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REVIEW ARTICLE

Cumulative Evidence for Association Between IL-8 -251T>A and IL-18 -607C>A Polymorphisms and Colorectal Cancer Susceptibility: a Systematic Review and Meta-analysis

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Abstract

Purpose The correlation of IL-8 and IL-18 gene polymorphisms with colorectal cancer (CRC) was investigated by previous studies, though the results remained conflicting. Thus, the meta-analysis was performed to investigate the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with CRC risk.

Methods A comprehensive search of the PubMed, Web of Science, CNKI, SciELO, and Wanfang databases was performed up to February 20, 2020. The strength of the associations was calculated with odds ratios (ORs) and their corresponding 95% of confidence intervals (CIs).

Results A total of 16 case-control studies including 13 studies with 3908 cases and 5005 controls on IL-8 -251T>A polymorphism and three studies with 396 cases and 560 controls on IL-18 -607C>A polymorphism were selected. Pooled data revealed that the IL-8 -251T>A and IL-18 -607C>A polymorphisms were not significantly associated with an increased risk of CRC in global population. When stratified by ethnicity, source of controls, sample size, and Hardy-Weinberg equilibrium (HWE), there were still no significant association between IL-8 -251T>A polymorphism and risk of CRC.

Conclusions Our results revealed that the IL-8 -251T>A and IL-18 -607C>A polymorphisms were not associated with an increased susceptibility to CRC. We strongly call for further studies with larger sample sizes and different ethnicities to confirm our findings.

Keywords Colorectal cancer · Interleukin · Cytokine · Association · Meta-analysis

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Introduction

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity worldwide, accounting for an estimated 1.8 million new cases and 881,000 deaths in 2018 [1–3]. Globally, CRC represents the most common cancer of the digestive system, and about 1 in 10 cancer deaths is due to CRC [4, 5]. CRC is the third cause of cancer after prostate and lung cancer in men (10% of total) and the second most common diagnosed cancer type after breast cancer in women (9.4% of total) [6, 7]. Despite decades of investigations, the etiology, pathogenesis, and risk factors of CRC remain unknown [8]. CRC is a complex disease that develops as a complex interactions between genetic and environmental factors [9–11]. Hereditary predisposition plays an obvious part in development of CRC, although 80% of colorectal neoplasms occur in the absence of a family history of CRC [12].

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Several prior studies have demonstrated that cytokine levels in plasma or serum varied significantly between CRC patients and healthy individuals, indicating that cytokine levels may be useful in screening or detecting CRC [13–15]. Interleukin 8 (IL-8), also named C-X-C motif chemokine ligand 8 (CXCL8), is located on chromosome 4q-13-21, contains 10 exons, and spans 5.2 kb in length [16, 17]. IL-8 plays important role in tumor formation processes such as angiogenesis, tumorigenesis, tissue invasion, and metastasis [18]. Moreover, the IL-18 was initially identified as a protein that induces interferon γ (IFNγ) production which is an ambiguous role of the immune system in cancer progression [19, 20]. The human IL-18 gene is located on chromosome 11q22.2-q22.3, contains six exons, and encompasses several polymorphisms within the promoter region [21].

Some epidemiologic studies evaluated the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with susceptibility to CRC. However, the results were inconsistent or even contradictory. Some reasons may be due to ethnic background of population, small sample size, inclusion or exclusion criteria, study design, and genotyping methods [22]. Moreover, the reason for this disagreement may be related to gene-gene and gene-environment interactions on development of CRC. Therefore, we performed a comprehensive meta-analysis to identify statistical evidence of the association between IL-8 -251T>A and IL-18 -607C>A polymorphisms and risk of CRC by retrieving all eligible studies.

Materials and Methods

Identification of Relevant Studies

A comprehensive literature search from PubMed, Goggle Scholar, EMBASE, Cochrane Library database, Springer Link, Chinese Biomedical Database (CBD), China National Knowledge Infrastructure (CNKI) platforms, Wanfang, and VIP database was conducted to identify all relevant studies on IL-8 -251T>A and IL-18 -607C>A polymorphisms with CRC risk up to February 20, 2020. We used the combination of the following search terms and keywords: ("Colorectal Cancer" OR "CRC" OR "Bowel Cancer" OR "Colon Cancer" OR "Rectal Cancer" OR "Tumor" OR "Cancer" OR "Neoplasm") AND ("Interleukin-8" OR "IL-8" OR "chemokine (C-X-C motif) ligand 8" OR "CXCL8") AND ("-251T>A" OR "rs4073") AND ("Interleukin-18" OR "IL-18" OR " Interferon-Gamma Inducing Factor") AND ("-607C>A" OR "rs1946518") AND ("Gene" OR "Polymorphism" OR "SNPs" OR "Mutation" OR "Variation" OR "Allele"). We have also manually screened the reference lists of eligible articles and reviews to retrieve additional articles. There was no language, ethnicity, or country restriction, and the literature search was limited to humans.

Inclusion and Exclusion Criteria

The following inclusion criteria were used to select literatures for the meta-analysis: (1) studies with case-control and cohort design, (2) studies evaluated the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with CRC risk, and (3) providing sufficient genotype data for both cases and controls to calculate the odds ratio (OR) with 95% confidence interval (CI). In addition, the following exclusion criteria were applied: (1) no usable data reported; (2) animal studies; (3) studies only involved a case population (without controls); (4) linkage studies and family-based studies; (5) repeated or overlapping studies; and (6) case report, reviews, commentaries, posters, abstracts, reviews, editorials, and conference papers.

Data Extraction

Data were carefully extracted independently and systematically from all eligible articles by two investigators. Any disagreements of the studies were resolved by third author. For each study, the following data were retrieved: first author's name, year of publication, country or region, ethnic group of the study population, source of controls, genotyping methods, sample size, genotype and allele frequencies for the IL-8 -251T>A and IL-18 -607C>A polymorphisms in cases and healthy subjects, and minor allele frequency (MAFs) and Hardy-Weinberg equilibrium (HWE) in healthy subjects. Ethnicity was categorized as Asian, Caucasian, and mixed. For studies including subjects of different ethnic groups or for both IL-8 -251T>A and IL-18 -607C>A polymorphisms, the data were extracted separately.

Statistical Analysis

The strength of the association of the IL-8 -251T>A and IL-18 -607C>A polymorphisms with risk of CRC was assessed by odds ratios (ORs) with 95% confidence intervals (CIs). The Z test was applied to assess the significance of pooled ORs, in which $P < 0.05$ defined as the significance. The pooled ORs were calculated under five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB + BA vs. AA), and the recessive (BB vs. BA + AA). A Cochran's Q statistic was used to assess between-study heterogeneity, in which $P \leq 0.10$ indicated significant heterogeneity was found. Moreover, we used the I^2 statistic to qualify (degree of heterogeneity) the 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). When $P < 0.1$ ($I^2 >$ 50%), statistically significant heterogeneity was assumed, and a random effect (DerSimonian and Laird's method) was used to calculate the pooled OR when heterogeneity was found; otherwise, a fixed-effect model (Mantel-Haenszel

method) in absence of heterogeneity was applied. The agreement of genotype frequencies in healthy subjects with Hardy-Weinberg equilibrium (HWE) was tested using the Pearson's χ^2 test. A P value of < 0.05 indicated deviation from HWE. Subgroup analyses were performed based on ethnicity, genotyping methods, source of controls (hospital- and population-based), and sample size (< 250 and ≥ 250). 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 was performed by excluding HWE violating studies to examine the stability of the pooled data. Egger's and Begg-Mazumdar's tests were used to identify possible publication bias. A nonsymmetrical funnel plot or P less than 0.05 indicated that there was significant publication bias. If the publication bias tests indicated bias existed, the Duval and Tweedie "trim and fill" method was used to adjust the 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

Study Characteristics

Figure 1 shows the flowchart of literature search and selection process. The initial literature searches retrieved 114 potentially relevant studies. After reading the titles and abstracts, 50 studies were excluded. Subsequently, 48 studies were excluded because not reporting useful data for the analysis, reviews, case only study, and not being case-control studies. Finally, 16 case-control studies including 13 case-control studies with 3908 CRC cases and 5005 controls on IL-8 -251T>A polymorphism [23–35] and three case-control studies with 396 CRC cases and 560 controls on IL-18 -607C>A polymorphism [14, 36, 37] were selected. The main characteristics of the studies were shown in Table 1. All included studies were published in English and Chinese between July 2003 and July 2015. The sample size of an individual cohort ranged from 191 to 1023 for CRC cases and 191 to 1121 for healthy controls. The subjects included Spanish, Grecian, US-American, Dane, Francis, Croatian, Dutch, Polish, Malaysian, Romanian, and Scottish individuals. As for ethnicity, eleven studies were conducted among Caucasians and one article among Asians. TaqMan, ARMS-PCR, PCR-RFLP, and AS-PCR methods were applied for genotyping. The genotype and minor allele frequency (MAF) distributions in the studies considered in the present meta-analysis 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 four studies (Table1).

Quantitative Data Synthesis

IL-8 -251T>A Polymorphism

The summary of the meta-analysis of the association of IL-8 -251T>A polymorphism with CRC risk is shown in Table 2. Overall, pooled ORs showed that IL-8 -251T>A polymorphism was not significantly associated with an increased risk of CRC under all five genetic models, i.e., allele (T vs. A: OR = 1.024, 95% CI 0.898–1.168, P = 0.724, Fig. 2a), homozygote (TT vs. AA: OR = 1.173, 95% CI 0.941–1.461, P = 0.156), heterozygote (TA vs. AA: OR = 1.060, 95% CI 0.876–1.283, P = 0.549), dominant (TT + TA vs. AA: OR = 1.190, 95% CI 0.980–1.447, P = 0.752), and recessive (TT + TA vs. AA: OR = 1.119, 95% CI 0.954–1.311, P = 0.167, Fig. 2b). Moreover, stratified analysis by ethnicity, source of controls, and genotyping methods still showed that IL-8 -251T>A polymorphism was not associated with risk of CRC (Table 2).

IL-18 -607C>A Polymorphism

The summary of the meta-analysis of the association of IL-18 -607C>A polymorphism with CRC risk is shown in Table 2. Overall, pooled results revealed that IL-18 -607C>A polymorphism was not significantly associated with risk of CRC under all five genetic models, i.e., allele (A vs. C: OR = 1.066, 95% CI 0.883–1.288, P = 0.506), homozygote (AA vs. CC: OR = 1.086, 95% CI 0.732–1.611, P = 0.682), heterozygote (AC vs. CC: OR = 1.349, 95% CI 0.706–2.578, P = 0.365), dominant (AA + AC vs. CC: OR = 1.207, 95% CI 0.906–1.608, P = 0.198), and recessive (AA + AC vs. CC: OR = 0.898, 95% CI 0.642–1.255, P = 0.528, Table 2).

Between-Study Heterogeneity Test

There were statistically significant heterogeneity for IL-8 -251T>A polymorphism under all five genetic models, i.e., allele (I^2 = 78.84; $P_H \leq 0.001$), homozygote (I^2 = 63.29; P_H = 0.002), heterozygote (I^2 = 67.57; $P_H \leq 0.001$), dominant (I^2 = 71.64; $P_H \leq 0.001$), and recessive (I^2 = 54.65; P_H = 0.012). Thus, subgroup analysis by ethnicity, genotyping methods, source of controls, and HWE was performed in order to determine the source of heterogeneity among the studies and to assess the effect of race on the association between IL-8 -251T>A polymorphism and CRC risk. As shown in Table 2, most of the heterogeneity disappeared in the subgroup analysis in group of studies used TaqMan approach, indicating that genotyping methods might be the major source of heterogeneity in this meta-analysis.

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

First author	Country (ethnicity)	Genotyping method	SOC	Case/control	Cases					Control					MAFs	HWE
					Genotypes			Alleles		Genotypes			Alleles			
IL-8 -251T>A					TT	TA	AA	T	A	TT	TA	AA	T	A		
Landi 2003 [23]	Spain (Caucasian)	TaqMan	HB	352/308	117	167	68	401	303	83	170	55	336	280	0.455	0.047
Theodoropoulos 2006 [24]	Greece (Caucasian)	ARMS-PCR	PB	222/196	76	106	40	258	186	64	90	42	218	174	0.444	0.327
Gunter 2006 [25]	USA (Caucasian)	PCR-RFLP	PB	205/191	52	87	66	191	209	65	94	32	224	158	0.414	0.840
Vogel 2007 [26]	Denmark (Caucasian)	TaqMan	PB	355/753	83	178	94	344	366	160	367	226	687	819	0.544	0.627
Kury 2008 [27]	France (Caucasian)	TaqMan	PB	1023/1121	307	511	205	1125	721	375	516	230	1266	976	0.435	0.032
Cacev 2008 [28]	Croatia (Caucasian)	TaqMan	PB	160/160	46	75	39	167	153	53	73	34	179	141	0.441	0.346
Wilkening 2008 [29]	Germany (Caucasian)	TaqMan	PB	300/580	71	133	96	275	325	115	296	169	526	634	0.547	0.475
Tsilidis 2009 [30]	USA (Caucasian)	TaqMan	PB	205/362	65	88	52	218	192	114	162	86	390	334	0.461	0.058
Walczak 2012 [31]	Poland (Caucasian)	PCR-RFLP	HB	191/205	50	104	37	204	178	99	71	35	259	141	0.344	≤ 0.001
Mustapha 2012 [32]	Malaysia (Asian)	AS-PCR	HB	255/255	40	183	32	263	247	54	189	12	297	213	0.418	≤ 0.001
Dumitrescu 2012 [35]	Romania (Caucasian)	TaqMan	NS	108/150	38	50	20	126	90	52	68	30	172	128	0.427	0.368
Burada 2013 [33]	Romania (Caucasian)	TaqMan	HB	144/233	50	67	27	167	121	81	106	46	268	198	0.425	0.291
Basavaraju 2015 [34]	Scotland (Caucasian)	PCR-RFLP	PB	388/491	113	183	92	409	367	133	249	109	515	467	0.476	0.711
IL-18 -607C>A					CC	CA	AA	C	A	CC	CA	AA	C	A		
Nikiteas 2007 [36]	Greece (Caucasian)	PCR-RFLP	PB	84/89	19	47	18	85	83	35	32	22	102	76	0.427	0.012
Haghshenas 2009 [14]	Iran (Asian)	AS-PCR	PB	142/311	55	72	15	182	102	119	144	48	382	240	0.386	0.684
Guo 2012 [37]	China (Asian)	PCR-RFLP	HB	170/160	36	85	49	157	183	42	76	42	160	160	0.500	0.527

PCR polymerase chain reaction, *RFLP* polymorphism chain reaction-restriction fragment length polymorphism, *ARMS* amplification refractory mutation system, *AS* Allele-specific polymerase chain reaction, *SOC* source of control, *PB* population based, *HB* hospital based, *NS* not stated, *MAF* minor allele frequency, *HWE* Hardy-Weinberg equilibrium

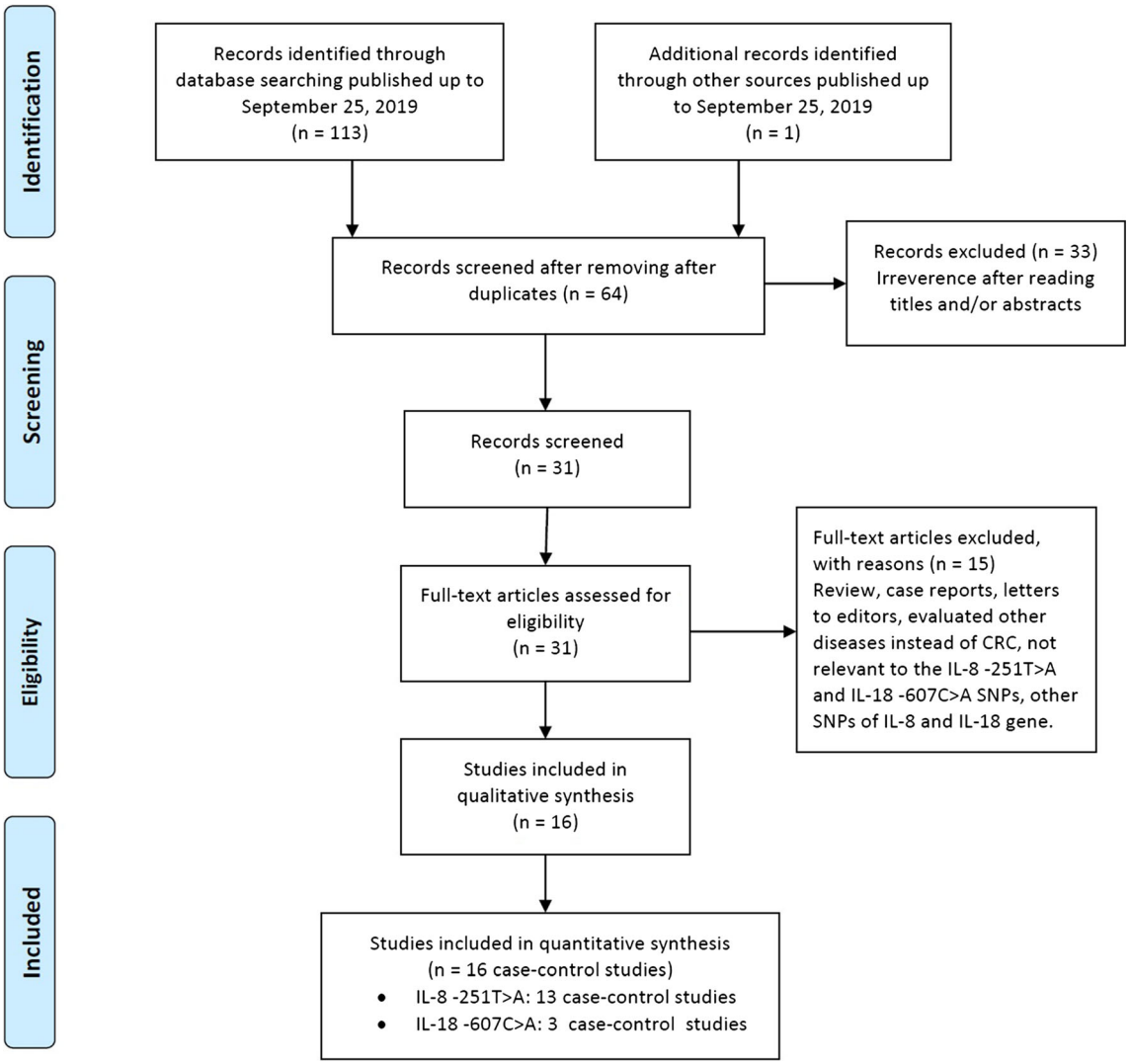


Fig. 1 Flowchart of literature search and selection process

Sensitivity Analysis

Sensitivity analysis was performed by excluding one study at a time and subsequently recalculating the overall effect to assess the influence of each study on pooled results and robustness of the pooled ORs. The results showed that the significance of the OR was not affected by any single study. Then, sensitivity analysis was conducted by excluding those studies departure from the HWE. Therefore, the sensitivity analysis suggested that the current meta-analysis were relatively consistent even when a single study or some studies were excluded.

Publication Bias

Publication bias was assessed with Begg's funnel plots and Egger's test (Table 2). The shape of the funnel plots and Egger's regression tests revealed evidence of publication bias for IL-8 -251T>A under allele model (A vs. T: $P_{Beggs} = 0.046$; $P_{Eggers} = 0.002$, Fig. 3) and for IL-18 -607C>A under two genetic models, i.e., heterozygote (AC vs. CC: $P_{Beggs} = 0.296$; $P_{Eggers} = 0.020$) and dominant (AA + AC vs. CC: $P_{Beggs} = 0.296$; $P_{Eggers} = 0.029$). Thus, to adjust these biases, we have used a trim-and-fill method developed by Duval and Tweedie. However, after trimming we have yield similar results, indicating that the publication bias has little effect on the results of our study and the results of our meta-analysis are relatively stable.

Discussion

To date, some epidemiological association studies have been performed to evaluate the potential roles of IL-8 -251T>A and IL-18 -607C>A polymorphisms in development of CRC, but the results of these studies were inconsistent and the sample

Table 2 Summary of meta-analysis for the association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with CRC 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}
IL-8 -251T>A										
Overall	A vs. T	Random	76.94	≤ 0.001	1.024	0.898–1.168	0.353	0.724	0.099	0.002
	AA vs. TT	Random	63.29	0.002	1.173	0.941–1.461	1.420	0.156	0.149	0.128
	AC vs. TT	Random	67.57	≤ 0.001	1.060	0.876–1.283	0.599	0.549	0.149	0.610
	AA + AT vs. TT	Random	71.64	≤ 0.001	1.190	0.980–1.447	1.752	0.752	0.080	0.576
	AA vs. AT +	Random	51.04	0.017	1.119	0.954–1.311	1.383	0.167	0.337	0.222
Ethnicity										
Caucasians	A vs. T	Random	77.73	≤ 0.001	1.005	0.872–1.159	0.070	0.944	0.061	0.004
	AA vs. TT	Random	51.26	0.025	1.093	0.902–1.325	0.906	0.365	0.436	0.373
	AC vs. TT	Random	69.72	≤ 0.001	1.043	0.851–1.277	0.405	0.695	0.161	0.981
	AA + AT vs. TT	Random	73.49	≤ 0.001	1.173	0.954–1.442	1.511	0.131	0.275	0.511
	AA vs. AT + TT	Fixed	37.81	0.097	1.052	0.946–1.171	0.937	0.349	0.533	0.288
Genotyping methods										
TaqMan	A vs. T	Random	66.78	0.006	0.917	0.797–1.054	− 1.218	0.223	0.071	0.012
	AA vs. TT	Fixed	0.00	0.764	0.987	0.852–1.144	− 0.175	0.861	0.763	0.813
	AC vs. TT	Fixed	47.05	0.079	0.991	0.876–1.121	− 0.144	0.885	0.763	0.276
	AA + AT vs. TT	Random	65.22	0.008	1.094	0.877–1.365	0.794	0.427	0.763	0.967
	AA vs. AT + TT	Fixed	0.00	0.776	1.003	0.886–1.136	0.052	0.958	0.763	0.447
PCR-RFLP	A vs. T	Random	78.90	0.009	1.276	0.934–1.742	1.532	0.125	0.296	0.190
	AA vs. TT	Random	79.09	0.008	1.699	0.906–3.185	1.653	0.098	1.000	0.141
	AC vs. TT	Random	89.19	≤ 0.001	1.410	0.688–2.892	0.938	0.348	1.000	0.481
	AA + AT vs. TT	Random	88.16	≤ 0.001	1.514	0.798–2.872	1.270	0.204	1.000	0.322
	AA vs. AT + TT	Random	72.48	0.026	1.418	0.882–2.280	1.442	0.149	1.000	0.596
Source of controls										
Population-based	A vs. T	Random	74.76	≤ 0.001	0.963	0.832–1.116	− 0.496	0.620	0.035	0.004
	AA vs. TT	Random	50.86	0.047	1.069	0.867–1.317	0.624	0.532	0.386	0.488
	AC vs. TT	Fixed	16.82	0.297	1.020	0.908–1.145	0.329	0.742	0.265	0.325
	AA + AT vs. TT	Random	56.22	0.025	1.145	0.955–1.373	1.463	0.143	0.265	0.613
	AA vs. AT + TT	Random	55.29	0.028	1.086	0.904–1.306	0.882	0.378	0.536	0.257
Hospital-based	A vs. T	Random	82.75	0.003	1.246	0.881–1.761	1.243	0.214	0.296	0.123
	AA vs. TT	Random	82.96	0.003	1.806	0.792–4.118	1.405	0.160	0.296	0.178
	AC vs. TT	Random	91.55	≤0.001	1.370	0.595–3.153	0.740	0.459	1.000	0.341
	AA + AT vs. TT	Random	90.75	≤ 0.001	1.401	0.654–3.001	0.866	0.386	1.000	0.399
	AA vs. AT + TT	Random	67.15	0.048	1.458	0.864–2.462	1.412	0.158	0.296	0.273
Sample size										
≥ 250	A vs. T	Random	79.98	≤ 0.001	0.936	0.790–1.108	− 0.767	0.443	0.132	0.004
	AA vs. TT	Random	61.84	0.022	1.048	0.809–1.357	0.352	0.725	1.000	0.343
	AC vs. TT	Random	61.34	0.024	0.936	0.759–1.154	− 0.621	0.534	0.707	0.260
	AA + AT vs. TT	Random	74.49	0.001	1.115	0.867–1.435	0.848	0.396	0.707	0.741
	AA vs. AT + TT	Random	57.36	0.039	1.090	0.889–1.336	0.828	0.408	0.259	0.044
< 250	A vs. T	Random	58.83	0.033	1.149	0.957–1.380	1.491	0.136	1.000	0.986
	AA vs. TT	Random	61.94	0.022	1.334	0.917–1.943	1.506	0.132	1.000	0.907
	AC vs. TT	Random	70.15	0.005	1.249	0.882–1.770	1.253	0.210	0.452	0.916
	AA + AT vs. TT	Random	70.64	0.004	1.283	0.925–1.779	1.495	0.135	1.000	0.894
	AA vs. AT + TT	Random	55.41	0.047	1.185	0.875–1.605	1.096	0.273	1.000	0.831
HWE*										
	A vs. T	Fixed	0.045	0.429	0.998	0.918–1.083	− 0.057	0.954	0.386	0.236
	AA vs. TT	Random	50.74	0.048	1.057	0.831–1.343	0.450	0.653	0.265	0.280
	AC vs. TT	Fixed	0.00	0.795	0.932	0.810–1.072	− 0.985	0.325	0.035	0.078
	AA + AT vs. TT	Random	55.96	0.026	1.127	0.915–1.386	1.125	0.261	0.107	0.200
	AA vs. AT + TT	Random	54.00	0.033	1.100	0.893–1.356	0.897	0.370	1.000	0.510
IL-18 -607C>A										
	A vs. C	Fixed	25.29	0.262	1.066	0.883–1.288	0.665	0.506	0.296	0.466
	AA vs. CC	Fixed	35.27	0.213	1.086	0.732–1.611	0.410	0.682	1.000	0.847
	AC vs. CC	Random	75.35	0.017	1.349	0.706–2.578	0.907	0.365	0.296	0.020
	AA + AC vs. CC	Fixed	55.64	0.105	1.207	0.906–1.608	1.288	0.198	0.296	0.029
	AA vs. AC + CC	Fixed	2.30	0.359	0.898	0.642–1.255	− 0.631	0.528	1.000	0.468

*By excluding the HWE-violating studies

size. *Meta-analysis* is a statistical procedure for combining data from individual studies to increase the sample size and enhance statistical power. Therefore, in order to resolve this conflict, a meta-analysis was conducted to explore the

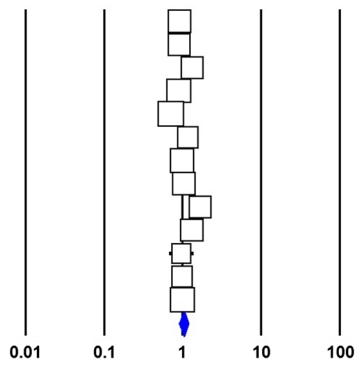
association of IL-8 -251T>A and IL-18 -607C>A polymorphisms with CRC risk. When all the eligible studies were pooled into the meta-analysis of polymorphism, no significant association was found between IL-8 -251T>A and IL-18 -607C>A polymorphisms and an increased risk of CRC. In further stratified and sensitivity analyses, no significant association was found in any subgroup analysis.

Up to now, there are two previous meta-analyses which have been done on the association of IL-8 -251T>A polymorphism with CRC risk [38, 39]. However, the number of original studies regarding this issue was statistically less for the estimation of the association. In 2012, Hu et al., in a meta-analysis of nine case-control studies with 3019 CRC cases and 3984 controls, evaluated the association between IL-8 -251T>A polymorphism and CRC risk. Their result revealed that IL-8 -251T>A polymorphism was not associated with an increased risk of CRC. Moreover, their subgroup analysis by ethnicity (Caucasians) and source of controls showed that there was no significant association between the polymorphism and CRC risk [38]. In the same year, Wang et al., in another meta-analysis of five studies with 1242 CRC cases and 1880 healthy subjects, have evaluated the association of IL-8 -251T>A polymorphism with CRC risk in Europeans. Similarly, their results showed that IL-8 -251T>A polymorphism was not significantly associated risk of CRC. However, the results of our meta-analysis are in accordance with those reported the previous two meta-analyses on IL-8 -251T>A polymorphism [39]. Our meta-analysis included more studies than previous two meta-analyses; there are 3908 CRC cases and 5005 controls from 13 case-control studies. From a statistical perspective, the previous meta-analyses with relatively inadequate sample sizes have low power to identify genetic association. Moreover, we have performed subgroup analysis by sample size and by excluding the HWE-violating studies.

IL-18 is a pleiotropic cytokine which is involved in the regulation of innate and acquired immune responses and plays key role in autoimmune diseases by controlling Th1- and Th2-type immune response [19]. Moreover, it induces the productions of TNF-α, granulocyte/macrophage colony-stimulating factor, and IFN-γ and increases the cytotoxic effects of NK

a

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Landi 2003	0.912	0.734	1.134	0.828-	0.407	8.16
Theocloropoulos 2006	0.903	0.687	1.188	0.727-	0.467	7.22
Gunter 2006	1.317	1.001	1.734	1.966	0.049	7.21
Vogel 2007	0.892	0.746	1.067	1.247-	0.212	8.80
Kury 2008	0.706	0.624	0.798	5.539-	0.000	9.62
Cacev 2008	1.163	0.852	1.588	0.952	0.341	6.62
Wilkening 2008	0.980	0.804	1.195	0.195-	0.845	8.49
Tsilidis 2009	1.028	0.807	1.311	0.226	0.821	7.74
Walczak 2012	1.665	1.250	2.216	3.489	0.000	7.02
Mustapha 2012	1.310	1.023	1.677	2.138	0.033	7.67
Dumitrescu 2012	0.960	0.673	1.368	0.227-	0.821	5.97
Burada 2013	0.981	0.728	1.320	0.128-	0.898	6.84
Basavaraju 2015	0.990	0.820	1.195	0.109-	0.913	8.64
	1.024	0.898	1.168	0.353	0.724	



b

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Landi 2003	1.101	0.743	1.633	0.481	0.631	8.20
Theocloropoulos 2006	0.806	0.497	1.307	0.875-	0.381	6.54
Gunter 2006	2.359	1.460	3.811	3.508	0.000	6.60
Vogel 2007	0.840	0.633	1.114	1.211-	0.226	10.85
Kury 2008	0.971	0.786	1.199	0.275-	0.783	12.80
Cacev 2008	1.194	0.708	2.016	0.666	0.506	5.92
Wilkening 2008	1.144	0.847	1.547	0.877	0.380	10.36
Tsilidis 2009	1.091	0.733	1.622	0.429	0.668	8.14
Walczak 2012	1.167	0.700	1.945	0.592	0.554	6.10
Mustapha 2012	2.906	1.461	5.781	3.039	0.002	4.04
Dumitrescu 2012	0.909	0.485	1.705	0.297-	0.767	4.60
Burada 2013	0.938	0.553	1.591	0.237-	0.813	5.85
Basavaraju 2015	1.089	0.794	1.494	0.530	0.596	9.99
	1.119	0.954	1.311	1.383	0.167	

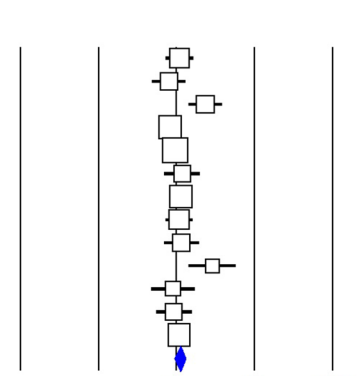


Fig. 2 Forest plot for association between the IL-8 -251T>A polymorphism and CRC risk. **a** Allele model (A vs. T) and **b** recessive model (AA vs. AT + TT)

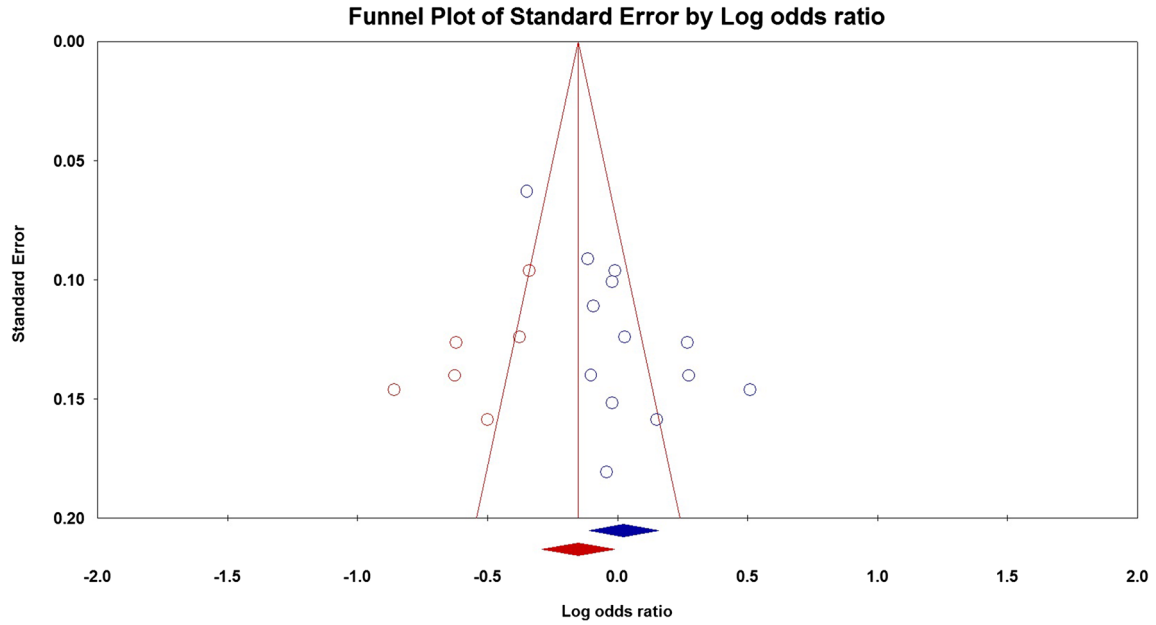


Fig. 3 Funnel plot for publication bias in the meta-analysis of IL-8 -251T>A polymorphism with risk of CRC under allele model (A vs. T)

and T cells in some disease. It was shown that IL-18 -607C>A polymorphism disrupts a potential cAMP-responsive element-binding protein-binding site [40]. These meta-analysis results showed that IL-18 -607C>A polymorphism was not significantly associated with CRC risk. Our results are in consistence with the previous meta-analysis. In 2015, Yao et al., in a meta-analysis of five case-control studies with 1618 cases and 1155 healthy controls, evaluated the relationship of IL-18 -607C>A polymorphism with gastrointestinal cancer risk. Their results showed that the polymorphism did not significantly associate with gastric cancer and CRC risk. However, they have revealed that IL-18 -607C>A polymorphism may be associated with susceptibility to esophageal cancer [41]. Guo et al., in a case-control study, showed that the distributions of IL-18 -607C>A polymorphism did not differ between CRC cases and healthy subjects in Chinese population. However, they found that the IL-18 -137C/-607A haplotype was associated with increased risk of CRC [41].

The heterogeneity is a crucial issue when elucidating the outcomes of a meta-analysis, and finding the possible sources for the high heterogeneity is very important [42]. The studies included in the current meta-analysis probably have different ethnic backgrounds, environmental exposures, methodology, and sample size, thus causing inconsistent conclusions. Moreover, it is evident that other factors such as diversity in source of controls, genotyping , and Hardy-Weinberg equilibrium (WHE) might contribute to potential sources of heterogeneity. In this meta-analysis, there was a significant heterogeneity under all five genetic models in the overall population. Thus, we attempted to minimize this issue by developing strict criteria and subgroup analyses. In the subgroup analysis based on ethnicity, the subgroup results were consistent with the overall results. However, due to the limitation of small sample size of the study in Asians, African, and mixed population, further epidemiological studies should be conducted in different ethnicities to clarify this issue. Moreover, stratification analysis revealed that genotyping methods may be source of heterogeneity in this study. Both funnel plot and Egger's test were used to assess the publication bias of our meta-analysis. The shape of funnel plot and statistical results revealed an obvious publication bias under the allele genetic model. Therefore, to adjust this bias, we have used a trim-and-fill method developed by Duval and Tweedie. However, after trimming we have found similar results. This indicates that the publication bias has little effect on the results of our study and the results of our meta-analysis are relatively stable.

Although the current study has collected available data on the association between IL-8 -251T>A polymorphism with CRC risk, several limitations could not be neglected. First, the sample size for IL-18 -607C>A polymorphism was considerably small; there are only three studies with a total of 396 cases and 560 controls were selected. Thus, more studies with large sample size and well-designed are needed to further identify the association more comprehensively. Second, studies included in this meta-analysis mainly provided data on Caucasian populations, and the subgroup analyses for other ethnicities were not applicable. Therefore, other ethnicities including Asians, Africans, and mixed populations should be evaluated in future studies. Third, only published studies in English were included in the current study, which might have led to publication and also potential language biases. Fourth, considering the diversity of CRC etiology, its pathogenesis is likely to be affected by factors such as age, gender, ethnicity, environmental factors, and other variables.

However, due to lack of the mentioned confounding factors in the original articles, we could not perform the corresponding subgroup analysis. Finally, we were also unable to evaluate the interactions among gene-gene and gene-environment, and the lack of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between the IL-8 -251T>A and IL-18 -607C>A polymorphisms and risk of CRC.

In summary, our pooled data revealed that the IL-8 -251T>A and IL-18 -607C>A polymorphisms were not associated with susceptibility to CRC. Moreover, stratified analysis by ethnicity, source of controls, and genotyping methods showed that the IL-8 -251T>A polymorphism was not associated with risk of CRC. Given the limited sample size and ethnicities included in the meta-analysis, we strongly call for f further larger scaled, well-designed studies in different ethnicities to confirm these findings.

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Authors' Contribution M.H.A and F.A are responsible as the guarantor of integrity of the entire study, study design and concepts, definition of intellectual content, and literature research. H.N, Y.G, and S.K. are responsible for the clinical studies, experimental studies, data acquisition, and manuscript preparation. S.A.D and H.N are responsible for the data analysis, statistical analysis, and manuscript review. J.S.Y is responsible for the manuscript editing. All authors have read and agreed with the final version of this manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

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