Polymorphisms of Tumour necrosis factor- α -308 (rs 1800629) and gastric cancer susceptibility: A meta- analysis of associations studies with trial sequential analysis

Norah Htet Htet

International Medical University, Kuala Lumpur, Malaysia

Cho Naing (✉ cho3699@gmail.com)

International Medical University, Kuala Lumpur, Malaysia

Wong Siew Tung

International Medical University, Kuala Lumpur, Malaysia

Thin Thin Win

International Medical University, Kuala Lumpur, Malaysia

Joon Wah Mak

International Medical University, Kuala Lumpur, Malaysia

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Abstract

Background: Gastric cancer is globally the fifth most common cancer. Several studies have assessed the relationship between tumour necrosis factor-alpha (TNF- α -308) and the risk of gastric cancer. These individual genetic association studies showed inconclusive results. The objective of the present study was to synthesis evidence on the association between TNF- α -308 polymorphisms and gastric cancer risk by meta-analysis of data from eligible studies.

Methods: We performed a meta-analysis of genetic association studies, according to the PLOS One checklist. We searched relevant case-control studies in health-related electronic databases. The methodological quality of included studies was assessed by the Newcastle-Ottawa quality assessment scale. The strength of association was calculated as odds ratios (ORs) with 95% confidence intervals (CIs). Pooled ORs and 95 % CIs were estimated using random-effects model or fixed effect model, based on between-study heterogeneity. We analysed the strength of association under four genetic models (allele, dominant, recessive and additive models). Subgroup analyses on ethnic groups, *Hardy-Weinberg equilibrium* (HWE) status, status of *Helicobacter pylori* infection and study quality were done for robustness of the estimates. Publication bias was detected by inspection of funnel plot asymmetry. To estimate the required information size, we performed trial sequential analysis (TSA) that classified the effect estimates as 'firm evidence of effect' or 'potentially spurious evidence of effect'.

Results: A total of 35 studies, comprising 11353 cases and 12827 controls were identified. Based on 28 studies that met HWE, there was overall significant association between *TNF- α -308* polymorphisms and gastric cancer risk under the dominant model (OR 1.19, 95%CI 1.1-1.29, P :37%), as well as Asians (OR 1.2, 95%CI 1.05-1.38, P :53%) and Cassian subgroups (OR 1.19, 95%CI 1.07-1.31, P :28%). Based on 13 high quality studies under the dominant model, overall significant association was also found (OR 1.38, 95%CI 1.07, 1.77). The TSA plot indicated the analyses was with the required information size. There was no publication bias. In the subgroup analysis by ethnic groups, the quality of studies impacted on the estimates.

Conclusions: The findings suggest that *TNF- α -308* gene polymorphism plays an important predisposing role for gastric carcinogenesis, and can serve as a useful screening marker.

Introduction

Gastric cancer (ICD10: C16) is globally the fifth most common cancer with the highest prevalence in both sexes in Asia (74.5%) and the third leading cause of cancer death. In 2018, the estimated number of deaths attributed to gastric cancer was 782,685 [1]. As such, a greater understanding of the risk factors that play a role in gastric carcinogenesis can improve preventive and therapeutic interventions [2].

Epidemiologic studies showed that gastric cancer is multifactorial in aetiology [3, 4], in which dietary factors and *Helicobacter pylori* infection may contribute to its development [3]. Of note is that a high prevalence of these risk factors do not always correspond to a high incidence of gastric cancer, suggesting that other susceptible factors such as genetic variations and environmental differences may be involved in gastric carcinogenesis [5]. For instance, it has appeared that only 1-2% of the infected will develop gastric cancer in their lifetime, albeit with more than half of the world's population being infected with *H. pylori* infection [6].

Gastric neoplasms are composed of cancer cells and other "non-cancer" compartments (including immune cells), which are the major players in gastric cancer disease progression and aggressiveness [7]. Tumour necrosis factor (TNF) is a pro-inflammatory cytokine, which is produced mainly by the immune cells such as macrophages, dendritic cells, lymphocytes and mast cells [8]. The tumour microenvironment, composed mainly of inflammatory cells, is a crucial player in the neoplastic process, fostering proliferation, survival and migration [9]. Thus, TNF- α may act as a tumour promoter through inflammation. Moreover, TNF- α can induce the transcription of a wide range of other proinflammatory cytokines and chemokines, amplifying the inflammatory cascade against the infection [2]. Individual studies reported the significant relationship between TNF- α -308 (rs 1800629) and the risk of gastric cancer [10, 11]. However, other studies reported differently [12-14]. The published reviews in this field [15-16], did not report the required information size leading to concerns over confidence in estimates. We have also found more individual studies on this. Taken together, the objective of this study was to summarize the evidence of association between TNF- α -308 and the risk of gastric cancer by meta-analysis of data from eligible studies.

Materials And Methods

This is a meta-analysis of genetic association studies (GAS), following the Plos One checklist (S 1 Table).

Study search

We searched relevant studies in the health-related databases of PubMed, Ovid Medline, Embase, Google scholar and Web of science. To maximize search scope, we used a simple term combination strategy: ("gastric cancer" OR "gastric carcinoma" OR "stomach cancer" OR gastric adenocarcinoma AND "tumour necrosis factor- alpha-308" OR "rs1800629" OR "TNF- α -308 G>A" OR "TNF- α -307 G>A"). The search strategy in PubMed database is provided (S2 Table). The search was limited to the publications in English until November 2020. We also manually searched the references of included studies and relevant systematic reviews to capture any additional studies.

Inclusion criteria

Human studies that assessed gastric cancer, irrespective of site or histological type were included, if they met all the following criteria:

1. The study investigated TNF- α -308 G>A (rs 1800629) or TNF- α -307 G>A;
2. The study was a case-control design (retrospective or nested case-control);

3. The study recruited healthy people as the controls;
4. The study assessed histopathologically confirmed gastric cancer as an outcome;
5. The study reported the genotype frequency in cases and controls;
6. The study provided sufficient data to compute odds ratio (OR) and its 95% confidence interval (CI) as the outcome measurement.

Gastric cancer is as defined in the primary studies. Studies which did not meet the inclusion criteria were excluded. Studies done on family or sibling-pairs were also excluded. Studies on gastric adenoma are not considered.

Data extraction

One investigator (WST) screened the titles and abstracts and selected the relevant full-text articles, following the inclusion criteria. Two investigators extracted the data (NHH, WST) from each study individually, by using a pretested data extraction sheet. Information collected included: first author, publication year, country, study setting, the number of cases/controls, ethnicity (Asian or Caucasians), method of genotyping and genotype/allele frequencies in cases/controls. If an allele frequency was zero in both case and control, we added 1 to that allele, following the Laplace approximation [17]. Any discrepancy between the two investigators was discussed with the third investigator (CN) to reach consensus.

Assessment of the methodology quality

The two investigators (WST, CN) independently evaluated the methodological quality of studies, using the Newcastle-Ottawa Scale (NOS) [18]. The assessment is based on the three domains such as 'selection of the study groups' (4 points), 'comparability of the groups' (2 points) and 'ascertainment of the exposure' (3 points). A total score for each study can vary from 0 (the worst) to 9 (the best). A score achieved ≥ 7 , 6-5 or ≤ 4 is regarded as good, moderate or low quality study, respectively. Any discrepancy between the two investigators was resolved by consensus.

Statistical analysis

We assessed *Hardy-Weinberg equilibrium* (HWE) in the control populations of the included studies using the goodness-of-fit test and $p > 0.05$ was considered to indicate consistency with HWE [19]. As described elsewhere [20], the strength of the association between TNF- α 308 G>A and the risk of gastric cancer in each study was estimated using OR and its 95% CI. Between- study heterogeneity was determined with the I^2 test, which indicates the percentage of total variation across studies attributed to the heterogeneity rather than chance. I^2 values $> 50\%$ is regarded as substantial heterogeneity [21]. For pooling of the estimates, the summary ORs and its 95% CIs were calculated with the random-effects model (The Der Simonian and Laird method) in the presence of substantial heterogeneity. Otherwise, we used the fixed-effect model. We calculated the summary ORs and its 95% CIs in four genetic models: the allelic contrast model (A vs G), the dominant model (AA+GA vs GG), the recessive model (AA vs GA+GG), and the additive model (AA vs GG). In order to investigate the source of heterogeneity, subgroup analyses were employed under the dominant model for ethnicity, *H. pylori* infection status and study quality. Due to inconsistent reporting, we were unable to analyse by location or histological type of gastric cancer. For sensitivity analysis, we reassessed the relationship between TNF- α 308 and the risk of gastric cancer in all four genetic models only with studies in conformity of HWE. The publication bias was assessed by visual inspection of funnel plots under dominant model [22, 23].

Trial sequential analysis

To estimate the required information size, we performed trial sequential analysis (TSA) [24]. It is classified as 'firm evidence of effect' or 'potentially spurious evidence of effect', depending on whether the cumulative Z-curve cross the monitoring boundaries or not [23]. Meta-analysis was done with RevMan 5.3 (The Cochrane collaboration, Copenhagen) and *rworldmap* package in *R*[®] version 3.6.1 (The R Foundation). TSA plot was done with TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen).

Results

Study search

Fig 1 illustrates a four-phase study selection process. The initial search yielded a total of 1335 records. After removing the duplicates and screening of abstracts, 45 potentially eligible full-text articles that were retrieved. We included a final of 35 studies (with 11353 cases and 12827 controls) in this review [2, 5, 10-14, 25-52]. Summary of the 10 excluded studies were provided (S3 Table).

Study characteristics

Table 1 shows the characteristics of 35 studies identified. Of these, slightly more than half (54.3%, 19/35) were from the Asian region. The years of publication spanned from 2001 to 2017. The participants were adults with male predominance in all these studies. Eighty percent of the studies were consistent with HWE in genotype distribution of the controls.

The most frequent five studies were performed in China, South Korea or Brazil. Fig 2 shows geographical distribution of the studies included.

Of 35 studies, less than half (40%, 14/35) were categorized as high quality in methodology (14 studies). Eight studies (22.8%) were gastric adenocarcinomas. Only five studies provided (2, 10, 13, 34, 44) anatomical location or histological type of gastric cancers. Twelve studies (34%) used TaqMan

method for genotyping. The majority of studies (24/35, 68.6%) included *H. pylori* infected gastric cancer cases, albeit with variation in distribution. For instance, all cases (100%) were infected with *H. pylori* in one study [32], while this was only 46% in another study [2] (Table 1).

Effect estimations

The genotype frequencies in individual studies are presented in Table 2. Overall, there were significant associations between TNF- α -308 G>A and the gastric cancer risk under the allele model (OR, 1.17, 95% CI, 1.0-1.38, I^2 :80%) and the dominant model (OR, 1.2, 95% CI: 1.03–1.4, I^2 : 70%), but not under the recessive model (OR, 1.1, 95% CI; 0.9–1.35, I^2 :16%) or the additive model (OR, 1.25, 95% CI: 1.01-1.54, I^2 :0%). On stratification, only the Caucasian population showed susceptible to the gastric cancer risk under the allelic model (OR, 1.25, 95% CI, 1.0-1.55, I^2 :80%) and the dominant model (OR: 1.24, 95% CI; 1.08-1.42 I^2 :40%) (Fig 3A, Fig 3B, Fig 3C and Fig 3D).

Subgroup analyses

Under dominant model, TNF- α -308 G>A has significantly associated with an increased risk of gastric cancer with the high or moderate quality studies, but not with poor quality studies (S1 Fig). Based on 24 studies in which patients were infected with *H. pylori*, a significant association was observed between TNF- α -308 G>A and gastric cancer risk (OR, 1.17, 95% CI, 1.05-1.29). On further stratification, this was only with the Caucasian group (OR, 1.17, 95% CI, 1.04-1.32) (Table 3).

A sensitivity analysis based on 28 studies that were consistent with HWE, showed TNF- α -308 G>A polymorphism was significantly associated with an increased risk of gastric cancer under the dominant model in overall analysis (OR, 1.19, 95% CI: 1.1–1.29, I^2 :37%), regardless of ethnic groups. Moreover, this association showed a decreased statistical heterogeneity (i.e. I^2 values from 69% to 37%) (Table 3, S2 Fig). In the allele and recessive model, there was no significant association in overall analysis even in the absence of statistical heterogeneity (I^2 :0%). Under the additive model, there was a significant association in overall analysis (OR, 1.31; 95% CI: 1.02–1.69, I^2 :0%), but not in any particular ethnic group (Table 3). A funnel plot showed no evidence of publication bias (S3 Fig).

TSA plot

We performed TSA of the dominant model with the use of an overall type I error of 5% and type II error of 20%. The included total participants in this meta-analysis reached the required information size (for an expected RRR 26%). Briefly, a TSA monitoring boundary crossed with Z curve, confirms the presence of robust evidence (Fig 4). In such case further studies are not needed to provide sufficient information.

Discussion

Summary information

The present study provides evidence on the relationship between TNF- α -308 G>A and the risk of gastric cancer, comprising 11353 cases and 12827 controls from 35 individual studies. The major observations are as follows;

1. Based on 28 studies that met HWE, TNF- α -308 G>A SNP was significantly associated with the gastric cancer risk under the dominant and additive models.
2. On stratification, the HWE status of the controls, ethnicity, *pylori* infection status or study quality had an impact on the effect estimates.
3. The TSA plot revealed that the required information size for evidence of effect was sufficient. Any future studies in this field will less likely change the direction of estimates.

The association was statistically significant only for the Caucasians in overall allele model, indicating a dominance of racial specific factors. This difference may be explained partly due to variations in the frequency of the A allele between the different ethnic groups that could contribute to the diverse results. Moreover, it might also be related to difference in environmental factors such as smoking and diet between these two major ethnic groups. This was indirectly supported by an individual study in Poland, in which 72% of the gastric cancer cases were smokers (ex-smokers or current smokers) [39] as the effects of inflammatory polymorphisms might have been masked by smoking [35]. Due to paucity of data, we were not able to perform subgroup analysis with the smoking status of participants included in the studies identified. A published meta-analyses [53] reported that *H. pylori* infected cases had higher risk of developing gastric cancer. This was also observed in the present review. This could be explained based on immune-biological plausibility. *H. pylori* infection activates the cytokines production in the lining of the stomach including inflammatory-related genes such as TNF- α in the present analysis.

Our findings were comparable with earlier reviews, in which the significant association was limited to the Caucasians [53, 54] in the dominant models [11, 54]. Although there are more studies in this analysis, the results in general, retained the evidence of association. The most commonly studied inflammatory-related genes in gastric diseases include TNF- α , among others. TNF- α has been shown to inhibit the gastric acid secretion which is important in inducing cell apoptosis and promoting epithelial cell damage [57].

Public health Implications

The difference in association between the ethnic groups observed in the current analysis has implications. Studies had reported that the regulation of tumor immunity factors at the genetic and gene expression level may be different in the Asian and non-Asian gastric cancer populations, and this can affect the region-specific effects on therapy outcome and prognosis [58].

Study limitations

We acknowledge the study limitations. Only 36% of the studies in this review used TaqMan SNP genotyping assays, which is the preferred technology due to its high throughput and high accurate [59] compared to other methods. Hence, accuracy of genotype frequency is a concern. Some studies included were with small sample sizes. Hence, there might be type II statistical error. Meta-analysis is a retrospective pooling of published studies, and type II errors are, therefore, less likely than in individual studies.

There might be other confounding factors that were not included in our subgroup analyses. For example, infections with carcinogenic potentials (e.g. EBV) or smoking and alcohol drinking of the participants were not addressed due to limited data. This bias was likely to be pronounced as the calculations used unadjusted assessment of ORs. The effects of inflammatory polymorphisms might have been masked by smoking [35]. Moreover, it is likely to miss relevant studies that are available in non-English or non-indexed databases. Furthermore, there might be interactions of TNF- α and other genes such as interleukins (gene-gene interaction/synergism) or other potential confounding factors such as nutritional status and life style of the patients that might have significant roles in the gastric cancer risk. Due to limited number of studies, we could not perform pooled analysis with these potential confounding factors. Hence, findings in this meta-analysis should be interpreted with caution to these factors.

Nevertheless, there are strengths in our present meta-analysis study. More than half of the included studies were carried out in the Asia region, in which the gastric cancer was more prevalent. Moreover, the majority of gastric cancer patients in the primary studies identified were males. The current analysis reflected geographical and gender representativeness. The vast majority of included studies had evidence of HWE. Numerous studies had highlighted the issue of deviations from HWE in genetic association studies such as genotyping error, population admixture/substructure, among others [60-62]. Furthermore, for robustness of the findings, we have attempted several subgroup analyses. There are strengths in this meta-analysis compared with published reviews in this field [11, 53, 54, 60-63]. To be comprehensive, we have attempted the TSA technique, which is useful to adjust random-error risk. Moreover, we introduced TSA for confirmation of the estimates to assess a required information size. TSA plots indicated that there was sufficient information to provide conclusive results. An add-on TSA approach to this field will highlight to researchers the optimal sample size to make judgement of the effect estimates. This will help the researchers and policy makers to determine the need for future similar studies, which can save limited resources.

Conclusions

The current findings suggest that *TNF- α -308* gene polymorphism plays an important role as host genetic factor predisposing to gastric carcinogenesis, and it could be useful as a screening marker. As the relationship of gastric cancer risk is ethnic specific, the consideration as a biomarker should be tailored to the specific population group. To substantiate this, studies only from the Asian regions, using more reliable genotyping technique are recommended.

Declarations

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Ethics approval (and consent to participate)

The need for approval was waived as this study solely used published human data.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Tables

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

	Author, Year	Ref no.	Country	Ethnicity	Cases/ Controls	Age group	Males	Type of cancer	Smokers	Study design	Genotyping method	HP +ve	HWE, <i>p</i> value
1	El-Omar, 2003	2	USA	Caucasian	314/210	adult	87% 77%	GC-C GC- NC	Yes (80%)	CC	TaqMan	46%	0.548
2	Hong, 2013	5	China	Asian	1686/1894	adult	73%	GC-C GC- NC	NA	CC	TaqMan	NA	0.376
3	Machado, 2003	10	Portugal	Caucasian	287/306	adult	58.3%	GC	NA	CC	PCR	61.3%	0.649
4	Du, 2017	11	China	Asian	400/400	adult	70%	GC	Yes	CC, MA	allele- specific PCR	NA	0.000
5	Jang, 2001	12	South Korea	Asian	52/92	adult	NA	GAC	NA	CC	Nested PCR	NA	0.704
6	Glas, 2004	13	Germany	Caucasian	88/145	adult	46.6%	GC	NA	CC	PCR	88%	0.669
7	Whiteman, 2010	14	Australia	Caucasian	307/1355	adult	88%	GAC	76%	CC	PCR	25%	0.979
8	Wu, 2002	25	Taiwan	Asian	120/220	adult	NA	GC	NA	CC	PCR, dir seq	NA	0.000
9	Fei, 2004	26	China	Asian	56/164		76.8%	GAC	NA	CC	PCR	NA	0.743
10	Lee, 2004	27	South Korea	Asian	341/261	adult	58.4%	GC	NA	CC	PCR	NA	0.493
11	Wu, 2004	28	Taiwan	Asian	204/210	adult	61.8%	GAC	NA	CC	PCR, dir seq	80.4%	0.000
12	Garcia- Gonzalez, 2005	29	Spain	Caucasian	63/215	adult	64.1%	GC	NA	CC	PCR	49.2%	0.607
13	Lee, 2005	30	South Korea	Asian	122/120	adult	59%	GC	NA	CC	PCR	81%	0.403
14	Li, 2005	31	China	Asian	59/264	adult	66.1%	GC- NC	NA	CC	PCR-RFLP	93.2%	0.559
15	Lu, 2005	32	China	Asian	250/300	adult	73.2%	GC	57.2%	CC	PCR	70.4%	0.559
16	Perri, 2005	33	Italy	Caucasian	184/366	adult	59.8%	GAC	NA	CC	PCR	77.1	0.145
17	Rocha, 2005	34	Brazil	Caucasian	166/536	adult	69.9%	GC- NC	NA	CC	PCR-RFLP	100%	0.345
18	Zambo, 2005	35	Italy	Caucasian	129/ 792 (benign gastro- duodenal diseases)	adult	60.5%	GC- NC	NA	CC	Taqman	84%	0.909
19	Kamangar, 2006	36	Finland	Caucasian	112/208	adult	100%	GC	100%	CC	Taqman	91% (NC); 68% (C)	0.292
20	Kim, 2006	37	South Korea	Asian	237/474	adult	62.9	GC	NA	CC	Taqman and PCR- RFLP	86.5%	0.911
21	Morgan, 2006	38	Honduras	Caucasian	170/162	adult	69%	GC	NA	CC	TaqMan	80%	0.623
22	Garcia- Gonzalez, 2007	39	Spain	Caucasian	404/404	adult	65.8%	GC	Yes	CC	TaqMan	70.3%	0.35
23	Hou, 2007	40	Poland	Caucasian	305/427	adult	66.2%	GC	Yes (71.1%)	CC	TaqMan_	NA	0.186
24	Sugimoto, 2007	41	Japan	Asian	105/172	adult	80.9%	GC	NA	CC	PCR-RFLP	100%	0.908

25	Canedo, 2008	42	Portugal	Caucasian	508/713	adult	58.3%	GC	NA	CC	Taqman	NA	0.000
26	Crusiu, 2008	43	Europe ¹	Caucasian	248/770	adults	NC (47%) C (74%)	GC-C GC-NC	Yes	Nested CC	RT-PCR	NA	0.165
27	Melo, 2009	44		Caucasian	30/100	adults	63%	GAC	NA	CC	PCR-RFLP	97%	0.528
28	Yang, 2009	45	South Korea	Asian	84/336	adult	70%	GC	55%	CC	PCR	86%	0.317
29	Burada, 2012	46	Romania	Caucasian	105/242	adult	62.9%	GAC	NA	CC	TaqMan	100% (Only HP +ve)	0.784
30	Santos, 2012	47	Brazil	Caucasian	64/202	adult	NA	GC	NA	CC	PCR	100%	0.67
31	Oliveira, 2015	48	Brazil	Caucasian	207/240	adult	77.8%	GC	Yes	CC	SYBR Green& Taqman	NA	0.296
32	Bhayal, 2013	49	India	Asian	114/229	adult	68.4%	GC	42.1%	CC	PCR	75.44%	0.007
33	Yu, 2014	50	China	Asian	360/300	adults	62.2%	GC	NA	CC	PCR	0.2%	0.000
34	Stubljär, 2015	51	Slovenia	Caucasian	58/200	adult	55.17%	GAC	NA	CC	PCR	100%	0.528
35	Zabaglia, 2015	52	Brazil	Caucasian	24/40	adult	45.5%	GC	NA	CC	Taqman	87.5%	0.000

Ref no.: Reference number; CC: case-control design; dir seq: direct sequencing HP +ve: *H. pylori* positive; GAC: gastric adenocarcinoma; GC: gastric cancer in general, not specified; NC: non-cardia cancer; C: cardia; Europe: Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden and the UK; MA: meta-analysis; HWE: Hardy-Weinberg Equilibrium; NOS criteria: 0-9 score; RT-PCR: Real-time PCR; NA: not available/not reported/not shown.

Table 2: Distribution of gene frequencies in the studies

Study	Year	Ref. No.	Cases			Controls		
			G/G	G/A	A/A	G/G	G/A	A/A
Jang	2001	12	46	4	2	85	7	0
Wu	2002	24	96	17	7	180	27	13
El-Omar	2003	2	201	87	26	152	52	6
Machado	2003	10	179	105	3	231	69	4
Fei	2004	25	53	3	0	143	20	1
Glas	2004	13	66	19	3	105	36	4
Lee	2004	26	218	43	1	297	42	1
Wu	2004	27	163	29	12	171	26	13
Garcia-Gonzalez	2005	28	0	8	55	1	35	179
Lee	2005	29	112	10	0	103	17	0
Li	2005	30	55	4	0	228	34	2
Lu	2005	31	214	36	0	274	24	2
Perri	2005	32	71	14	1	118	24	4
Rocha	2005	33	120	37	4	399	123	13
Zambo	2005	34	95	31	3	496	138	10
Kamangar	2006	35	86	23	3	154	52	2
Kim	2006	36	199	34	4	400	59	2
Morgan	2006	37	151	17	0	149	12	0
Garcia-Gonzalez	2007	38	309	84	11	320	77	7
Hou	2007	39	186	98	21	304	109	15
Sugimoto	2007	40	101	4	0	169	3	0
Canedo	2008	41	330	178	0	544	169	0
Crusiu	2008	42	170	64	2	820	274	31
Melo	2009	43	24	5	1	86	13	1
Yang	2009	44	75	8	0	288	34	0
Whiteman	2010	14	196	93	6	842	403	48
Burada	2010	45	78	26	1	196	44	2
Santos	2012	46	44	20	0	22	4	0
Bhayal	2013	47	32	76	6	76	128	25
Hong	2013	5	1335	333	18	1585	295	14
Oliveira	2015	48	138	66	3	167	69	4
Zabaglia	2015	49	17	4	3	33	4	3
Du	2017	11	204	184	12	326	60	14

Table 3 Subgroup analysis

Genetic model	Number of studies included	OR (95%CI)		
		Overall	Asians	Caucasians
Studies consistent with HWE	28 (Asians 10 + Caucasians 18)			
Allele		1.11 [0.97, 1.27]R	1.06 [0.81, 1.39]R	1.12 [0.95, 1.33] R
Dominant		1.19 [1.10, 1.29]F	1.20 [1.05,1.38]F	1.19 [1.07, 1.31]F
Recessive		1.24 [0.98, 1.56] F	1.50 [0.88, 2.55] F	1.18 [0.90, 1.53]F
Additive		1.31 [1.02, 1.69] F	1.53 [0.91, 2.56]F	1.25 [0.94, 1.67]F
Studies based on <i>H. Pylori</i> infection status	24 (Asians 8 + Caucasians 16)			
Dominant		1.17 [1.05, 1.29] F	1.15 [0.93, 1.42] F	1.17 [1.04, 1.32] F

HWE: Hardy-Weinberg equilibrium; F : Fixed- effect model; R: random-effects model; Significant association is in bold;

Figures

Figure 1

Figure 2

Geographical distribution of included studies. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

A)

B)

Figure 3

Forest plot of gastric cancer risk associated with TNF- α 308 G/A polymorphism by ethnic group. (A) Allelic model. (B) Dominant model. (C) Recessive model. (D) Additive model Footnote: The circle and horizontal lines correspond to the study-specific OR and 95% CI. The diamond represents the summary OR and 95% CI.

Figure 4

Trial sequential monitoring plot of TNF- α -308 in gastric cancer risk under dominant model

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