 [0.33, 2.28] W 36 150 40 220 2.1% 1.42 [0.86, 2.36] W 5 41 204 39 210 2.1% 1.01 [0.68, 1.80] httotal (95%C1) 4363 6049 39.9% 1.24 [0.99, 1.56] terogeneity: Tat ² = 0.21; χ^2 = 76.40, $d'' = 26$ ($P < 0.0001$); $J' = 66%$ st for overall effect: $Z = 1.87$ ($P = 0.06$) Lacardia 27 105 46 242 2.0% 1.47 [0.86, 2.54] medo 178 508 169 713 2.28 ($J'' = 0.06$) Local (95%C1) 4363 305 1125 2.6% 1.04 [0.76, 1.43] medo 178 508 169 713 2.28 ($J'' = 0.06$) teroid effect: $Z = 1.87$ ($P = 0.06$) Local (95%C1) 43 508 169 713 2.26% 1.04 [0.76, 1.43] medo 178 508 169 713 2.27% 0.46 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.57, 1.41] Orna FM 39 161 58 210 2.4% 0.48 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.48 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.44 [0.52, 1.34] Orna FM 39 161 58 210 2.4% 0.48 [0.40, 1.60] minghere 26 112 54 208 2.0% 0.80 [0.50, 1.48] nd 18 53 63 86 320 2.5% 0.87 [0.55, 1.07] as 22 88 40 145 1.8% 0.88 [0.48, 1.60] minghere 26 112 54 208 2.0% 0.86 [0.55, 1.07] abo 6 30 14 100 0.9% 1.54 [0.55, 1.07] bio 16 30 12 50 1.2% 0.54 [0.54, 1.34] or 6 6 30 14 100 0.9% 1.54 [0.55, 1.07] bio 12 50 120 350 122 350 2.2% 0.65 [0.54, 1.34] or 6 6 30 14 100 0.9% 1.54 [0.55, 1.07] bio 12 50 120 350 122 350 2.2% 0.65 [0.54, 1.34] bio 16 13 156 535 2.4% 1.00 [0.67, 1.50] bio 12 150 120 350 122 350 120 350 123 350 120 350 1	đ	58	88	43	88	1.8%	2.02 [1.10, 3.71]	│ ─── ⊷
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	gimoto	4	105	3	172	0.5%	2.23 [0.49, 10.17]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	ang BB	33	230	15	158	1.75%	1.60 [0.84, 3.05]	
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$t_{a} = 1200000000000000000000000000000000000$			$\chi^{2} = 15$		= 57 (P	< 0.00001); $I^2 = 64\%$	
$\begin{array}{c} \text{base} \text{constraint} \\ \text{constraint} \\$					v		,,	

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	Ca	se	Cor	ntrol		Odds ratio	Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95%CI	M-H, random, 95%CI
1.2.1 Gastric cance							
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]	\longrightarrow
Crusius	66	236	305	1125	2.6%	1.04 [0.76, 1.43]	
El-Omar Fei	113 3	314 56	58 21	210 164	2.4% 0.7%	1.47 [1.01, 2.16] 0.39 [0.11, 1.35]	
Garcia-Gonzalez	95	404	84	404	2.6%	1.17 [0.84, 1.63]	
Garza-Gonzalez	63	-0- 63	214	215	0.1%	0.89 [0.04, 22.07]	
Glas	22	88	40	145	1.8%	0.88 [0.48, 1.60]	e
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]	\longrightarrow
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	535 172	2.4%	1.00 [0.67, 1.50]	
Sugimoto Torres	4 3	105 44	3 10	172 66	0.5% 0.6%	2.23 [0.49, 10.17] 0.41 [0.11, 1.58]	
Wu M	3 36	44 150	10 40	220	0.6% 2.1%	0.41 [0.11, 1.58] 1.42 [0.86, 2.36]	
Wu MS	41	204	39	220	2.1%	1.42 [0.88, 2.30]	
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)	51	5061	110	8885	49.6%	1.17 [1.02, 1.34]	
Total events	1204	5001	1932	0005	191070	1.17 [1.02, 1.5 1]	
Heterogeneity: Tau		5; $\gamma^2 =$		f = 27	(P = 0.00)	(9); $I^2 = 43\%$	
Test for overall effe						- //	
				,			
1.2.2 Colorectal car	ncer						
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)	562	2029	650	2486	20.7%	1.17 [0.87, 1.57]	
Total events Heterogeneity: Tau	563	2_	659	+F _ O ()	2 ~ 0 000	$(01), t^2 = 760/$	
Test for overall effe					< 0.000	(01); 1 = 76%	
		1.02 (/	0.51)			
1.2.3 Hepatocellula	r carcin	oma					
Akkiz	38	110	11	110	1.5%	4.75 [2.27, 9.92]	
Ben-Ari	1	110	6	48	0.3%	0.78 [0.08, 7.28]	<hr/>
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]	
Но	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]	<u>د او </u>
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					(<i>P</i> < 0.00	001); <i>I</i> ² = 73%	
Test for overall effe	ect: <i>Z</i> =	2.89 (/	P = 0.00	4)			

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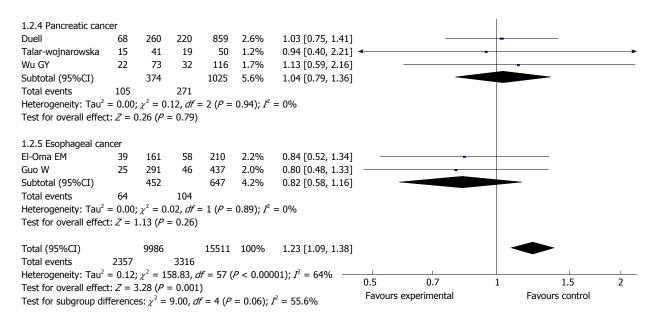


Figure 3 Subgroup analysis of tumor necrosis factor α -308 polymorphism by cancer type (dominant model).

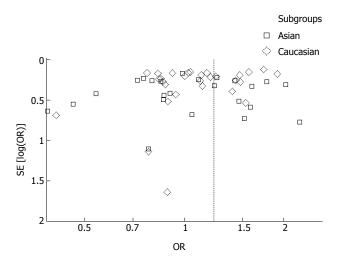


Figure 4 Funnel plots analysis to detect publication bias. Each point represents an independent study for the indicated association.

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 $TNF \cdot \alpha - 308G/A$ polymorphism increases the risk of gastric carcinoma. However, some studies have reported that no statistically significant association exists between the $TNF \cdot \alpha - 308G/A$ polymorphism and cancer risk^[14,20].

The current meta-analysis, which included 58 casecontrol 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

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Table 1 Characteristics of studies included in the meta-analysis														
Ref.	Year	Country	Ethnicity	Cancer type	Genotyping method		Ca	se			Р			
						Total	otal GG GA AA T		Total GG GA A			AA		
Burada et al ^[6]	2012	Romania	Caucasian	Gastric	TaqMan	105	78	26	1	242		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 <i>et al</i> ^[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		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 <i>et al</i> ^[15]	2004	China	Asian	Gastric	PCR	56	53	3	0	164		20	1	0.74
Garcia-Gonzalez <i>et al</i> ^[16]	2007	Spain	Caucasian	Gastric	TaqMan	404	309		11	404		77	7	0.35
Garza-Gonzalez et al ^[17] Glas et al ^[18]	2005	Mexico	Caucasian	Gastric	PCR-RFLP	63	0	8	55	215	1		179	0.61
Hou et al ^[19]	2004 2007	Germany	Caucasian Caucasian	Gastric	PCR-RFLP	88 305	66 186	19 98	3 21	145		36 109	4 15	0.67 0.19
Kamangar <i>et al</i> ^[20]	2007	Poland Finland	Caucasian	Gastric Gastric	TaqMan TaqMan	305 112	86	98 23	3	428 208	304 154	109 52	15	0.19
Kim et al ^[21]	2006	South Korea	Asian	Gastric	PCR-RFLP	237	199	34	4	208 461		52 59	2	0.29
Lee et al ^[22]	2000	South Korea	Asian	Gastric	PCR	341	297	43	1	261		42	1	0.49
Lee et al ^[23]	2001	South Korea	Asian	Gastric	PCR-RFLP	122	112	10	0	120		17	0	0.40
Li et al ^[24]	2005	China	Asian	Gastric	PCR-RFLP	59	55	4	0	264		34	2	0.56
Lu et al ^[25]	2005	China	Asian	Gastric	PCR-DHPLC	250	214	36	0		274	24	2	0.08
Machado <i>et al</i> ^[26]	2003	Portugal	Caucasian	Gastric	PCR-SSCP	287	179	105	3	304		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 <i>et al</i> ^[36]	2005	Italy	Caucasian	Gastric	TaqMan	129	95	31	3		496	138	10	0.91
Garrity-Park et al ^[37]	2008	Ireland	Caucasian	Colorectal	PCR, sequencing	114	52		13	114	92	20	2	0.46
Jang <i>et al</i> ^[14]	2001	South Korea	Asian	Colorectal	PCR-RFLP	27	24	3	0	92	85	7	0	0.70
Landi <i>et al</i> ^[38]	2003	Spain	Caucasian	Colorectal	TaqMan	363	278	80	5		234	76	10	0.22
Li M <i>et al</i> ^[39]	2011	China	Asian	Colorectal	PCR-RFLP	180	156	15	9	180		19	1	0.60
Macarthur <i>et al</i> ^[40] Park <i>et al</i> ^[41]	2005	Scotland	Caucasian	Colorectal	TaqMan	246	157		15		224	145	20	0.58
Suchy <i>et al</i> ^[42]	1998 2008	South Korea Poland	Asian Caucasian	Colorectal Colorectal	PCR-RFLP PCR-RFLP	140 350	115 254	24 87	1 9	328 350	252	72 95	4 7	0.65 0.55
Theodoropoulos <i>et al</i> ^[43]	2008	Greece	Caucasian	Colorectal	PCR-RFLP		152		9 14	200		93 44	10	0.05
Toth <i>et al</i> ^[44]	2000	Hungary	Caucasian	Colorectal	PCR-SSP	183	132	48	3		111	30	0	0.01
Tsilidis <i>et al</i> ^[45]	2007	United States	Caucasian	Colorectal	TaqMan	204	146	55	3	372		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 <i>et al</i> ^[47]	2003	United States		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 <i>et al</i> ^[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 <i>et al</i> ^[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		270	5	0	0.88
Shi <i>et al</i> ^[58]	2011	China	Asian	Hepatocellular	PCR-RFLP	88	30		15	88	45	35	8	0.75
Wang <i>et al</i> ^[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		15	0	0.53
Duell <i>et al</i> ^[61]	2006	United States	Caucasian	Pancreatic	PCR-RFLP	260	192	63	5		639	198	22	0.16
Talor-wojnarowska <i>et al</i> ^[62]	2009	Poland	Caucasian	Pancreatic	PCR-RFLP	41 72	26 51	12	3	50	31	17	2	0.86
Wu GY <i>et al</i> ^[63] El-Omar <i>et al</i> ^[9]	2010	Germany	Caucasian	Pancreatic Ecophagoal	PCR-RFLP	73 161	51	20	2	116 210	84 152	30 52	2	0.72
	2003	United States		Esophageal	TaqMan	161	122	34	5	210		52	6	0.55
Guo et al ^[13]	2005	China	Asian	Esophageal	PCR-RFLP	291	266	21	4	437	391	40	6	< 0.01

¹Numbers 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; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

are accurate.

Some limitations of this meta-analysis should be ad-

dressed. First, the number of published studies, especially for oesophageal and pancreatic cancers, was not suf-

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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	

¹Test for heterogeneity; ²Random-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.

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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 $TNF-\alpha$ -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.

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