REVIEW

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Association of IL-8 -251T>A (rs4073) polymorphism with susceptibility to gastric cancer: a systematic review and meta-analysis based on 33 case-control studies

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ABSTRACT – **Background** – The role of -251A>T polymorphism in the anti-inflammatory cytokine interleukin-8 (IL-8) gene in gastric cancer was intensively evaluated, but the results of these studies were inconsistent. **Objective** – Therefore, we performed a meta-analysis to provide a comprehensive data on the association of IL-8 -251T>A polymorphism with gastric cancer. **Methods** – All eligible studies were identified in PubMed, Web of Science, EMBASE, Wanfang and CNKI databases before September 01, 2019. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were derived from a fixed effect or random effect model. **Results** – A total of 33 case-control studies with 6,192 cases and 9,567 controls were selected. Overall, pooled data showed that IL-8 -251T>A polymorphism was significantly associated with an increased risk of gastric cancer under all five genetic models, i.e., allele (A vs T: OR=1.189, 95% CI 1.027–1.378, *P*=0.021), homozygote (AA vs TT: OR=1.307, 95% CI 1.111–1.536, *P*=0.001), heterozygote (AT vs TT: OR=1.188, 95% CI 1.061–1.330, *P*=0.003), dominant (AA+AT vs TT: OR=1.337, 95% CI 1.115–1.602, *P*=0.002) and recessive (AA vs AT+TT: OR=1.241, 95% CI 1.045–1.474, *P*=0.014). The stratified analysis by ethnicity revealed an increased risk of gastric cancer in Asians and mixed populations, but not in Caucasians. Moreover, stratified by country found a significant association in Chinese, Korean and Brazilian, but not among Japanese. **Conclusion** – This meta-analysis suggests that the IL-8 -251T>A polymorphism is associated with an increased risk of gastric cancer, especially by ethnicity (Asian and mixed populations) and country (Chinese, Korean and Brazilian).

HEADINGS – Stomach neoplasms. Interleukin 8. Genetic polymorphism. Meta-analysis.

INTRODUCTION

Gastric cancer is the 4th most common malignancy and the second leading cause of cancer-related death worldwide[1,2], accounting for more than one million new patients and an estimated 783,000 deaths in 2018[3]. There is considerable variation in gastric cancer incidence rates according to age, gender, socioeconomical factors and geographical location[4]. Several factors have been suggested as risk factors for gastric cancer, which by establishing complex interactions may ultimately lead to development of this disease. The exact etiology of gastric cancer is multifactorial and both host genetic variants and environmental factors, including inflammation, *Helicobacter pylori* (*H. pylori*) infection, cigarette smoking, alcohol consumption, dietary and nutritional aspects have been shown to play a role in the development of this disease[5,6].

Interleukin-8 (IL-8, also known as CXCL8) is a member of the alpha (C-X-C) subfamily of small basic heparin-binding chemokines[7]. These group of proteins are proinflammatory and primarily mediate the activation and migration of neutrophils into tissue from peripheral blood[8]. IL-8 was originally discovered and purified as a neutrophil chemotactic and activating factor and secreted by several hematopoietic cells, fibroblasts, hepatocytes, and various cell lines and interacts with two specific seven-transmembrane span, G-protein-coupled receptors, CXCR1 and CXCR2[9,10]. Moreover, IL-8 is produced by several types of tumor cells and has been shown to be involved in angiogenesis and neovascularization-dependent tumor growth[11]. Hence, IL-8 gene variants may be the important determinants of development of different cancers, especially gastric cancer. IL-8 is associated with both the immune response and the inflammatory process against *H. pylori*[12]. An increased IL-8 expression has been detected in patients with *H. pylori* infection and gastric disorders[12,13].

The human IL-8 gene is mapped to 4q12-q21 by somatic cell hybridization and in situ hybridization, spanning 5.2 kb in length and contains 10 exons[14]. The 3' untranslated region (UTR) of IL-8 contains a A/U-rich element that makes it extremely unstable under certain conditions. The -251T>A (rs4073) polymorphism in the IL-8 promoter is one of the most extensively studied genetic variant in several inflammatory conditions[15]. Although several studies have been previously performed to evaluate whether the IL-8 -251T>A (rs4073) polymorphism increases the risk of gastric cancer, the results from these studies are inconsistent and controversial. Therefore, this study aimed to perform a meta-analysis including the update data to evaluate the association of IL-8 -251T>A (rs4073) polymorphism and gastric cancer.

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METHODS

Search strategy

We have performed this meta-analysis in adherence with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was conducted in PubMed, EMBASE, Cochrane Library database, SID, CBM, WanFang Chinese Biomedical Database (CBD), China National Knowledge Infrastructure (CNKI) and VIP database to collect all the eligible studies evaluating the association of IL-8 -251T>A (rs4073) polymorphism and gastric cancer until to September 01, 2019. The following terms, keywords and their combinations were used: ("gastric" OR "stomach") AND ("cancer" OR "malignancy" OR "tumor" OR "carcinoma" or "neoplasm" OR "adenocarcinoma") AND ("interleukin-8" OR "IL-8" OR "C-X-C motif chemokine ligand 8" OR "CXCL8" OR "neutrophil chemotactic factor") AND ("polymorphism" OR "SNP" OR "variant" OR "genotype" OR "mutation" OR "allele"). The whole search process was carried out in English, Chinese and Farsi. Ethical approval was not necessary since this study was based on previous publications.

Inclusion and exclusion criteria

The studies were considered eligible if the following criteria are met: 1) studies with case-control and cohort design; 2) studies were performed on human beings; 3) studies evaluated the association between the IL-8 -251T>A polymorphism and gastric cancer; and 4) provide adequate data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Studies were excluded if one of the following criteria was fulfilled: 1) studies that had no control group; 2) abstracts, review, letters, comments, conference presentations, case reports or case series; 3) studies without detailed raw data regarding IL-8 -251T>A polymorphism; 4) family-based, sibling, twins and linkage studies. For duplicate reports, only the study with the largest sample size was included.

Data extraction

All the available data were extracted from each study by two of the authors independently and carefully according to the criteria and any disagreement was resolved by discussion with third author. For each included study, the following information was collected: first author's name, year of publication, ethnicity (Asian, Caucasian, African and mixed populations), country of origin, source of the controls (hospital based or population based), genotyping methods, numbers of cases and controls, frequencies of genotypes in cases and controls, minor allele frequency (MAF) in controls, and Hardy-Weinberg equilibrium (HWE) in controls. The "mixed" group means mixed or unknown populations. When studies included sample of more than one ethnicity or population, the data was extracted separately according to ethnicities. If necessary data were not reported in the primary manuscripts, we contacted the corresponding authors by email to request the missing data.

Methodological quality assessment

Quality assessments for eligible studies were conducted by two investigators independently using the Newcastle-Ottawa Scale (NOS). In this methodological quality assessment scale, nine items, each with a score value between one and nine, are included. The NOS has a score range of zero to nine, and studies with a NOS score of ≥6 stars is generally considered of high-quality.

Statistical analysis

The strength of association between IL-8 -251T>A polymorphism and gastric cancer was assessed by odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance of the pooled effect size was determined by Z-test, in which $P<0.05$ was considered statistically significant. The association was evaluated in five genetic models, i.e., allele (A vs T), homozygote (AA vs TT), heterozygote (AT vs TT), dominant (AA+AT vs TT), and the recessive (AA vs AT+TT). Between-study heterogeneity was evaluated by the Cochran Q-test, in which $P\leq0.10$ indicated significant heterogeneity was found. In addition, the I^2 statistic we applied to qualify between-study heterogeneity (range of 0 to 100%: I^2=0–25%, no heterogeneity; I^2=25%–50%, moderate heterogeneity; I^2=50%–75%, large heterogeneity; I^2=75%–100%, extreme heterogeneity). The random effects model shows more flexibility with respect to variable effect size in different studies and study populations. Thus, we have applied a random-effects model, using the DerSimonian and Laird method to calculate the pooled OR when heterogeneity was found; otherwise, affixed effect model was applied to use the Mantel-Haenszel method in absence of heterogeneity. A Hardy-Weinberg equilibrium (HWE) test in controls was tested using chi-square test (P-values <0.05). Subgroup analyses were conducted by stratification of ethnicity to identifying potential source of heterogeneity. Sensitivity analyses were performed to assess influence of each single study on pooled ORs and the stability of the meta-analysis results by sequential remove of individual studies. In addition, sensitivity analysis by excluding those studies HWE violating was performed to examine the stability of the results. Funnel plots and Egger's linear regression test were used to estimate evidence for potential publication bias. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Characteristics of selected studies

FIGURE 1 shows the flowchart of literature search and selection process. The initial literature searches retrieved 158 potentially relevant studies. After reading titles and abstracts, 67 irrelevant and duplicate articles were excluded. Another 32 articles were subse-

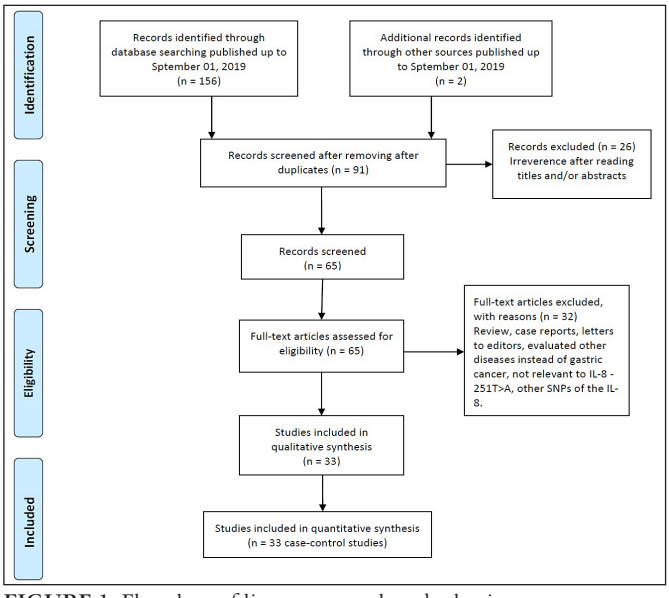

FIGURE 1. Flowchart of literature search and selection process.

quently excluded because not reporting useful data for meta-analysis, review, case only study, and not being case-control studies. Finally, a total of 33 eligible studies with 6,192 gastric cancer cases and 9,567 controls were included in the meta-analysis[16-39]. Characteristics of included studies are shown in TABLE 1. All eligible studies were published in English and Chinese. The NOS score of included studies ranged from 7 (19 studies) to 8 (14 studies), which suggested that all included studies were of relatively high quality. Among them, 21 studies were based on Asians (Taiwan, Japan, Korea, Iran, and India), seven based on Caucasians (USA, Finland, France, Portugal, Hungary, Romanian), and five were based on mixed populations (Mexico and Brazil). The allele, genotype and minor allele frequency (MAF) distributions in the cases and controls are shown in TABLE 1. Moreover, the distribution of genotypes in the controls was in agreement with Hardy-Weinberg equilibrium (HWE) for all selected studies, except for one study (TABLE 1).

Overall and subgroup analyses

The summary of the meta-analysis of the association of between IL-8 -251T>A polymorphism and gastric cancer are shown in TABLE 2. Overall, pooled ORs showed that there was a significant association between IL-8 -251T>A polymorphism and gastric can-

TABLE 1. Main characteristics of studies included in the meta-analysis.

First author	Country (Ethnicity)	Genotyping Method	SOC	Case/ Control	Cases					Controls					MAFs	HWE	NOS
					Genotypes			Allele		Genotypes			Allele				
					TT	TA	AA	T	A	TT	TA	AA	T	A			
Savage 2004	USA (Caucasian)	SBE	PB	88/429	26	39	23	91	85	147	207	75	501	357	0.416	0.884	7
		TaqMan	PB	287/428	76	140	71	282	292	117	205	106	439	417	0.487	0.391	7
Lee 2005	Taiwan (Asian)	PCR-RFLP	HB	364/291	156	164	44	609	331	108	127	56	354	262	0.411	0.093	8
Taguchi 2005	Japan (Asian)	PCR-RFLP	HB	396/215	161	191	44	513	279	125	105	22	355	149	0.296	0.994	7
Lu 2005	China (Asian)	PCR-DHPLC	PB	250/300	94	102	54	290	210	119	144	37	382	218	0.363	0.515	8
Zeng 2005	China (Asian)	PCR-RDB	PB	206/504	37	110	59	184	228	43	114	39	200	192	0.490	0.021	8
Leung 2006	China (Asian)	TaqMan	NS	123/179	44	56	23	144	102	51	92	36	194	164	0.467	0.835	7
Ohyauchi 2005	Japan (Asian)	DS	HB	212/244	93	106	13	292	132	149	84	11	534	158	0.217	0.847	7
Shirai 2005	Japan (Asian)	PCR-RFLP	HB	181/468	83	78	20	244	118	211	208	49	630	306	0.327	0.830	7
Kamali-Sarvestani 2006	Iran (Asian)	ASO-PCR	HB	19/153	4	6	9	14	24	57	74	22	188	118	0.386	0.797	7
Kamangar 2006	Finland (Caucasian)	TaqMan	PB	112/207	42	56	14	140	84	72	111	24	255	159	0.384	0.054	8
Garza-Gonzalez 2007	Mexico (Mixed)	ARMS-PCR	HB	78/189	15	47	16	77	79	69	87	33	225	153	0.405	0.538	7
Crusius 2008	France (Caucasian)	Real-Time	PB	236/1139	75	113	48	263	209	315	574	250	1204	1074	0.471	0.705	8
Canedo 2008	Portugal (Caucasian)	TaqMan	PB	333/693	111	169	53	391	275	203	353	137	759	627	0.452	0.459	7
Szoke 2008	Hungary (Caucasian)	ARMS-PCR	NS	35/168	11	15	9	37	33	38	93	37	169	167	0.497	0.164	7
Kang 2009	Korea (Asian)	PCR-RFLP	PB	334/322	126	159	49	411	257	147	148	27	442	202	0.314	0.225	8
Ko 2009	Korea (Asian)	Snapshot	PB	81/308	34	35	12	103	59	135	146	27	416	200	0.325	0.155	8
Ye 2009	Korea (Asian)	PCR-RFLP	HB	153/206	54	82	17	190	116	97	86	23	280	132	0.320	0.552	7
Song 2009	China (Asian)	PCR-RFLP	HB	125/140	33	72	20	138	112	47	70	23	164	116	0.414	0.720	8
Liu 2009	China (Asian)	TaqMan	HB	138/137	26	89	23	141	135	50	72	15	172	102	0.372	0.145	7
Li 2010	China (Asian)	PCR-DHPLC	NS	101/137	25	65	11	115	87	59	64	14	184	92	0.336	0.579	7
Bo 2010	China (Asian)	PCR-RFLP	HB	208/190	64	108	36	236	180	68	96	26	232	148	0.386	0.389	8
Zhang 2010	China (Asian)	PCR-RFLP	PB	519/504	130	261	128	521	517	160	251	93	571	437	0.434	0.754	8
Vinagre 2011	Brazil (Mixed)	PCR-RFLP	HB	102/103	21	56	25	98	106	42	42	19	126	80	0.387	0.122	8
Felipe 2012	Brazil (Mixed)	PCR-RFLP	PB	104/196	31	58	15	120	88	59	85	52	203	189	0.482	0.065	7
Burada 2012	Romania (Caucasian)	Real-Time	HB	105/242	31	54	20	116	94	82	112	48	276	208	0.430	0.385	7
Pan 2014	China (Asian)	SBE	HB	308/308	92	168	48	352	264	101	148	59	350	266	0.432	0.715	7
Qadri 2014	India (Asian)	PCR-CTPP	PB	130/200	50	68	12	168	92	94	94	12	282	118	0.295	0.066	8
Kumar 2015	India (Asian)	ASO-PCR	HB	200/250	67	86	47	220	180	93	122	35	308	192	0.384	0.618	8
de Oliveira 2015	Brazil (Mixed)	PCR-RFLP	HB	240/207	61	134	45	222	192	62	98	47	256	224	0.464	0.488	7
Wang 2016	China (Asian)	MassARRAY	HB	132/296	47	59	26	153	111	102	144	50	348	244	0.412	0.945	7
Ramis 2017	Brazil (Mixed)	PCR-RFLP	PB	9/38	4	1	4	9	9	11	20	7	42	34	0.447	0.691	7
Chang 2017	Korea (Asian)	PCR-RFLP	HB	283/176	81	168	34	330	236	70	89	17	229	123	0.349	0.136	8

SBE: allele-specific single base extension; PCR: polymerase chain reaction; RFLP: polymerase chain reaction restriction fragment length polymorphism; DHPLC: denaturing high performance liquid chromatography; DS: direct sequencing; ASO: Allele-specific oligonucleotide; ARMS: amplification refractory mutation system; SOC: source of controls; HB: hospital-based; PB: population-based; NS: not stated; MAFs: minor allele frequencies; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa Scale.

TABLE 2. Summary of meta-analysis for association between IL-8 -251T>A polymorphism and gastric cancer risk.

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs T	Random	87.85	≤0.001	1.189	1.027-1.378	2.312	0.021	0.245	0.926
	AA vs TT	Random	55.20	≤0.001	1.307	1.111-1.536	3.239	0.001	0.117	0.029
	AT vs TT	Random	50.86	≤0.001	1.188	1.061-1.330	2.987	0.003	0.258	0.528
	AA+AT vs TT	Random	83.25	0.020	1.337	1.115-1.602	3.141	0.002	0.060	0.228
	AA vs AT+TT	Random	69.17	≤0.001	1.241	1.045-1.474	2.457	0.014	0.141	0.233
Ethnicity										
Asians	A vs T	Random	89.49	≤0.001	1.299	1.068-1.580	2.614	0.009	0.650	0.520
	AA vs TT	Random	51.39	0.004	1.458	1.200-1.771	3.800	≤0.001	0.319	0.140
	AT vs TT	Random	45.31	0.013	1.222	1.076-1.388	3.089	0.002	0.607	0.574
	AA+AT vs TT	Random	86.93	≤0.001	1.470	1.151-1.878	3.088	0.002	0.074	0.262
	AA vs AT+TT	Random	72.40	≤0.001	1.394	1.106-1.756	2.819	0.005	0.927	0.755
Caucasians	A vs T	Fixed	19.86	0.278	0.972	0.883-1.070	-0.579	0.562	0.763	0.366
	AA vs TT	Fixed	10.68	0.348	0.927	0.762-1.127	-0.759	0.448	0.763	0.310
	AT vs TT	Fixed	0.00	0.654	0.925	0.791-1.080	-0.987	0.323	1.000	0.962
	AA+AT vs TT	Fixed	0.00	0.530	0.924	0.797-1.070	-1.062	0.288	0.367	0.627
	AA vs AT+TT	Fixed	3.701	0.398	0.974	0.822-1.154	-0.300	0.764	0.367	0.196
Mixed	A vs T	Random	86.72	≤0.001	1.044	0.642-1.696	0.173	0.862	0.220	0.391
	AA vs TT	Random	64.18	0.025	1.310	0.715-2.401	0.874	0.382	0.806	0.565
	AT vs TT	Fixed	56.82	0.055	1.639	1.244-2.153	3.518	≤0.001	0.806	0.528
	AA+AT vs TT	Random	58.36	0.048	1.526	0.990-2.352	1.913	0.056	0.806	0.919
	AA vs AT+TT	Random	60.55	0.038	0.984	0.601-1.611	-0.064	0.949	0.086	0.271
Country										
Chinese	A vs T	Random	93.30	≤0.001	1.390	0.999-1.933	1.954	0.051	0.591	0.905
	AA vs TT	Fixed	36.37	0.117	1.427	1.194-1.704	3.921	≤0.001	1.000	0.966
	AT vs TT	Random	54.56	0.019	1.225	0.993-1.510	1.898	0.058	0.474	0.463
	AA+AT vs TT	Random	92.61	≤0.001	1.701	1.051-2.752	2.163	0.031	0.591	0.556
	AA vs AT+TT	Random	78.97	≤0.001	1.409	0.993-2.000	1.918	0.055	0.720	0.657
Korean	A vs T	Fixed	0.00	0.936	1.315	1.143-1.514	3.816	≤0.001	0.089	0.035
	AA vs TT	Fixed	0.00	0.782	1.773	1.282-2.452	3.462	0.001	0.734	0.270
	AT vs TT	Fixed	0.00	0.391	1.263	1.026-1.554	2.200	0.028	0.734	0.794
	AA+AT vs TT	Fixed	0.00	0.547	1.438	1.182-1.749	3.639	≤0.001	0.734	0.761
	AA vs AT+TT	Fixed	0.00	0.429	1.488	1.098-2.016	2.561	0.010	0.734	0.534
Brazilian	A vs T	Random	86.03	≤0.001	0.943	0.547-1.626	-0.212	0.832	0.308	0.481
	AA vs TT	Random	64.91	0.036	1.142	0.573-2.276	0.377	0.706	0.734	0.704
	AT vs TT	Fixed	56.82	0.055	1.636	1.244-2.153	3.518	≤0.001	0.734	0.474
	AA+AT vs TT	Fixed	57.09	0.072	1.360	1.026-1.803	2.138	0.033	0.734	0.789
	AA vs AT+TT	Random	67.23	0.027	0.949	0.511-1.764	-0.165	0.869	0.308	0.392
Japanese	A vs T	Random	92.09	≤0.001	0.549	0.229-1.317	-1.344	0.179	0.296	0.007
	AA vs TT	Fixed	0.00	0.440	1.374	0.955-1.977	1.710	0.087	1.000	0.597
	AT vs TT	Random	74.20	0.021	1.391	0.923-2.096	1.578	0.115	1.000	0.775
	AA+AT vs TT	Random	79.38	0.008	1.246	0.796-1.948	0.962	0.336	1.000	0.152
	AA vs AT+TT	Fixed	0.00	0.864	1.129	0.796-1.601	0.679	0.497	0.122	1.000
Source of controls										
HB	A vs T	Random	81.06	≤0.001	1.139	0.959-1.351	1.484	0.138	0.111	0.901
	AA vs TT	Random	53.23	0.004	1.402	1.117-1.760	2.913	0.004	0.002	0.001
	AT vs TT	Random	49.95	0.010	1.346	1.150-1.576	3.693	≤0.001	0.063	0.103
	AA+AT vs TT	Random	67.52	≤0.001	1.397	1.158-1.684	3.496	≤0.001	0.007	0.003
	AA vs AT+TT	Random	48.38	0.013	1.135	0.933-1.380	1.264	0.206	0.015	0.002
PB	A vs T	Random	92.79	≤0.001	1.255	0.958-1.645	1.652	0.099	1.000	0.814
	AA vs TT	Random	62.35	0.001	1.277	0.989-1.648	1.875	0.061	0.951	0.530
	AT vs TT	Fixed	5.38	0.393	1.040	0.930-1.162	0.684	0.494	0.760	0.345
	AA+AT vs TT	Random	90.77	≤0.001	1.278	0.896-1.824	1.355	0.175	0.951	0.846
	AA vs AT+TT	Random	82.21	≤0.001	1.407	1.020-1.941	2.079	0.038	0.951	0.481
Genotyping methods										
PCR-RFLP	A vs T	Random	82.90	≤0.001	1.081	0.881-1.327	0.747	0.455	0.427	0.154
	AA vs TT	Random	60.54	0.002	1.271	0.970-1.665	1.740	0.082	1.000	0.968
	AT vs TT	Fixed	31.91	0.123	1.248	1.113-1.400	3.797	0.001	0.360	0.988
	AA+AT vs TT	Random	49.25	0.023	1.250	1.065-1.467	2.732	0.006	0.669	0.681
	AA vs AT+TT	Random	58.77	0.004	1.070	0.843-1.358	0.558	0.577	0.760	0.986
TaqMan	A vs T	Random	67.36	0.016	1.025	0.831-1.264	0.227	0.821	0.220	0.488
	AA vs TT	Random	61.83	0.033	1.024	0.678-1.546	0.111	0.911	0.220	0.304
	AT vs TT	Random	66.24	0.019	1.032	0.741-1.437	0.187	0.852	0.806	0.525
	AA+AT vs TT	Random	84.10	≤0.001	1.140	0.715-1.816	0.549	0.583	0.462	0.293
	AA vs AT+TT	Fixed	0.00	0.413	0.947	0.771-1.163	-0.519	0.604	0.462	0.224
Others	A vs T	Random	91.42	≤0.001	1.370	1.049-1.789	2.310	0.021	0.060	0.550
	AA vs TT	Random	41.04	0.049	1.458	1.167-1.822	3.317	0.001	0.488	0.016
	AT vs TT	Random	55.10	0.005	1.181	0.978-1.427	1.725	0.085	0.428	0.583
	AA+AT vs TT	Random	89.22	≤0.001	1.494	1.048-2.131	2.217	0.027	0.234	0.646
	AA vs AT+TT	Random	75.20	≤0.001	1.531	1.134-2.067	2.783	0.005	0.692	0.490

cer under all five genetic models, i.e., allele (A vs T: OR=1.189, 95% CI 1.027–1.378, *P*=0.021, FIGURE 2A), homozygote (AA vs TT: OR=1.307, 95% CI 1.111–1.536, *P*=0.001), heterozygote (AT vs TT: OR=1.188, 95% CI 1.061–1.330, *P*=0.003), dominant (AA+AT vs TT: OR=1.337, 95% CI 1.115–1.602, *P*=0.002) and recessive (AA vs AT+TT: OR=1.241, 95% CI 1.045–1.474, *P*=0.014).

Moreover, we have performed subgroup analysis by ethnicity, country (China, Korea, Japan and Brazil), source of controls, and genotyping methods. Stratified analysis by ethnicity revealed that there was a significant association between IL-8 -251T>A polymorphism and gastric cancer in Asian (A vs T: OR=1.299, 95% CI 1.068–1.580, *P*=0.009; AA vs TT: OR=1.458, 95% CI 1.200–1.771, *P*≤0.001, FIGURE 2B; AT vs TT: OR=1.222, 95% CI 1.076–1.388, *P*=0.002; AA+AT vs TT: OR=1.470, 95% CI 1.151–1.878, *P*=0.002; and AA vs AT+TT: OR=1.394, 95% CI 1.106–1.756, *P*=0.005), mixed populations (AT vs TT: OR=1.639, 95% CI 1.244–2.153, *P*≤0.001), but not in Caucasians. Moreover, subgroup analysis by country showed a significant association between IL-8 -251T>A polymorphism and gastric cancer in Chinese (AA vs TT: OR=1.427, 95% CI 1.194–1.704, *P*≤0.001; and AA+AT vs TT: OR=1.701, 95% CI 1.051–2.752, *P*=0.031, FIGURE 2C), Korean (A vs T: OR=1.315, 95% CI 1.143–1.514, *P*≤0.001; AA vs TT: OR=1.773, 95% CI 1.282–2.452, *P*=0.001; AT vs TT: OR=1.263, 95% CI 1.026–1.554, *P*=0.028; AA+AT vs TT: OR=1.438, 95% CI 1.182–1.749, *P*≤0.001; and AA vs AT+TT: OR=1.488, 95% CI 1.098–2.016, *P*=0.010) and in Brazilian (AT vs TT: OR=1.636, 95% CI 1.244–2.153, *P*≤0.001, FIGURE 2D; and AA+AT vs TT: OR=1.360, 95% CI 1.026–1.803, *P*=0.033), but not in Japanese. When stratified by source of controls, the results showed a significant association between IL-8 -251T>A polymorphism and gastric cancer in hospital based studies (AA vs TT: OR=1.402, 95% CI 1.117–1.760, *P*=0.004; AT vs TT: OR=1.346, 95% CI 1.150–1.576, *P*≤0.001; and AA+AT vs TT: OR=1.397, 95% CI 1.158–1.684, *P*≤0.001) and population based studies (AA vs AT+TT: OR=1.407, 95% CI 1.020–1.941, *P*=0.038). Subgroup analysis by genotyping methods revealed that there was a significant association between IL-6 -176G>C polymorphism and gastric cancer risk in PCR-RFLP group of studies (AT vs TT: OR=1.248, 95% CI 1.113–1.400, *P*=0.001; and AA+AT vs TT: OR=1.250, 95% CI 1.065–1.467, *P*=0.006) and in group of studies used other genotyping methods (A vs T: OR=1.370, 95% CI 1.049–1.789, *P*=0.021; AA vs TT: OR=1.457, 95% CI 1.167–1.822, *P*=0.001; AA+AT vs TT: OR=1.494, 95% CI 1.048–2.131, *P*=0.027; and AA vs AT+TT: OR=1.531, 95% CI 1.134–2.067, *P*=0.005).

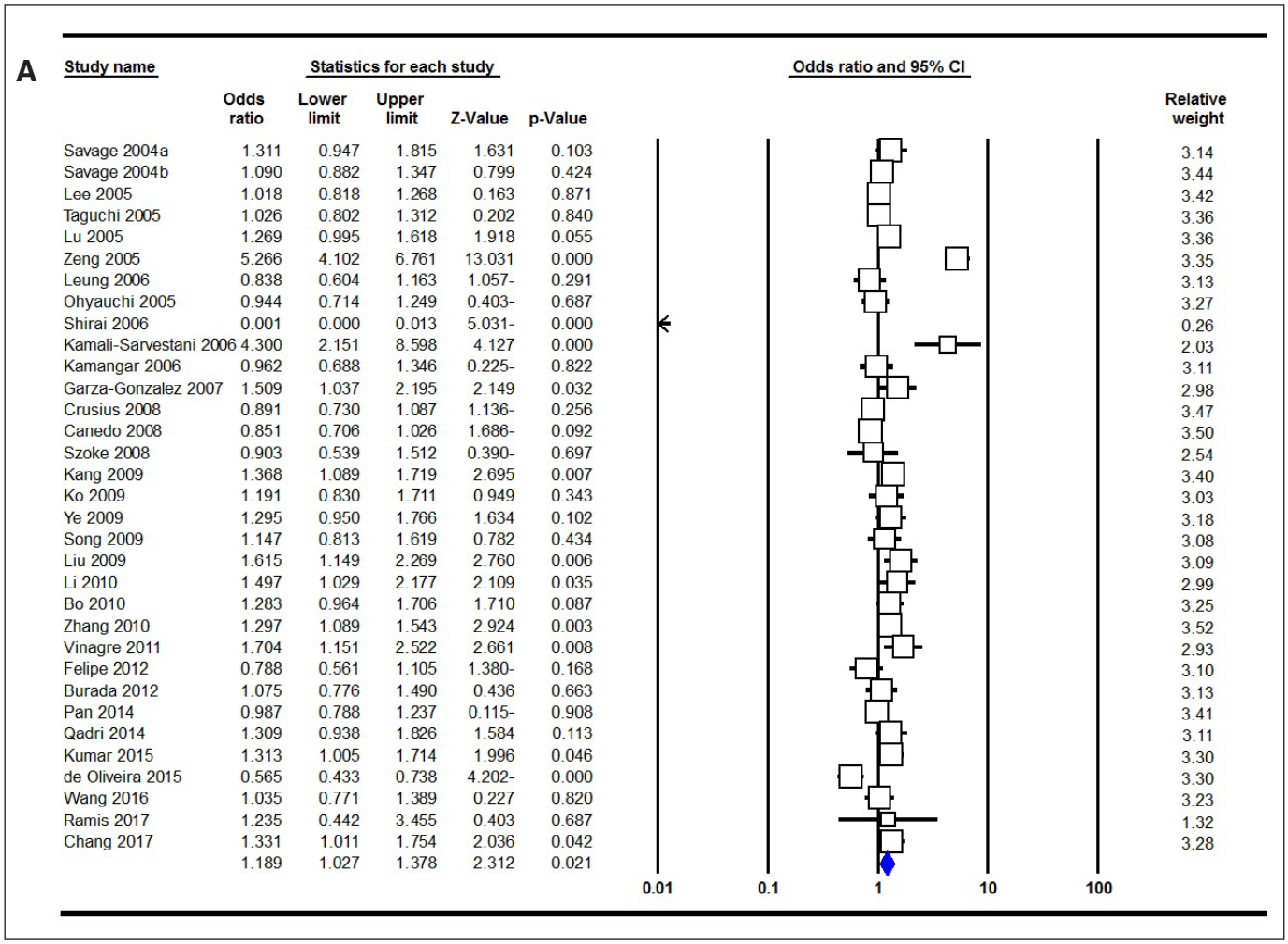

FIGURE 2. Forest plot for association of IL-8 -251T>A polymorphism and gastric cancer. **A:** in overall population (A vs T).

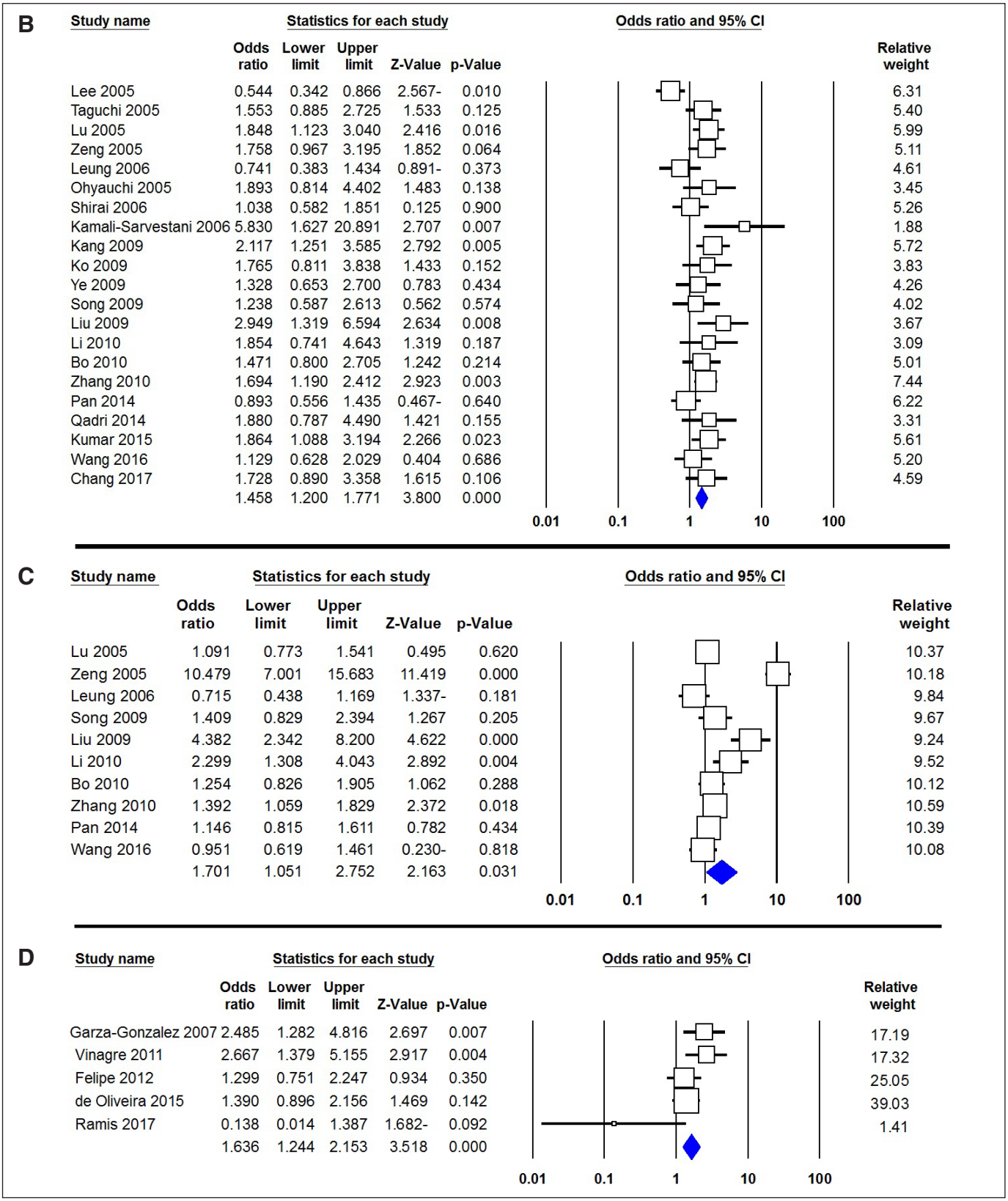

FIGURE 2. Forest plot for association of IL-8 -251T>A polymorphism and gastric cancer. **B:** in Asians (AA vs TT). **C:** in Chinese (AA+AT vs TT). **D:** in Brazilian (AT vs TT).

Between-study heterogeneity

There was statistically moderate to high heterogeneity among the studies under all five genetic models, i.e., allele (I^2=87.85, P_H≤0.001), homozygote (I^2=55.20, P_H≤0.001), heterozygote (I^2=50.86, P_H≤0.001), dominant (I^2=83.25, P_H≤0.001), and recessive (I^2=69.17, P_H≤0.001) in overall population. To explore the sources of heterogeneity, we performed subgroup analyses using ethnicity, country, source of controls and genotyping methods. The results suggested that ethnicity and country (population) may contribute to the heterogeneity in this meta-analysis.

Sensitivity analysis

To evaluate the sensitivity of the meta-analysis, we omitted each study at a time and checked for significant differences. There were no significant differences observed upon removal of any of the studies, indicating that our results are statistically reliable and stable. Deviation of HWE may reflect methodological problem such as genotyping errors, population stratification or selection bias. Moreover, we performed sensitivity analysis by excluding the HWE-violating study. When this study was excluded, the results were not changed in overall population and also by subgroup analyses, indicating that our meta-analysis was statistically robust and reliable.

Publication bias

Publication bias was assessed with Begg's funnel plots and Egger's test (TABLE 2). The results of Begg's funnel plots and Egger's regression test suggested evidence of publication bias in overall population under homozygote genetic model (AA vs TT: P_{Beggs}=0.117; P_{Eggers}=0.029; FIGURE 3), and by subgroup analysis in Korean under allele model (A vs T: P_{Beggs}=0.089; P_{Eggers}=0.035), Japanese under allele model (A vs T: P_{Beggs}=0.296; P_{Eggers}=0.007), hospital based studies under homozygote model (AA vs TT: P_{Beggs}=0.002; P_{Eggers}=0.001), dominant (AA+AT vs TT: P_{Beggs}=0.007; P_{Eggers}=0.003) and recessive (AA vs AT+TT: P_{Beggs}=0.015; P_{Eggers}=0.002), and by other genotyping methods under homozygote model (AA vs TT: P_{Beggs}=0.488; P_{Eggers}=0.016). Thus, we utilized the trim-and-fill method developed by Duval and Tweedie to adjust these biases. However, after trimming we have yield similar results, indicating that the results were statistically reliable.

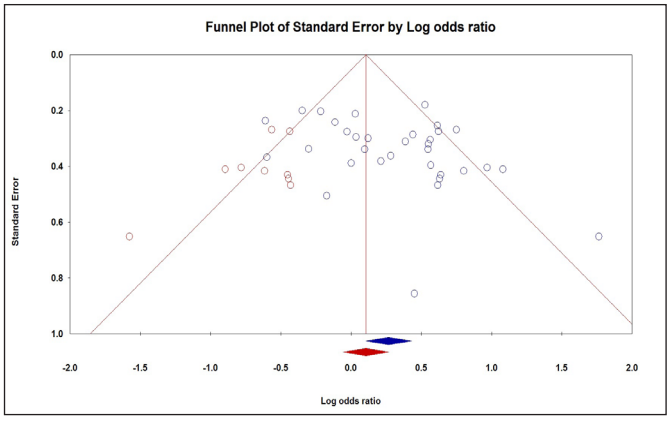

FIGURE 3. Begg's funnel of the Egger's test for publication bias test before (Blue) and after (Red) Trim-and-Fill method for association of IL-8 -251T>A polymorphism with gastric cancer under homozygote model (AA vs TT). Each point represents a separate study for the indicated association.

DISCUSSION

In this meta-analysis, we included 33 case-control studies with 6,192 cases and 9,567 controls about association between IL-8 -251T>A polymorphism and gastric cancer. Our pooled data showed that there was a significant association between IL-8 -251T>A polymorphism and gastric cancer under all five genetic models. Our subgroup meta-analysis also demonstrates that the IL-8 -251T>A polymorphism was associated with gastric cancer in Asians and mixed populations. Moreover, the IL-8 -251T>A polymorphism is associated with gastric cancer in Chinese, Korean and Brazilian. Although, meta-analyses have revealed evidence that IL-8 -251T>A polymorphism is associated with significantly increased risk of gastric cancer in overall analyses, none reported the association between IL-8 -251T>A polymorphism in mixed population and by country.

In 2015, Zhang et al., in meta-analysis of 26 studies with 5286 cases and 8000 controls have evaluated association between IL-8 -251T>A polymorphism and gastric cancer[40]. Their results showed that IL-8 -251T>A polymorphism was significantly associated with increased risk of gastric cancer. Similarly, they have found that this polymorphism was associated with gastric cancer in Asians, but not in Caucasians. However, inconsistence with our pooled data, their results failed to show an association in PCR-RFLP studies. In 2018, Wang et al., in a meta-analysis of 31 studies with 5848 cases and 8926 controls have evaluated of IL-8 -251T>A polymorphism with gastric cancer[41]. Their results showed a significant association between IL-8 -251T>A polymorphism and gastric cancer risk in overall and in Asians. However, their pooled data were based on crude pooled ORs, not adjusted OR values such as genotyping methods and source of controls, which might be caused to inaccurate results. Our results seem to confirm and establish the trend in the meta-analysis of association between IL-8 -251T>A polymorphism and gastric cancer risk that the data by previous meta-analyses had indicated. Moreover, the previous meta-analyses have not performed subgroup analysis by ethnicity in mixed populations and by country. Although, our subgroup analysis showed that IL-8 -251T>A polymorphism with gastric cancer, there was no significant association in Japanese. It is suggested that the lack of an increased risk of gastric cancer in Japanese might be attributing to genetic backgrounds and environmental factors of the population. In addition, other factors such as gene-gene interactions may be modulating the IL-8 -251T>A polymorphism functionality in Japanese populations.

The possibility of publication bias in a meta-analysis is always a concern, especially when the number of incorporated studies is small[42-44]. Although, large number of studies included in this meta-analysis, publication bias have distorted our results. It seems the studies that found any negative results of the association between IL-8 -251T>A polymorphism with gastric cancer may not have been published. Moreover, heterogeneity and confounding factors may have affected the meta-analysis. In this meta-analysis, there was a mild to high between-study heterogeneity under all five genetic models that could affect our results. This may be attributed to variations in confounding factors such as age, gender, source of controls, tumor stage, pathological type, and genotyping method[45-47]. We were unable to take most of these confounders into consideration in our meta-analysis because the majority of studies either did not report these baseline data. However, subgroup analyses by ethnicity, country, source of controls and genotyping methods revealed that ethnicity and country (population) may contribute to the heterogeneity in this meta-analysis.

Our meta-analysis has several strengths. First, a systematic review of the association of IL-8 -251T>A polymorphism with gastric cancer risk is statistically more powerful than any previous meta-analysis. Second, the quality of eligible studies included in this meta-analysis was satisfactory and met the inclusion criterion. Although, we performed a comprehensive meta-analysis with several subgroup analyses, there were still several limitations to be taken into consideration in this meta-analysis. First, we only selected published studies electronically in some databases, so it is possible that some pertinent studies not included in these databases or unpublished studies with negative results may have been missed. Second, only small numbers of studies were included in some subgroups such as subsets of studies among Caucasians and TaqMan. Therefore, these subgroup analyses may not have enough statistical power with the small sample size and the conclusions must be interrupted by caution. Third, although the overall sample size is large, the size of study performed in Caucasians mixed populations was relatively small. Therefore, more studies in Caucasians mixed populations are required in other populations. Finally, the mechanism of gastric cancer is considered to be sophisticated, including gene-gene and gene-environment interactions. More studies with enough statistical power are needed for deeply evaluation.

In summary, this meta-analysis suggested that the IL-8 -251T>A polymorphism might contribute to susceptibility and development of gastric cancer in overall population, especially in Asians and mixed populations. Moreover, there was a significant association between IL-8 -251T>A polymorphism and an increased risk of gastric cancer in Chinese, Korean and Brazilian populations. However, it is necessary to conduct large sample studies using standardized unbiased genotyping methods, homogeneous cancer patients and well-matched controls. Moreover, further studies estimating the effect of gene-gene and gene-environment interactions may eventually lead to our better, comprehensive understanding of the association between IL-8 -251T>A polymorphism and gastric cancer risk.

Authors' contribution

Moghimi M and Dastgheib SA contributed to the concept and design of the study. Neamatzadeh H and Zare M contributed to data acquisition, analysis, and interpretation. Heiranizadeh N and Sheikhpour E contributed to writing and editing the manuscript. All authors commented on drafts of the paper and have approved the final draft of the manuscript.

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Moghimi M, Dastgheib SA, Heiranizadeh N, Zare M, Sheikhpour E, Neamatzadeh H. Associação de polimorfismo IL-8 -251T>A (rs4073) com suscetibilidade ao câncer gástrico: uma revisão sistemática e meta-análise com base em 33 estudos caso controle. Arq Gastroenterol. 2020;57(1):91-9.

RESUMO – **Contexto** – O papel do polimorfismo -251A>T no gene anti-inflamatório citocina interleucina-8 (IL-8) no câncer gástrico foi intensamente avaliado, mas os resultados desses estudos foram inconsistentes. **Objetivo** – Portanto, realizamos uma meta-análise para fornecer dados abrangentes sobre a associação de IL-8 -251T>A polimorfismo com câncer gástrico. **Métodos** – Todos os estudos elegíveis foram identificados nos bancos de dados PubMed, Web of Science, EMBASE, Wanfang e CNKI antes de 01 de setembro de 2019. As relações de probabilidades agrupadas (ORs) com intervalos de confiança de 95% (IC) foram derivadas de um modelo de efeito fixo ou efeito aleatório. **Resultados** – Foram selecionados 33 estudos de controle de caso com 6.192 casos e 9.567 controles. No geral, dados agrupados mostraram que o polimorfismo IL-8 -251T>A foi significativamente associado a um risco aumentado de câncer gástrico em todos os cinco modelos genéticos, isto é, alelo (A vs T: OR=1,189; 95% CI 1,027–1,378; *P*=0,021), homozigoto (AA vs TT: OR=1,307; 95% CI 1,111–1,536; *P*=0,001), heterozigoto (AT vs TT: OR=1,188; 95% CI 1,061–1,330; *P*=0,003), dominante (AA+AT vs TT: OR=1,337; 95% CI 1,115–1,602; *P*=0,002) e recessivo (AA vs AT+TT: OR=1,241; 95% CI 1,045–1,474; *P*=0,014). A análise estratificada por etnia revelou um risco aumentado de câncer gástrico em asiáticos e populações mistas, mas não em caucasianos. Além disso, estratificado por país. Encontrou-se uma associação significativa em chineses, coreanos e brasileiros, mas não entre os japoneses. **Conclusão** – Esta meta-análise sugere que o polimorfismo IL-8 -251T>A está associado a um risco aumentado de câncer gástrico, especialmente por etnia (populações asiáticas e mistas) e por país (chinês, coreano e brasileiro).

DESCRITORES – Neoplasias gástricas. Interleucina-8. Polimorfismo genético. Metanálise.

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