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The associations between interleukin-17 single-nucleotide polymorphism and colorectal cancer susceptibility: a systematic review and meta-analysis

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Abstract

Background: Numerous case-control studies have reported 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 the electronic databases PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and the Chinese Biomedical Literature Database (CMB) up to April 2021. The odds ratio and 95% confidence interval were used to estimate the strength of the associations.

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

Conclusion: The IL-17A rs2275913 polymorphism may be an independent risk factor contributing to colorectal cancer susceptibility, while the IL-17F rs763780 polymorphism may decrease susceptibility to colorectal cancer. Future studies with large-scale samples are warranted to identify these associations.

Keywords: Colorectal cancer, IL-17, Polymorphism, Susceptibility, Meta-analysis

Introduction

Epidemiological data from the last year showed that colorectal cancer has become the third most common and the second most lethal malignant tumor. With a high morbidity and mortality, colorectal cancer causes almost 2 million diagnosed cases and approximately 1 million

cancer-related deaths throughout the world per year [1], posing a major threat to normal life and imposing a heavy global burden on human health [2]. Although the specific mechanism of colorectal cancer tumorigenesis remains uncertain, accumulative evidence has demonstrated that factors, such as the environment, diet, smoking, alcohol, and some precancerous lesions, are 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

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cancer, which suggests that genetic factors might play a crucial role in the pathogenesis of colorectal cancer. Some current studies have indicated that single-nucleotide polymorphisms, especially polymorphisms from inflammatory cytokines, interfere with and modify protein expression and increase colorectal malignant tumor susceptibility [6, 7].

The synergy of the tumor microenvironment and some inflammatory cytokines is well recognized in cancer progression [8, 9]. Chronic inflammation has been proven to be strongly associated with genetic instability and related mechanisms in the cancer inflammatory microenvironment, indicating that gene mutation and inflammation may closely participate in the pathogenesis and progression of malignant tumors [10]. IL-17, also called IL-17A or CTLA-8, is an inflammatory cytokine secreted by T-helper 17 cells. As the named subspecies in the IL-17 gene family, it was first discovered from the cDNA of hybrid rodent T cells [11]. The IL-17 family contains at least six members, IL-17A to F, with all of them having similar gene sequences and biological functions [12]. Recently, a number of studies have confirmed the effects of IL-17 on the initiation and development of multiple types of malignancies, including hepatocellular carcinoma [13], lung cancer [14], pancreatic cancer [15], and cervical cancer [16]. Although IL-17A and IL-17F were clarified as risk factors for colorectal cancer during the most recent decades [17], the concrete reasons were unclear.

It is widely reported that IL-17A and IL-17F polymorphic variants are correlated with increased susceptibility to several digestive system primary malignancies, such as gastric cancer [18], esophageal cancer [19], hepatocellular carcinoma [20, 21], and oral squamous cell carcinoma [22]. Additionally, some scholars proposed that the IL-17F polymorphism might confer poor survival for advanced pancreatic cancer patients [23]. Positive relationships were observed between inflammatory bowel diseases, regarded as precancerous lesions of colorectal cancer, and IL-17A and IL-17F polymorphisms in several previous studies [24, 25], and an increasing number of studies have been performed to investigate whether these polymorphisms contribute to colorectal cancer; however, the results were still inconclusive. Hence, this meta-analysis was conducted to first explore the association between IL-17A rs2275913 and IL-17F rs763680 polymorphisms and colorectal cancer.

Materials and methods

Search strategy for the literature

An Internet search for the literature published in English or Chinese was conducted from the establishment date of the PubMed, Web of Science, Embase, CNKI,

and CMB databases to April 2021, with the following keywords: “interleukin-17 or IL-17 or CTLA-8,” “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 the National Library of China by a manual search.

Inclusion and exclusion criteria

All of the eligible studies included in this meta-analysis met the following criteria:

- (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 the following criteria were 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 were identified as reviews, case reports, letters to editors, and brief communications.

Data extraction

Available data were extracted by two independent investigators from the enrolled articles, including the 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 studies with the largest sample size and highest quality or the most exhaustive information were selected. If any disagreement appeared, a third investigator was involved in the discussion until a final agreement was reached.

Quality score assessment

The quality of each enrolled study 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) [26]. The total score ranged from 0 to 18, and the score for each aspect ranged from 0 to 3. Literature with a total score ≥ 12 was considered high quality; otherwise, literature with a total score < 12 was considered low quality.

Statistical analysis

All statistical tests in this study were bilateral, and differences with $P < 0.05$ were considered statistically significant unless otherwise stated. The association of mutation sites with colorectal cancer risk was assessed by the odds ratio (OR) and its corresponding 95% confidence interval (CI), and the Z-test was used for the statistical significance test of the combined OR value. The χ^2 test was used to test whether the genotypes of the control group met HWE. The Cochran 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 degrees of freedom

(k was the number of studies). A P-value less than 0.10 suggested that heterogeneity existed among studies. At the same time, heterogeneity was quantitatively evaluated by combining the I^2 values. The I^2 value ranged from 0 to 100%, and the larger the value was, 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% indicated 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 estimating whether the results changed. The funnel plots drawn by effect size and standard error were carried out to evaluate possible publication bias, and Begg's rank correlation was used to test the asymmetry of the funnel plots. All statistical analyses were calculated using Stata version 13.0 software (STATA Corporation, College Station, TX, USA).

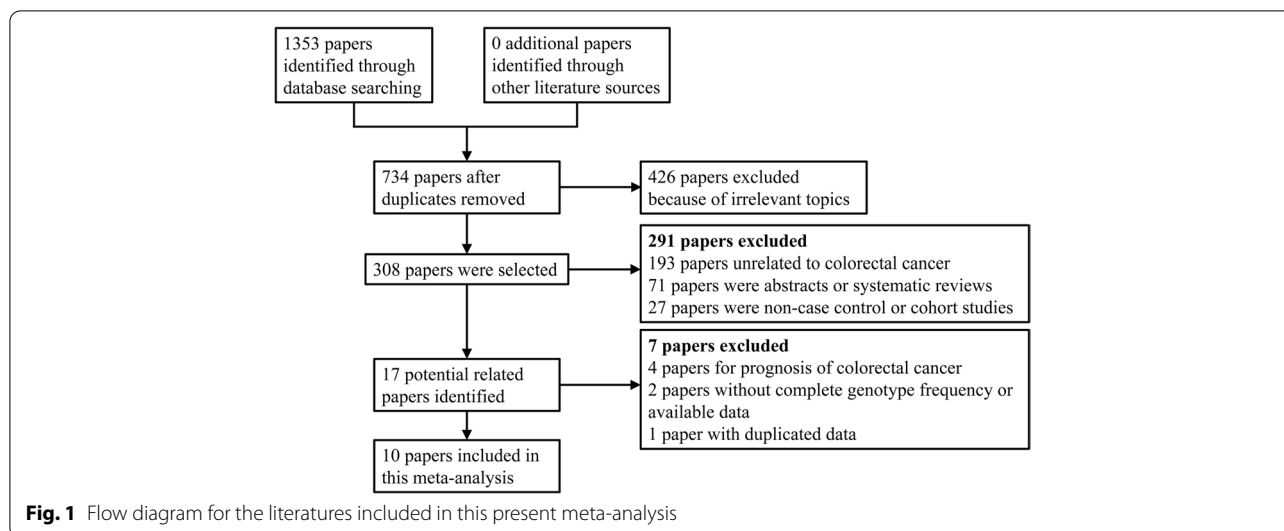
Results

Characteristics of publications

In total, 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 further reading the full text, 298 articles were excluded, including 193 studies unrelated to colorectal cancer, 71 abstracts or systematic reviews, 27 non-case-control or cohort studies, 4 prognostic studies of colorectal cancer, 2 without complete genotype frequency or 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 [27–36] (Fig. 1). The first authors for each included paper were from 6 different nations, and the geographical areas consisted of East Asia, West Asia, and North Africa. The number of coauthors in each paper ranged from 2 to 13, and the researchers of 6 papers received explicit funding support. Among the included studies, 8 were conducted for the IL-17A rs2275913 polymorphism, and 6 were conducted for the IL-17F rs763780 polymorphism; meanwhile, 6 were conducted on Asians, and 8 were conducted on Caucasians. A total of 9 studies were considered high quality (≥ 12) via quality score assessment. The basic characteristics of each included study are summarized in Table 2.

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



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

Overall, the analysis revealed that all five genetic models (allelic, dominant, recessive, homozygous, and heterozygous models) of the IL-17A rs2275913 polymorphism were related to 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, a higher risk of colorectal cancer was observed not only in the 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 the 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, $P = 0.017$) (Fig. 2, Supplementary Fig. 1 A–D). 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 model.

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

No significant associations between the IL-17F rs763780 polymorphism and colorectal cancer were detected in the overall analysis (Table 3). We also failed to find any correlations in further subgroup analyses based on the source of controls and genotyping methods. Interestingly, when stratified analysis was classified by ethnicity (Fig. 3, Supplementary Fig. 2 A–D), 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, $P = 0.019$).

Sensitivity analysis and cumulative meta-analysis

The goal of the sensitivity analysis was to detect whether the pooled OR results could be affected by any single enrolled study. We found no significant alteration in the pooled OR for the 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 the literature, and the results showed that as the number of studies increased, the combined effect sizes and confidence intervals tended to be stable.

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

Study author	Study year	Country	Ethnicity	Cancer type	Design	Source of controls	Genotyping method	Matching criteria	Cases		Controls		HWE	Quality score	
									AA	AG	AA	AG			
IL-17A rs2275913															
Omrane et al.	2014	Tunisia	Caucasian	Colorectal cancer	Retro-spective study	HB	PCR-RFLP	Not mentioned	3 (2.9%)	51 (50.0%)	6 (4.3%)	38 (27.4%)	95 (68.3%)	0.387	10
Nemati et al.	2015	Iran	Caucasian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Age, sex, ethnic, geo-graphic origin	82 (27.0%)	100 (32.9%)	50 (17.4%)	110 (38.2%)	128 (44.4%)	0.002	14
Samiei et al.	2018	Malaysia	Asian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Not mentioned	27 (38.6%)	33 (47.1%)	12 (15.0%)	41 (51.2%)	27 (33.8%)	0.577	11
Al Obeed et al.	2018	Saudi Arabia	Caucasian	Colorectal cancer	Retro-spective study	PB	qRT-PCR	Gender, age	17 (14.5%)	40 (34.2%)	7 (7.0%)	23 (23.0%)	70 (70.0%)	0.018	12
Bedoui et al.	2018	Tunisia	Caucasian	Colorectal cancer	Retro-spective study	PB	TaqMan	Ethnic origin	14 (4.8%)	79 (27.1%)	9 (3.5%)	58 (22.2%)	194 (74.3%)	0.084	14
Feng et al.	2019	China	Asian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Sex, age	37 (10.5%)	154 (43.9%)	31 (7.2%)	169 (39.2%)	231 (53.6%)	0.991	16
Moundir et al.	2019	Morocco	Caucasian	Colorectal cancer	Retro-spective study	HB	TaqMan	Not mentioned	41 (58.6%)	22 (31.4%)	27 (38.6%)	18 (25.7%)	25 (35.7%)	<0.001	6
Zhang et al.	2020	China	Asian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Gender, age	41 (19.7%)	110 (52.9%)	45 (14.4%)	149 (47.8%)	118 (37.8%)	0.854	16
IL-17F rs763780															
Omrane et al.	2014	Tunisia	Caucasian	Colorectal cancer	Retro-spective study	HB	PCR-RFLP	Not mentioned	1 (0.7%)	38 (27.8%)	1 (1.0%)	27 (27.0%)	72 (72.0%)	0.374	10
Nemati et al.	2015	Iran	Caucasian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Age, sex, ethnic, geo-graphic origin	337 (93.6%)	0 (0.0%)	391 (97.3%)	0 (0.0%)	11 (2.7%)	<0.001	14
Li et al.	2016	China	Asian	Colorectal cancer	Retro-spective study	PB	PCR-HRM	Sex, age	0 (0.0%)	13 (26.0%)	0 (0.0%)	10 (20.0%)	40 (80.0%)	0.432	14

Table 2 (continued)

Study author	Study year	Country	Ethnicity	Cancer type	Design	Source of controls	Genotyping method	Matching criteria	Cases			Controls			HWE	Quality score
									AA	AG	GG	AA	AG	GG		
Samiei et al.	2018	Malaysia	Asian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Not mentioned	5 (7.2%)	25 (35.7%)	40 (57.1%)	1 (1.2%)	23 (28.8%)	56 (70.0%)	0.419	11
Al Obeed et al.	2018	Saudi Arabia	Caucasian	Colorectal cancer	Retro-spective study	PB	qRT-PCR	Gender, age	110 (94.0%)	7 (6.0%)	0 (0.0%)	94 (94.0%)	6 (6.0%)	0 (0.0%)	0.757	15
Feng et al.	2019	China	Asian	Colorectal cancer	Retro-spective study	PB	PCR-RFLP	Sex, age	10 (2.8%)	100 (28.5%)	241 (68.7%)	16 (3.7%)	132 (30.6%)	284 (65.7%)	0.892	16

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			Homozygous model			Heterozygous model				
	OR (95% CI)	P	P _h	OR (95% CI)	P	P _h	OR (95% CI)	P	P _h	OR (95% CI)	P	P _h	OR (95% CI)	P	P _h	I ² (%)	
IL-17A rs2275913 (G197A)	A vs. G			AA/AG vs. GG			AA vs. GG/AG			AA vs. GG			AG vs. GG				
Total	1.59 (1.34, 1.89)*	< 0.001	0.035	1.75 (1.36, 2.25)*	< 0.001	0.018	1.74 (1.41, 2.15)*	< 0.001	0.437	2.05 (1.62, 2.60)*	< 0.001	0.117	1.60 (1.23, 2.09)*	0.001	0.020	58.0	
Ethnicity																	
Asian	1.52 (1.16, 2.01)*	0.003	0.067	1.62 (1.18, 2.23)*	0.003	0.186	1.72 (1.26, 2.34)*	0.001	0.131	2.10 (1.49, 2.96)*	< 0.001	0.078	1.43 (1.14, 1.80)*	0.002	0.516	0	
Caucasian	1.67 (1.30, 2.14)*	< 0.001	0.058	1.88 (1.26, 2.81)*	0.002	0.009	1.76 (1.32, 2.36)*	< 0.001	0.585	2.01 (1.46, 2.77)*	< 0.001	0.171	1.76 (1.11, 2.80)*	0.017	0.004	73.9	
Genotyping method																	
PCR-REL	1.47 (1.24, 1.74)*	< 0.001	0.156	1.61 (1.23, 2.11)*	0.001	0.075	1.68 (1.33, 2.14)*	< 0.001	0.219	1.90 (1.46, 2.47)*	< 0.001	0.172	1.50 (1.08, 2.08)*	0.015	0.028	63.2	
qRT-PCR	2.04 (1.30, 3.20)*	0.002	0.002	2.22 (1.27, 3.88)*	0.005	0.084	2.26 (0.90, 5.69)	0.084	0.084	2.83 (1.10, 7.29)*	0.031	0.031	3.76)*	0.025			
TaqMan	1.84 (0.90, 3.76)	0.092	0.017	2.42 (0.68, 8.68)	0.174	0.174	1.88 (1.10, 3.19)*	0.020	0.400	2.71 (1.44, 5.08)*	0.002	0.054	2.17 (0.69, 6.86)	0.186	0.036	77.1	
Source of controls																	
PB	1.47 (1.25, 1.72)*	< 0.001	0.138	1.50 (1.23, 1.83)*	< 0.001	0.197	1.74 (1.39, 2.18)*	< 0.001	0.465	1.96 (1.53, 2.50)*	< 0.001	0.260	1.35 (1.11, 1.65)*	0.003	0.247	25.0	
HB	2.15 (1.41, 3.29)*	< 0.001	0.200	3.15 (1.59, 6.21)*	0.001	0.182	1.77 (0.98, 3.21)	0.060	0.129	3.20 (1.52, 6.76)*	0.002	0.053	2.95 (1.82, 4.79)*	< 0.001	0.408	0	
IL-17F rs763780 (T7488C)	C vs. T			CC/CT vs. TT			CC vs. TT/CT			CC vs. TT			CT vs. TT				
Total	0.94 (0.63, 1.41)	0.776	0.009	0.96 (0.64, 1.44)	0.845	0.058	0.71 (0.45, 1.12)	0.141	0.180	0.78 (0.32, 1.92)	0.588	0.104	1.01 (0.79, 1.29)	0.929	0.491	0	
Ethnicity																	
Asian	1.21 (0.73, 2.01)	0.466	0.067	1.17 (0.72, 1.89)	0.527	0.142	1.07 (0.53, 2.18)	0.844	0.076	1.80 (0.20, 15.89)	0.598	0.056	1.01 (0.77, 1.32)	0.964	0.300	17.0	
Caucasian	0.71 (0.36, 1.36)	0.317	0.043	0.67 (0.27, 1.63)	0.376	0.055	0.54 (0.30, 0.98)*	0.042	0.421	0.43 (0.21, 0.87)*	0.019	0.694	1.03 (0.58, 1.85)	0.910			
Genotyping method																	
PCR-REL	0.89 (0.54, 1.46)	0.649	0.002	0.91 (0.58, 1.43)	0.683	0.040	0.67 (0.41, 1.09)	0.109	0.125	0.78 (0.32, 1.92)	0.588	0.104	0.99 (0.76, 1.27)	0.918	0.385	0	
qRT-PCR	1.00 (0.33, 3.03)	0.996	0.002	1.00 (0.33, 3.03)	0.996	0.002	1.00 (0.33, 3.03)	0.996	0.002	1.00 (0.33, 3.03)	0.996	0.002	1.00 (0.33, 3.03)	0.996	0.002	0	

Table 3 (continued)

	Allele model			Dominant model			Recessive model			Homozygous model			Heterozygous model		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
TaqMan	1.34 (0.56, 3.23)	0.507		1.41 (0.55, 3.59)	0.477		1.41 (0.55, 3.59)	0.477		1.41 (0.55, 3.59)	0.477		1.41 (0.55, 3.59)	0.477	
Source of controls															
PB	0.94 (0.57, 1.55)	0.804	73.6	0.95 (0.56, 1.63)	0.854	66.7	0.71 (0.45, 1.12)	0.146	52.1	0.83 (0.29, 2.40)	0.733	0.046	1.01 (0.77, 1.32)	0.964	17.0
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		0.73 (0.05, 11.94)	0.828		1.03 (0.58, 1.85)	0.910	

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

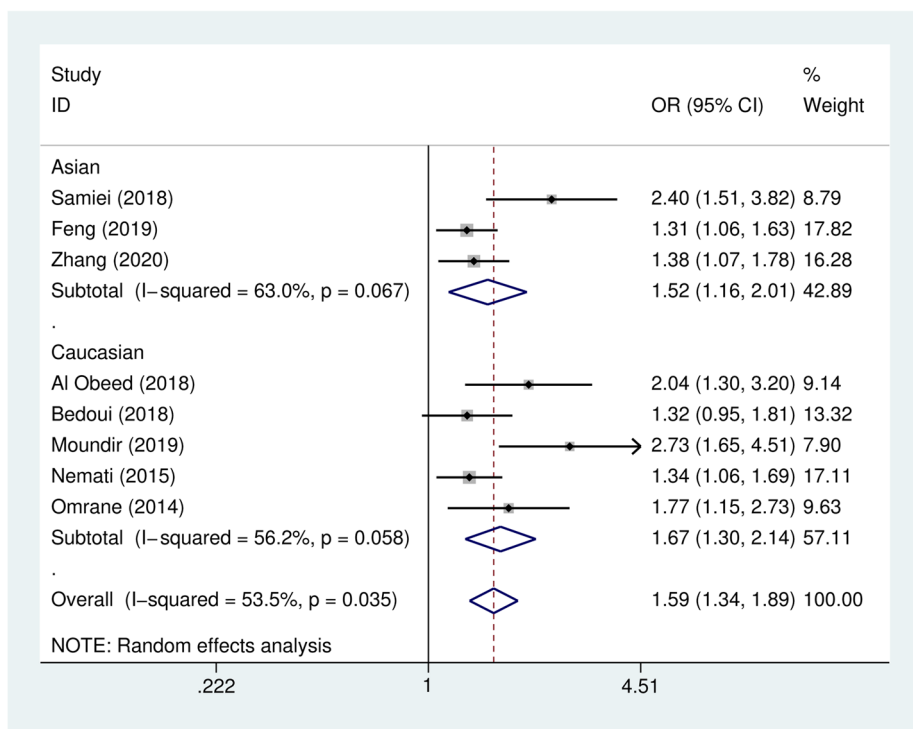


Fig. 2 The forest plot of the allelic model (A vs. G) for the associations between IL-17A rs2275913 polymorphism and colorectal cancer. The study-specific ORs are represented as squares. The size of the square indicates the weight of each study. The horizontal lines represent 95% CIs. Diamonds show the overall estimate or pooled ORs in subgroups with their corresponding 95% CIs

Publication bias

For the assessment of publication bias, Begg’s funnel plot and Egge’s test were conducted (Fig. 4, Supplementary Fig. 3 A–D). The results for the IL-17A rs2275913 polymorphism displayed a certain publication bias in the allelic model ($P = 0.001$) (Fig. 4) and dominant model ($P = 0.001$) (Supplementary Fig. 3A), and a slight publication bias was observed in the heterozygous model ($P = 0.021$) (Supplementary Fig. 3D). Regarding the IL-17F rs763780 polymorphism, the funnel plots for all of the models were symmetrical and suggested the absence of significant publication bias (Fig. 5, Supplementary Fig. 4 A–D).

Discussion

Growing evidence has revealed a positive influence of the inflammatory cytokine IL-17 on colorectal cancer development, leading to a poor prognosis for patients. Further studies explicitly determined that IL-17 is involved in colorectal cancer cell proliferation [37], migration and invasion [38], angiogenesis [39], and enhanced drug resistance [40, 41] 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 increasing attention.

Among the six members of the IL-17 family, IL-17F shared the most similar amino acid sequence and overlapping functions with IL-17A [42]. Each of the two genes consisted of 3 exons and 2 introns and was located on chromosome 6p12.3-q13. The genetic variant of IL-17A rs2275913 was located in the 5'-UTR, which is involved in gene transcription regulation and changes the roles of some cytokines [43]. The IL-17F rs763780 polymorphism was identified as a missense mutation located in the coding region, with the amino acid modification of the conversion of His to Arg, resulting in potential changes in protein expression and possible cancer risk [30]. An increasing number of studies and meta-analyses have been performed to explore associations between the IL-17A rs2275913 and IL-17F rs763780 polymorphisms and various types of malignant tumors in recent years [44–46]; however, the related findings for colorectal cancer display no consensus. Thus, this meta-analysis was performed to detect whether both polymorphisms contribute to colorectal cancer susceptibility.

Our present research was comprised of 2599 cases and 2845 controls from the 10 selected case-control studies. The overall analysis results revealed highly

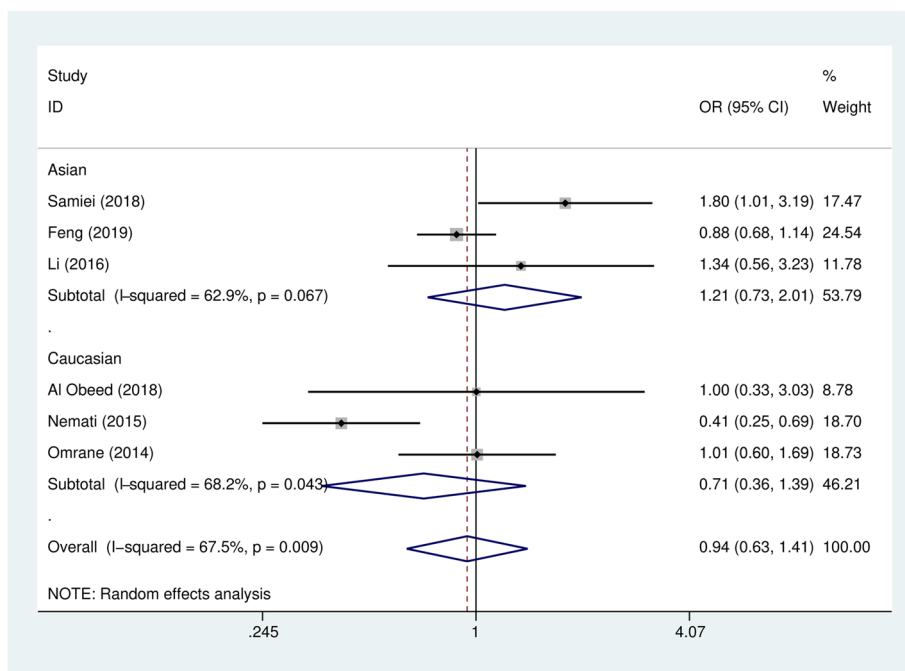


Fig. 3 The forest plot of the allelic model (C vs. T) for the associations between IL-17F rs763780 polymorphism and colorectal cancer. The study-specific ORs are represented as squares. The size of the square indicates the weight of each study. The horizontal lines represent 95% CIs. Diamonds show the overall estimate or pooled ORs in subgroups with their corresponding 95% CIs

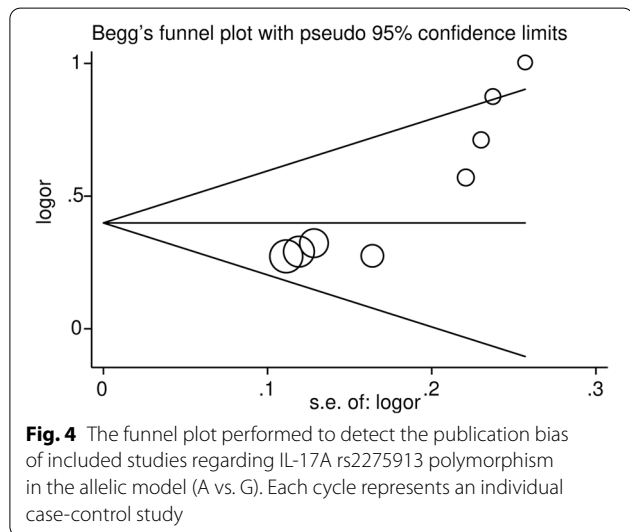


Fig. 4 The funnel plot performed to detect the publication bias of included studies regarding IL-17A rs2275913 polymorphism in the allelic model (A vs. G). Each cycle represents an individual case-control study

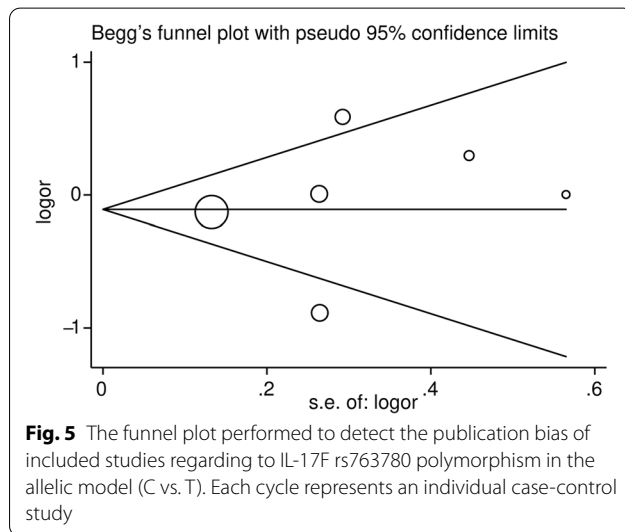


Fig. 5 The funnel plot performed to detect the publication bias of included studies regarding to IL-17F rs763780 polymorphism in the allelic model (C vs. T). Each cycle represents an individual case-control study

significantly positive associations between the IL-17A rs2275913 polymorphism and colorectal cancer in all 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 for the 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. In addition, it was

noteworthy that heterogeneities existed in the 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 analyses based on the aspects of race, source of controls, and genotyping method were conducted. The results of the analysis classified by ethnicity displayed an increased colorectal cancer risk from the IL-17A rs2275913 polymorphism in both the Asian and Caucasian subgroups, revealing that this mutation might independently increase 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 the Caucasian subgroup was observed in the recessive and homozygous models, which suggested that the biological functions of the IL-17F rs763780 polymorphism for populations from various races were possibly discrepant and provided a negative predictor for colorectal cancer occurrence in Caucasians; however, due to the insufficient sample size, such a result needs 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 the IL-17A rs2275913 polymorphism showed no significant relationship with elevated colorectal cancer risk. Since patients with self-underlying diseases were included, potential selection bias was likely to decrease the representativeness of controls in the HB group compared to those in the PB group [47]. In the models of the 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 the IL-17A rs2275913 polymorphism. The explanation may be that various gene detection methods have different theories and advantages, which possibly lead to different testing results [48].

Although this meta-analysis was performed with rigorous design and exact calculations, several inevitable limitations should be noted. First, some heterogeneities were observed in the overall analyses for both polymorphisms, and stratified analyses classified by ethnicity, the source of controls, and some other subgroups failed to completely eliminate these heterogeneities. Second, systematic reviews using case-control studies are prone to error of inappropriate selection of control groups for comparison. The data of age, sex, living styles, and exposures to smoking or drinking were unable to be further extracted, and since such factors may also impact the occurrence and development of cancer, available information of these

unadjusted estimates was essential for a more accurate analysis. Third, all of the selected studies were conducted in Asian and Caucasian populations, and the geographic areas were limited to East Asia, West Asia, and North Africa. Such geographical bias might be attributed to more attention given to colorectal cancer prevention due to the substantially increased colorectal cancer incidence in Arab and eastern Asian countries during recent years [49–52]. In addition, a candidate gene association study was a cost-effective and convenient hypothesis-driven approach, which may make it readily available to investigate genetic susceptibility to colorectal cancer in these countries [53]. Therefore, studies with related data from other races and geographic areas are required to verify these findings. Fourth, all of the included literature was published in English and Chinese, and papers written in other languages and unpublished data due to negative results were not obtained, which may be responsible for the publication bias detected in the IL-17A rs2275913 polymorphism. Future analysis with more enrolled studies would likely overcome this issue. Moreover, the sample size of this meta-analysis was relatively small, and the findings need to be discussed in further studies with large samples.

Admittedly, the results should be interpreted with caution due to these limitations, but some possible benefits of our present study may be worthy of attention. First, to the best of our knowledge, this was the first meta-analysis to specifically detect the relationships between IL-17 polymorphisms and colorectal cancer risk. Furthermore, in this study, we sought to systematically evaluate previous studies by a meta-analysis to obtain reliable conclusions about the association of IL-17A rs2275913 and IL-17F rs763780 polymorphisms with susceptibility to colorectal cancer, which probably provides a new perspective for mechanistic research and a novel direction for the clinical treatment of this life-threatening malignancy. Finally, the potential uses of our findings also included earlier screening and family genetic testing for identifying high-risk patients.

In conclusion, this meta-analysis displayed a significant association between the IL-17A rs2275913 polymorphism and susceptibility to colorectal cancer among Asians and Caucasians, which provided a potential risk factor for colorectal cancer for the two populations. Although we failed to discover any positive effects of the IL-17F rs763780 polymorphism on colorectal cancer occurrence, this mutation may decrease the colorectal cancer risk in Caucasians. The analysis results shown in our present research should be confirmed 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.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12957-022-02586-2>.

Additional file 1: Supplementary Figure 1. Forest plots of the genetic models for the associations between IL-17A rs2275913 polymorphism and colorectal cancer. **A.** dominant model (AA/AG vs. GG). **B.** recessive model (AA vs. GG/AG). **C.** homozygous model (AA vs. GG). **D.** 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.

Additional file 2: Supplementary Figure 2. Forest plots of the genetic models for the associations between IL-17F rs763780 polymorphism and colorectal cancer. **A.** dominant model (CC/CT vs. TT). **B.** recessive model (CC vs. TT/CT). **C.** homozygous model (CC vs. TT). **D.** 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.

Additional file 3: Supplementary Figure 3. Funnel plots performed to detect the publication bias of included studies regarding to IL-17A rs2275913 polymorphism in the genetic models. **A.** dominant model (AA/AG vs. GG). **B.** recessive model (AA vs. GG/AG). **C.** homozygous model (AA vs. GG). **D.** heterozygous model (AG vs. GG). Each cycle represents an individual case-control study.

Additional file 4: Supplementary Figure 4. Funnel plots performed to detect the publication bias of included studies regarding to IL-17F rs763780 polymorphism in the genetic models. **A.** dominant model (CC/CT vs. TT). **B.** recessive model (CC vs. TT/CT). **C.** homozygous model (CC vs. TT). **D.** heterozygous model (CT vs. TT). Each cycle represents an individual case-control study.

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Not applicable

Authors' contributions

Study concept and design, interpretation of data, and critical revision: GL and YJ. Literature 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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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Not applicable since our study is a meta-analysis.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–49.
- Ladabaum U, Dominitz JA, Kahi C, Schoen RE. Strategies for colorectal cancer screening. *Gastroenterology.* 2020;158:418–32.
- Song M, Chan AT. Environmental factors, gut microbiota, and colorectal cancer prevention. *Clin Gastroenterol Hepatol.* 2019;17:275–89.
- Hansen RD, Sorensen M, Tjonneland A, Overvad K, Wallin H, Raaschou-Nielsen O, et al. XPA A23G, XPC Lys939Gln, XPD Lys751Gln and XPD Asp312Asn polymorphisms, interactions with smoking, alcohol and dietary factors, and risk of colorectal cancer. *Mutat Res.* 2007;619:68–80.
- Conteduca V, Sansonno D, Russi S, Dammacco F. Precancerous colorectal lesions (review). *Int J Oncol.* 2013;43:973–84.
- Liu L, Zhai Z, Wang D, Ding Y, Chen X, Wang Q, et al. The association between IL-1 family gene polymorphisms and colorectal cancer: a meta-analysis. *Gene.* 2021;769:145187.
- Cheng H, Fan X, Ye E, Chen H, Yang J, Ke L, You M, Liu M, Zhang YW, Wu YL et al. Dual tumor microenvironment remodeling by glucose-contained radical copolymer for MRI-guided photodynamic therapy. *Adv Mater.* 2021:e2107674. <https://doi.org/10.1002/adma.202107674>.
- Trivedi S, Rosen CA, Ferris RL. Current understanding of the tumor micro-environment of laryngeal dysplasia and progression to invasive cancer. *Curr Opin Otolaryngol Head Neck Surg.* 2016;24:121–7.
- Cao L, Zhu Y, Wang W, Wang G, Zhang S, Cheng H. Emerging nano-based strategies against drug resistance in tumor chemotherapy. *Front Bioeng Biotechnol.* 2021;9:798882.
- Kawanishi S, Ohnishi S, Ma N, Hiraku Y, Murata M. Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. *Int J Mol Sci.* 2017;18(8):1808.
- Singh RK, Lee KM, Vujkovic-Cvijin I, Ucmak D, Farahnik B, Abrouk M, et al. The role of IL-17 in vitiligo: a review. *Autoimmun Rev.* 2016;15:397–404.
- McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. *Immunity.* 2019;50:892–906.
- Zarogoulidis P, Katsikogianni F, Tsiouda T, Sakkas A, Katsikogiannis N, Zarogoulidis K. Interleukin-8 and interleukin-17 for cancer. *Cancer Invest.* 2014;32:197–205.
- Wu F, Xu J, Huang Q, Han J, Duan L, Fan J, et al. The role of interleukin-17 in lung cancer. *Mediators Inflamm.* 2016;2016:8494079.
- Hu F, Guo F, Zhu Y, Zhou Q, Li T, Xiang H, et al. IL-17 in pancreatic disease: pathogenesis and pharmacotherapy. *Am J Cancer Res.* 2020;10:3551–64.
- Alves JJP, De Medeiros Fernandes TAA, De Araujo JMG, Cobucci RNO, Lanza DCF, Bezerra FL, et al. Th17 response in patients with cervical cancer. *Oncol Lett.* 2018;16:6215–27.
- Razi S, Baradaran Noveiry B, Keshavarz-Fathi M, Rezaei N. IL-17 and colorectal cancer: from carcinogenesis to treatment. *Cytokine.* 2019;116:7–12.
- Chen L, Li XG, Wang JF, Hao RS, Xiang WY, Tan PF, et al. Potential effects of IL-17A rs2275913 and IL-17F rs763780 polymorphisms on susceptibility to gastric cancer in Chinese population: a meta-analysis. *Eur Rev Med Pharmacol Sci.* 2020;24:3633–41.
- Yin J, Wang L, Shi Y, Shao A, Tang W, Wang X, et al. Interleukin 17A rs4711998 A>G polymorphism was associated with a decreased risk of esophageal cancer in a Chinese population. *Dis Esophagus.* 2014;27:87–92.
- Gheshlaghi A, Haghshenas MR, Safarpour AR, Hosseini SY, Fattahi MR, Sarvari J. IL-17 genetic variations increase the risk of cirrhotic/hepatocellular carcinoma in patients with hepatitis B virus infection. *Iran J Immunol.* 2021;18:130–40.

21. Wu W, Zeng Y, Lin J, Chen T, Xun Z, Li B, et al. IL-17 and IL-21 polymorphisms in relation to HBV related hepatocellular carcinoma in Chinese Han population. *Infect Genet Evol.* 2021;87:104638.
22. Li N, Zhang C, Chen Z, Bai L, Nie M, Zhou B, et al. Interleukin 17A and interleukin 17F polymorphisms are associated with oral squamous cell carcinoma susceptibility in a Chinese population. *J Oral Maxillofac Surg.* 2015;73:267–73.
23. Innocenti F, Owzar K, Cox NL, Evans P, Kubo M, Zembutsu H, et al. A genome-wide association study of overall survival in pancreatic cancer patients treated with gemcitabine in CALGB 80303. *Clin Cancer Res.* 2012;18:577–84.
24. Chen B, Zeng Z, Hou J, Chen M, Gao X, Hu P. Association of interleukin-17F 7488 single nucleotide polymorphism and inflammatory bowel disease in the Chinese population. *Scand J Gastroenterol.* 2009;44:720–6.
25. Kim SW, Kim ES, Moon CM, Park JJ, Kim TI, Kim WH, et al. Genetic polymorphisms of IL-23R and IL-17A and novel insights into their associations with inflammatory bowel disease. *Gut.* 2011;60:1527–36.
26. Thakkestian A, McEvoy M, Minelli C, Gibson P, Hancox B, Duffy D, et al. Systematic review and meta-analysis of the association between {beta}2-adrenoceptor polymorphisms and asthma: a HuGE review. *Am J Epidemiol.* 2005;162:201–11.
27. Samiei G, Yip WK, Leong PP, Jabar MF, Dusa NM, Mohtarrudin N, et al. Association between polymorphisms of interleukin-17A G197A and interleukin-17F A7488G and risk of colorectal cancer. *J Cancer Res Ther.* 2018;14:S299–305.
28. Al Obeid OA, Vaali-Mohamed MA, Alkhalaf KA, Bin Traiki TA, Zubaidi AM, Arafah M, et al. IL-17 and colorectal cancer risk in the Middle East: gene polymorphisms and expression. *Cancer Manag Res.* 2018;10:2653–61.
29. Bedoui SA, Barbiro M, Stayoussef M, Dallel M, Mokrani A, Makni L, et al. Association of interleukin-17A polymorphisms with the risk of colorectal cancer: a case-control study. *Cytokine.* 2018;110:18–23.
30. Feng H, Ying R, Chai T, Chen H, Ju H. The association between IL-17 gene variants and risk of colorectal cancer in a Chinese population: a case-control study. *Biosci Rep.* 2019;39(11):BSR20190013.
31. Nemati K, Golmoghaddam H, Hosseini SV, Ghaderi A, Doroudchi M. Interleukin-17FT7488 allele is associated with a decreased risk of colorectal cancer and tumor progression. *Gene.* 2015;561:88–94.
32. Omrane I, Marrakchi R, Baroudi O, Mezlini A, Ayari H, Medimegh I, et al. Significant association between interleukin-17A polymorphism and colorectal cancer. *Tumour Biol.* 2014;35:6627–32.
33. Omrane I, Baroudi O, Bougateg K, Mezlini A, Abidi A, Medimegh I, et al. Significant association between IL23R and IL17F polymorphisms and clinical features of colorectal cancer. *Immunol Lett.* 2014;158:189–94.
34. Liu Z, Suo C, Mao X, Jiang Y, Jin L, Zhang T, et al. Global incidence trends in primary liver cancer by age at diagnosis, sex, region, and etiology, 1990-2017. *Cancer.* 2020;126:2267–78.
35. Issiki Z, Moundir C, Marnissi F, Seddik N, Benjelloun N, Zaid Y, et al. Toxicological evaluation of the aqueous extract of *Caralluma europaea* and its immunomodulatory and inflammatory activities. *Pharmacognosy Res.* 2017;9:390–5.
36. Li B, Xu A, Gan A, Zhang X, Huang W, Yu Z, Chen X. Application of high resolution melting assay to explore the correlation between the single nucleotide polymorphisms of IL-23/IL-17 gene and colorectal cancer. *J New Med.* 2016;47(10):661–5.
37. Straus DS. TNFalpha and IL-17 cooperatively stimulate glucose metabolism and growth factor production in human colorectal cancer cells. *Mol Cancer.* 2013;12:78.
38. Ren H, Wang Z, Zhang S, Ma H, Wang Y, Jia L, et al. IL-17A promotes the migration and invasiveness of colorectal cancer cells through NF-kappaB-mediated MMP expression. *Oncol Res.* 2016;23:249–56.
39. Liu J, Duan Y, Cheng X, Chen X, Xie W, Long H, et al. IL-17 is associated with poor prognosis and promotes angiogenesis via stimulating VEGF production of cancer cells in colorectal carcinoma. *Biochem Biophys Res Commun.* 2011;407:348–54.
40. Chung AS, Wu X, Zhuang G, Ngu H, Kasman I, Zhang J, et al. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. *Nat Med.* 2013;19:1114–23.
41. Sui G, Qiu Y, Yu H, Kong Q, Zhen B. Interleukin-17 promotes the development of cisplatin resistance in colorectal cancer. *Oncol Lett.* 2019;17:944–50.
42. Sarkar S, Cooney LA, Fox DA. The role of T helper type 17 cells in inflammatory arthritis. *Clin Exp Immunol.* 2010;159:225–37.
43. Ruiz de Morales JMG, Puig L, Dauden E, Canete JD, Pablos JL, Martin AO, Juanatey CG, Adan A, Montalban X, Borrueal N, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: an updated review of the evidence focusing in controversies. *Autoimmun Rev.* 2020;19(1):102429.
44. Liu J, Xu Q, Yuan Q, Wang Z, Xing C, Yuan Y. Association of IL-17A and IL-17F polymorphisms with gastric cancer risk in Asians: a meta-analysis. *Hum Immunol.* 2015;76:6–12.
45. Dai ZM, Zhang TS, Lin S, Zhang WG, Liu J, Cao XM, et al. Role of IL-17A rs2275913 and IL-17F rs763780 polymorphisms in risk of cancer development: an updated meta-analysis. *Sci Rep.* 2016;6:20439.
46. Elshazli RM, Salman DO, Kamel MM, Toraih EA, Fawzy MS. Genetic polymorphisms of IL-17A rs2275913, rs3748067 and IL-17F rs763780 in gastric cancer risk: evidence from 8124 cases and 9873 controls. *Mol Biol Rep.* 2018;45:1421–44.
47. Wu T, Zhang ZT, Li L, Liu RY, Bei BT. Correlation between hypoxia-inducible factor-1alpha C1772T/G1790A polymorphisms and head and neck cancer risk: a meta-analysis. *World J Surg Oncol.* 2021;19:210.
48. Miao Z, Wang K, Wang X, Zhang C, Xu Y. TNF-alpha-308G/A polymorphism and the risk of colorectal cancer: a systematic review and an updated meta-analysis. *J BUON.* 2018;23:1616–24.
49. Al-Shamsi HO, Jones J, Fahmawi Y, Dahbour I, Tabash A, Abdel-Wahab R, et al. Molecular spectrum of KRAS, NRAS, BRAF, PIK3CA, TP53, and APC somatic gene mutations in Arab patients with colorectal cancer: determination of frequency and distribution pattern. *J Gastrointest Oncol.* 2016;7:882–902.
50. Ghorbanoghli Z, Jabari C, Sweidan W, Hammoudeh W, Cortas G, Sharara AI, et al. A new hereditary colorectal cancer network in the Middle East and eastern mediterranean countries to improve care for high-risk families. *Fam Cancer.* 2018;17:209–12.
51. Makhoulf NA, Abdel-Gawad M, Mahros AM, Lashen SA, Zaghoul M, Eliwa A, et al. Colorectal cancer in Arab world: a systematic review. *World J Gastrointest Oncol.* 2021;13:1791–8.
52. Yang Y, Yang L, Zhou L, Tang S. A critical review of the effect of dietary fiber intake on the prevention of colorectal cancer in eastern Asian countries. *J Healthc Eng.* 2021;2021:6680698.
53. Li G, Song Q, Jiang Y, Cai A, Tang Y, Tang N, et al. Cumulative evidence for associations between genetic variants and risk of esophageal cancer. *Cancer Epidemiol Biomarkers Prev.* 2020;29:838–49.

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