REVIEW

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Association of promoter region polymorphisms of interleukin-10 gene with susceptibility to colorectal cancer: a systematic review and meta-analysis

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ABSTRACT – **Background** – Several epidemiological studies have investigated the association of promoter region polymorphisms of Interleukin-10 (IL-10) gene with colorectal cancer (CRC), while the conclusion is still conflicting and inconclusive. **Objective** – We conducted this meta-analysis to evaluate the association of promoter region polymorphisms of IL-10 with CRC. **Methods** – Eligible articles were identified by a search of several bibliographic databases for the period up to March 15, 2018. The strength of the association was measured by odd ratios with 95% confidence intervals. **Results** – A total of 28 case-control studies with 5,647 CRC cases and 6,908 controls were selected, including 14 studies for IL-10 -1082A>G (rs1800896) polymorphism (2,702 cases and 3,649 controls), eleven studies for -592C>A (rs1800872) polymorphism (3,259 cases and 4,992 controls), and three studies for -819T>C (rs1800871) polymorphism (477 cases and 544 controls). By pooling all eligible studies, we found that the IL-10 -1082A>G and -592C>A polymorphisms were not associated with increased CRC risk in overall population. However, there was significant associations between the IL-10 -819T>C polymorphism and CRC susceptibility under the allele model (A vs G: OR=1.278, 95% CI 1.043-1.566, *P*=0.018) and the recessive model (AA vs AG+GG: OR=1.709, 95% CI 1.026-2.845, *P*=0.039). **Conclusion** – In this meta-analysis we found that IL-10 -819T>C polymorphism was associated with significantly increased risk of CRC; while the IL-10 -1082A>G and -592C>A polymorphisms were not associated with CRC risk. The IL-10 -819T>C polymorphism may be important as suspected predictive factor of CRC occurrence.

HEADINGS – Interleukin-10. Colorectal neoplasms. Genetic polymorphism. Meta-analysis.

INTRODUCTION

Colorectal cancer (CRC) ranks among the three most common cancers in terms of both cancer incidence and cancer-related deaths worldwide[1-4]. CRC is the cancer of the colon and the rectum and approximately two thirds are located in the colon. Differences in the CRC death rates relate to differences in socioeconomic factors, diet, population life span, genetic factors, and to the quality of medical care available[5,6]. The most common risk factors for to CRC include age, the presence of polyps, inflammatory bowel disease, lifestyle, genetic background and family medical history[7]. Life style relating factors such as obesity, physical inactivity, poor diet, cigarette smoking and heavy alcohol consumption account for approximately 80% of all colorectal cancer cases[8]. The sequence of genetic alterations in CRC development is well documented[9]. Genetic conditions such as familial adenomatous polyposis (FAP), Lynch syndrome (HNPCC; hereditary nonpolyposis colorectal cancer) and Gardner's syndrome (considered a subtype of FAP) are genetic risk factors[10], which accounts for 10% of all colorectal cancer cases[11].

Several cytokines that modulate the immunologic response have been implicated in the development of cancer[12]. Interleukin-10 (IL-10) is a multifunctional cytokine involved in both innate and adaptive immune response, and a wealth of evidence supports its regulatory role in carcinogenesis and tumor growth[13,14]. In addition, increased circulating IL10 has been shown in patients diagnosed with different malignancies, such as hepatocellular carcinoma, autoimmune cancers, and leukemia. The IL10 gene (Gene ID: 3586) has been mapped to human chromosome 1q31–q32, spans 5.2 kb and contains five exons[14]. Many SNPs in the promoter and coding region of IL-10 gene were shown to be associated with cancer risk, and also, studies have showed that the genetic variants played important roles in the transcription and protein expression[15].

It is well known that IL-10 gene production can be influenced by the SNPs located within the promoter regions of the gene[15,16]. The IL-10 promoter is highly polymorphic and three single nucleotide polymorphisms (SNPs) have been confirmed in the promoter region of IL-10 including IL-10 -1082A>G (rs1800896), -592C>A (rs1800872) and -819T>C (rs1800871). In recent decade, accumulating evidence has supported the hypothesis that the promoter region of IL-10 polymorphisms correlates with genetic susceptibility of CRC[16,17]. However, the results from the studies were often inconsistent and inconclusive. This inconsistency may derive from a number of issues, including limited sample size of single

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study, different characteristics among studies (such as ethnicity, pathological types, and sources of controls), false-positive errors, lack of power, and minor impacts of IL-10 gene polymorphisms on CRC susceptibility. Therefore, we performed a meta-analysis to comprehensively assess the association of promoter region polymorphisms of IL-10 with CRC risk.

METHODS

Identification of eligible studies

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. We carried out a search in the internet covering well-known biomedical databases such as PubMed, Excerpta Medica Database (EMBASE), Elsevier Science Direct, Cochrane Library, and Chinese Biomedical Literature Database (CBM) regarding the association of IL-10 polymorphisms with CRC risk up to March 15, 2018. The following keywords were used for searching: (''Interleukin- 10'' OR ''IL-10'') AND (''colorectal cancer'' OR ''CRC'' OR 'colon cancer'') AND (''promoter region'' OR ''promoter'') AND (''polymorphism'' OR ''mutation'' OR ''genotype'' OR ''allele'' OR ''variation'' OR ''variant''). All searched studies were retrieved and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand searched to find additional eligible studies. We also conducted a manual search of references of original or reviewed articles on this subject to identify additional studies. No language restrictions were applied. Abstracts, case reports and editorials were excluded.

Inclusion criteria

The following criteria were used for the literature selection: (1) evaluating the association between promoter region polymorphisms of IL-10 and CRC risk; (2) case–control or cohort studies comparing CRC cases with healthy or non-cancer controls; (3) the numbers of CRC case and healthy subjects for each genotype were reported or the relevant data was available, and adequate data was provided for calculating the pooled odds ratios (OR) with 95% confidence intervals (CI). Studies was excluded if they were the following: (1) case-only studies; (2) animal studies, abstracts, seminar posters, case reports, letters, or reviews; (3) incomplete data or no usable data were reported; (4) duplicated or studies containing overlapping data; (5) family-based design studies. After deliberate searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data extraction

Information was carefully extracted from all eligible papers by two of the authors independently according to the inclusion criteria mentioned above. Data included the following: first author, publication year, country, cancer type, source of control, each genotype frequency of the case and control groups, genotype methods, and the Hardy–Weinberg equilibrium (HWE) value in the control group. Disagreement was resolved by discussion until consensus was reached. If these two authors could not reach a consensus, then a third author was consulted to resolve the dispute.

Statistical analysis

The strength of the association between the IL-10 polymorphisms and the risk of CRC was measured by odd ratios (ORs) with 95% confidence intervals (CI). Z-test was carried out to evaluate the statistical significance of pooled ORs. The pooled ORs were performed for the allele model (B vs A), homozygote model (BB vs AA), heterozygote model (BA vs AA), dominant model (BB + BA vs AA) and recessive model (BB vs BA + AA), respectively. The heterogeneity between studies was assessed with the chi-squared based Q-test. A significant *P* value (<0.10) was used to indicate heterogeneity among studies. Moreover, the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were used, according to the criteria from the Cochrane Handbook, which categorized it into unimportant (0%–40%), moderate (30%–60%), substantial (50%–90%) and considerable (75%–100%). When the effects were assumed to be homogenous, the fixed-effects model was used (Mantel-Haenszel method)[18]. If obvious heterogeneity was present, the random effects model was used (DerSimonian-Laird method)[19]. Stratification and meta-regression analyses were used to detect the potential heterogeneity among studies. In case–control studies, Hardy–Weinberg equilibrium (HWE) was tested using an online program (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl) to evaluate the study quality of genotype data, and $P<0.05$ was considered statistically significant. A high-quality study was said that its control group was in HWE. Sensitivity analysis by sequentially omitting the single studies and recounting the pooled ORs and 95% confidence intervals (CIs) was performed to estimate the effect of individual studies on overall risk of CRC. The funnel plot was utilized to test the publication bias and Egger's test (linear regression analysis) was used to check the symmetry of funnel plots[20,21]. The statistical analysis for the current meta-analysis study was performed by using the comprehensive meta-analysis (CMA) version 2.0 software (Biostat, USA). All *P*-values in the meta-analysis were two-sided, and statistical significance was considered when the *P*-value was less than 0.05.

RESULTS

The initial search of online databases yielded 253 relevant articles, and an additional 4 articles were identified through manually search. A total of 157 articles were excluded after reading the title or abstract because of obvious irrelevance to our criteria, lack of data for calculation and duplication. Finally, a total of 28 case-control studies in 17 publications[22-38] with 5,647 CRC cases and 6,908 controls were selected for the current meta-analysis, including 14 studies[22-35] for IL-10 -1082A>G (rs1800896) polymorphism (2,702 cases and 3,649 controls), eleven case-control studies[22,23,25,26,28,29,32,34,36–38] for -592C>A (rs1800872) polymorphism (3,259 cases and 4,992 controls), and three case-control studies[24,25,28] for -819T>C (rs1800871) polymorphism (477 cases and 544 controls). All of these 28 case-control studies provided sufficient data to calculate the possible relationship between the three polymorphisms of the IL-10 gene and CRC risk. The baseline characteristics of the case-control studies are shown in TABLE 1. Two ethnicities were addressed: 24 studies focused on Caucasian populations and four on Asian populations. The countries of these studies included Scotland, Italy, USA, Spain, Romania, Brazil, Canada, China, India, Korea, Egypt, and Turkey. Three genotyping methods were applied in the present case-control studies such as TaqMan, ARMS-PCR, Sequencing, AS-PCR, MassARRAY, PCR-RFLP, and KASP assay. The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for three case-control studies for IL-10 -1082A>G[24,28,33].

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

First Author/Year	Country (Ethnicity)	SOC	Genotyping Technique	Case/ Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
IL10 -1082A>G (rs1800896)					**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**		
Macarthur 2005[22]	Scotland (Caucasian)	PB	TaqMan	257/403	61	125	71	247	267	86	202	115	374	432	0.536	0.877
Crivello 2006[23]	Italy (Caucasian)	PB	ARMS-PCR	62/124	16	34	12	66	58	38	60	26	136	112	0.451	0.796
Guntar 2006[24]	USA (Caucasian)	HB	TaqMan	222/207	61	114	47	236	208	55	123	29	233	181	0.437	0.002
Cozar 2007 [25]	Spain (Caucasian)	PB	TaqMan	126/175	42	62	22	146	106	58	87	30	203	147	0.420	0.787
Talseth 2007[26]	Mixed (Caucasian)*	HB	Sequencing	118/100	36	61	21	133	103	33	50	17	116	84	0.420	0.792
Wilkening 2008[27]	Sweden (Caucasian)	PB	TaqMan	304/579	83	146	75	312	296	164	283	132	611	547	0.472	0.639
Cacev 2008[28]	Croatia (Caucasian)	PB	TaqMan	160/160	54	86	20	194	126	43	92	25	178	142	0.443	0.037
Tsilidis 2009 [29]	USA (Caucasian)	PB	TaqMan	205/372	69	101	35	239	171	98	187	87	383	361	0.485	0.903
Miteva 2014[30]	Bulgaria (Caucasian)	PB	ARMS-PCR	119/154	40	57	22	137	101	54	79	21	187	121	0.392	0.349
Burada 2013[31]	Romania (Caucasian)	HB	TaqMan	144/233	65	60	19	190	98	80	118	35	278	188	0.403	0.426
Basavaraju 2015[32]	Scotland (Caucasian)	PB	TaqMan	388/496	58	210	92	351	394	103	261	130	471	521	0.527	0.183
Li 2015[33]	China (Asian)	HB	AS-PCR	102/105	26	66	10	118	86	20	77	8	117	93	0.442	≤0.001
Cai 2016[34]	China (Asian)	HB	MassARRAY	375/382	323	50	2	696	54	343	39	0	725	39	0.051	0.293
Gulubova 2018[35]	Bulgaria (Caucasian)	NS	ARMS-PCR	120/159	47	57	16	151	89	59	78	22	196	122	0.383	0.638
IL-10 -592C>A (rs1800872)					**CC**	**AC**	**AA**	**C**	**A**	**CC**	**AC**	**AA**	**C**	**A**		
Macarthur 2005[22]	Scotland (Caucasian)	PB	TaqMan	258/403	151	99	8	401	115	248	133	22	629	177	0.219	0.455
Crivello 2006[23]	Italy (Caucasian)	PB	ARMS-PCR	62/124	31	28	3	90	34	69	48	7	186	62	0.250	0.719
Talseth 2007[26]	Mixed (Caucasian)	HB	Sequencing	117/99	62	51	4	175	59	50	45	4	145	53	0.267	0.112
Vogel 2007[36]	Danish (Caucasian)	PB	TaqMan	355/753	224	109	22	557	153	455	256	42	1166	340	0.225	0.450
Cozar 2007[25]	Spain (Caucasian)	PB	TaqMan	95/175	52	41	2	145	45	98	63	14	259	91	0.260	0.393
Cacev 2008[28]	Croatia (Caucasian)	PB	PCR-RFLP	160/160	83	64	13	230	90	104	52	4	260	60	0.187	0.399
Tsilidis 2009[29]	USA (Caucasian)	PB	TaqMan	203/361	123	71	9	317	89	213	131	17	557	165	0.228	0.579
Andersen 2012[36]	Danish (Caucasian)	PB	KASP assay	949/1748	596	297	56	1489	409	1072	580	96	2724	772	0.226	0.134
Yu 2014[38]	China (Asian)	PB	PCR-RFLP	298/291	153	114	31	420	176	118	135	38	371	211	0.362	0.949
Basavaraju 2015[32]	Scotland (Caucasian)	HB	TaqMan	387/496	241	134	12	616	158	311	168	17	790	202	0.203	0.323
Cai 2016[34]	China (Asian)	HB	MassARRAY	375/382	221	128	26	570	180	184	158	40	526	238	0.311	0.484
IL-10 -819T>C (rs1800871)					**TT**	**TC**	**CC**	**T**	**C**	**TT**	**TC**	**CC**	**T**	**C**		
Guntar 2006[24]	USA (Caucasian)	HB	TaqMan	222/209	125	76	21	326	118	117	79	13	313	105	0.251	0.944
Cozar 2007 [25]	Spain (Caucasian)	PB	TaqMan	95/175	81	37	9	199	55	98	63	14	259	91	0.260	0.393
Cacev 2008 [28]	Croatia (Caucasian)	PB	PCR-RFLP	160/160	83	64	13	230	90	106	51	3	263	57	0.178	0.262

SOC: source of control, PB: Population based; HB: hospital based; NA: not available; PCR: Polymerase chain reaction; ASPCR: Allele-specific PCR; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium. * Australia and Poland.

Quantitative synthesis

The evaluation of the associations of IL-10 -1082A>G, -592C>A and -819T>C polymorphisms with CRC risk are presented in TABLE 2. The results showed that no association of IL-10 polymorphism was observed with the risk of CRC in five genetic models, i.e., allele (A vs G: OR=0.9623, 95% CI 0.893-1.038, *P*=0.318, FIGURE 1.A), homozygote (AA vs GG: OR=0.983, 95% CI 0.836-1.155, *P*=0.835), heterozygote (AC vs GG: OR=0.953, 95% CI 0.843-1.078, *P*=0.444), dominant (AA+AG vs GG: OR=0.921, 95% CI 0.821-1.034, *P*=0.165) and recessive model (AA vs AG+GG: OR=0.986, 95% CI 0.861-1.129, *P*=0.839).

TABLE 2 listed the main results of the meta-analysis of IL-10 polymorphism and CRC risk. When all the eligible studies were pooled into the meta-analysis of IL-10 polymorphism, significantly increased risk of CRC was observed in all the five genetic comparison models, i.e., allele (A vs G: OR=1.497, 95% CI 0.838-1.064, *P*=0.349), homozygote (AA vs GG: OR=2.153, 95% CI 0.705-1.047, *P*=0.132), heterozygote (AC vs GG: OR=1.494, 95% CI 0.826-1.094, *P*=0.481), dominant (AA+AG vs GG: OR=1.584, 95% CI 0.693-1.145, *P*=0.368, FIGURE 1.B) and recessive (AA vs AG+GG: OR=1.753, 95% CI 0.747-1.099, *P*=0.319).

TABLE 2. Results of the association of IL-10 promoter region 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-10 -1082A>G (rs1800896)										
	G vs A	Fixed	10.58	0.337	0.962	0.893-1.038	-0.999	0.318	0.228	0.422
	GG vs AA	Fixed	3.88	0.408	0.983	0.836-1.155	-0.208	0.835	0.826	0.664
	GA vs AA	Fixed	16.60	0.272	0.953	0.843-1.078	-0.766	0.444	0.826	0.688
	GG+GA vs AA	Fixed	0.00	0.458	0.921	0.821-1.034	-1.387	0.165	0.324	0.826
	GG vs GA+AA	Fixed	0.00	0.561	0.986	0.861-1.129	-0.203	0.839	0.228	0.260
IL-10 -592C>A (rs1800872)										
	A vs C	Random	53.69	0.017	0.945	0.838-1.064	-0.937	0.349	0.533	0.544
	AA vs CC	Fixed	37.90	0.097	0.859	0.705-1.047	-1.507	0.132	1.000	0.863
	AC vs CC	Random	45.87	0.047	0.951	0.826-1.094	-0.704	0.481	0.275	0.328
	AA+AC vs CC	Random	84.90	≤0.001	0.891	0.693-1.145	-0.900	0.368	0.350	0.005
	AA vs AC+CC	Fixed	24.83	0.207	0.906	0.747-1.099	-0.997	0.319	0.436	0.625
IL-10 -819T>C (rs1800871)										
	C vs T	Fixed	57.07	0.097	1.278	1.043-1.566	2.368	0.018	1.000	0.636
	CC vs TT	Random	66.94	0.049	1.682	0.651-4.348	1.074	0.283	1.000	0.533
	CT vs TT	Fixed	66.43	0.051	1.011	0.779-1.312	0.083	0.934	1.000	0.988
	CC+CT vs TT	Fixed	52.19	0.123	1.253	0.974-1.611	1.757	0.079	1.000	0.653
	CC vs CT+TT	Fixed	33.49	0.222	1.709	1.026-2.845	2.060	0.039	1.000	0.411

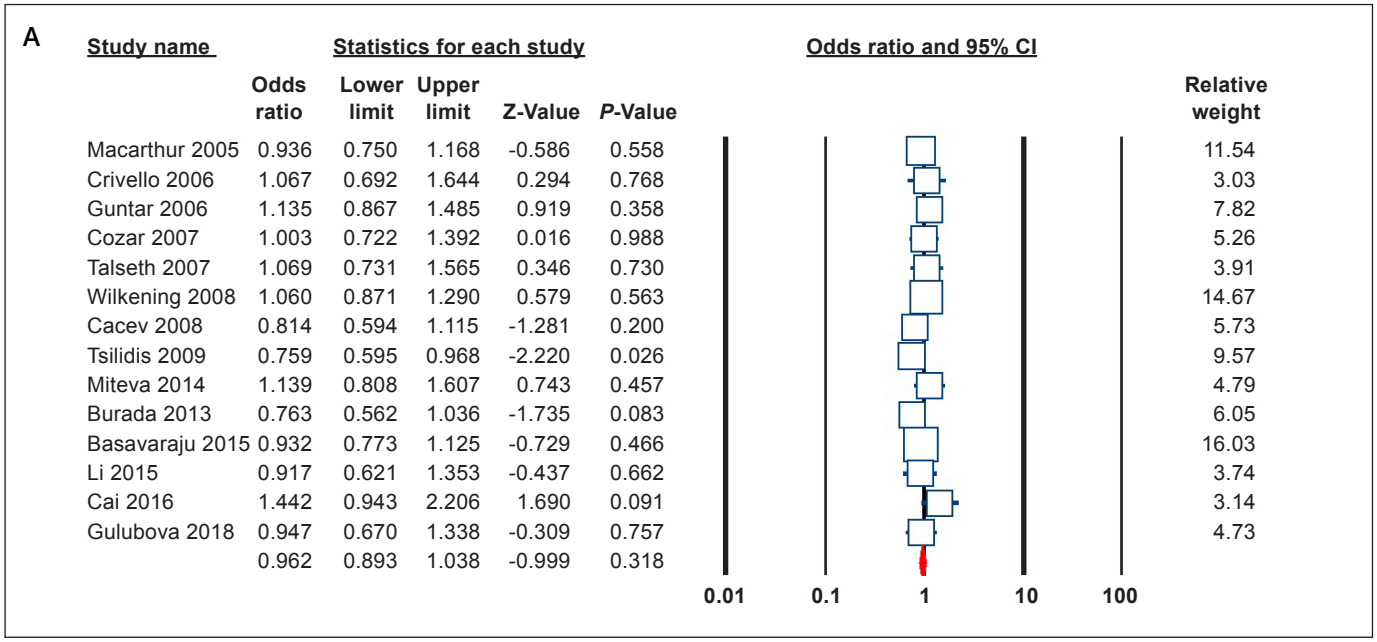

FIGURE 1.A. Forest plots for association of IL-10 -1082A>G and -592C>A polymorphisms with CRC risk. (A) -1082A>G under allele model (G vs. A).

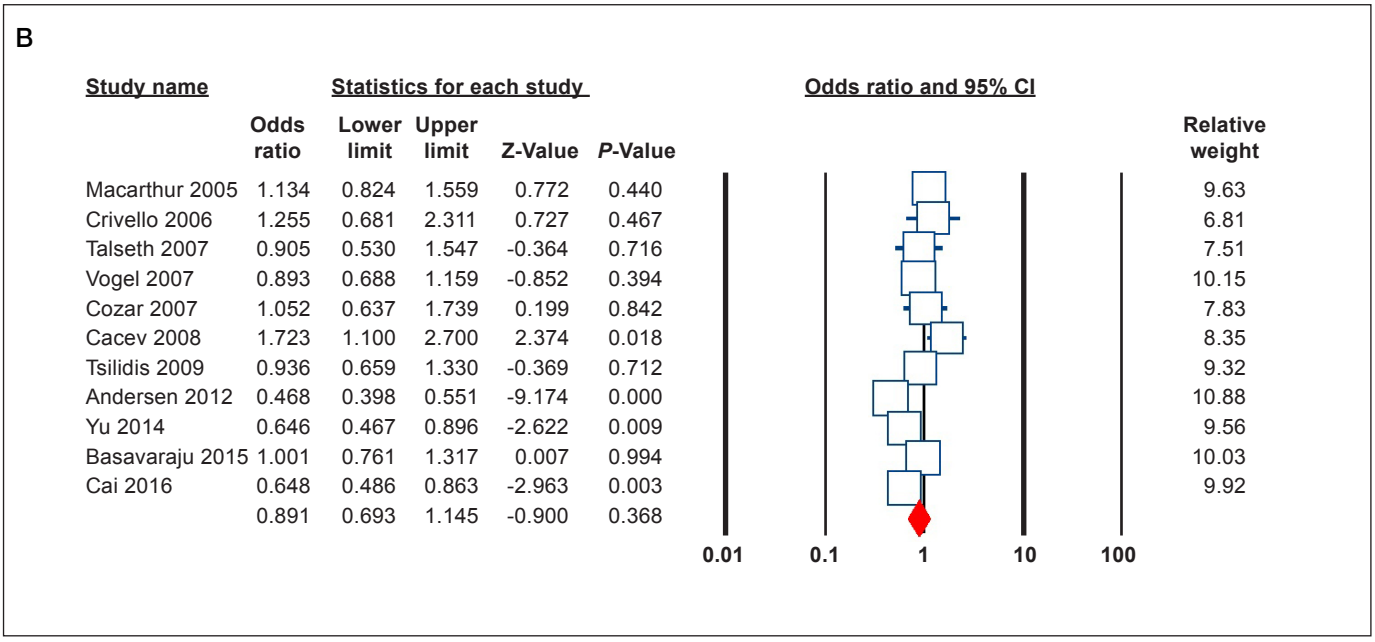

FIGURE 1.B. -592C>A under dominant model (AA+AC vs. CC).

TABLE 2 listed the main results of the meta-analysis of IL-10 -819T>C (rs1800871) polymorphism and CRC risk. When all the eligible studies were pooled into the meta-analysis of IL-10 -819T>C (rs1800871) polymorphism, significantly increased risk of CRC was observed in the two genetic models, i.e., allele (A vs G: OR=1.278, 95% CI 1.043-1.566, *P*=0.018) and recessive (AA vs AG+GG: OR=1.709, 95% CI 1.026-2.845, *P*=0.039).

The studies were further stratified on the basis of ethnicity, source of control, genotyping technique and HWE status. Subgroup analysis did not showed the IL-10 -1082A>G and -592C>A polymorphisms significantly increased risk of CRC (data not showed).

Heterogeneity and sensitivity analyses

TABLE 2 summarizes the results of this meta-analysis for heterogeneity test. For IL-10 -1082A>G polymorphism, there was no a significant heterogeneity in all five genetic models. Our meta-analysis showed little evidence of genetic heterogeneity in the homozygote model of IL-10 -819T>C. We detected significant between-study heterogeneity in the three genetic models, i.e., allele, heterozygote and dominant for -592C>A. One-way sensitivity analyses were performed by iteratively removing one study at a time to assess the stability of the meta-analysis results. The result showed that there was still no significant association of IL-10 -1082A>G and -819T>C polymorphisms with CRC. Significant between-study heterogeneity was still significant after removing one study under the genetic models (data not shown).

Publication bias

We performed Begg's test and Egger's test to assess the publication bias. As shown in the TABLE 2, no obvious publication bias was found according to the obtained *P* values for all the genetic models for IL-10 -1082A>G and -819T>C polymorphisms. However, the results of Egger's regression test and relative asymmetry of funnel plot showed evidence of publication bias for IL-10 -592C>A under the dominant model ($P_{Begg's}$=0.350, P_{Eggers}=0.005, FIGURE 2), suggesting that there was obvious publication bias in the genetic model. Therefore, we have performed the Duval and Tweedie nonparametric "trim and fill" method to adjust for publication bias. The "trim and fill" method did not change conclusion, indicating that our results were statistically robust.

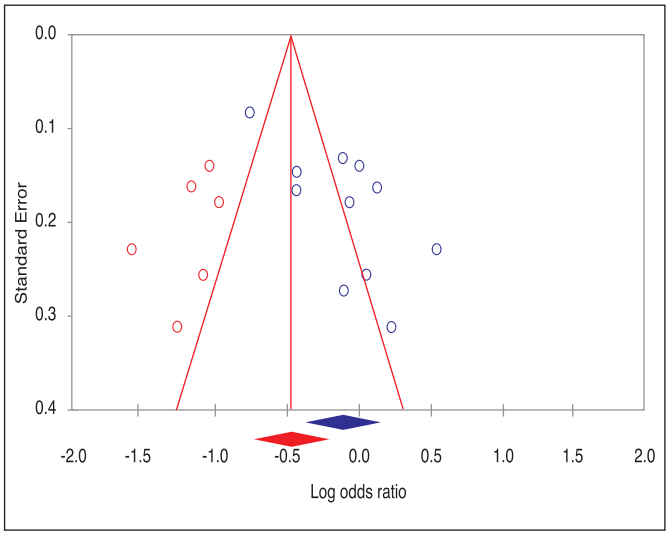

FIGURE 2. Begg's funnel plot of publication bias test before (blue) and after (red) trim-and-fill method for IL10 -592C>A polymorphism with CRC risk under dominant model (AA+AC vs. CC).

Minor Allele Frequencies (MAFs)

The minor allele frequencies (MAFs) of the IL-10 polymorphisms are presented in TABLE 1. The IL10 -1082G, -592A and -819C allele frequencies in the overall populations were 29.35% (5.10%-53.60%), 27.45% (18.70%-36.20%), and 21.9% (17.80%-26.0%), respectively.

DISCUSSION

To date, numerous molecular epidemiological studies have been conducted to evaluate the association between polymorphisms of IL-10 promoter polymorphisms and the risk of CRC, but results have remained conflicting. In this meta-analysis, we identified 28 eligible studies, including 5,647 CRC cases and 6,908 controls, and analyzed the association of IL-10 -1082A>G, -592C>A and -819T>C polymorphisms with susceptibility to CRC. We found that the IL-10 -1082A>G and -592C>A polymorphisms were not associated with CRC risk in overall population. We suggested that the IL-10 -1082A>G and -592C>A polymorphisms could play a protective role in the development of CRC due to a higher incidence found in controls than in cases from the included studies in the meta-analysis.

Previously, association of the IL-10 polymorphisms with CRC risk has been investigated by two meta-analyses. In 2013, Yu et al. performed a comprehensive meta-analysis about IL-10 -819C>T polymorphism and cancer susceptibility. They have found that the IL-10 -819C>T polymorphism was not significantly associated with CRC, breast cancer, lung cancer, hepatocellular carcinoma, prostate cancer, lymphoma, or melanoma[16]. Compared with Yu et al., we only focused on the association of IL-10 polymorphisms with CRC cancer, while Yu et al. analyzed a variety of human malignancies. In 2012, Zhang et al. performed a meta-analysis about IL-10 -1082 A>G and -592 C>A polymorphisms and CRC risk[17]. Compared with Yu et al. and Zhang et al. studies, we have focused on the association of three promoter region polymorphisms with CRC. On the other hand, we also analyzed the association of IL-10 -819T>C polymorphism with CRC risk. Additionally, we identified more eligible studies undertaken to assess the association IL-10 gene promoter polymorphisms and CRC risk.

To the best knowledge, this is the first comprehensive meta-analysis to assess the association of IL-10 -819T>C polymorphism with CRC risk. The current meta-analysis, which included a total of three case–control studies with 477 cases and 544 controls, investigated the association of IL-10 -819T>C polymorphism with CRC risk. We found that the IL-10 -819T>C polymorphism significantly increased risk of CRC in the two genetic models, i.e., allele (A vs G: OR=1.278, 95% CI 1.043-1.566, P=0.018) and recessive (AA vs AG+GG: OR=1.709, 95% CI 1.026-2.845, P=0.039). However, a small number of eligible studies were enrolled for IL-10 -819T>C polymorphism, which may fail to provide enough statistical power to detect a possible or effect of IL-10 -819T>C polymorphism on CRC. Therefore, to achieve more precise correlation, future studies should take ethnic difference in to consideration. However, we suggests that the IL-10 -819T>C polymorphism may be important as suspected predictive factor for CRC occurrence.

Between-study heterogeneity is a potential problem that might affect the interpretation of the results. thus, one of the most important goals of the meta-analysis is to identify the source of heterogeneity[39-42]. Through conducting meta-regression, we found that the heterogeneity could not be explained by ethnicity, source of control, genotyping methods and HWE status in the current meta-analysis. Therefore, we suggested that the heterogeneity may have resulted due to something more than these factors. It is known that the existence of publication bias can influence the conclusions of a meta-analysis. Therefore, the "trim and fill" methods have been developed to deal with publication bias. In the current meta-analysis, we have found possible publication bias between IL-10 -592C>A polymorphism and CRC risk under the dominant model ($P_{Begg's}$=0.350, P_{Eggers}=0.005), adjusting for possible publication bias using the Duval and Tweedie nonparametric "trim and fill" method showed that the results did not adjust, indicating that the overall pooled results should be unbiased.

In interpreting the results, some cautions should be applied. First, there was limited number of eligible studies in the meta-analysis of the association between IL-10 -819T>C polymorphism and risk of CRC. The limited sample size in the meta-analysis may fail to provide enough statistical power to detect a possible or weak effect of IL-10 -819T>C polymorphism on CRC. Therefore, more studies with large sample are needed to give a more precise estimation of the association between IL-10 -819T>C polymorphism and risk of CRC. Second, the included studies involved in the meta-analysis were mainly Caucasian, so it is uncertain whether these results are generalizable to other populations. Moreover, the stratification by ethnicity had little or no information for other ethnicities, which may limited the strength of our results. Thus, strengthening the statistical power will require more data from different ethnicities. Third, although no significant publication bias was detected, we have included only published studies in this meta-analysis, and it is possible that some relevant published and unpublished studies in other languages might be missed, which also publication bias may occur. Fourth, our results were based on unadjusted estimates without adjustment for other risk factors such as age, gender, drinking consumption, environmental factors and other variables, while a more precise analysis should be conducted according to potentially confounding factors. Finally, lack of the original data of the included studies, the interaction of different susceptibility genes, gene-to-environment, and even different polymorphic loci of the same gene interactions due to the limited information of included studies.

In conclusion, this meta-analysis indicated that IL-10 -1082A>G and -592C>A polymorphisms could play a protective role in the development of CRC. However, we found that there was a significant association between IL-10 -819T>C polymorphism and CRC risk. The IL-10 -819T>C polymorphism may be important as suspected predictive factor of CRC occurrence. More extensive studies with large sample sizes, gene-gene and gene-environment interactions are necessary to provide a more reliable estimation of these associations in overall and by ethnicity.

Authors' contributions

Mirjalili SA, Moghimi M and Neamatzadeh H conceived and research design. Abolbaghaei SM and Mazaheri M selected the articles and extracted the data. Aghili K, Jafari M and Zare-Shehneh M performed data analysis. The manuscript was drafted by Mirjalili SA and Neamatzadeh H. Moghimi M and Abolbaghaei SM critically reviewed the manuscript and discussed with the other co-authors. All the authors read and approved the final manuscript.

Mirjalili SA, Moghimi M, Aghili K, Jafari M, Abolbaghaei SM, Neamatzadeh H, Mazaheri M, Zare-Shehneh M. Associação de polimorfismos da região do promotor do gene interleucina-10 com susceptibilidade ao câncer colorretal: uma revisão sistemática e meta-análise. Arq Gastroenterol. 2018,55(3):306-13.

RESUMO – **Contexto** – Vários estudos epidemiológicos têm investigado a associação de polimorfismo da região promotora do gene interleucina-10 (IL-10) com câncer colorretal (CRC), mas por enquanto a conclusão ainda é conflitante e inconclusiva. **Objetivo** – Foi realizada esta meta-análise para avaliar a associação de polimorfismo da região promotora do Il-10 com o câncer colorretal. **Métodos** – Os artigos elegíveis foram identificados por uma pesquisa de várias bases de dados bibliográficas para o período até 15 de março de 2018. A força da associação foi medida por odds ratio (OR) com intervalos de 95% de confiança (IC). **Resultados** – Um total de 28 estudos de casos-controles com 5.647 casos de câncer colorretal e 6.908 controles foram selecionados, incluindo 14 estudos para o polimorfismo de IL-10-1082A>G (rs1800896) (2.702 casos e 3.649 controles), 11 estudos para-592C>A (rs1800872) polimorfismo (3.259 casos e 4.992 controles), e três estudos para-819T>C (rs1800871) polimorfismo (477 casos e 544 controles). Ao reunir todos os estudos elegíveis, verificou-se que o Il-10-1082A>G e-592C>A polimorfismo não foram associados com o aumento do risco de câncer colorretal na população global. No entanto, houve associações significativas entre o polimorfismo IL-10-819T>C e a susceptibilidade de câncer colorretal o modelo alelo (A vs G: OR=1,278; 95% CI 1,043-1,566; *P*=0,018) e o modelo recessivo (AA vs AG + GG: ou =1,709; 95% CI 1,026-2,845; *P*=0,039). **Conclusão** – Nesta meta-análise revelou-se que o polimorfismo IL-10-819T>C foi associado a um risco significativamente maior de câncer colorretal; enquanto o Il-10-1082A>G e-592C>A polimorfismos não foram associados com o risco de câncer colorretal. O polimorfismo IL-10-819T>C pode ser importante como fator preditivo suspeito da ocorrência de câncer colorretal.

DESCRITORES – Interleucina-10. Neoplasias colorretais. Polimorfismo genético. Metanálise.

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