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Original Article

Association between Interleukin-8-251A/T polymorphism and gastric cancer susceptibility: a meta-analysis based on 5286 cases and 8000 controls

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Abstract: Objectives: Published data on the association between Interleukin-8-251A/T polymorphism and gastric cancer (GC) risk are inconclusive. Thus, we conducted a meta-analysis to evaluate the relationship between cyclin D1 G870A polymorphism and GC risk. Methods: We searched PubMed, EMBASE, Web of science and the Cochrane Library up to July 12, 2015 for relevant studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of associations. Results: Twenty-six studies published from 2004 to 2015, with a total of 5286 cases and 8000 controls, were included in this meta-analysis. The pooled results showed that there was significant association between Interleukin-8-251A/T polymorphism and GC risk in any genetic model. In the subgroup analysis by ethnicity, the effects remained in Asians. However, no genetic models reached statistical association in Europeans. The subgroup analysis stratified by Source of controls showed an increased breast cancer risk in hospital-based (HB) studies in any genetic model except recessive model. However, there was no association in any genetic model in population based (PB) studies. When stratifying by Genotyping method, we found statistical association in Non-RFLP (restriction fragment length polymorphism) in any genetic model except heterozygote comparison, the effect was remain in PCR-RFLP in dominant model and heterozygote comparison. Conclusions: This meta-analysis suggests that Interleukin-8-251A/T polymorphism is a risk factor for susceptibility to GC in overall population, especially in Asians, in hospital populations and in Non-RFLP. While, there was no association in Europeans and in general population. Further large scale multicenter epidemiological studies are warranted to confirm this finding.

Keywords: Interleukin-8-251A/T, polymorphism, gastric cancer, susceptibility, meta-analysis

Introduction

Gastric cancer (GC) is one of the most common malignant tumors and the third leading cause of cancer-related death in the word, the 5-year survival rate is low, especially for advanced GC [1, 2]. In the majority of developing countries, the incidence of GC is constantly increasing, as well as mortality [3, 4]. For most GCs are diagnosed to be advanced stages, early detection seems particularly important [5]. While, the determination of the association between Interleukin-8-251A/T polymorphism and GC risk provides us a promising approach to achieve this goal.

Interleukin-8 is an important member of the chemokine superfamily, which belongs to the CXC chemokine family. Under the stimulation of a variety of factors (such as lipopolysaccharide, IL.1, etc.), many cells can produce IL-8, such as monocytes, endothelial cells and tumor cells [6, 7]. In recent years, the expression of IL-8 in tumor cells was significantly increased. It is found that IL-8 can induce the migration and proliferation of endothelial cells to mediate tumor angiogenesis, which can promote tumor [8-10]. Human IL-8 gene is located on fourth chromosome, composed of four exons, three introns, and a proximal promoter region. In the promoter region of IL-8, there is a genetic poly-

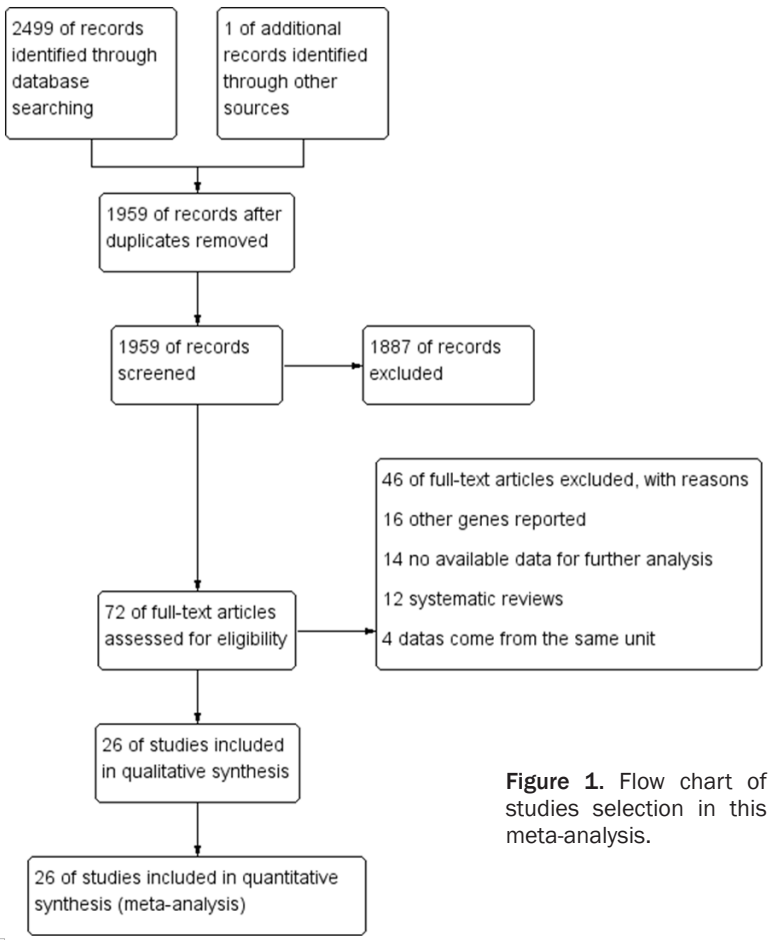

Figure 1. Flow chart of studies selection in this meta-analysis.

morphism in -251T, which has been reported to be closely associated with altered expression levels of IL-8 through gene transcription regulation [11].

Previous functional studies have reported the association between Interleukin-8-251A/T polymorphism and GC risk, but the results remain inconclusive [12-37]. To clarify the role of Interleukin-8-251A/T polymorphism in GC risk, four meta-analysis on the associations between Interleukin-8-251A/T polymorphism and cancers [38-41]. However, number of their studies included in their meta-analysis about GC is small, and GC is just a small part of their study. In the subgroup of their analyses the sample size is extremely small, and some just no subgroup. Therefore, we decided to carry out a meta-analysis on all eligible case-control studies to make a more precise estimation of the association. Furthermore, we conducted the subgroup analysis by stratification according to the ethnicity, source of controls and genotyping method.

Materials and methods

Literature searching strategy

We searched PubMed, EMBASE, Web of science, the Cochrane Library for relevant studies published before July 12, 2015. The following keywords were used: interleukin*/IL*, variant/genotype/polymorphism/SNP, Gastric/stomach/cardia, cancer/carcinom*/neoplasm*/tumor and the combined phrases for all genetic studies on the association between the Interleukin-8-251A/T polymorphism and GC risk. The reference lists of all articles were also manually screened for potential studies. Abstracts and citations were screened independently by two authors, all the agreed articles need a second screen for full-text reports. The searching was done without restriction on language.

Selection and exclusion criteria

Inclusion criteria: A study was included in this meta-analysis if it meets the following criteria: *i*) independent case-control studies for humans; *ii*) the study evaluated the association between Interleukin-8-251A/T polymorphism and GC risk; *iii*) has available genotype frequencies in cancer cases and control subjects for risk estimate. We excluded comments, editorials, systematic reviews or studies lacking sufficient data. If the publications were duplicated or shared in more than one study, the most recent publications were included. All identified studies were screened by two investigators independently. What's more, there was no limitation for publication language.

Data extraction and synthesis

We used endnote bibliographic software to construct an electronic library of citations identified in the literature search. All the PubMed, EMBASE, Web of science and the Cochrane Library searches were performed using Endnote; duplicates were found automatically by

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

First author	Year	Country	Ethnicity	Source of controls	Genotyping method	Number (case/control)	HWE	Quality assessment score	Published language
Bo [37]	2010	China	Asian	HB	PCR-RFLP	208/190	0.389403209	7	English
Canedo [36]	2008	Portugal	European	PB	Taq Man-PCR	333/693	0.459719109	8	English
Crusius [35]	2008	Caucasia	European	PB	Real-time	236/1139	0.705567725	8	English
de Oliveira [34]	2015	Brazil	European	HB	PCR-RFLP	207/240	0.059480986	7	English
Felipe [33]	2012	Brazil	European	PB	PCR-RFLP	104/196	0.065528611	8	English
Garza-Gonzalez [32]	2007	Mexico	European	HB	ARMS-PCR	78/189	0.538816094	7	English
Kamali-Sarvestani [31]	2006	Iran	Asian	HB	ASO-PCR	19/153	0.797575578	7	English
Kamangar [30]	2006	Finland	European	PB	TaqMan-PCR	112/207	0.054934096	8	English
Kang [29]	2009	Korea	Asian	PB	PCR-RFLP	334/322	0.22569954	8	English
Ko [28]	2009	Korea	Asian	PB	Snapshot	81/308	0.155354832	8	English
Lee [27]	2005	Taiwan	Asian	HB	PCR-RFLP	470/308	0.14303682	7	English
Liu [12]	2009	China	Asian	HB	Taq Man-PCR	138/137	0.145093518	7	Chinese
Lu [26]	2005	China	Asian	PB	PCR-DHPLC	250/300	0.515848398	8	English
Ohyauchi [25]	2005	Japan	Asian	HB	Direct	212/346	0.549317592	7	English
Pan [24]	2014	China	Asian	HB	SBE	308/308	0.715713139	7	English
Qadri [23]	2014	India	Asian	PB	PCR-CTPP	130/200	0.066109789	8	English
Ramis [22]	2015	Brazil	European	PB	PCR-RFLP	9/38	0.691258974	8	English
Savage [21]	2004	China	Asian	PB	SBE	88/429	0.884813104	8	English
Savage [20]	2006	Poland	European	PB	Taqman or MGB Eclipse	287/428	0.391465014	8	English
Shirai [19]	2006	Japan	Asian	HB	PCR-RFLP	181/468	0.830460367	7	English
Song [18]	2009	China	Asian	HB	PCR-RFLP	125/140	0.720157181	7	English
Taguchi [17]	2005	Japan	Asian	HB	PCR-RFLP	396/252	0.994013656	7	English
Vinagre [16]	2011	Brazil	European	HB	PCR-RFLP	102/103	0.150502334	7	English
Ye [15]	2009	Korea	Asian	HB	PCR-RFLP	153/206	0.552934095	7	English
Zeng [14]	2005	China	Asian	PB	PCR-RDB	206/196	0.02187681	8	Chinese
Zhang [13]	2010	China	Asian	PB	PCR-RFLP	519/504	0.75413968	8	English

HWE: Hardy-Weinberg equilibrium; PB: population based; HB: hospital-based; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; SBE, single base extension; PCR-RDB, polymerase chain reaction-reverse dot blot. DHPLC: PCR-based denaturing high-performance liquid chromatography; Direct: Direct sequence analysis of polymerase chain reaction; ASO: oligonucleotide allele specific polymerase chain reaction; MGB Eclipse: MGB Eclipse Assay polymerase chain reaction method; ARMS: Amplification refractory mutation system polymerase chain reaction; Snapshot: the Snapshot assay which provides detection of certain SNPs. CTPP: confronting two-pair primers. The quality of studies included in this meta-analysis was assessed using Newcastle-Ottawa scale, which graded the quality of a study from 0 to 10 points. Articles exceeding 6 points were considered as high quality.

endnote and deleted manually. All data extraction were checked and calculated twice according to the inclusion criteria listed above by two independent investigators. Data extracted from the included studies were as follows: First author, year of publication, country, ethnicity, Source of controls, Genotyping method, number of cases and controls and evidence of HWE in controls. A third reviewer would participate if some disagreements were emerged, and a final decision was made by the majority of the votes.

Statistical analysis

All statistical analyses were performed using STATA version 11.0 software (StataCorp LP, College Station, TX) and Review Manage version 5.2.0 (The Cochrane Collaboration, 2012). Hardy-Weinberg equilibrium (HWE) was assessed by χ^2 test in the control group of each study [42]. The strength of associations between the Interleukin-8-251A/T polymorphism and GC risk were measured by odds ratio (ORs) with 95% confidence interval (CIs). Z test was used to assess the significance of the ORs, I^2 and Q statistics was used to determine the statistical heterogeneity among studies. A random-effect model was used if *P* value of heterogeneity tests was no more than 0.1 ($P \leq 0.1$), otherwise, a fixed-effect model was selected [42, 43]. Sensitivity analyses were performed to assess the stability of the results. We used Begg's funnel plot and Egger's test to evaluate the publication bias [44, 45]. The strength of the association was estimated in the allele model, the dominant model, the recessive model, the homozygous genetic model, and the heterozygous genetic model, respectively. $P < 0.05$ was considered statistically significant.

Table 2. Interleukin-8-251A/T polymorphisms genotype distribution and allele frequency in cases and controls

First author	Genotype (N)								Allele frequency (N)			
	Case				Control				Case		Control	
	Total	AA	AT	TT	Total	AA	AT	TT	A	T	A	T
Bo	208	36	108	64	190	26	96	68	180	236	148	232
Canedo	333	53	169	111	693	137	353	203	275	391	627	759
Crusius	236	48	113	75	1139	250	574	315	209	263	1074	1204
de Oliveira	207	47	98	62	240	45	134	61	192	222	224	256
Felipe	104	15	58	31	196	52	85	59	88	120	189	203
Garza-Gonzalez	78	16	47	15	189	33	87	69	79	77	153	225
Kamali-Sarvestani	19	9	6	4	153	22	74	57	24	14	118	188
Kamangar	112	14	56	42	207	24	111	72	84	140	159	255
Kang	334	49	159	126	322	27	148	147	257	411	202	442
Ko	81	12	35	34	308	27	146	135	59	103	200	416
Lee	470	59	213	198	308	62	138	108	331	609	262	354
Liu	138	23	89	26	137	15	72	50	135	141	102	172
Lu	250	54	102	94	300	37	144	119	210	290	218	382
Ohyauchi	212	13	106	93	346	20	118	208	132	292	158	534
Pan	308	48	168	92	308	59	148	101	264	352	266	350
Qadri	130	12	68	50	200	12	94	94	92	168	118	282
Ramis	9	4	1	4	38	7	20	11	9	9	34	42
Savage	88	23	39	26	429	75	207	147	85	91	357	501
Savage	287	76	140	71	428	117	205	106	292	282	439	417
Shirai	181	20	78	83	468	49	208	211	118	244	306	630
Song	125	20	72	33	140	23	70	47	112	138	116	164
Taguchi	396	44	191	161	252	22	105	125	279	513	149	355
Vinagre	102	25	56	21	103	19	42	42	106	98	80	126
Ye	153	17	82	54	206	23	86	97	116	190	132	280
Zeng	206	59	110	37	196	39	114	43	228	184	192	200
Zhang	519	128	261	130	504	93	251	160	517	521	437	571

We performed subgroup according to Ethnicity, Source of controls, Genotyping method.

Results

Characteristics of included studies

Detailed search procedures are summarized in **Figure 1**. A total of 2499 references were preliminarily identified at first based on our selection strategy. We also identified 1 paper through other source. After excluding duplicate articles, we reviewed titles and abstracts of all identified studies to exclude those that were clearly irrelevant. Next, the full texts of the remaining articles were examined according to the inclusion and exclusion criteria. Finally, 26 studies [12-37] on Interleukin-8-251A/T polymorphism and GC risk were finally identified in this meta-analysis, including 5286 cases and 8000 controls. The characteristics of the included studies are listed in **Table 1**. The 26 case-control studies were published between 2004 and 2015, among them, 9 studies were performed in European and 17 in Asians. All studies were case-controlled. 13 studies were hospital-based and 13 were population-based studies.

Meta-analysis results

Table 2 shows the interleukin-8-251A/T polymorphisms genotype distribution and allele frequency in cases and controls. The main results of this meta-analysis were listed in **Table 3**. There were 26 studies with 5286 cases and 8000 controls for Interleukin-8-251A/T polymorphism. As shown in **Table 3**, The pooled results showed that there was significant association between Interleukin-8-251A/T polymor-

Table 3. Meta-analysis results

Subgroup		OR	95% CI	*P* value	Heterogeneity		Effects model
					I^2	*P* value	
Allele model A vs. T							
Overall		1.16	1.05-1.27	0.002	66%	P<0.00001	R
Ethnicity	European	1.01	0.87-1.17	0.90	54%	0.03	R
	Asian	1.23	1.10-1.37	0.0002	61%	0.0005	R
Source of controls	PB	1.10	0.98-1.24	0.09	58%	0.004	R
	HB	1.23	1.05-1.43	0.01	72%	P<0.0001	R
Genotyping method	PCR-RFLP	1.13	0.98-1.30	0.10	68%	0.0003	R
	Non-RFLP	1.18	1.04-1.35	0.01	66%	0.0002	R
Dominant model AA + AT vs. TT							
Overall		1.22	1.07-1.39	0.003	61%	P<0.0001	R
Ethnicity	European	1.05	0.81-1.35	0.71	64%	0.005	R
	Asian	1.30	1.13-1.49	0.0002	49%	0.01	R
Source of controls	PB	1.09	0.98-1.21	0.13	27%	0.17	F
	HB	1.40	1.12-1.76	0.004	73%	P<0.0001	R
Genotyping method	PCR-RFLP	1.20	1.00-1.46	0.06	62%	0.002	R
	Non-RFLP	1.23	1.02-1.49	0.03	63%	0.0007	R
Recessive model AA vs. AT + TT							
Overall		1.20	1.01-1.41	0.03	60%	P<0.0001	R
Ethnicity	European	0.94	0.80-1.10	0.43	38%	0.12	F
	Asian	1.33	1.07-1.64	0.009	61%	0.0005	R
Source of controls	PB	1.25	0.99-1.58	0.06	65%	0.0005	R
	HB	1.14	0.90-1.44	0.29	54%	0.01	R
Genotyping method	PCR-RFLP	1.12	0.87-1.45	0.39	63%	0.002	R
	Non-RFLP	1.27	1.01-1.58	0.04	60%	0.002	R
Homozygous genetic model AA vs. TT							
Overall		1.31	1.08-1.59	0.006	63%	P<0.00001	R
Ethnicity	European	1.01	0.76-1.34	0.97	50%	0.04	R
	Asian	1.49	1.18-1.87	0.0009	60%	0.0008	R
Source of controls	PB	1.27	0.98-1.64	0.07	63%	0.001	R
	HB	1.38	1.02-1.88	0.04	66%	0.0005	R
Genotyping method	PCR-RFLP	1.24	0.91-1.67	0.17	67%	0.0005	R
	Non-RFLP	1.38	1.06-1.80	0.02	62%	0.001	R
Heterozygote comparison AT vs. TT							
Overall		1.19	1.04-1.35	0.01	57%	0.0002	R
Ethnicity	European	1.07	0.81-1.42	0.63	67%	0.002	R
	Asian	1.25	1.09-1.43	0.001	41%	0.04	R
Source of controls	PB	1.04	0.93-1.16	0.54	5%	0.39	F
	HB	1.39	1.11-1.74	0.004	68%	0.0002	R
Genotyping method	PCR-RFLP	1.20	1.00-1.45	0.05	55%	0.01	R
	Non-RFLP	1.18	0.97-1.42	0.09	60%	0.002	R

F-fixed effects model; R-random effects model.

phism and GC risk in any genetic model: Allele model (A vs. T: OR=1.16, 95% CI=1.05-1.27, P=0.002), dominant model (AA + AT vs. TT: OR=1.22, 95% CI=1.07-1.39, P=0.003) recessive model (AA vs. AT + TT: OR=1.20, 95% CI=1.01-1.41, P=0.03) homozygous genetic model (AA vs. TT: OR=1.31, 95% CI=1.08-1.59, P=0.006) heterozygote comparison (AT vs. TT:

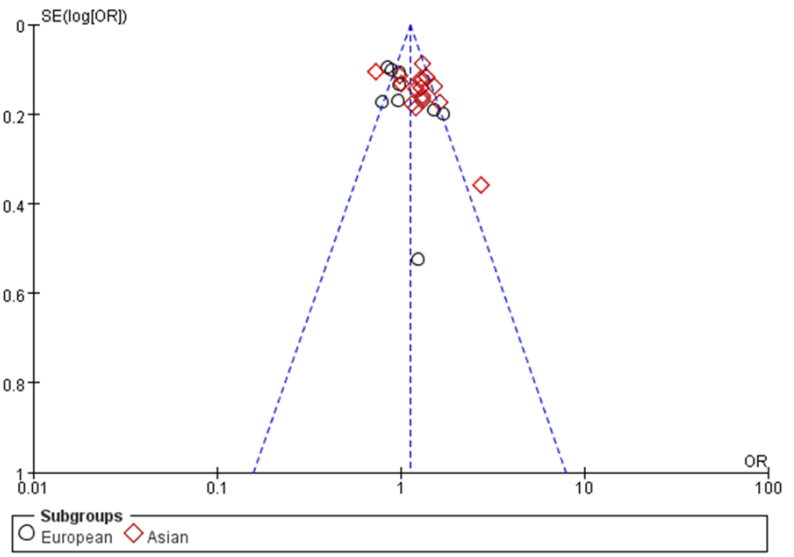

Figure 2. Funnel plot assessing evidence of publication bias from 26 studies (A vs. T). Abbreviations: SE, standard error; OR, odds ratio; A vs. G, Allele model.

OR=1.19, 95% CI=1.04-1.35, P=0.01). In the subgroup analysis by ethnicity, the effects remained in Asians (A vs. T: OR=1.23, 95% CI=1.10-1.37, P=0.0002; AA + AT vs. TT: OR=1.30, 95% CI=1.13-1.49, P=0.0002; AA vs. AT + TT: OR=1.33, 95% CI=1.07-1.64, P=0.009; AA vs. TT: OR=1.49, 95% CI=1.18-1.87, P=0.0009; AT vs. TT: OR=1.25, 95% CI=1.09-1.43, P=0.001). However, no genetic models reached statistical association in Europeans (**Table 3**).

The subgroup analysis stratified by Source of controls showed an increased breast cancer risk in hospital-based (HB) studies in any genetic model except recessive model (A vs. T: OR=1.23, 95% CI=1.05-1.43, P=0.01; AA + AT vs. TT: OR=1.40, 95% CI=1.12-1.76, P=0.004; AA vs. TT: OR=1.38, 95% CI=1.02-1.88, P=0.04; AT vs. TT: OR=1.39, 95% CI=1.11-1.74, P=0.004). However, there was no association in any genetic model in population based (PB) studies (**Table 3**).

When stratifying by Genotyping method, we found statistical association in Non-RFLP (restriction fragment length polymorphism) in any genetic model except heterozygote comparison (A vs. T: OR=1.18, 95% CI=1.04-1.35, P=0.01; AA + AT vs. TT: OR=1.23, 95% CI=1.02-1.49, P=0.03; AA vs. AT + TT: OR=1.27, 95% CI=1.01-1.58, P=0.04; AA vs. TT: OR=1.38, 95% CI=1.06-1.80, P=0.02), the effect was remain in PCR-RFLP in dominant model and heterozygote comparison (AA + AT vs. TT: OR=1.20, 95% CI=1.00-1.46, P=0.06; AT vs. TT: OR=1.20, 95% CI=1.00-1.45, P=0.05).

Sensitivity analyses

As shown in **Table 1**, all the studies conformed to he balance of Hardy-Weinberg equilibrium (HWE) in controls except Zeng's (P< 0.05), however, after performing the sensitivity analyses, The overall results did not show quantitative changes when excluding any study, suggesting the stability and reliability of this meta-analysis.

Detection for heterogeneity

Statistically significant heterogeneity was observed between trials of the following analyses using Q statistic: allele model (A vs. T: P< 0.00001, I^2=66%), the dominant model (AA + AT vs. TT: P<0.0001, I^2=61%), the recessive model (AA vs. AT + TT: P<0.0001, I^2=60%), the homozygous genetic model (AA vs. TT: P< 0.00001, I^2=63%), and the heterozygous genetic model (AT vs. TT: P=0.0002, I^2=57%), and the random-effects model was performed in these studies.

Publication bias

Begg's funnel plot and Egger's test were employed to assess the publication bias. As shown in **Figure 2**, the funnel plots failed to reveal any obvious asymmetry in all genotypes in overall population. Neither Begg's test nor Egger's test showed statistical evidence for publication bias in our meta-analysis (P>0.05).

Discussion

A large amount of evidence suggests that genetics is important in determining the risk of cancer. Related research is to search for the susceptibility genes associated with cancer [46]. It is believed that single nucleotide polymorphism is the most common source of human genetic variation, which may contribute to

the susceptibility of individuals to cancer [38-41, 47]. In recent years, genetic susceptibility to cancer has caused people's great interest, and the study on the genetic polymorphism of the tumor is increasing.

Recently, a growing number of epidemiological studies have been performed to assess the association of Interleukin-8-251A/T polymorphisms with GC risk [12-37]. However, the results are conflicting. Thus, we conducted a comprehensive meta-analysis involving published data, to assess the strength of association between the polymorphisms and GC risk.

In this present meta-analysis, 26 studies with 5286 cases and 8000 controls were included. And we explored the association between the potentially functional polymorphisms of Interleukin-8-251A/T and GC risk. In the overall population, the pooled results showed that there was significant association between Interleukin-8-251A/T polymorphism and GC risk in any genetic model: Allele model (A vs. T: OR=1.16, 95% CI=1.05-1.27, P=0.002), dominant model (AA + AT vs. TT: OR=1.22, 95% CI=1.07-1.39, P=0.003) recessive model (AA vs. AT + TT: OR=1.20, 95% CI=1.01-1.41, P=0.03) homozygous genetic model (AA vs. TT: OR=1.31, 95% CI=1.08-1.59, P=0.006) heterozygote comparison (AT vs. TT: OR=1.19, 95% CI=1.04-1.35, P=0.01). In a previous meta-analysis by Wang et al. [39], they failed to find association between Interleukin-8-251A/T polymorphism and gastric cancer susceptibility. This contradiction may result from different sample size and ethnic groups.

In the subgroup analysis by ethnicity, the effects remained in Asians (A vs. T: OR=1.23, 95% CI=1.10-1.37, P=0.0002; AA + AT vs. TT: OR=1.30, 95% CI=1.13-1.49, P=0.0002; AA vs. AT + TT: OR=1.33, 95% CI=1.07-1.64, P=0.009; AA vs. TT: OR=1.49, 95% CI=1.18-1.87, P=0.0009; AT vs. TT: OR=1.25, 95% CI=1.09-1.43, P=0.001). However, no genetic models reached statistical association in Europeans (**Table 3**). It was partially in line with the results of Cheng (2013)'s [41], Xue (2012)'s [38] and Wang (2012)'s [40] finding. However, there were only 18 studies respectively in their meta-analysis, while 26 studies were involved in our meta-analysis.

The subgroup analysis stratified by Source of controls showed an increased breast cancer risk in hospital-based (HB) studies in any genetic model except recessive model (A vs. T: OR=1.23, 95% CI=1.05-1.43, P=0.01; AA + AT vs. TT: OR=1.40, 95% CI=1.12-1.76, P=0.004; AA vs. TT: OR=1.38, 95% CI=1.02-1.88, P=0.04; AT vs. TT: OR=1.39, 95% CI=1.11-1.74, P=0.004). However, there was no association in any genetic model in population based (PB) studies (**Table 3**). When stratifying by Genotyping method, we found statistical association in Non-RFLP (restriction fragment length polymorphism) in any genetic model except heterozygote comparison (A vs. T: OR=1.18, 95% CI=1.04-1.35, P=0.01; AA + AT vs. TT: OR=1.23, 95% CI=1.02-1.49, P=0.03; AA vs. AT + TT: OR=1.27, 95% CI=1.01-1.58, P=0.04; AA vs. TT: OR=1.38, 95% CI=1.06-1.80, P=0.02), the effect was remain in PCR-RFLP in dominant model and heterozygote comparison (AA + AT vs. TT: OR=1.20, 95% CI=1.00-1.46, P=0.06; AT vs. TT: OR=1.20, 95% CI=1.00-1.45, P=0.05). Above findings was reported first by the paper.

There are some limitations in this meta-analysis. Firstly, this meta-analysis was based on pooled data. We could not assess the risk of cancer according to stratification of age, Sex and H. pylori infection, smoking, alcohol consumption, environment factors, and other risk factors. Secondly, we just included the published studies in the meta-analysis. It is possible that we missed some related unpublished studies that might meet the inclusion criteria. Moreover, small study effect, in which effects reported in small studies are larger, could not be avoided in that some studies were of a relative small size. Further large scale multicenter studies are warranted to further validate on Interleukin-8-251A/T polymorphisms and GC risk.

Conclusions

In conclusion, this meta-analysis suggests that Interleukin-8-251A/T polymorphism is a risk factor for susceptibility to GC in overall population, especially in Asians, in hospital populations and in Non-RFLP. While, there was no association in Europeans and in general population. Further large scale multicenter epidemi-

ological studies are warranted to confirm this finding.

Disclosure of conflict of interest

None.

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