

## ORIGINAL ARTICLE

# TNF- $\alpha$ -308G/A polymorphism and the risk of colorectal cancer: A systematic review and an updated meta-analysis

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## Summary

**Purpose:** This study aimed to explore the relationship between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and the risk of colorectal cancer (CRC) by meta-analysis.

**Methods:** Articles on exploring the relationship between TNF- $\alpha$ -308G/A polymorphism and CRC risk were searched from PubMed, Web of Science and Embase. The timeliness and authority of the included articles were evaluated. 95% confidence interval (95% CI) and odds ratio (OR) were calculated using fixed effect model or random effect model. Subgroup analysis was performed based on the ethnicity, source of control and method of genotyping. Finally, meta-analysis was conducted using STATA 12.0 software.

**Results:** Sixteen articles were selected (all case-control studies) with 3391 CRC patients and 3995 normal individuals (controls). No significant correlation was found between TNF- $\alpha$ -308G/A polymorphism and CRC risk (dominant gene model, OR=0.96, 95%CI, 0.86-1.07,  $p>0.05$ ; recessive gene model, OR=1.32, 95%CI, 0.99-1.76,  $p>0.05$ ; homozygous model, OR=1.28, 95%CI, 0.95-1.72,  $p>0.05$ ; heterozygous

model, OR=0.92, 95%CI, 0.82-1.04,  $p>0.05$ ; allele model, OR=0.96, 95%CI, 0.87-1.07,  $p>0.05$ ). Besides, we did not observe remarkable correlation in subgroup analysis of Asian and Caucasian CRC patients. Subgroup analysis of source of control showed no significance in hospital-based subgroup. However, TNF- $\alpha$ -308G/A polymorphism could reduce CRC risk in population-based subgroup (dominant gene model, OR=0.80, 95%CI, 0.63-1.00,  $p<0.05$ ; heterozygous model, OR=0.76, 95%CI, 0.60-0.97,  $p<0.05$ ; allele model, OR=0.80, 95%CI, 0.66-0.98,  $p<0.05$ ). On the contrary, TNF- $\alpha$ -308G/A polymorphism could increase CRC risk in subgroup analysis of method of genotype detected by PCR-RFLP (recessive gene model, OR=1.77, 95%CI, 1.10-2.86,  $p<0.05$ ; homozygous model, OR=1.79, 95%CI, 1.10-2.89,  $p<0.05$ ).

**Conclusions:** Our analysis indicated no significant correlation between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk.

**Key words:** colorectal cancer, meta-analysis, polymorphism, Rs1800629, TNF- $\alpha$ -308G/A

## Introduction

In recent years, incidence and mortality of malignant tumors have been increased astonishingly, and have become a major public health problem in China [1-3]. CRC (colon cancer, rectal cancer and anal cancer) is a common digestive tract tumor. Globally, it ranks third and second in incidence in males and females, respectively. There are 1.2

million newly diagnosed and 600,000 death cases of CRC each year in China [1,4-6]. Region, race, living environment and lifestyle all could affect the morbidity and mortality of CRC [7,8]. The incidence of CRC has gradually decreased in developed countries because of the widespread application of early detection and intervention. However, CRC

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incidence has increased in developing countries, especially in South Korea, China and some Eastern European countries [9-12]. Current treatment methods of CRC include surgery, chemotherapy, radiotherapy and targeting agents. CRC patients with distant metastasis have a poor prognosis [13,14].

Inflammatory cells secrete a variety of cytokines that promote cell proliferation, migration and angiogenesis, so as to repair damaged tissues [15,16]. TNF- $\alpha$  is an important inflammatory cytokine that is mainly secreted by macrophages. Functionally, TNF- $\alpha$  regulates immune cells and is a risk factor for the progression of malignant tumors [17]. Poor prognosis is frequently seen in cancer patients with positive expression of TNF- $\alpha$ , such as breast cancer, prostate cancer, lung cancer, colorectal cancer, liver cancer, lymphoma, and leukemia [18-21]. Experiments have shown that intra-peritoneal injection of TNF- $\alpha$  promotes the growth of papilloma and angiogenesis [20]. In chemically carcinogen-induced skin cancers, TNF- $\alpha$  promotes the development of malignant tumors. In an article, TNF- $\alpha$  knockout mice showed resistance to chemical carcinogens [22]. Moreover, SNP (single nucleotide polymorphisms) loci and GWAS (genome-wide association studies) found that rs1800629 was the locus most strongly associated with CRC ( $p < 0.05$ ) [23].

In this study, we analyzed the differentially expressed TNF- $\alpha$ -308G/A rs1800629 in CRC tissues. The effect of rs1800629 on the risk of CRC patients was also explored. Previous studies have pointed out that TNF- $\alpha$ -308G/A can affect the development of tumors [24-26]. Therefore, our analysis intended to further verify the relationship between rs1800629 polymorphism and CRC risk.

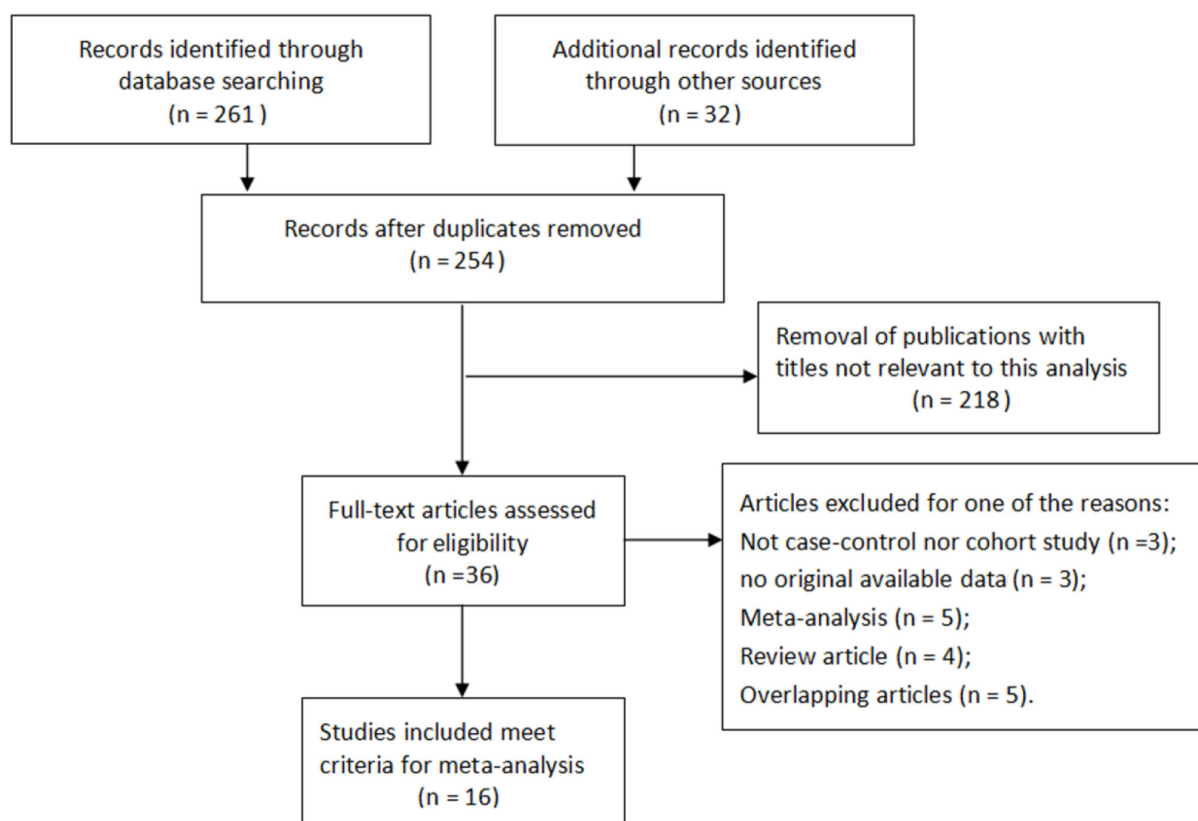
## Methods

### Literature search

Articles that explored the relationship between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk were searched in PubMed, Web of Science and Embase until April 1, 2018, without language restrictions. "TNF- $\alpha$ -308G/A" or "rs1800629", "single nucleotide polymorphism" or "variants", and "colorectal cancer" were used as the key words in literature search. Besides, we also included relative references of these articles. If repeated or overlapped data appeared in several articles, the articles with larger sample size or latest published were included.

### Inclusion and exclusion criteria

Completely published articles were selected and case-control studies focusing on the relationship between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk detected by effective biological methods were



**Figure 1.** Flowchart of literature search and selection process.

**Table 1.** Characteristics of individual studies included in the meta-analysis

TNF- $\alpha$ -308G/A(rs1800629)					Cases (n)			Controls (n)			HWE		
Year	First author	Ethnicity	SOC	Genotyping	Case	Control	GG	GA	AA	GG		GA	AA
2017	Li	Asian	HB	PCR-RFLP	569	570	500	66	3	493	75	2	Y
2016	Hamadien	Asian	HB	TaqMan	124	138	42	54	28	45	67	26	Y
2016	Gutiérrez-Hurtado	Caucasian	PB	PCR-RFLP	164	209	139	21	4	180	27	2	Y
2016	Banday	Caucasian	PB	PCR-RFLP	142	184	124	18	0	150	34	0	Y
2014	Stanilov	Caucasian	HB	PCR-RFLP	119	177	88	28	3	135	40	2	Y
2011	Li	Asian	HB	PCR-RFLP	180	180	156	15	9	160	19	1	Y
2009	Tsilidis	Caucasian	HB	TaqMan	204	372	146	55	3	275	90	7	Y
2008	Suchy	Caucasian	HB	PCR-RFLP	350	350	254	87	9	248	95	7	Y
2008	Garrity-Park	Caucasian	PB	PCR-RFLP	114	114	52	49	13	92	20	2	Y
2007	Toth	Caucasian	HB	PCR-RFLP	183	141	132	48	3	111	30	0	Y
2006	Gunter	Caucasian	HB	TaqMan	244	231	146	59	12	139	57	6	Y
2006	Theodoropoulos	Caucasian	HB	PCR-RFLP	222	200	152	56	14	146	44	10	Y
2005	Macarthur	Caucasian	PB	TaqMan	246	389	157	74	15	224	145	20	Y
2003	Landi	Caucasian	HB	TaqMan	363	320	278	80	5	234	76	10	Y
2001	Jang	Asian	PB	PCR-RFLP	27	92	24	3	0	85	7	0	Y
1998	Park	Asian	PB	PCR-RFLP	140	328	115	24	1	252	72	4	Y

SOC:source of controls, PB:population-based controls, HB:hospital-based controls

**Table 2.** Meta-analysis results of association between TNF- $\alpha$ -308G/A rs1800629 polymorphism and colorectal cancer risk after the elimination of the study conducted by Garrity-Park et al

Variables	rs1800629	All	Ethnicity		Source of control	
			Caucasian	Asian	PB	HB
No. of studies		15	10	5	5	10
Allele model	A vs.G					
OR (95% CI)		0.96 (0.87,1.07)	0.98 (0.88,1.11)	0.91 (0.7,1.14)	0.80 (0.66,0.98)	1.02 (0.91,1.15)
p values		0.405	0.420	0.290	0.421	0.705
I-square (%)		4.2	2.1	19.6	<0.1	<0.1
Dominant model	(GA+AA) vs. GG					
OR (95% CI)		0.96 (0.86,1.07)	0.98 (0.86,1.11)	0.91 (0.7,1.14)	0.80 (0.63,1.00)	1.02 (0.90,1.16)
p values		0.616	0.405	0.691	0.598	0.764
I-square (%)		<0.1	3.8	<0.1	<0.1	<0.1
Heterozygous model	GA vs. GG					
OR (95% CI)		0.92 (0.82,1.04)	0.95 (0.83,1.09)	0.84 (0.66,1.07)	0.76 (0.60,0.97)	0.719
p values		0.766	0.518	0.910	0.99(0.86 , 1.13)	0.868
I-square (%)		<0.1	<0.1	<0.1	<0.1	<0.1
Homozygous model	AA vs. GG					
OR (95% CI)		1.28 (0.95,1.72)	1.21 (0.85,1.72)	1.48 (0.85,2.57)	1.14 (0.62,2.09)	1.33 (0.95,1.87)
p values		0.483	0.510	0.232	0.512	0.339
I-square (%)		<0.1	<0.1	30.0	<0.1	11.3
Recessive model	AA vs. (GA+GG)					
OR (95% CI)		1.32 (0.99,1.76)	1.23 (0.87,1.75)	1.53 (0.92,2.54)	1.25 (0.68,2.28)	1.35 (0.97,1.87)
p values		0.521	0.547	0.251	0.556	0.356
I-square (%)		<0.1	<0.1	26.8	<0.1	9.4

enrolled. The articles should be comprehensive and clear, and odds ratio (OR) of the detailed population could be calculated. Exclusion criteria included duplicate reports, studies with poor quality, reviews and abstracts.

*Data acquisition*

Data acquisition was independently carried out by two reviewers using accurate data acquisition table. Disagreements among the two reviewers were re-evaluated by a third reviewer. The extracted data included last name of the first author, publication data, country, ethnicity, case numbers, source of controls (population-based or hospital-based), genotyping methods and genotype frequency of TNF- $\alpha$ -308G/A polymorphism between cases and controls.

*Statistics*

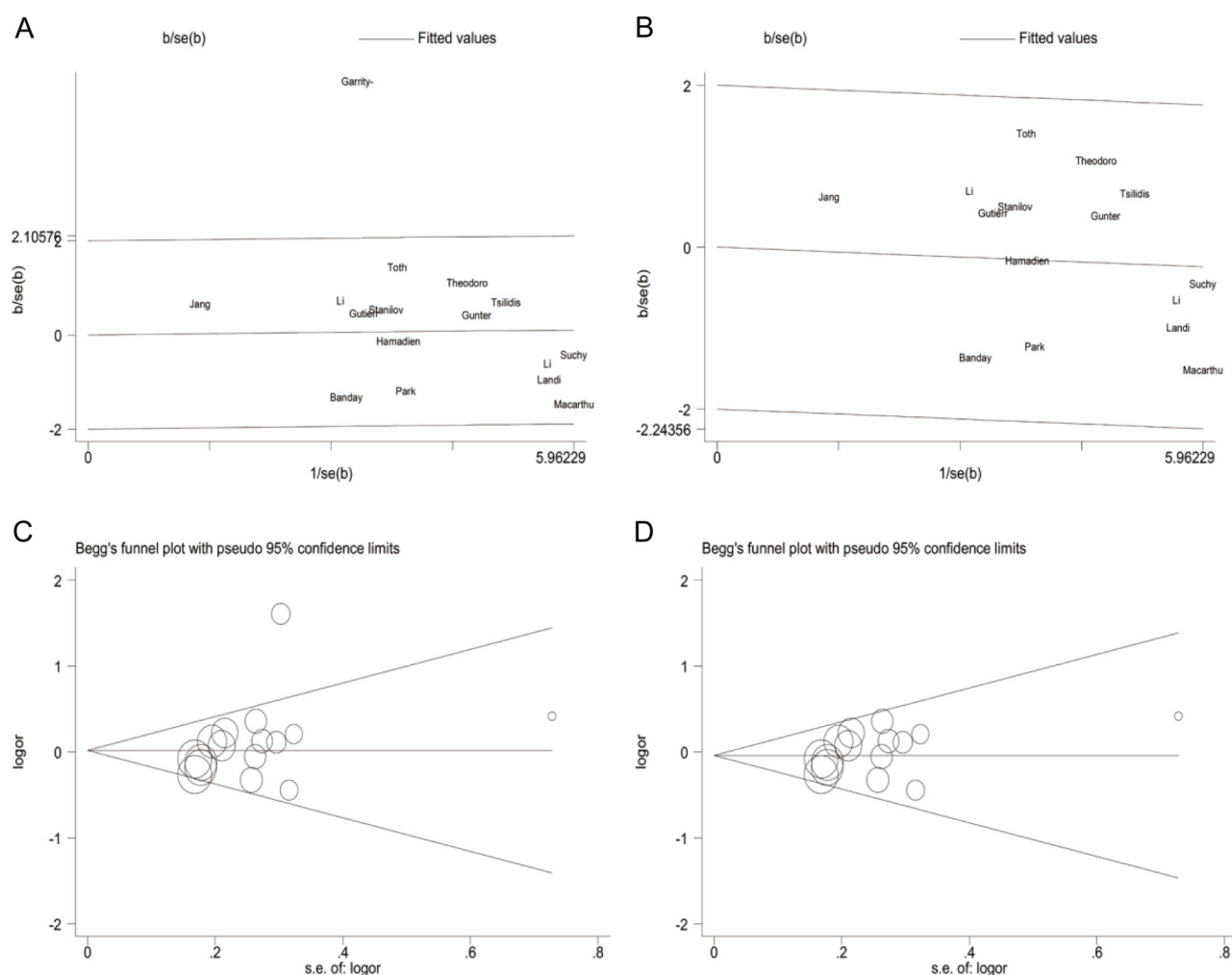
Stata software (version 12.0, Stata Corporation, College Station, TX, USA) was used to perform meta-analysis. Sensitivity analysis was performed to reflect the stability and reliability of results by excluding single

studies one by one and recalculating their ORs. Besides, the influence of publication bias between the studies was estimated by Begg's funnel plots and Egger's linear regression test. The degree of heterogeneity was evaluated based on the  $I^2$  value ( $I^2 < 25\%$ =low heterogeneity,  $25\% < I^2 < 50\%$ =moderate heterogeneity,  $I^2 > 75\%$ =high heterogeneity). Subgroup analysis was performed based on the ethnicity, source of control and method of genotype.  $P < 0.05$  was considered to be statistically significant.

**Results**

*Characteristics of the studies*

Flowchart of articles search and selection process was shown in Figure 1. A total of 16 studies were selected, which were all case-control studies with 3391 CRC patients and 3995 cases of controls [27-41]. Among them, 11 studies were conducted in Caucasian CRC patients and 5 in Asian CRC patients. In addition, 6 studies were population-based

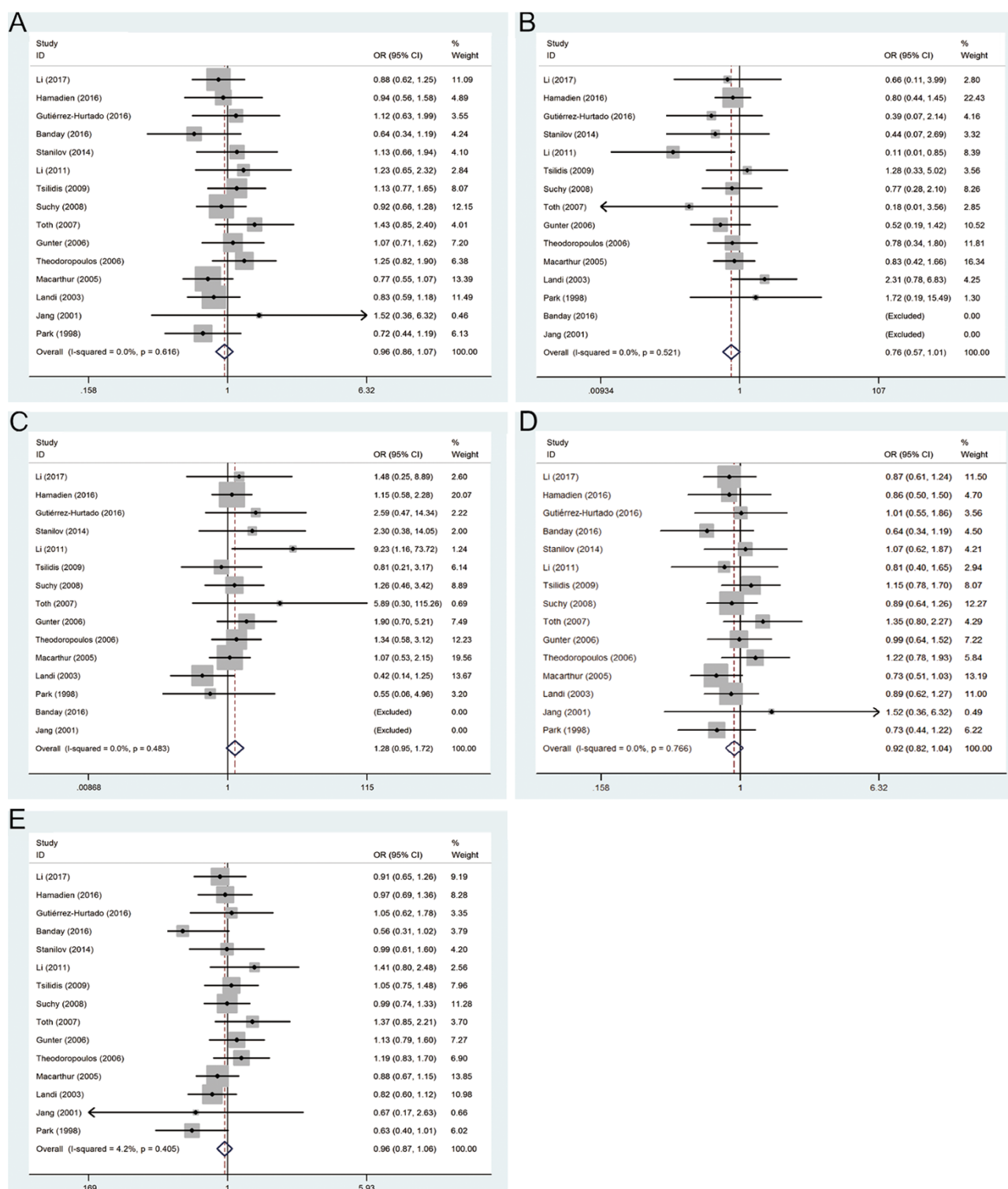


**Figure 2.** Galbraith plot of the association between TNF- $\alpha$ -308G/A rs1800629 polymorphism and colorectal cancer susceptibility in dominant model. **A:** Before removing the study conducted by Garrity-Park et al. **B:** After the exclusion of the study; Begg's funnel plot of publication bias test. **C:** Before omitting the study of Garrity-Park et al. **D:** After exclusion of the study.

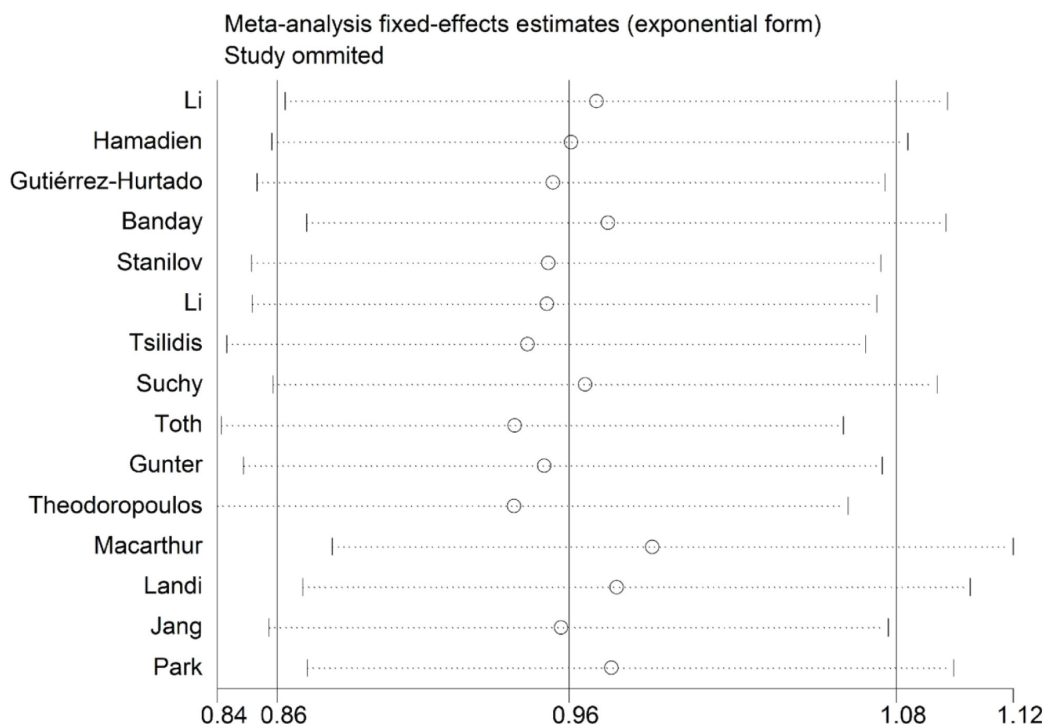
and 10 were hospital-based. Different genotyping methods were registered in the present analysis, namely TaqManSNP (TaqMan) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Characteristics of individual studies selected in the analysis, including specific distribution of genotypes are listed in Table 1.

### Quantitative synthesis results

Meta-analysis showed no significant relationship between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk (Table 2). We therefore performed heterogeneity analysis and detected publication bias in order to search for possible



**Figure 3.** Forest plots of the association between TNF- $\alpha$ -308G/A rs1800629 polymorphism and colorectal cancer susceptibility **A:** Dominant model; **B:** Recessive model; **C:** Homozygote model; **D:** Heterozygote model; **E:** Allele model. These results show no obvious correlation between TNF- $\alpha$ -308G/A and CRC risk in any of the 5 models.



**Figure 4.** Sensitivity analysis under the dominant model. These results show no substantial change in pooled ORs, indicating that our analysis was reliable and robust.

factors. As shown in Figure 3, after ruling out the study performed by Garrity-Park et al. [34], we still did not observe an obvious correlation between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk (dominant gene model, OR=0.96, 95%CI, 0.86-1.07,  $p>0.05$ ; recessive gene model, OR=1.32, 95%CI, 0.99-1.76,  $p>0.05$ ; homozygous model, OR=1.28, 95%CI, 0.95-1.72,  $p>0.05$ ; heterozygous model, OR=0.92, 95%CI, 0.82-1.04,  $p>0.05$ ; allele model, OR=0.96, 95%CI, 0.87-1.07,  $p>0.05$ ). Besides, no remarkable correlation in subgroup analysis of Asian and Caucasian CRC patients was found. Subgroup analysis of source of control showed no significance in hospital-based subgroup. However, TNF- $\alpha$ -308G/A polymorphism could reduce CRC risk in population-based subgroup (dominant gene model, OR=0.80, 95%CI, 0.63-1.00,  $p<0.05$ ; heterozygous model, OR=0.76, 95%CI, 0.60-0.97,  $p<0.05$ ; allele model, OR=0.80, 95%CI, 0.66-0.98,  $p<0.05$ ). On the contrary, TNF- $\alpha$ -308G/A polymorphism could increase CRC risk in subgroup analysis of method of genotyping detected by PCR-RFLP (recessive gene model, OR=1.77, 95%CI, 1.10-2.86,  $p<0.05$ ; homozygous model, OR=1.79, 95%CI, 1.10-2.89,  $p<0.05$ ).

#### Heterogeneity test

The overall heterogeneity was lower after ruling out the study conducted by Garrity-Park et al. [34], indicating the origin of heterogeneity

( $p=0.616$ , Figure 2). More interestingly, subgroup analysis could obviously reduce heterogeneity.

#### Sensitivity analysis

Sensitivity analysis was carried out to assess the stability and reliability of results by excluding single studies one by one and recalculating their ORs. No substantial change was found in pooled ORs, indicating that our analysis was reliable and robust (Figure 4).

#### Publication bias

Publication bias was determined by Begg's funnel plot and Egger's test. We found that the funnel plot was nearly symmetrically distributed after ruling out the study conducted by Garrity-Park et al. [34], suggesting that no remarkable publication bias was observed in our study ( $p=0.218$ , Figure 2).

## Discussion

CRC is one of the common malignancies of the digestive tract and exploring its occurrence and development mechanisms is of great significance [1]. Molecular genetic changes in CRC cells, such as changes in gene copy number and disruption of coding sequences, have crucial effects on tumor phenotype [2,3]. Current studies of signaling pathways in tumors have promoted the development of many new therapeutic targets. In recent years,

the incidence and mortality of CRC in China have gradually increased. The early diagnosis rate of CRC patients in China is extremely low, and most of them are in middle to late stages when first diagnosed and CRC in advanced stage accounts for the majority of the patients [13]. CRC is characterized with easy relapse, metastasis and poor prognosis. Early diagnosis and accurate prognosis of CRC contribute to timely and effective treatment. Hence, searching for proper biomarkers of CRC is extremely important in clinical practice [13,14]. Genetics, diet, unhealthy lifestyles and precancerous lesions are closely related to the occurrence of CRC [7,8]. Therefore, investigations on diagnosis, metastasis, recurrence and adjuvant treatment of advanced CRC have become the focus of current researches [12]. Recent studies have found that SNPs exert an essential role in many tumors. Multiple abnormally expressed SNP sites have already been found in CRC which may serve as new targets for the treatment of CRC [13,14].

Our results indicated no significant relationship between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk. After sensitivity and subgroup analysis to rule out small-size, replicate studies, we still did not observe an obvious correlation between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk, suggesting our analysis was reliable and robust. The results have shown that TNF- $\alpha$ -308G/A locus neither increases the transcriptional activity of the gene, nor leads to TNF- $\alpha$ -308G/A overexpression and proliferation of inflammation or cancer cells, suggesting that they are not risk factors of CRC.

Multiple studies have been carried out to explore the relationship between TNF- $\alpha$ -308G/A polymorphism and CRC risk but the results varied a lot. Li et al. [21] showed that TNF- $\alpha$ -308G/A increases CRC risk, and significant difference is found in the alleles of TNF- $\alpha$ -308G/A and distant metastasis even after adjusting for other clinical characteristics. On the contrary, Banday et al. [24] demonstrated no relationship between TNF- $\alpha$ -308G/A and distant metastasis of CRC in Kashmir. In the present study, we enrolled 16 relative articles and the results revealed no significant correlation between TNF- $\alpha$ -308G/A polymorphism and CRC risk (dominant gene model, OR=0.96, 95%CI, 0.86-1.07,

p>0.05; recessive gene model, OR=1.32, 95%CI, 0.99-1.76, p>0.05; homozygous model, OR=1.28, 95%CI, 0.95-1.72, p>0.05; heterozygous model, OR=0.92, 95%CI, 0.82-1.04, p>0.05; allele model, OR=0.96, 95%CI, 0.87-1.07, p>0.05). Besides, we did not observe remarkable correlation in subgroup analysis of Asian and Caucasian CRC patients. Subgroup analysis of the source of controls showed no significance in hospital-based subgroup. However, TNF- $\alpha$ -308G/A polymorphism could reduce CRC risk in population-based subgroup (dominant gene model, OR=0.80, 95%CI, 0.63-1.00, p<0.05; heterozygous model, OR=0.76, 95%CI, 0.60-0.97, p<0.05; allele model, OR=0.80, 95%CI, 0.66-0.98, p<0.05). On the contrary, TNF- $\alpha$ -308G/A polymorphism could increase CRC risk in subgroup analysis of method of genotyping detected by PCR-RFLP (recessive gene model, OR=1.77, 95%CI, 1.10-2.86, p<0.05; homozygous model, OR=1.79, 95%CI, 1.10-2.89, p<0.05). Different genotyping methods have different advantages, but may also lead to different statistical results. Therefore, meta-analysis results would be more meaningful and reliable only if the same suitable genotyping method is used.

To sum up, no significant correlation was found between TNF- $\alpha$ -308G/A polymorphism and CRC risk. It is worth noting that we could not cover all relative studies because of the limited number of clinical trials and objective conditions, which would decrease the strength of argument to some extent. Further explorations need to be carried out in case-control studies with large sample size and different races or prospective studies. Meanwhile, genetic and environmental factors should also be considered, so as to fully elucidate the underlying mechanism of CRC.

## Conclusions

Our analysis indicated no significant correlation between TNF- $\alpha$ -308G/A polymorphism (rs1800629) and CRC risk. Further studies with large sample size are needed to be carried out.

## Conflict of interests

The authors declare no conflict of interests.

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