The Associations between Interleukin-17 Single Nucleotide Polymorphism and Colorectal Cancer Susceptibility: A Systematic Review and Meta-Analysis

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Abstract

Backgrounds: Numerous of case-control studies have reported the associations between Interleukin-17 (IL-17) polymorphisms and colorectal cancer, however, the results were inconsistent. The aim of this meta-analysis was to further clarify the effects of IL-17 polymorphisms on colorectal cancer susceptibility.

Materials and method: Relevant Studies were extracted from electronic databases of Pubmed, Embase, Web of science, China National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database (CMB) up to April 2021. The Odds ratio and 95% confidence interval were conducted to estimate the strength of the associations and the Stata 13.0 software was used to perform the meta-analysis.

Results: Ten articles including 2599 cases and 2845 controls were enrolled in our research after strictly literature screening. Highly significant associations between IL-17A rs2275913 polymorphism and increased colorectal cancer susceptibility were observed in all the five gene models (allelic, dominant, recessive, homozygous and heterozygous models), subgroup analysis based on ethnicity revealed that these associations existed not only in Asia population, but also in Caucasian population. However, the results showed no significantly elevated colorectal cancer risk correlated to IL-17F rs763780 polymorphism and a slightly lower colorectal cancer susceptibility for Caucasian population was discovered in the recessive and homozygous models of this mutation.

Conclusion: IL-17A rs2275913 polymorphism may be an independent risk factor contributed to colorectal cancer susceptibility, while IL-17F rs763780 polymorphism displayed a possible decreased susceptibility to colorectal cancer. Future studies with large-scale samples were warranted to identify these associations.

1. Introduction

Epidemiological data from last year showed that colorectal cancer has become the third most common and the second lethal malignant tumor. With a high morbidity and mortality, colorectal cancer caused almost 2 million diagnosed cases and approximately 1 million cancer-related deaths throughout the world per year[1], posing a major threat to the normal lives and providing a heavy global burden of human health[2]. Although the specific mechanism of colorectal cancer tumorigenesis remains uncertain presently, accumulative evidence demonstrated that these factors, such as environment, diet, smoking, alcohol and some precancerous lesions, were closely associated with the occurrence of colorectal cancer[3-5]. However, even if exposed to the same environmental factors, only a small proportion of people suffer from colorectal cancer, which suggested that genetic factors might play a crucial role in the pathogeny of colorectal cancer. Some current studies have indicated that single nucleotide polymorphisms, especially the polymorphisms from inflammatory cytokines, had access to interfere and modify the protein expressions and increased the colorectal malignant tumor susceptibility[6].

The synergy of inflammatory microenvironment and some carcinogenic cytokines was well recognized in the cancer progression[7]. Chronic inflammation was proved to be strongly associated with the genetic instability and related mechanism in cancer inflammatory microenvironment, indicating that gene mutation and inflammation may closely participated in the pathogenesis and progression of malignant tumors[8]. IL-17, also called as IL-17A or CTLA-8, was an inflammatory cytokine secreted by T helper 17 cells. As the named subspecies in the IL-17 gene family, it was firstly discovered from the cDNA of a hybrid rodent T cells[9]. The IL-17 family contained at least six members, which was IL-17A to F, each of them had the similar gene sequences and biological functions[10]. Recently, a number of researches has confirmed the effects of IL-17 on the initiation and development of multiple types of malignancies, including Hepatocellular carcinoma[11], lung cancer[12], pancreatic cancer[13] and cervical cancer[14]. Although IL-17A and IL-17F was clarified as risk factors for colorectal cancer during the recent decade[15], the concrete reasons were unclear.

It is widely reported that IL-17A and IL-17F polymorphic variants were positively correlated with increased susceptibility of some primary malignancies [16-18]. Furthermore, the positive relationships were observed between inflammatory bowel diseases, regarding as the precancerous lesions of colorectal cancer, and IL-17A and IL-17F polymorphisms in several previous literatures[19, 20], and increasing numbers of studies has performed to investigate whether these polymorphisms contribute to colorectal cancer, however, the results were still controversy. Hence, this meta-analysis was conducted to firstly explore the association between IL-17A rs2275913 and IL-17F rs763680 polymorphisms and colorectal cancer.

2. Materials And Methods

2.1 Search strategy of literatures

An Internet search for the literatures published in English or Chinese was conducted from the establishment date of databases of Pubmed, Web of science, Embase, CNKI and CMB to April 2021, with the following key words: “Interleukin-17 or IL-17 or CTLA-8” and “CRC or colorectal cancer or colon cancer or rectal cancer” and “SNP or polymorphism or single nucleotide polymorphism or gene mutation or gene variant”. Relevant conference papers were retrieved using the journal database of National library of China by a manual search.

2.2 Inclusion and exclusion criteria

All the eligible studies including in this meta-analysis should meet the criteria as: (1). The studies were set out to investigate the associations between IL-17A rs2275913 or IL-17F rs763780 polymorphisms and colorectal cancer susceptibility. (2). The studies were case-control studies. (3). There were available and adequate genotype frequencies to evaluate the odds ratio (OR) and 95% confidence interval (CI). (4). The studies were carried out only on human beings.

The studies with following criteria should be excluded from this meta-analysis: (1). The aims of the studies were not to detect the effect of IL-17A rs2275913 or IL-17F rs763780 polymorphism on colorectal cancer. (2). Non-case-control studies. (3). Duplicated publications or studies with overlapping data. (4). The studies without extractable data of genotype frequencies. (5). The publications identified to be review, case-reports, letter to editors and brief communications.

2.3 Data extraction

Available data were extracted by two independent investigators from the enrolled articles, including study author, study year, study design, ethnicity of population, source of controls, genotyping methods, Matching criteria of cases and controls, genotype frequencies and the calculated Hardy-Weinberg equilibrium (HWE). For repeated publications, only the researches with the largest sample size and highest quality or the most exhaustive information was selected. If any disagreement appeared, a third investigator may involve in the discussion until the final agreement reached.

2.4 Quality score assessment

The quality of each enrolled literatures was assessed by the developed standard consisting of 6 aspects of representativeness of cases, source of controls, case-control matching, specimens used for determining genotypes, HWE, and total sample size as previously reported（Table 1）[21]. The total score ranged from 0 to 18 and score for each aspects ranged from 0 to 3, literatures with a total score ≥12 was considered high quality, otherwise, literatures with a total score ＜12 was considered low quality.

2.5 Statistic analysis

All statistical tests in this study were bilateral, and the difference with P<0.05 was considered statistically significant unless otherwise stated. The association of mutation sites with colorectal cancer risk was assessed by odds ratio OR and its corresponding 95% confidence interval CI, and the Z test was used for the statistical significance test of combined OR value. χ^2 test was used to test whether the genotypes of the control group met HWE. The Cochrane Q test was used to detect whether heterogeneity existed among the studies and its statistical quantity Q approximately followed the χ^2 distribution with k-1 degree of freedom (k was the number of studies), P value less than 0.10 suggested that heterogeneity existed among studies. At the same time, the heterogeneity was quantitatively evaluated by combining the I^2 value. The I^2 value ranged from 0 to 100% and the larger the value, the higher the heterogeneity. In general, I^2 less than 25% indicated mild heterogeneity, I^2 between 25% and 50% indicated moderate heterogeneity and I^2 more than 50% indicates high heterogeneity. When the heterogeneity test in various studies was P<0.10 or I^2> 50%, the random effect model (DerSimonian-Laird method) was employed for Meta-analysis, otherwise, the fixed effect model (Mantel-Haenszel method) was employed. Sensitivity analysis was performed to determine the stability of conclusions by removing the enrolled studies one by one and estimated whether the results changed. The funnel plots drawn by effect size and standard error was carried out to evaluated possible publication bias and Begg's rank correlation was used to test the asymmetry of the funnel plots. All the statistical analysis was calculated using the software of Stata version 13.0 (STATA Corporation, College Station, TX, USA).

3. Results

3.1 Characteristics of publications

Totally, 1353 related articles were obtained in the preliminary examination, and the remaining 619 articles were excluded from repeated articles. According to the inclusion and exclusion criteria, the preliminary screening for articles was conducted by reading titles and abstracts, and 426 articles unrelated to the research topic were excluded. After then further reading the full text, 298 articles were excluded, including 193 researches unrelated to colorectal cancer, 71 abstracts or systematic reviews, 27 non-case control or cohort studies, 4 prognosis studies of colorectal cancer, 2 without complete genotype frequency or data available data and 1 with duplicated data. Finally, 14 case-control studies including 2599 cases and 2845 controls from 10 papers meeting the inclusion criteria were selected for this meta-analysis[22-31]（Figure 1）. Among included studies, 8 were conducted for IL-17A rs2275913 polymorphism and 6 were conducted for IL-17F rs763780 polymorphism, 6 were regarding to Asian and 8 were regarding to Caucasian. A total of 9 studies were considered high-quality (≥12) via quality score assessment. The basic characteristics of each included study were summarized in Table 2.

3.2 Associations between IL-17A rs2275913 polymorphism and colorectal cancer

Overall analysis revealed that all the five genetic models (allelic, dominant, recessive, homozygous and heterozygous models) of IL-17A rs2275913 polymorphism were related with an elevated colorectal cancer risk (A vs. G: OR = 1.59, 95% CI = 1.34–1.89, P<0.001; AA/AG vs. GG: OR = 1.75, 95% CI = 1.36–2.25, P<0.001; AA vs. GG/AG: OR = 1.74, 95% CI = 1.41–2.15, P<0.001; AA vs. GG: OR = 2.05, 95% CI = 1.62–2.60, P<0.001; AG vs. GG: OR = 1.60, 95% CI = 1.23–2.09, P = 0.001)(Table 3). when subgroup analysis was performed according to ethnicity, the higher risk of colorectal cancer was observed not only in Asian population (A vs. G: OR = 1.52, 95% CI = 1.16–2.01, P =0.003; AA/AG vs. GG: OR = 1.62, 95% CI = 1.18–2.23 P =0.003; AA vs. GG/AG: OR = 1.72, 95% CI = 1.26–2.34, P =0.001; AA vs. GG: OR = 2.10, 95% CI = 1.49–2.96, P<0.001; AG vs. GG: OR = 1.43, 95% CI = 1.14–1.80, P = 0.002), but also in Caucasian population (A vs. G: OR = 1.67, 95% CI = 1.30–2.14, P<0.001; AA/AG vs. GG: OR = 1.88, 95% CI = 1.26–2.81 P =0.002; AA vs. GG/AG: OR = 1.76, 95% CI = 1.32–2.36, P<0.001; AA vs. GG: OR = 2.01, 95% CI = 1.46–2.77, P<0.001; AG vs. GG: OR = 1.76, 95% CI = 1.11–2.80, P = 0.017) (Figure 2A-E). The result from stratified analysis classified by the source of controls exhibited a significant colorectal cancer susceptibility correlated to IL-17A rs2275913 polymorphism in population-based (PB) (A vs. G: OR = 1.47, 95% CI = 1.25–1.72, P<0.001; AA/AG vs. GG: OR = 1.50, 95% CI = 1.23–1.83, P<0.001; AA vs. GG/AG: OR = 1.74, 95% CI = 1.39–2.18, P<0.001; AA vs. GG: OR = 1.96, 95% CI = 1.53–2.50, P<0.001; AG vs. GG: OR = 1.35, 95% CI = 1.11–1.65, P = 0.003) and in hospital-based (HB) controls (A vs. G: OR = 2.15, 95% CI = 1.41–3.29, P<0.001; AA/AG vs. GG: OR = 3.15, 95% CI = 1.59–6.21, P =0.001; AA vs. GG: OR = 3.20, 95% CI = 1.52–6.76, P =0.002; AG vs. GG: OR = 2.95, 95% CI = 1.82–4.79, P<0.001) except for the recessive models.

3.3 Associations between IL-17F rs763780 polymorphism and colorectal cancer

No significant associations between IL-17F rs763780 polymorphism and colorectal cancer were detected in the overall analysis (Table 3). We also failed to found any correlations in the further subgroup analyses based on source of controls and genotyping methods. Interestingly, when stratified analysis was classified by ethnicity (Figure 3A-E), we discovered a decreased colorectal cancer risk for the Caucasian population in the recessive model (CC vs. CT/TT: OR = 0.54, 95% CI = 0.30–0.98, P =0.042) and homozygous model (CC vs.TT: OR = 0.43, 95% CI = 0.21–0.87, P =0.019).

3.4 Sensitive analysis and cumulative meta-analysis

The destination of sensitive analysis was to detect whether the pooled OR results could be affected by any single enrolled study, we found no significant alteration exist in the pooled OR for IL-17A rs2275913 and IL-17F rs763780 polymorphisms when any one study was eliminated from this meta-analysis, indicating the reliability of our results. The cumulative analysis was performed on the basis of the publication year of literatures and the result showed that with the number of studies increased, the combined effect sizes and confidence intervals trended to be stable.

3.5 Publication bias

For the assessment of publication bias, the Begg's funnel plot and Egge's test were conducted (Figure 4 and Figure 5). The results for IL-17A rs2275913 polymorphism displayed a certain publication bias in the allelic model (P=0.001) (Figure 4A) and dominant model (P=0.001) (Figure 4B), a slight publication bias was observed in the heterozygous model (P=0.021) (Figure 4E). Regarding to IL-17F rs763780 polymorphism, the funnel plots for all the models were symmetrical and suggested the absence of significant publication bias (Figure 5A-E).

4. Discussion

Growing evidence revealed positive influence of inflammatory cytokine IL-17 on the colorectal cancer development, leading a poor prognosis for the patients. Further studies explicitly determined IL-17 involved in the colorectal cancer cells proliferation[32], migration and invasion[33], angiogenesis[34] and enhanced drug resistance[35, 36] by regulating a series of downstream signaling pathways, significantly improving the tumorigenesis, invasive and distant metastasis capabilities of colorectal cancer. The role of IL-17 in the occurrence of colorectal cancer has also received more and more attention.

Among the six members of IL-17 family, IL-17F shared the highest similar amino acid sequence and overlapping functions with IL-17A[37]. Each of the two genes was consisted of 3 exons and 2 introns and located on the chromosome 6p12.3-q13. The genetic variant of IL-17A rs2275913 was located in the 5'-UTR, involving in the gene transcription regulations and changing the roles of some cytokines[38], IL-17F rs763780 polymorphism was identified to be a missense mutation located on the coding region, with the amino acid modifying conversion of His to Arg, resulting in the potential changing of protein expressions and possible cancer risk[25]. An increasing number of studies and meta-analysis were performed to explore associations between the IL-17A rs2275913 and IL-17F rs763780 polymorphisms and virous kinds of malignant tumors in recent years[39–41], however, the related findings for colorectal cancer displayed no consensus. Thus, this meta-analysis was to detect whether both the two polymorphisms contribute to colorectal cancer susceptibility.

Our present research was comprised of 2599 cases and 2845 controls from the selected 10 case-control studies, the overall analysis results revealed a highly significantly positive associations between IL-17A rs2275913 polymorphism and colorectal cancer in all the five genetic models (A vs. G, AA/AG vs. GG, AA vs. AG /GG, AA vs. GG and AG vs. GG), suggesting that this mutation may be a remarkable genetic risk factor in the tumorigenesis of colorectal cancer. However, when the analysis was performed in IL-17F rs763780 polymorphism, no associations for colorectal cancer were observed in any genetic models (C vs. T, CC/CT vs. TT, CC vs. CT /TT, CC vs. TT and CT vs. TT). The combined effect size did not change significantly when the enrolled studies were excluded one by one, ensuring the reliability of these associations. Besides, it was noteworthy that heterogeneities existed in statistical results for some genetic models.

To explore the origin of heterogeneities and further explain the impact of different factors on the contributions of IL-17A rs2275913 and IL-17F rs763780 polymorphisms to colorectal cancer susceptibility, a series of subgroup analysis based on the aspects of race, source of controls and genotyping method were conducted. The results of analysis classified by ethnicity displayed an increased colorectal cancer risk from IL-17A rs2275913 polymorphism in both Asian and Caucasian subgroups, revealing that this mutation might independently rise the susceptibility to colorectal cancer risk in Asian and Caucasian populations. However, for the IL-17F rs763780 polymorphism, a decreased risk correlated with colorectal cancer in Caucasian subgroup was observed in the recessive and homozygous models, which suggested that the biological functions of IL-17F rs763780 polymorphism for populations from various races was possibly discrepant and provided a negative predictor for colorectal cancer occurrence in Caucasians, however, the insufficient sample size advised that such result was necessary to be identified by further studies. When stratified analysis was performed in terms of the source of controls, we found that only the HB population in the recessive model of IL-17A rs2275913 polymorphism showed no significant relationship with elevated colorectal cancer risk, since these cases were underwent the influence of self-underlying diseases, radioactive examinations and drug treatment during the hospitalization, such factors had access to potentially affect the results of genetic assessment[42]. In the models from IL-17F rs763780 polymorphism, no significant association with colorectal cancer susceptibility was observed in either PB or HB populations. We further discovered some statistical discrepancies among the subgroups divided by genotyping methods for IL-17A rs2275913 polymorphism, which indicated that various detection methods may also impact genotyping results.

Despite this meta-analysis was performed with rigorous design and exact calculations, several inevitable limitations should be noted. Firstly, some heterogeneities were observed in the overall analyses for both the two polymorphism, stratified analyses classified by ethnic, source of controls and some other subgroups failed to completely eliminate these heterogeneities. Secondly, the data of age, sex, living styles and exposures to smoking or drinking were unable to be further extracted, such factors may also impact the occurrence and development of cancer, available information of these unadjusted estimates was essential for a more accurate analysis. Thirdly, all the selected studies were conducted in the races of Asian and Caucasian and the geography areas were limited to East Asia, West Asia and North Africa, therefore, the studies with related data from some other races and geography areas were required to verify these findings. Fourthly, all the included literatures were published in English and Chinese, papers written in other languages and unpublished data due to negative results were not obtained, which may responsible for the publication bias detected in IL-17A rs2275913 polymorphism, future analysis with more enrolled studies probably overcome this issue. Moreover, the sample size of this meta-analysis was relatively small and the findings need to be discussed in further researches with large samples.

In conclusion, this meta-analysis displayed a significant association between IL-17A rs2275913 polymorphism and susceptibility to colorectal cancer among Asians and Caucasians, which provided a potential risk factor of colorectal cancer for the two populations. Although we failed to discovered no positive

effects of IL-17F rs763780 polymorphism on the colorectal cancer occurrence, this mutation may have access to decrease the colorectal cancer risk in Caucasians. The analysis results showed in our present research were warranted to be identified by continued well-designed and high-level studies, especially some prospective studies in the future.

Abbreviations

IL-17, interleukin-17
CBM, Chinese Biomedical Literature Database
CNKI, China National Knowledge Infrastructure
OR, odds ratio
CI, confidence interval
HWE, Hardy
Weinberg genetic equilibrium law
PB, population-based
HB, hospital-based.

Declarations

1. Ethics approval and consent to participate

Our analysis is based on previously published data, so the ethical approval may be not concerned.

2. Consent for publication

Not applicable

3. Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

4. Competing interests

The authors declare that they have no competing interests

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6. Authors' contributions

Study concept and design, interpretation of data and critical revision: GL and YJ. Literatures review and data analysis: GL, NZ, XL and FL. Drafting of the manuscript: GL and YJ. Revision of the manuscript: YJ. Obtained funding: JM and YJ. All authors read and approved the final manuscript.

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Not applicable

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Tables

Table 1. The criteria list of quality score for included studies

Criterion	Score
Representativeness of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Case-control match	
Matched by age and gender	3
Not matched by age and gender	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium (HWE)	
Hardy-Weinberg equilibrium in control subjects	3
Hardy-Weinberg disequilibrium in control subjects	0
Total sample size	
>1000	3
>500 and <1000	2
>200 and <500	1
<200	0

Table 2. Basic characteristics of included studies for this meta-analysis.

IL-17A rs2275913

Study author	Study year	Country	Ethnicity	Cancer type	Design	Source of controls	Genotyping method	Matching criteria	Cases		
									AA	AG	GG
Omrane	2014	Tunisia	Caucasian	colorectal cancer	Retrospective study	HB	PCR-RFLP	Not mentioned	3(2.9%)	51(50.0%)	48(47
Nemati	2015	Iran	Caucasian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Age, Sex, Ethnic, Geographic origin	82(27.0%)	100(32.9%)	122(4
Samiei	2018	Malaysia	Asian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Not mentioned	27(38.6%)	33(47.1%)	10(14
Al Obeed	2018	Saudi Arabia	Caucasian	colorectal cancer	Retrospective study	PB	qRT-PCR	Gender, Age	17(14.5%)	40(34.2%)	60(51
Bedoui	2018	Tunisia	Caucasian	colorectal cancer	Retrospective study	PB	TaqMan	Ethnic origin	14(4.8%)	79(27.1%)	199(6
Feng	2019	China	Asian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Sex, age	37(10.5%)	154(43.9%)	160(4
Moundir	2019	Morocco	Caucasian	colorectal cancer	Retrospective study	HB	TaqMan	Not mentioned	41(58.6%)	22(31.4%)	7(10.
Zhang	2020	China	Asian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Gender, Age	41(19.7%)	110(52.9%)	57(27

IL-17F rs763780

Study author	Study year	Geographic area	Ethnicity	Cancer type	Design	Source of controls	Genotyping method	Matching criteria		Cases	
									CC	CT	TT
Omrane	2014	Tunisia	Caucasian	colorectal cancer	Retrospective study	HB	PCR-RFLP	Not mentioned	1(0.7%)	38(27.8%)	98(71
Nemati	2015	Iran	Caucasian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Age, Sex, Ethnic, Geographic origin	337(93.6%)	0(0.0%)	23(6.
Li	2016	China	Asian	colorectal cancer	Retrospective study	PB	PCR-HRM	Sex, Age	0(0.0%)	13(26.0%)	37(74
Samiei	2018	Malaysia	Asian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Not mentioned	5(7.2%)	25(35.7%)	40(57
Al Obeed	2018	Saudi Arabia	Caucasian	colorectal cancer	Retrospective study	PB	qRT-PCR	Gender, Age	110(94.0%)	7(6.0%)	0(0.0
Feng	2019	China	Asian	colorectal cancer	Retrospective study	PB	PCR-RFLP	Sex, Age	10(2.8%)	100(28.5%)	241(6

Table 3. Pooled ORs and 95% CIs of this meta-analysis for the effect of IL-17A rs2275913 and IL-17F rs763780 polymorphism on colorectal cancer.

	Allele model				Dominant model				Recessive model			
	OR(95% CI)	P	P_h	I^2(%)	OR(95% CI)	P	P_h	I^2(%)	OR(95% CI)	P	P_h	I^2(%)
IL-17A rs2275913 (G197A)	**A vs. G**				**AA / AG vs. GG**				**AA vs. GG /AG**			
Total	**1.59(1.34,1.89)***	<0.001	0.035	53.5	**1.75(1.36,2.25)***	<0.001	0.018	58.5	**1.74(1.41,2.15)***	<0.001	0.437	0
Ethnicity												
Asian	**1.52(1.16,2.01)***	0.003	0.067	63.0	**1.62(1.18,2.23)***	0.003	0.186	40.6	**1.72(1.26,2.34)***	0.001	0.131	50.8
Caucasian	**1.67(1.30,2.14)***	<0.001	0.058	56.2	**1.88(1.26,2.81)***	0.002	0.009	70.3	**1.76(1.32,2.36)***	<0.001	0.585	0
Genotyping Method												
PCR-RFLP	**1.47(1.24,1.74)***	<0.001	0.156	39.8	**1.61(1.23,2.11)***	0.001	0.075	52.9	**1.68(1.33,2.14)***	<0.001	0.219	30.4
qRT-PCR	**2.04(1.30,3.20)***	0.002	—	—	**2.22(1.27,3.88)***	0.005	—	—	**2.26(0.90,5.69)***	0.084	—	—
TaqMan	1.84(0.90,3.76)	0.092	0.017	82.5	**2.42(0.68,8.68)**	0.174	0.01	85.0	**1.88(1.10,3.19)***	0.02	0.4	0
Source of Controls												
PB	**1.47(1.25,1.72)***	<0.001	0.138	40.1	**1.50(1.23,1.83)***	<0.001	0.197	31.8	**1.74(1.39,2.18)***	<0.001	0.465	0
HB	**2.15(1.41,3.29)***	<0.001	0.2	39.0	**3.15(1.59,6.21)***	0.001	0.182	43.9	1.77(0.98,3.21)	0.06	0.129	56.5
IL-17F rs763780 (T7488C)	**C vs. T**				**CC/ CT vs. TT**				**CC vs. TT / CT**			
Total	0.94(0.63,1.41)	0.776	0.009	67.5	0.96(0.64,1.44)	0.845	0.058	56.2	0.71(0.45,1.12)	0.141	0.18	36.2
Ethnicity												
Asian	1.21(0.73,2.01)	0.466	0.067	62.9	1.17(0.72,1.89)	0.527	0.142	48.8	1.07(0.53,2.18)	0.844	0.076	68.2
Caucasian	0.71(0.36,1.36)	0.317	0.043	68.2	0.67(0.27,1.63)	0.376	0.055	72.8	**0.54(0.30,0.98)***	0.042	0.421	0
Genotyping Method												
PCR-RFLP	0.89(0.54,1.46)	0.649	0.002	79.3	0.91(0.58,1.43)	0.683	0.04	64.0	0.67(0.41,1.09)	0.109	0.125	47.8
qRT-PCR	1.00(0.33,3.03)	0.996	—	—	—	—	—	—	1.00(0.33,3.09)	0.996	—	—
TaqMan	1.34(0.56,3.23)	0.507	—	—	1.41(0.55,3.59)	0.477	—	—	—	—	—	—
Source of Controls												
PB	0,94(0.57,1.55)	0.804	0.004	73.6	0.95(0.56,1.63)	0.854	0.029	66.7	0.71(0.45,1.12)	0.146	0.099	52.1
HB	1.01(0.60,1.69)	0.976	—	—	1.02(0.58,1.81)	0.937	—	—	0.73(0.04,11.78)	0.823	—	—

N: number of studies included; OR: odds ratio; CI: confidence interval; P_h: p value for heterogeneity;

*:OR with statistical significance, P<0.05 was considered statistically significant.

Figures

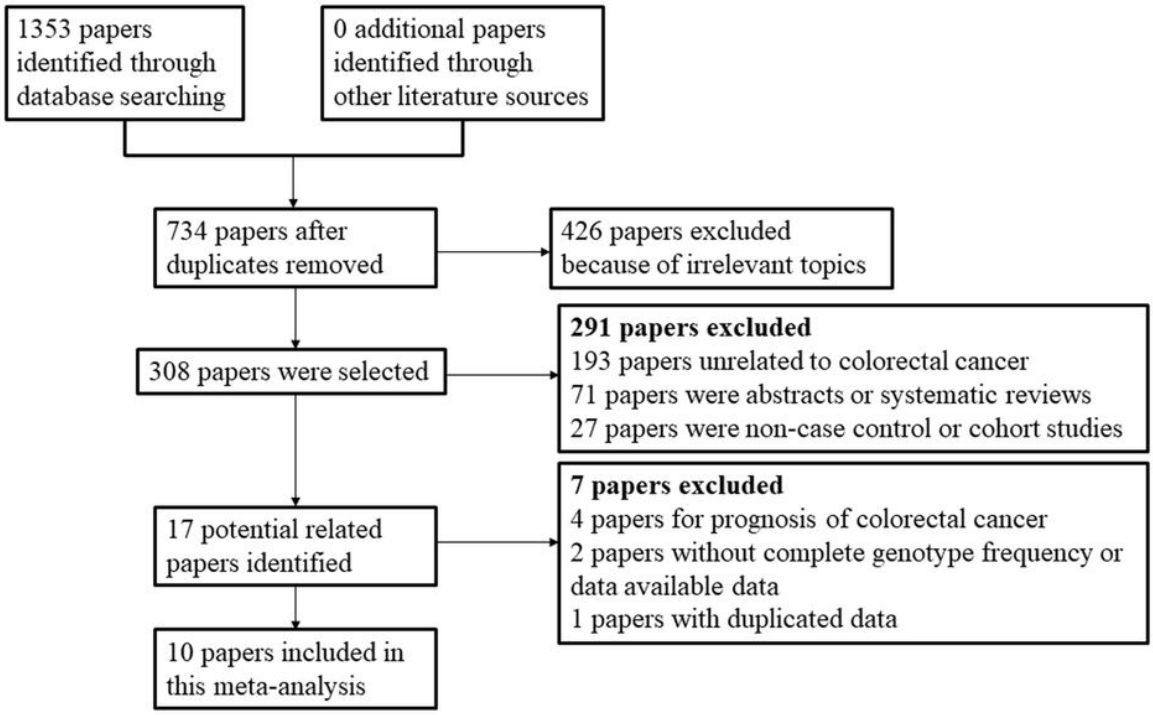

Figure 1

Flow diagram for the literatures included in this present meta-analysis

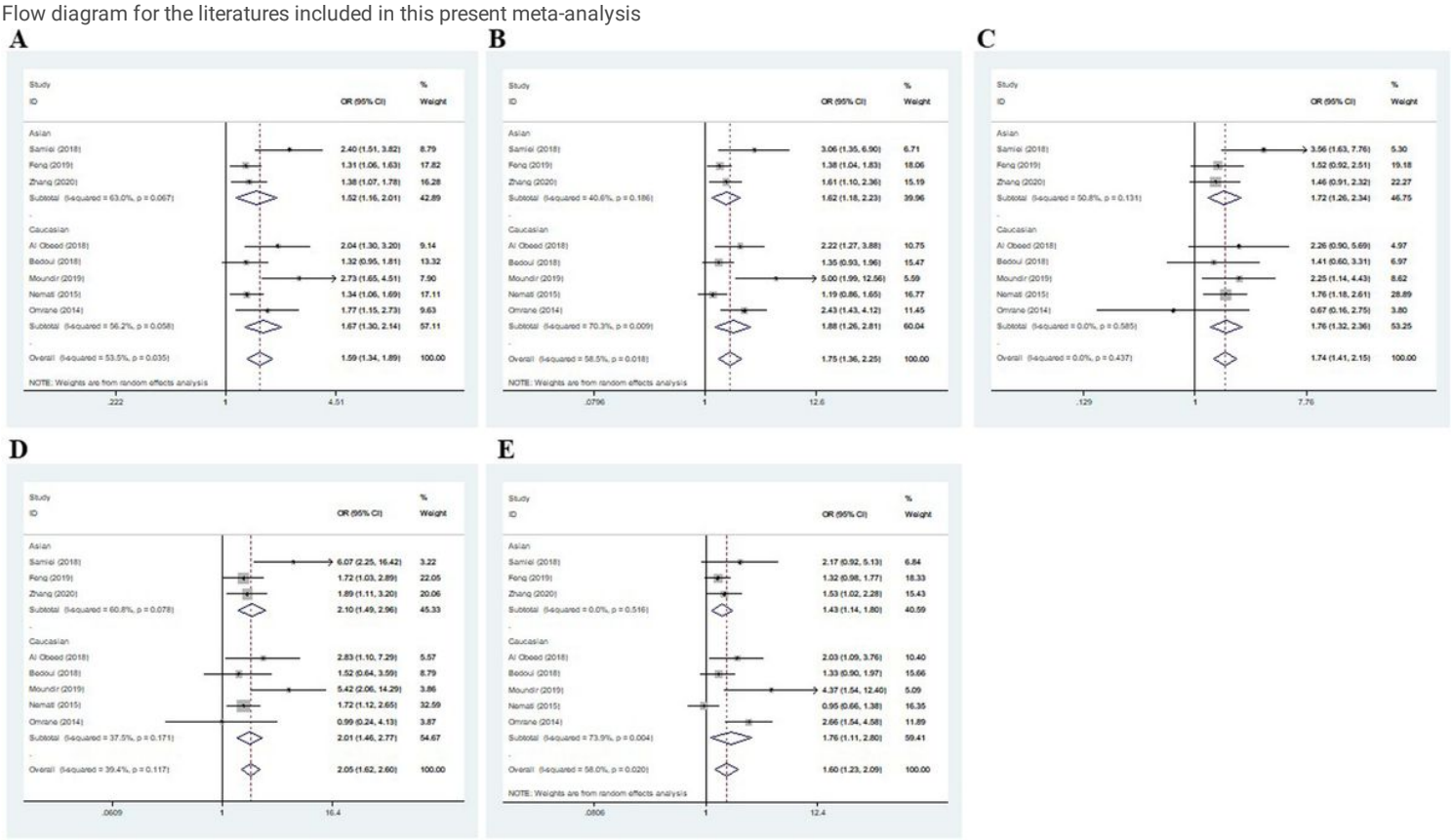

Figure 2

Forest plots of all the genetic models for the associations between IL-17A rs2275913 polymorphism and colorectal cancer. A. allelic model (A vs. G). B. dominant model (AA/AG vs. GG). C. recessive model (AA vs. GG/AG). D. homozygous model (AA vs. GG). E. heterozygous model (AG vs. GG). The study-specific ORs are represented as squares. The size of the square indicates the weight of each study. The horizontal lines represent 95% CIs. Diamonds show the overall estimate or pooled ORs in subgroups with their corresponding 95% Cis.

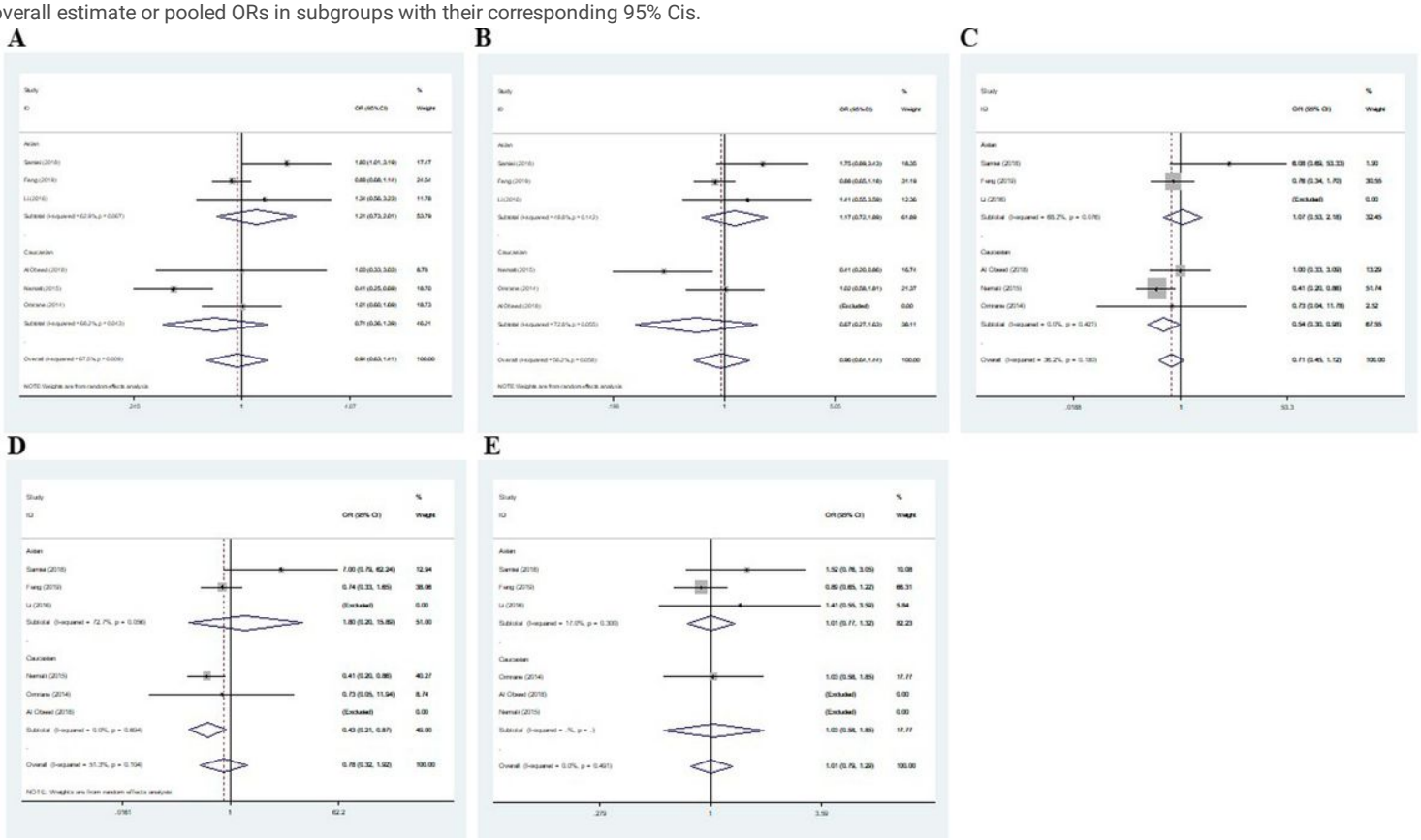

Figure 3

Forest plots of all the genetic models for the associations between IL-17F rs763780 polymorphism and colorectal cancer. A. allelic model (C vs. T). B. dominant model (CC/CT vs. TT). C. recessive model (CC vs. TT/CT). D. homozygous model (CC vs. TT). E. heterozygous model (CT vs. TT). The study-specific ORs are represented as squares. The size of the square indicates the weight of each study. The horizontal lines represent 95% CIs. Diamonds show the overall estimate or pooled ORs in subgroups with their corresponding 95% Cis.

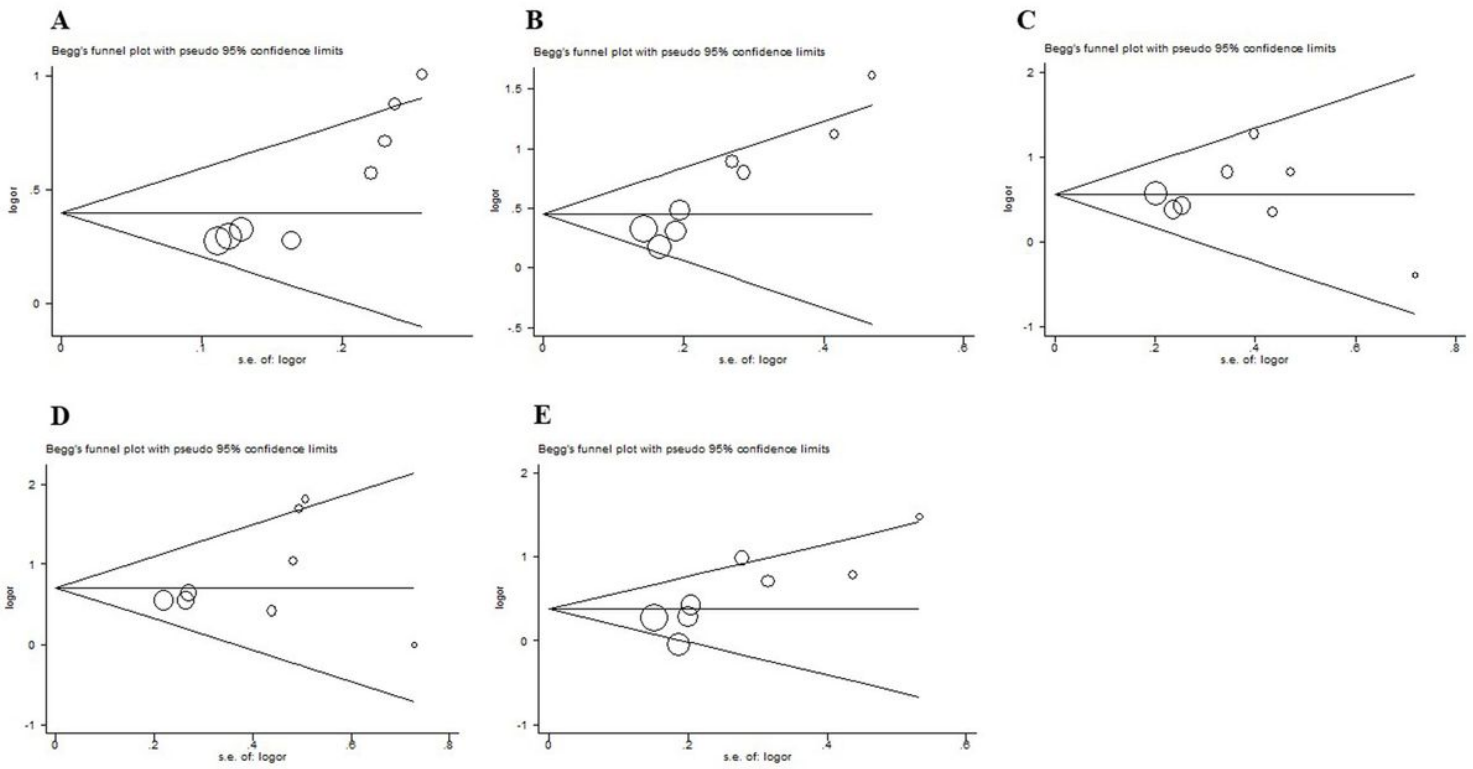

Figure 4

Funnel plots performed to detect the publication bias of included studies regarding to IL-17A rs2275913 polymorphism. A. allelic model (A vs. G). B. dominant model (AA/AG vs. GG). C. recessive model (AA vs. GG/AG). D. homozygous model (AA vs. GG). E. heterozygous model (AG vs. GG). Each cycle represents an individual case-control study.

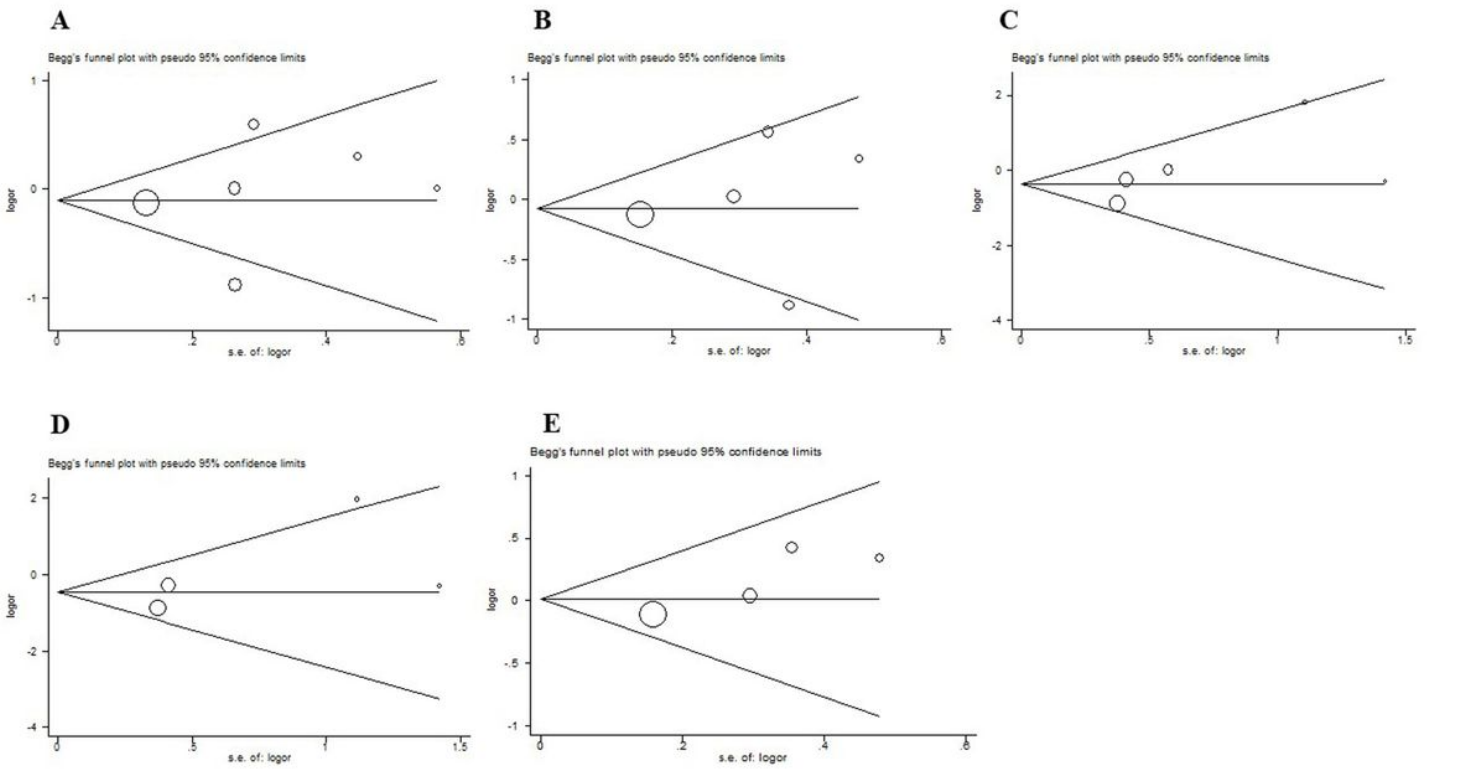

Figure 5

Funnel plots performed to detect the publication bias of included studies regarding to IL-17F rs763780 polymorphism. A. allelic model (C vs. T). B. dominant model (CC/CT vs. TT). C. recessive model (CC vs. TT/CT). D. homozygous model (CC vs. TT). E. heterozygous model (CT vs. TT). Each cycle represents an individual case-control study.