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Positive association between Interleukin-8 -251A > T polymorphism and susceptibility to gastric carcinogenesis: a meta-analysis

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Abstract

Backgrounds: The associations between the polymorphisms of interleukin-8 (IL-8) gene and gastric carcinogenesis have been extensively investigated in recent years. However, the results remain conflicting rather than conclusive.

Methods: A meta-analysis of 18 eligible studies was performed to evaluate the association of IL-8 -251A > T polymorphism with risk of gastric carcinogenesis. A systematic literature search of MEDLINE, Embase, and Web of Science, CNKI databases was conducted. Statistical analysis was performed by using the Revman 5.1 software and the Stata 12.0 software.

Results: Of the 293 unique studies identified using our search criteria, 18 studies fulfilled our inclusion criteria and were included in the meta-analysis. These studies cumulatively reported 5,321 cases and 6,465 controls. The combined results based on all studies showed that the IL-8 -251A > T polymorphism was associated with the risk of gastric carcinogenesis (A vs. T: OR: 1.14 [1.02, 1.26], $P = 0.02$), especially gastric cancer (A vs. T: OR: 1.15 [1.03, 1.29], $P = 0.02$), but not associated with the risk of precancerous lesion (A vs. T: OR: 1.09 [0.99, 1.20], $P = 0.08$). Analysis stratified by ethnicity may seem that IL-8 -251A > T polymorphism was susceptible to gastric cancer in Asian population, but not in Caucasian population.

Conclusions: Our meta-analysis results provide evidence that IL-8 -251A > T polymorphism is significantly associated with increased risk of gastric carcinogenesis in Asian population, particularly in gastric cancer. Further large and well-designed studies are required to confirm this conclusion.

Keywords: Interleukin-8, Gastric cancer, Precancerous lesions, Meta-analysis

Backgrounds

Although the incidence of gastric cancer has recently declined in several countries, it is still a serious health problem and remains the world's fourth common malignancy and the second leading cause of cancer death [1-3]. Currently, many epidemiologic studies have demonstrated that gastric cancer has a multifactorial etiology and is modulated by different factors including *Helicobacter pylori* infection, life style, socioeconomic status, and environmental factors [4]. In addition, genetic factors are increasingly recognized as major contributors to gastric cancer risk [5], although not yet well understood. Perhaps, the genes involved in gastric cancer mutated

which intimately control cell growth and apoptosis, allowing cells to acquire the ability to invade and metastasize. Therefore, identification of biomarkers significantly related to development and progress of gastric cancer and elucidation of the molecular mechanisms for cancer prevention and control strategy are essential for better gastric treatment.

Chemotactic cytokines, produced by tumor and endothelial cells, could play an important role in cancer, such as increasing angiogenesis, stimulating tumor progression, enhancing tumor cell migration, and facilitating evasion of immune surveillance [6,7]. As a member of the chemokine family, interleukin-8 (IL-8) is well known for its leukocyte chemotactic properties and its tumorigenic and proangiogenic activities [8]. In vivo and in vitro experiments in melanoma [9], as well as breast [10], ovarian

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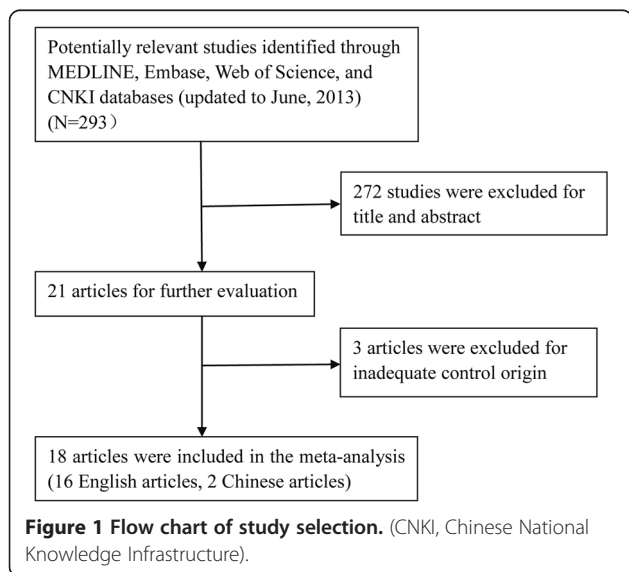
[11], prostate [12], endometrial [13], and colon cancer [14] have shown a direct correlation between IL-8 levels and tumor progression [8]. Moreover, it has been reported that expression of IL-8 in gastric cancer specimens was significantly higher than in corresponding normal gastric mucosa [15], and is associated with adhesion, migration and invasion in gastric cancer [15]. Therefore, it is reasonable to deduce that IL-8 plays a certain role in the formation and progression of gastric tumor.

IL-8 gene, which is located on chromosome 4q12-21, contains four exons and three introns, and exhibits functional polymorphisms, fifteen of which have been characterized [16]. Among these polymorphisms the presence of IL-8-251 A > T in the promoter region exerts the greatest influence on IL-8 production and is associated with the risk of prostate [17], breast [18], oral [19], colorectal cancer [20] and Kaposi's sarcoma [21]. To better understand this issue, we performed an updated systemic review and meta-analysis of all eligible case-control studies to provide insights into the association between IL-8 -251A > T polymorphism and susceptibility to gastric carcinogenesis, which may promote our understanding of the exact role of IL-8 gene in the etiology of gastric cancer.

Results

Search results

Of the 293 unique studies identified using our search criteria, 18 case-control studies fulfilled our inclusion criteria and were included in the meta-analysis [22-39]. These studies cumulatively reported 5,321 cases and 6,465 controls. The publication year of involved studies ranged from 2004 to 2012. Detailed search steps were described in Figure 1.



The characteristics of included studies

The main features of the studies included in the meta-analysis were shown in Table 1. Among these studies, six studies were performed in Caucasian populations [22-25,31,32], eleven studies in Asian populations [26-29,33-35,37-39], and one study in mixed population [36]. Ten studies used hospital-based controls, while the other eight studies used population-based controls (community populations). Most studies indicate that the distribution of genotypes in controls was consistent with Hardy-Weinberg equilibrium (HWE), and the subjects of controls were matched for age and gender. All cases were confirmed histologically or pathologically.

Quantitative data synthesis

Table 2 showed the summary odds ratio (OR) relating IL-8-251 A > T to gastric carcinogenesis risk based on 5,321 cases and 6,465 controls in all 18 studies.

Overall analysis

Eighteen studies involved the correlations between IL-8-251 A > T polymorphism and gastric carcinogenesis. The heterogeneity obviously existed under most genetic models, which might be a result of the difference in ethnicity, country, source of controls and genotype methods, so random effects model was conducted to pool the results. By allelic comparison, A-allele genotypes were associated with gastric carcinogenesis, with a pooled OR of 1.14 (95% CI: 1.02-1.26, $P = 0.02$) (Figure 2). There were also significant associations in the recessive model (AA + AT versus TT) (OR = 1.18, 95% CI: 1.02-1.36, $P = 0.03$), and homozygous comparison (AA versus TT) (OR = 1.26, 95% CI: 1.02-1.57, $P = 0.04$), respectively, but not in the dominant model (AA vs AT + TT) (OR = 1.17, 95% CI = 0.98-1.38, $P = 0.07$) and the heterozygous comparison (AT versus TT) (OR = 1.14, 95% CI: 1.00-1.31, $P = 0.05$) (Table 2). In the stratified analysis by ethnicity, we found that gastric carcinogenesis risk was significant increased in Asian population under allele comparison (OR = 1.20, 95% CI: 1.06-1.36, $P < 0.05$), dominant model (OR = 1.28, 95% CI: 1.02-1.61, $P = 0.04$), recessive model (OR = 1.26, 95% CI: 1.08-1.47, $P < 0.01$), homozygous comparison (OR = 1.40, 95% CI: 1.08-1.83, $P = 0.01$), and heterozygous comparison (OR = 1.21, 95% CI: 1.09-1.35, $P < 0.01$). However, no significant association between this polymorphisms and gastric carcinogenesis risk was observed in all comparison models in Caucasians population (Table 2).

Subgroup analysis

In the subgroup analysis, we evaluated the significance in patients with gastric cancer or precancerous lesion, respectively. In the gastric cancer group, we found that individuals with A-allele had significantly higher gastric

Table 1 Baseline characteristics of the 18 eligible studies for the analysis of IL-8-251 A > T polymorphism

Studies	Year	Country	Ethnicity	Source of controls	Number of controls	Number of case	Genotyping method	HWE
Burada F	2012	Romanian	Caucasian	HB	242	105	Real-time PCR	0.386
Canedo P	2007	Portugal	Caucasian	PB	693	401	Taqman	0.460
Crusius JB	2008	European	Caucasian	HB	1139	428	Real-time PCR	0.706
Kamangar F	2006	Finland	Caucasian	PB	207	112	Taqman	0.055
Kang JM	2009	Korea	Asian	HB	322	645	RFLP	0.226
Lee WP	2005	Taiwan	Asian	HB	308	461	RFLP	0.143
Liu J	2009	China	Asian	HB	137	417	Taqman	0.145
Lu W	2005	China	Asian	PB	300	250	DHPLC	0.516
Ohyauchi M	2005	Japan	Asian	PB	346	212	Direct sequence analysis	0.549
Savage SA	2004	Poland	Caucasian	PB	429	88	SBE	0.885
Savage SA	2006	Poland	Caucasian	PB	428	287	Taqman or MGB Eclipse	0.391
Shirai K	2005	Japan	Asians	HB	468	181	RFLP	0.830
Song B	2010	China	Asian	HB	190	208	RFLP	0.389
Taguchi A	2005	Japan	Asian	HB	252	611	RFLP	0.994
Vinagre RM	2011	Brazil	Mixed	HB	103	102	RFLP	0.151
Ye BD	2009	Korea	Asian	HB	206	399	RFLP	0.553
Zeng ZR	2005	China	Asian	PB	196	206	PCR-RDB	0.022
Zhang LW	2010	China	Asian	PB	504	519	PCR-RFLP	0.754

PB, population-based controls; HB, hospital-based controls. HWE, Hardy-Weinberg equilibrium. PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SBE, single base extension; PCR-RDB, polymerase chain reaction- reverse dot blot.

cancer risks (OR = 1.15, 95% CI: 1.03–1.29, $P = 0.02$) (Figure 3). The results also indicated the significant risk under three models (recessive model: OR = 1.21, 95% CI: 1.03–1.43, $P = 0.02$; homozygous comparison: OR = 1.29, 95% CI: 1.02–1.62, $P = 0.03$; heterozygous comparison: OR = 1.18, 95% CI: 1.01–1.38, $P = 0.03$), whereas no significant risk was observed under dominant model (OR = 1.18, 95% CI: 1.01–1.38, $P = 0.03$). Moreover, we found that gastric cancer risk was significant increased in Asian population under allele comparison (OR = 1.23, 95% CI: 1.07–1.40, $P < 0.01$), dominant model (OR = 1.28, 95% CI: 1.01–1.63, $P = 0.04$), recessive model (OR = 1.32, 95% CI: 1.09–1.59, $P < 0.01$), homozygous comparison (OR = 1.46, 95% CI: 1.09–1.95, $P = 0.01$), and heterozygous comparison (OR = 1.27, 95% CI: 1.06–1.52, $P = 0.01$). However, no significant association between this polymorphisms and gastric cancer risk was observed in all comparison models in Caucasians population (Table 2).

The information on the association between IL-8-251 A > T polymorphism and gastric precancerous lesions was available from four articles evaluated in this study (Figure 4). No remarkable association was presented between IL-8-251 A > T polymorphism and the presence of gastric precancerous lesions under the allele comparison (OR = 1.09, 95% CI: 0.99–1.20, $P = 0.08$), dominant model (OR = 1.15, 95% CI: 0.85–1.56, $P = 0.37$), recessive model (OR = 1.21, 95% CI: 0.99–1.49, $P = 0.07$), homozygous comparison (OR = 1.27, 95% CI: 0.91–1.76,

$P = 0.16$), and heterozygous comparison (OR = 1.19, 95% CI: 0.96–1.48, $P = 0.11$).

Publication bias

Begger's funnel plot and Egger's linear regression test were performed to assess the publication bias of included studies. The shapes of the funnel plots seemed symmetrical in the allele comparison model ($P = 0.484$) (Figure 5). Egger's test also did not show any significantly statistical evidence of publication bias under the allele comparison model ($P = 0.05$), which indicated low risk of publication bias in this meta-analysis.

Discussion

The pathogenesis of gastric carcinogenesis involves environmental factors, molecular signaling pathways, and host genetic factors [40]. The role of cytokine gene polymorphisms is currently a hot topic in gastric cancer research. Genome-wide association studies have identified several genetic loci associated with susceptibility to gastric carcinogenesis. Recently, a growing number of studies have suggested that SNPs of IL-8 251 allele, which is located at the promoter sequence of the IL-8 gene, might be associated with gastric tumorigenesis [41]. However, the results are contradictory. Hence, it is worth performing a meta-analysis of all eligible studies to investigate more precise estimation of this specific association.

Table 2 Main results for the IL-8-251 A > T polymorphism with the risk of gastric carcinogenesis based on OR and 95% CI

Genotype comparison	OR [95% CI]	Z (P value)	Heterogeneity of study design		Model
			χ^2	I ²	
Overall analysis (5,321 cases, 6,465 controls)					
A allele vs T allele	1.14 [1.02, 1.26]	2.33 (0.02)	59.55	71%	Random
Asian	1.20 [1.06, 1.36]	2.87 (<0.01)	29.42	66%	Random
Caucasian	0.95 [0.85, 1.07]	0.87 (0.38)	7.38	32%	Random
AA vs AT + TT (dominant model)	1.17 [0.98, 1.38]	1.78 (0.07)	40.15	58%	Random
Asian	1.28 [1.02, 1.61]	2.11 (0.04)	24.53	59%	Random
Caucasian	0.92 [0.79, 1.08]	1.02 (0.31)	6.42	22%	Fixed
AA + AT vs TT (recessive model)	1.18 [1.02, 1.36]	2.21 (0.03)	50.59	66%	Random
Asian	1.26 [1.08, 1.47]	2.86 (<0.01)	23.13	57%	Random
Caucasian	0.90 [0.78, 1.03]	1.53 (0.13)	5.29	70%	Random
AA vs TT (homozygous comparison)	1.26 [1.02, 1.57]	2.10 (0.04)	52.95	6%	Fixed
Asian	1.40 [1.08, 1.83]	2.50 (0.01)	27.43	64%	Random
Caucasian	0.87 [0.73, 1.05]	1.48 (0.14)	7.62	34%	Fixed
AT vs TT (heterozygous comparison)	1.14 [1.00, 1.31]	1.97 (0.05)	39.34	57%	Random
Asian	1.21 [1.09, 1.35]	3.55 (<0.01)	18.92	47%	Random
Caucasian	0.91 [0.78, 1.05]	1.29 (0.20)	3.64	0%	Fixed
Gastric cancer analysis (4,513 cases, 6,465 controls)					
A allele vs T allele	1.15 [1.03, 1.29]	2.43 (0.02)	63.29	73%	Random
Asian	1.23 [1.07, 1.40]	2.94 (<0.01)	32.40	69%	Random
Caucasian	0.95 [0.84, 1.07]	0.85 (0.40)	7.46	33%	Random
AA vs AT + TT (dominant model)	1.17 [0.98, 1.39]	1.75 (0.08)	40.38	58%	Random
Asian	1.28 [1.01, 1.63]	2.02 (0.04)	25.37	61%	Random
Caucasian	0.92 [0.79, 1.09]	0.95 (0.34)	6.31	21%	Fixed
AA + AT vs TT (recessive model)	1.21 [1.03, 1.43]	2.36 (0.02)	58.32	71%	Random
Asian	1.32 [1.09, 1.59]	2.88 (<0.01)	29.51	66%	Random
Caucasian	0.90 [0.78, 1.03]	1.55 (0.12)	5.40	7%	Fixed
AA vs TT (homozygous comparison)	1.29 [1.02, 1.62]	2.17 (0.03)	56.20	70%	Random
Asian	1.46 [1.09, 1.95]	2.52 (0.01)	30.52	67%	Random
Caucasian	0.87 [0.72, 1.05]	1.44 (0.15)	7.65	35%	Fixed
AT vs TT (heterozygous comparison)	1.18 [1.01, 1.38]	2.14 (0.03)	47.23	64%	Random
Asian	1.27 [1.06, 1.52]	2.57 (0.01)	25.47	61%	Random
Caucasian	0.90 [0.78, 1.05]	1.33 (0.18)	3.68	0%	Fixed
Precancerous lesions analysis (808 cases, 1,288 controls)					
A allele vs T allele	1.09 [0.99, 1.20]	1.66 (0.08)	2.98	0%	Fixed
AA vs AT + TT (dominant model)	1.15 [0.85, 1.56]	0.90 (0.37)	1.92	0%	Fixed
AA + AT vs TT (recessive model)	1.21 [0.99, 1.49]	1.84 (0.07)	1.42	0%	Fixed
AA vs TT (homozygous comparison)	1.27 [0.91, 1.76]	1.42 (0.16)	2.37	0%	Fixed
AT vs TT (heterozygous comparison)	1.19 [0.96, 1.48]	1.59 (0.11)	0.69	0%	Fixed

The present meta-analysis summarized the correlation between the IL-8-251 A > T polymorphism and susceptibility to gastric carcinogenesis in 18 studies. The results suggested that the AA and AT genotypes of IL-8 -251A > T polymorphism appears to be associated with an overall

increased risk of gastric carcinogenesis and is discovered as a risk factor of gastric cancer. Subgroup analysis by ethnicity allowed us to look for potential ethnic differences in the association. In the Asian population, the A-allele was associated with increased risk of gastric

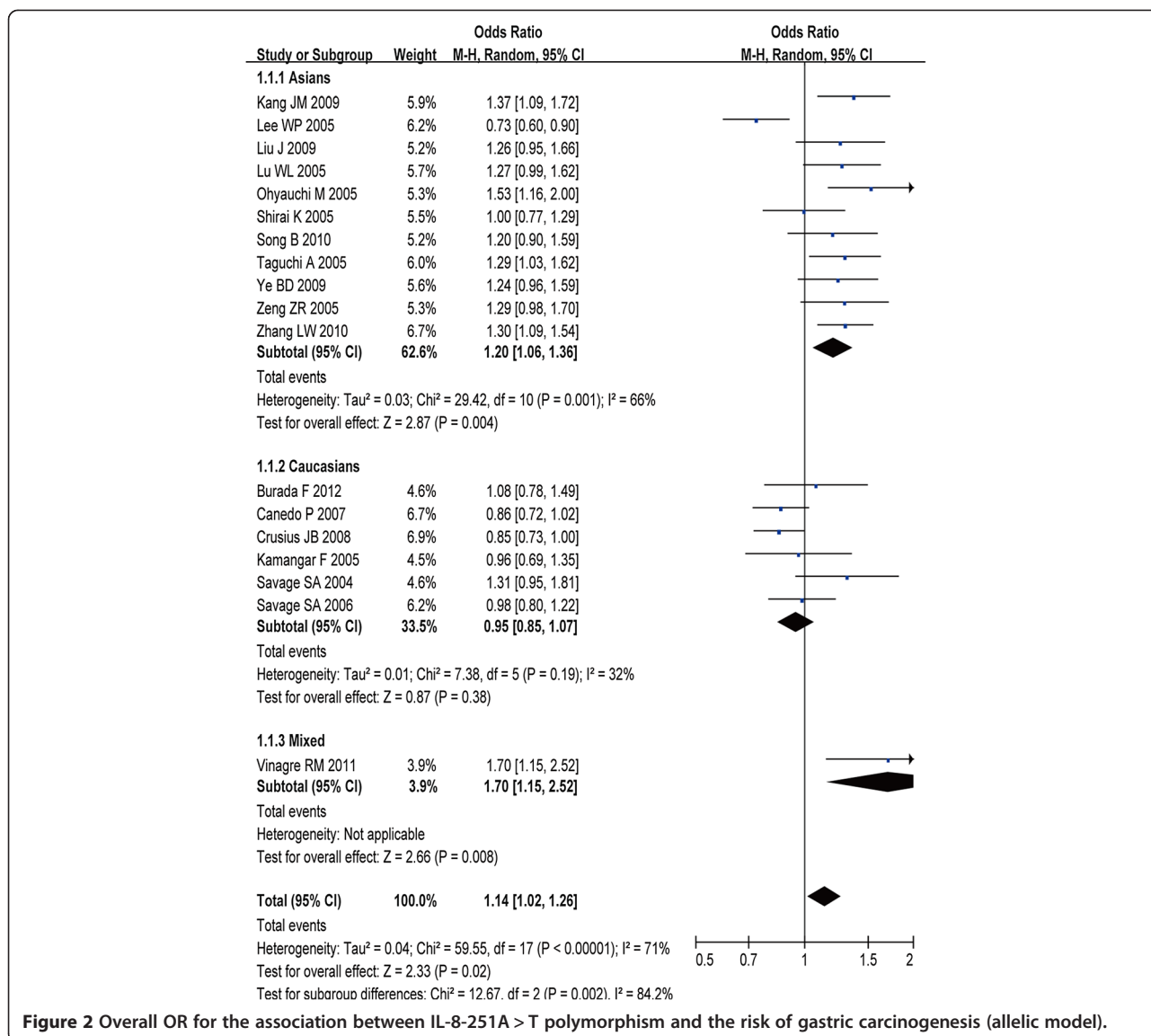


Figure 2 Overall OR for the association between IL-8-251A > T polymorphism and the risk of gastric carcinogenesis (allelic model).

carcinogenesis and gastric cancer based on allele comparison, dominant model, recessive model, homozygote comparison, and heterozygous comparison. However, for the Caucasian population, IL-8 -251A > T polymorphism was not associated with increased risk of gastric carcinogenesis and gastric cancer. The A allele seemed to be dominant, but in the precancerous lesion subgroup, no significance was noted for all models. The possible reason could be that genetic risk factors differ between gastric cancer and precancerous lesions.

The IL-8 promoter is estimated to be 1,500 bp. Several reports have shown relationship between IL-8 gene polymorphisms and human diseases, and all of them have focused on the A/T polymorphism at -251 upstream from the transcriptional start site. IL-8 -251A > T polymorphism has been associated with altered transcription levels of IL-8 by regulating the transcriptional activity of

the gene and then proved to affect susceptibility to a large number of diseases. In the present analysis, we found an overall increase in gastric carcinogenesis of one or two allele variants as compared to wild allele T and homozygous TT genotype. After stratification into dominant and recessive genetic models, the dominant model (AA vs. AT + TT) (P = 0.07) and the recessive model (AA + AT vs. TT) (P = 0.02) both showed increased (1.18 fold) risk of gastric carcinogenesis. Even though the precise role of IL-8 -251A > T polymorphism in the development of gastric carcinogenesis is unknown, a plausible mechanism is that the mutations of IL-8 gene might increase gene transcription after binding to its high affinity cell surface receptor, which eventually attribute to the correlation between IL-8 and gastric carcinogenesis risk.

In fact, 18 studies were conducted as gastric cancer subgroup, whereas only 4 studies were conducted as

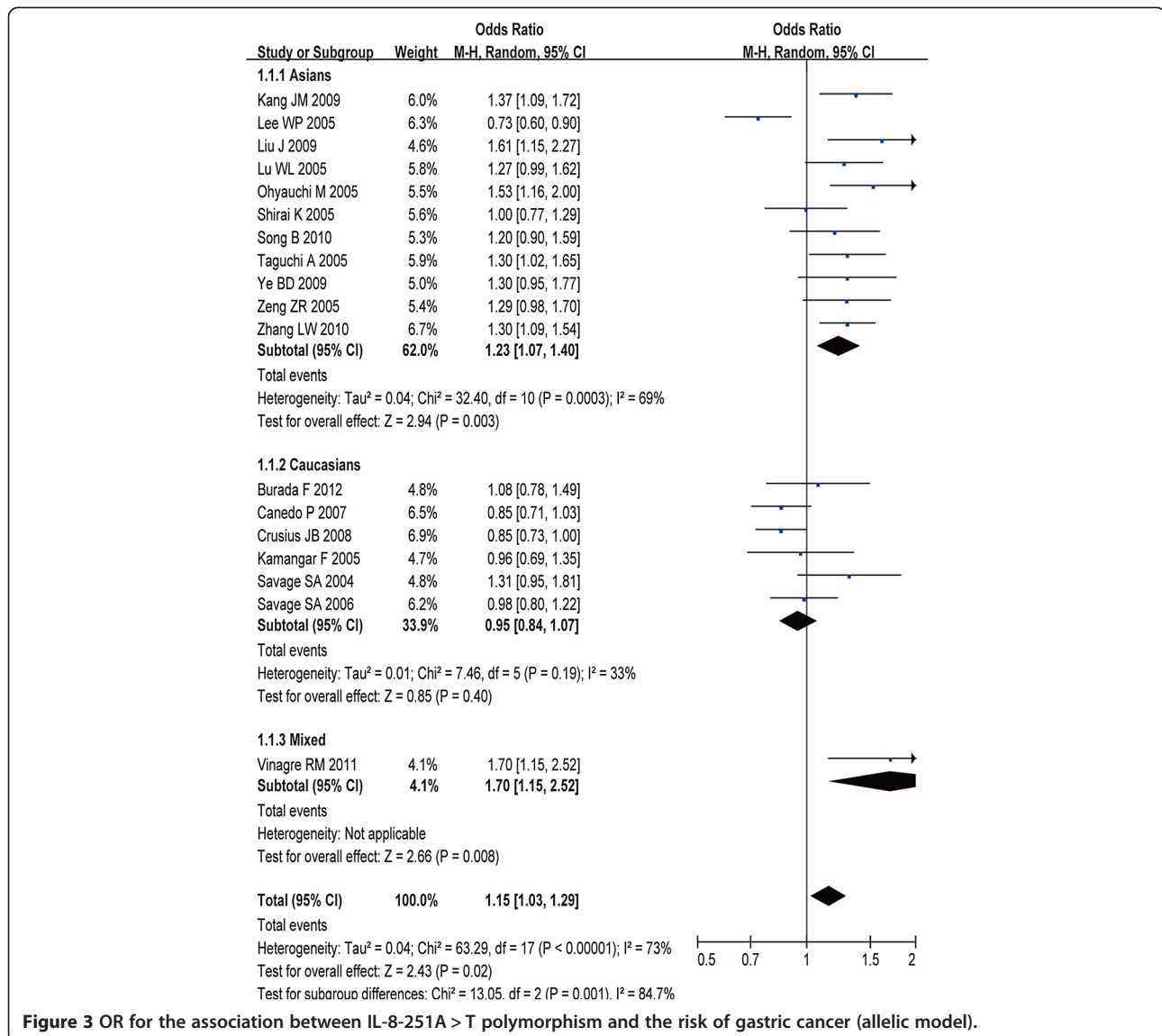


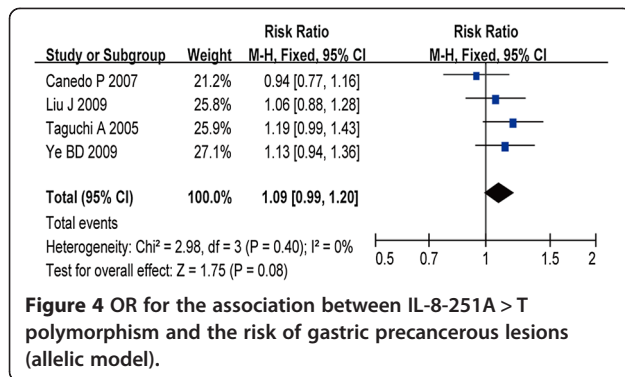
Figure 3 OR for the association between IL-8 -251A > T polymorphism and the risk of gastric cancer (allelic model).

precancerous lesions subgroup. We found that the pooled effect of studies of gastric cancer reported significant association between IL-8 -251A > T polymorphism and risk of gastric cancer. Moreover, the pooled effect of studies on patients with precancerous lesions did not show significant difference, the reasons for which might be deriving many elements and multiple mechanisms of gastric cancer and precancerous lesion disease. As is known, there are two mechanisms by which the gastric mucosa progresses to carcinoma, both starting from chronic gastritis. One mechanism is via precancerous lesions, such as gastric atrophy, intestinal metaplasia and adenomatous dysplasia leading to intestinal-type carcinomas characterized by glandular formation; the other is via hyperplastic or de novo changes leading to diffuse-type carcinomas characterized by isolated cancer cells with an infiltrative growth. However, our results showed that IL-8 -251A > T

polymorphism was only associated with gastric cancer risk, but not with precancerous lesion. Thus, our meta-analysis suggested that genetic risk factors differ between gastric cancer and precancerous lesions.

In addition, results differed when stratifying the data by ethnicity. Associations between IL-8 -251A > T polymorphism and gastric carcinogenesis and gastric cancer were generally stronger in Asian than Caucasian population. This discrepancy from our meta-analysis may reflect the complex multifactorial etiology of gastric carcinogenesis.

Our results should be interpreted cautiously since some limitations exist in this present meta-analysis. First, only published studies were included in the meta-analysis. Therefore, the publication bias may have occurred, even though the use of a statistical test did not show it. Second, the number of included studies was relatively small with only about 5,321 cases. Moreover, other clinical factors



such as age, ethics, and different chemotherapies in each study might lead to bias. Determining whether or not these factors influence the results of this meta-analysis would need further investigation. Third, the effect from our meta-analysis could be overestimated because many studies were retrospective cohort studies which had high risk of reporting biases. Therefore, more well-designed studies with large sample sizes are needed to further assess the precise effect of IL-8 -251A > T polymorphism in gastric carcinogenesis. Finally, the studies included in this meta-analysis were from different populations, it is possible that demographic factors can confound our results.

Conclusions

Despite the limitations listed above, our meta-analysis results provide evidence that IL-8 -251A > T polymorphism is significantly associated with increased risk of gastric carcinogenesis, particularly in gastric cancer. Nevertheless, gastric carcinogenesis is a multifactorial and multistep process, so our results should be examined cautiously by

an adequately designed prospective studies, and larger clinical trials with widely accepted assessment methods.

Materials and methods

Search strategy

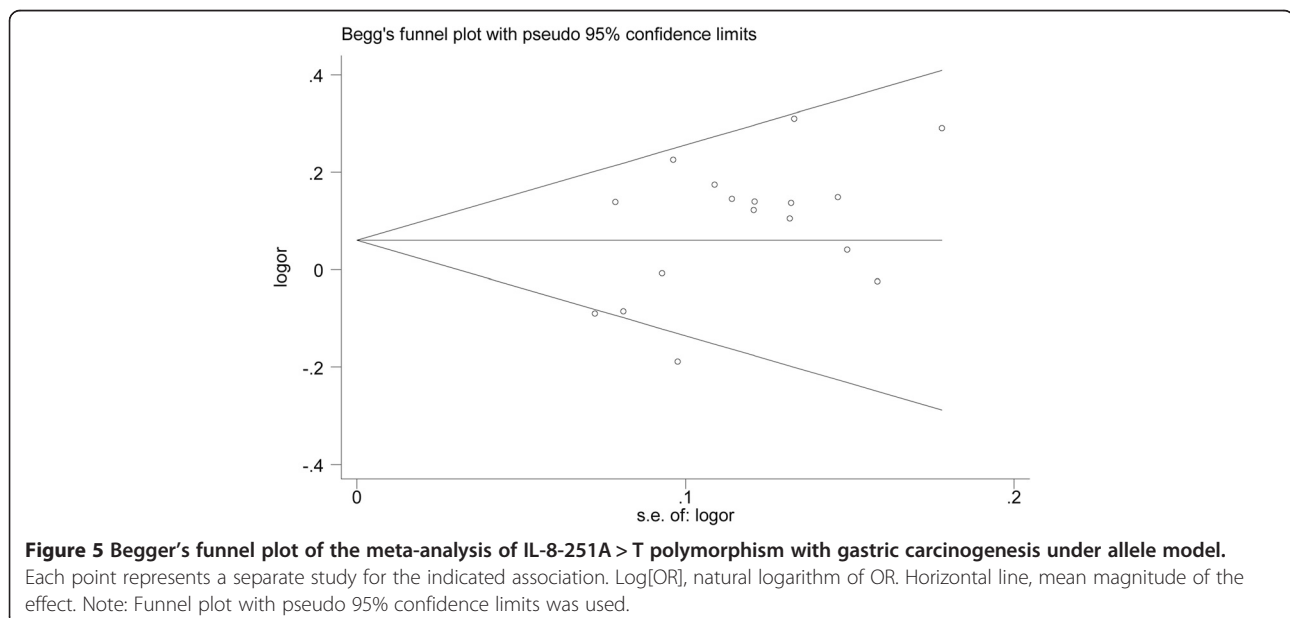
A systematic literature search of MEDLINE (updated to June, 2013), Embase (updated to June, 2013), and web of Science (updated to June, 2013), and CNKI (Chinese National Knowledge Infrastructure) databases was conducted by two study investigators (D.C. and Y. H.) independently for all relevant articles. Key words used in the research included “Interleukin-8”, “IL-8”, “CXCL8”, “gastric cancer”, “stomach cancer”, “precancerous lesion”, “polymorphism”, “SNP”, “gene variant”, “gene mutation”, and “gastric tumor”.

Inclusion and exclusion criteria

Studies eligible for inclusion in this meta-analysis should meet the following criteria: (a) case-control studies or cohort studies focused on association between IL-8-251 A > T polymorphism and risk of gastric carcinogenesis; (b) patients have pathologically or histological confirmed gastric cancer and/or precancerous lesions; (c) The studies provided the number of cases and controls for various genotypes. The exclusion criteria of the meta-analysis were: (a) animal studies; (b) meta-analyses, letters, reviews or editorial comments; (c) studies with duplicate data or incomplete date. When an individual author published several articles obtained from the same patient population, only the newest or most complete article was included in the analysis.

Data extraction

Information was carefully extracted from all the eligible publications. The following data were collected from each



study: first author's name, publication date, country, ethnicity, source of controls, genotyping method, total numbers of cases and controls, number of cases and controls for each IL-8-251 A>T polymorphism, and *P* value for HWE. An attempt was made to contact authors if data presentation was incomplete or if it was necessary to resolve an apparent conflict or inconsistency in the article. Any disagreements were resolved by consensus.

Statistical analysis

Review manager 5.1 program provided by the Cochrane Library and Stata (Version 12.0, Stata Corporation) were used to perform all the statistical analysis. The association was evaluated with the use of the allelic comparison (A versus T), as well as the dominant model (AA versus AT + TT), the recessive model (AA + AT versus TT), the homozygous comparison (AA versus TT), and heterozygous comparison (AT versus TT), respectively. Two models of pooling data for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model. The pooled statistical analysis was calculated using the fixed effects model, but a random-effect model was performed when the *P* value of heterogeneity test was <0.1 (or $I^2 > 50\%$). The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study, and the combined OR and 95% CI were calculated for all eligible studies. OR was the proportion of the exposed population in whom disease has developed over the proportion of the unexposed population in whom disease has developed in a case-control study. The significance of the combined OR was determined by the Z-test, in which $P < 0.05$ was considered significant. Heterogeneity assumption was assessed by the chi-square based Q test and was regarded to be statistically significant if $P < 0.10$. The potential publication bias was assessed by Begg's funnel plot and Egger's test [42,43].

Abbreviations

IL-8: Interleukin-8; OR: Odds ratio.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DC conceived and designed the study. DC and YH drafted the manuscript. WZ and YM collected the data. DC performed the data analysis. All authors have read and approved the final manuscript.

Acknowledgements

This study was supported by Liaoning Natural Science Fund, Liaoning Province, China (Topic No: 201102257).

Received: 12 July 2013 Accepted: 19 October 2013

Published: 22 October 2013

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doi:10.1186/1475-2867-13-100

Cite this article as: Cheng *et al*: Positive association between Interleukin-8 -251A > T polymorphism and susceptibility to gastric carcinogenesis: a meta-analysis. *Cancer Cell International* 2013 **13**:100.

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