RESEARCH ARTICLE

Lack of Association Between Interleukin-8-251 T>A Polymorphism and Colorectal Cancer Risk: a Meta-analysis based on 3,019 Cases and 3,984 Controls

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Abstract

Purpose: The results of recent published studies focusing on IL-8 polymorphism in colorectal cancer susceptibility have often been inconsistent. We therefore carried out a meta-analysis based on independent studies to assess the association. Methods: Nine case-control studies with 7,003 individuals (3,019 cases and 3,984 controls) were included in this meta-analysis through searching the databases of PubMed, Excerpta Medica Database (EMBASE), and Chinese Biomedical Literature Database (CBM; Chinese) (up to Aug 1st, 2012). The odds ratio (OR) and 95% confidence interval (95%CI) were used to assess the strength of the association. Meta-analysis was conducted in a fixed/random effect model. Results: No obvious associations were found for all genetic models when all studies were pooled into the meta-analysis (for A vs. T: OR = 1.084, 95% CI = 0.971-1.209, P = 0.019; for TA vs. TT: OR = 1.18, 95% CI = 0.943-1.475, P = 0.001; for AA vs. TT: OR = 1.155, 95% CI = 0.916-1.456, P = 0.014; for AA+TA vs. TT: OR = 1.170, 95% CI =0.953-1.437, P = 0.001; for AA vs. TT+TA: OR = 1.044, 95% CI = 0.886-1.230, P = 0.097). In the subgroup analyses by ethnicity (Caucasian) and source of controls (population based), also no significant associations were found for all genetic models. Conclusions: Result suggests that the IL-8-251T>A polymorphism is not associated with colorectal cancer risk. Because of the limitations of this meta-analysis, this finding demands further investigation.

Keywords: Colorectal cancer - polymorphism - meta-analysis - interleukin-8

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Introduction

Colorectal cancer(CRC) is the third most commonly diagnosed cancer in males and the second in females(Jemal et al., 2010). Ecologic and migrant studies have proved that the environment, life style, diet habit, and genetic factors all contribute to the carcinogenesis of colorectal cancer (Glade, 1999; Potter, 1999). Among the risk factors for CRC, inherited genetic susceptibility account for approximately 35% of all colorectal cancer (Tenesa et al., 2008). Genetics has a key role in predisposition to CRC in its initiation and progression. The identification of the important CRC-related genes may help facilitate the early diagnosis, prevention, and treatment of CRC (Cheah, 2009).

A number of researches have shown that single nucleotide polymorphism (SNP) may influence human susceptibility to colorectal cancer (Tomlinson et al., 2008; Abuli et al., 2010). Interleukin (IL)-8 is a chemokine and one of the major mediators of inflammatory responses, and is believed to play a role in the angiogenesis of cancer (Harada et al., 1994; Xie, 2001). IL-8 is produced by several types of tumor cells (Heinzmann et al., 2004) and has been involved in angiogenesis and neovascularization-dependent tumor growth (van Aken et al., 2002). It is also overexpressed in a variety of human tumors and is involved in tumor invasion and metastasis (Kitadai et al., 2000; Bendre et al., 2002; Li et al., 2003). Therefore, IL-8 may constitute a risk factor in the development and progression of tumors.

Several polymorphisms have been detected in the IL-8 gene, and a common polymorphism at the -251 position (251T>A) of the promoter region has been associated with transcriptional activity of the gene. The -251T>A polymorphism at the promoter region of IL-8 gene is associated with the transcriptional activity of the gene (Wei et al., 2007), and to influence production and expression of IL-8 (Ohyauchi et al., 2005; Taguchi et al., 2005).

To date, several studies were conducted to investigate the association between IL-8 251T>A (rs4073) polymorphism and CRC risk in humans, but the results of these studies are conflicting. To our best knowledge, rs4073 is the most extensively studied polymorphisms in the IL-8 gene in colorectal cancer susceptibility. To conclude, we performed the present meta-analysis to evaluate the association between the polymorphism and colorectal cancer risk.

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Materials and Methods

Publication search

PubMed, Excerpta Medica Database (EMBASE), and Chinese Biomedical Literature Database (CBM; Chinese) were searched for relevant reports on the association between interleukin 8 polymorphism and colorectal cancer (last search: Aug 1st, 2012). The search terms were used as follows: 'interleukin 8 or interleukin-8 or IL8 or IL-8', '-251T>A or rs4073', 'cancer or tumor or carcinoma', 'colorectal or colon or rectal' and 'polymorphism or polymorphisms'. Additional literature was collected from cross-references within both original and review articles. No language restrictions were applied.A study was included in the current meta-analysis if (1) evaluation of the IL-8 polymorphism and colorectal cancer risk, (2) it was a case-control study, (3) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval. The major exclusion criteria were (1) animal studies,reviews, tutorials, letters, and editorials; (2) duplicate data; (3) not a case-control design; (4) insufficient data were reported as IL-8 expression levels were provided without genotype data.We excluded family-based studies of pedigrees with several affected cases per family because the analysis was based on linkage considerations. When a study reported the results on different ethnicities, we treated them as separate studies.

Data extraction

Data were independently checked and extracted by two investigators. The following items were collected from each study: first author's name, year of publication, ethnicity (included Caucasian, Asian, African and Mixed) of the study population, sample size (total cases and controls),source of controls (population based and hospital based), evidence of Hardy-Weinberg equilibrium (HWE), genotype distributions in cases and controls.

Meta-Analysis Methods

Crude ORs with 95% CIs were calculated to assess the strength of the association between IL-8-251 T/A polymorphism and CRC risk. We explored the association for a homozygote comparison (AA vs. TT), a heterozygote comparison (TA vs. TT), a recessive model (AA vs. TA + TT), a dominant model (AA+TA vs. TT), and an allelic model (A allele vs. T allele). Subgroup analyses based on ethnicity and source of controls were also performed.

Heterogeneity among studies was assessed by the Chi-square test-based Q-statistic and I^2- statistic(Higgins et al., 2003). A random (DerSimonian-Laird method) (DerSimonian and Laird 1986)or fixed (Mantel-Haenszel method) (Mantel and Haenszel, 1959)effects model was used to calculate the pooled ORs in the presence ($p \leq 0.10$) or absence ($p > 0.10$) of heterogeneity. The Hardy-Weinberg equilibrium (HWE) was determined using the chi-square test in the control groups (Haber, 1981).

An estimate of potential publication bias was carried out by the funnel plot (Begg and Mazumdar, 1994) and Egger's linear regression test (Egger et al., 1997). An asymmetric funnel plot suggests a possible publication bias. Then, the funnel plot asymmetry was assessed by Egger's linear regression test, and the significance of the intercept was determined by the t test suggested by Egger ($p < 0.05$ was considered representative of statistically significant publication bias).

All statistic analyses were carried out using stata software, vision 10.0 (Stata corporation, College Station, TX, USA). A P-value less than 0.05 was considered statistically significant, and all the P values were two sided.

Results

Characteristics of Eligible Studies

A flow diagram illustrating the study selection process was shown in Figure 1.Through literature search and selection, a total of 9 publications (Landi et al., 2003; Theodoropoulos et al., 2006; Vogel et al., 2007; Cacev et al., 2008; Kury et al., 2008; Wilkening et al., 2008;

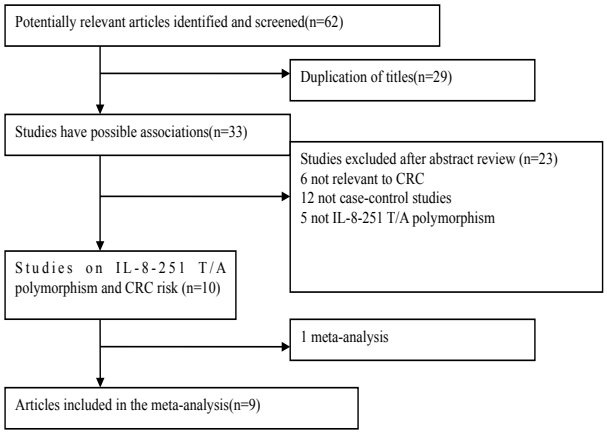

Figure 1. Flow Diagram of the Study Selection Process

Table 1. Characteristics of Primary Studies in the Meta-analysis

ID	First author	Year	Sample size (case/control)	Ethnicity	Cases			Controls			Source of control[a]	HWE[b]
					TT	TA	AA	TT	TA	AA		
1	Landi etal	2003	308/352	Caucasian	83	170	55	117	167	68	HCC	0.543
2	Theocloropoulos etal	2006	222/196	Caucasian	76	106	40	64	90	42	PCC	0.328
3	Vogel etal	2007	355/753	Caucasian	83	178	94	160	367	226	PCC	0.627
4	Kury etal	2008	1023/1121	Caucasian	307	511	205	375	516	230	PCC	0.033
5	Cacev etal	2008	160/160	Caucasian	46	75	39	53	73	34	PCC	0.346
6	Wilkening etal	2008	300/580	Caucasian	71	133	96	115	296	169	PCC	0.476
7	Tsilidis etal	2009	205/362	Caucasian	65	88	52	114	162	86	PCC	0.058
8	Walczak etal	2012	191/205	Caucasian	50	104	37	99	71	35	HCC	0.001
9	Mustapha etal	2012	255/255	Mixed	40	183	32	54	189	12	PCC	0.001

[a]HCC hospital-based case–control study; PCC population-based case–controls study; [b]HWE Hardy–Weinberg equilibrium

Table 2. Main Results of Pooled ORs in the Meta-analysis

Study groups(n)	Comparison	Test of association			Test of heterogeneity			Model
		OR(95%)	Z	P	χ^2	P	I^2	
Total(9)	A vs.T	1.084(0.971-1.209)	1.43	0.152	18.34	0.019	56.4	R
	TA vs.TT	1.180(0.943-1.475)	1.45	0.147	27.08	0.001	70.5	R
	AA vs.TT	1.155(0.916-1.456)	1.22	0.224	19.21	0.014	58.4	R
	AA+TA vs.TT	1.170(0.953-1.437)	1.5	0.135	25.84	0.001	69	R
	AA vs.TT+TA	1.044(0.886-1.230)	0.52	0.605	13.46	0.097	40.6	R
Ethnicity								
Caucasian (8)	A vs.T	1.060(0.947-1.186)	1.01	0.312	15.41	0.031	54.6	R
	TA vs.TT	1.168(0.913-1.493)	1.24	0.217	26.81	0	73.9	R
	AA vs.TT	1.048(0.911-1.206)	0.66	0.512	9.88	0.195	29.2	F
	AA+TA vs.TT	1.146(0.918-1.430)	1.2	0.229	24.75	0.001	71.7	R
	AA vs.TT+TA	0.984(0.873-1.108)	0.27	0.785	4.22	0.754	0	F
Source								
PCC(7)	A vs.T	1.029(0.955-1.108)	0.75	0.453	8.04	0.235	25.4	F
	TA vs.TT	1.057(0.933-1.198)	0.88	0.381	7.92	0.244	24.2	F
	AA vs.TT	1.076(0.838-1.382)	0.57	0.565	13.78	0.032	56.5	R
	AA+TA vs.TT	1.052(0.936-1.183)	0.85	0.394	7.99	0.239	24.9	F
	AA vs. TT+TA	1.064(0.869-1.304)	0.6	0.548	12.86	0.045	53.4	R
HCC(2)	A vs.T	1.340(0.896-2.005)	1.42	0.154	5.03	0.025	80.1	R
	TA vs.TT	2.009(1.009-4.002)	1.99	0.047	5.74	0.017	82.6	R
	AA vs.TT	1.437(1.009-2.048)	2.01	0.045	2.65	0.103	62.3	F
	AA+TA vs.TT	1.861(0.967-3.582)	1.86	0.063	5.89	0.015	83	R
	AA vs.TT+TA	0.997(0.730-1.361)	0.02	0.984	0.58	0.446	0	F

HCC hospital-based case–control study; PCC population-based case–controls study; OR, odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model

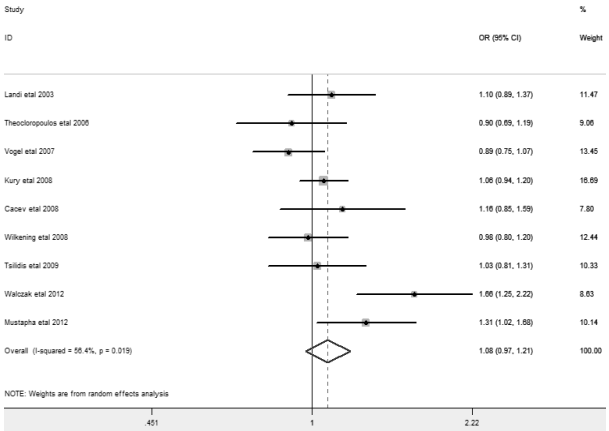

Figure 2. Forest Plot for the Overall Association Between IL-8-251 T>A Polymorphism and CRC Risk for an Allelic Model (A versus T). Each study was shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for the OR (extending lines); the pooled OR and 95% CI were shown by diamonds

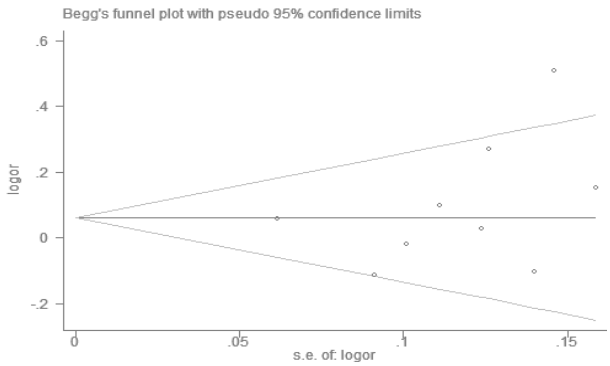

Figure 3. Begg's Funnel Plot Indicated that No Publication Bias was Observed for A vs. T Allele Comparison in IL-8 Polymorphism. Each point represents a separate study for the indicated association. Log[OR] natural logarithm of odds ratio. Horizontal line mean effect size

Tsilidis et al., 2009; Mustapha et al., 2012; Walczak et al., 2012) including 3,019 cases and 3,984 controls comparing the IL-8 T251A polymorphism and colorectal cancer susceptibility were identified based on MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000). Table 1 shows the basic information from these studies.There were two hospital-based studies and seven population-based studies. The genotype distribution of three studies (Kury et al., 2008; Mustapha et al., 2012; Walczak et al., 2012) did not conform to Hardy-Weinberg equilibrium expectations. However, the distribution of the genotype in overall control population was consistent with Hardy-Weinberg equilibrium ($P > 0.05$).

Meta-Analysis

Table 2 lists the main results of the meta-analysis and the heterogeneity test. We found no association between the IL-8-251T>A polymorphism and CRC in overall population (for A vs. T: OR = 1.084, 95% CI = 0.971-1.209, P = 0.019 and I^2 =56.4 for heterogeneity(Figure 2); for TA vs. TT: OR = 1.18, 95% CI = 0.943-1.475, P = 0.001 and I^2 = 70.5 for heterogeneity; for AA vs. TT: OR = 1.155, 95% CI = 0.916-1.456, P = 0.014 and I^2 = 58.4 for heterogeneity; for AA+TA vs. TT: OR = 1.170, 95% CI = 0.953-1.437, P = 0.001 and I^2 = 69.0 for heterogeneity; for AA vs. TT+TA: OR = 1.044, 95% CI = 0.886-1.230, P = 0.097 and I^2 = 40.6 for heterogeneity). In the subgroup analyses by ethnicity (Caucasian) and source of controls (population based and hospital based), also no significant associations were found for all genetic models, except among those studies from "hospital-based" in the

homozygote comparison (AA vs. TT) and the heterozygote comparison (TA vs. TT).

Evaluation of Publication Bias

Funnel plots and Egger's regression test were performed to assess the publication biases of the literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparisons (Figure 3). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. No evidence of publication bias was observed (for A vs. T: P = 0.351; for TA vs. TT: P = 0.780; for AA vs. TT: P = 0.146; for AA+TA vs. TT: P = 0.637; for AA vs. TT/TA: P = 0.133).

Discussion

Recently, the IL-8 polymorphism has attracted widespread attention, and many case-control studies were conducted to assess the association between this polymorphism and cancer in humans. However, these results were often conflicting. Several reasons may explain this discordance, such as small sample size, ethnic background and publication bias.

Meta-analysis is a statistical procedure for combining results from several studies to produce a single estimate of the major effect with enhanced precision. It is considered a powerful tool for summarizing inconsistent results from different studies. The aim of the present study was to investigate whether the IL-8-251T>A polymorphism is a risk factor to cancer susceptibility, using a meta-analysis.

Wang et al. (2012) performed a meta-analysis about the association of the IL-8-251T>A polymorphism with colorectal cancer. Their results suggested that there was lack of association between the IL-8- 251 T/A polymorphism and colorectal cancer. However, the authors have several concerns related to the article.

Firstly,in the article by Wang et al. (2012), though the genotype contrasts (TA genotype vs. AA genotype, AA genotype vs. TT genotype and (AA+TA) genotypes vs. TT genotype) were included, the allele (A genotype vs. T genotype and AA genotype vs. (TT+TA) genotypes) contrast were not included. Secondly, in the Statistical analysis section, they stated that ''the between-study heterogeneity across the eligible comparisons using the χ^2-based Q test and the heterogeneity was considered significant if P<0.05.'' P<0.10 rather than < 0.05 usually indicates the heterogeneity between studies (Kavvoura and Ioannidis, 2008) Thirdly, Gunter et al. (2006) should be excluded from the meta-analysis,because they conducted the association between IL-8-251 T>A polymorphism and colorectal adenoma risk,not colorectal cancer.To reach a precise conclusion, we present a more systematic review to further investigate the association of IL-8-251 T>A polymorphism and colorectal cancer risk.

The present meta-analysis, including 3,019 cases and 3,984 controls from 9 case-control studies, explored the association between the -251 T/A polymorphism of the IL-8 gene and CRC risk. Overall, we did not find any significant association between IL-8- 251 T/A polymorphism and CRC susceptibility. In the stratified analysis by ethnicity and source of controls, significant associations were still not observed in all genetic models, except among those studies from "hospital-based". Because only two studies were from hospital-based, the observed association may be due to small-study bias.

Although it is biologically plausible that -251T>A which affects IL-8 levels could influence the susceptibility to CRC, the current evidence provides a negative result. The potential explanation is that the effect of a single polymorphism/gene might have a limited impact on CRC susceptibility relative to the one that has been anticipated.

Some limitations of this meta-analysis should be acknowledged. First, the overall outcomes were based on individual unadjusted ORs. Lacking of the information of detailed individual data limited our further more precise analysis on adjusted estimates by other factors like age and sex. This limitation may cause serious confounding bias. Second, relatively limited study number made it impossible to perform subgroup analysis. There was no study of Asian population or American African population. Third, we could not construct funnel plot and Egger's test for the meta-analysis in hospital-based study because of small numbers of studies. Thus,publication bias might exist, distorting the results. Fourth,meta-analysis is a type of retrospective study, and the recall and selection bias may be present.

Despite these limitations, our meta-analysis also showed some advantages. First, the statistical power of the analysis was greatly increased as substantial number of cases and controls were pooled from different studies. Second, no publication bias was detected, indicating that the whole pooled result may be unbiased.

In conclusion, this meta-analysis evaluates the relationship between genetic polymorphism and CRC risk and reveals that IL-8 251T/A polymorphism is not associated with altered susceptibility to CRC among Caucasians. Since no study was from a non-Caucasian population, it is critical that larger and well-designed multicentric studies based on Asian and African-American patients should be performed to re-evaluate the association.

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