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Original Article

Insulin receptor substrate-2 (*IRS-2*) rs1805097 G>A polymorphism is associated with colorectal cancer susceptibility: a meta-analysis involving 11,234 subjects

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Abstract: To assess the role of the *insulin receptor substrate-2* (*IRS-2*) rs1805097 G>A polymorphism in colorectal cancer (CRC) susceptibility, we conducted a comprehensive meta-analysis, which included 5,220 CRC cases and 6,014 controls in six case-control studies published up to September 30, 2015. We used the crude odds ratios (ORs) with their 95% confidence intervals (95% CIs) to assess the relationship of *IRS-2* rs1805097 G>A variants with CRC risk. Overall, *IRS-2* rs1805097 G>A polymorphism was associated with the decreased risk of overall CRC risk (AA+GA vs. GG: OR, 0.91; 95% CI, 0.84-0.99; *P*=0.022). In a subgroup analysis by the region of CRC, *IRS-2* rs1805097 G>A polymorphism was associated with a significantly decreased risk of colon cancer (AA+GA vs. GG: OR, 0.84; 95% CI, 0.76-0.94; *P*=0.002), but not mixed colorectal cancer and rectal cancer. In a subgroup analysis by ethnicity, a significantly decreased CRC risk was identified among American populations (AA+GA vs. GG: OR, 0.88; 95% CI, 0.80-0.97; *P*=0.007), but not Caucasians. Our meta-analysis suggested the *IRS-2* rs1805097 G>A polymorphism might act as a CRC protective factor, especially in colon cancer and American populations subgroups.

Keywords: Polymorphism, *IRS-2*, colorectalcancer, susceptibility, meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common malignancy in males and the second in females worldwide, with an estimated 1.4 million CRC patients and 693,900 cancer-related-mortality occurring in 2012 [1]. Accumulating evidences demonstrate that insulin resistance (IR) and hyperinsulinemia are correlated with the pathogenesis of CRC, and high insulin secretion has been considered as a putative mechanism which links obesity, a vital susceptibility factor for a number of common diseases including cancer, with CRC [2, 3]. Numerous epidemiologic investigations have highlighted that individuals with type 2 diabetes mellitus which is correlated with hyperinsulinemia and IR are at increased susceptibility of CRC [4]. In addition, preclinical and experimental studies have shown that CRC patients have higher serum levels of insulin [4], and insulin therapy may increase the susceptibility and development of CRC by increasing cell proliferation and decreasing apoptosis [4-6].

The *insulin receptor substrate-2* (*IRS-2*) gene is located on chromosome 13q34. IRS-2, a member of IRS family (IRS1-6), shares some important structure with IRS-1, in that both IRS-1 and IRS-2 proteins possess a N-terminal pleckstrin homologydomain, several phosphotyrosine binding domains as well as a number of tyrosine and serine phosphorylation sites in a C-terminal tail [7, 8]. IRS-2 null mouse model showed metabolic defects in liver, muscle and adipose tissue, and then developed diabetes

[9]. IRS1 and IRS2, two types of cytoplasmic proteins, almost express in various cells and mediate the function of metabolism, proliferation, and anti-apoptosis [10, 11]. Some prior studies demonstrated that IRS-2 played important roles in tumorigenesis and progression, specifically by facilitating cancer cell motility, invasion and metastasis [11, 12]. Studies linking obesity, IR and CRC demonstrated that the insulin pathway might play a vital role in the etiology of CRC [6, 13, 14].

IRS-2 gene is polymorphic. More than one thousand single nucleotide polymorphisms (SNPs) in *IRS2* gene have been found (http://www.ncbi.nlm.nih.gov/SNP). Numerous SNPs have been studied, such as rs1805097 G>A, rs2289046 A>G, rs9515116 C>T, rs11069806 G>T, rs12429603 C>T, rs4773094 A>G, rs9521508 A>T and rs9559654 A>G polymorphisms etc. Among them, the *IRS-2* rs1805097 G>A, a non-synonymous SNP, was the most widely studied for its implication in the development of cancer. Several epidemiologic studies suggested that this SNP were involved in the aetiology of CRC [15-19]. Although these studies have focused on the relationship of the *IRS-2* rs1805097 G>A variants and the risk of CRC, allavailable results remain conflicting rather than conclusive. Recently, a meta-analysis have reported that *IRS-2* rs1805097 G>A variants may not contribute to the susceptibility of CRC [20]. However, only three publications were included in that study. Now, additional studies were conducted on the association between *IRS-2* rs1805097 G>A polymorphism and the susceptibility of CRC. To obtain a more precise assessment, an updated meta-analysis was carried out.

Materials and methods

Search strategy

We searched the publications using the terms 'insulin receptor substrate 2' or 'insulin receptor substrate-2' or 'IRS2' or 'IRS-2' and 'polymorphism' or 'variant' or 'SNP' and 'cancer' or 'carcinoma' or 'malignance' and 'colorectal' or 'rectal' or 'colon' in Pubmed and Embase databases, and the last search was updated in September 30, 2015. There was not limited for language. We examined all associated publications to retrieve the eligible papers. Their bibliographies were manually-searched to find additional publications.

Inclusion and exclusion criteria

Studies were selected according to the major inclusion criteria: (1) case-control studies; (2) evaluating the association between *IRS-2* rs1805097 G>A SNP and CRC risks; (3) CRC was confirmed by histopathology; (4) providing data on genotype frequencies. Accordingly, studies without detail genotype frequencies, not case-control study design, duplicated data, reviews and comments were excluded.

Data extraction

For each recruited study, data was collected by two authors (J. Lin and Y. Wang) independently in duplicate. The following original data were extracted: name of first author, publication year, country where the study was performed, source of control, adjusted factors, genotyping methods, ethnicity, the region of CRC, Hardy-Winberg equilibrium (HWE), number of cases/controls and genotype frequency. In addition, different ethnicity descents were defined as Caucasian and American populations. The regions of CRC were classified as mixed colorectal cancer, colon cancer and rectal cancer. An online chi-square test program (http://ihg.gsf.de/cgi-bin/hw/hwa1.p) was used to calculate the HWE in controls [21]. When came to duplicated data, these studies with larger sample sizes or according with HWE in controls were included. Two authors (J. Lin and Y. Wang) reached consensus on each item after a discussion.

Methodological quality assessment

The quality of included papers was independently assessed by two reviewers (J. Lin and Y. Wang) according to a 'methodological quality assessment scale' [22-24]. The quality scores ≥ 6, papers were defined as 'high quality'; otherwise, papers were defined as 'low quality' [24].

Statistical analysis

The correlation strength between *IRS-2* rs1805097 G>A polymorphism and CRC susceptibility was assessed by odds ratio (OR) with its 95% confidence intervals (95% CI). The pooled ORs and CIs were calculated for homozygote comparison (AA versus GG), allele comparison (A versus G), dominant (GA/AA versus GG) and recessive (AA versus GA/GG) genetic models, respectively. Subgroup analyses were carried

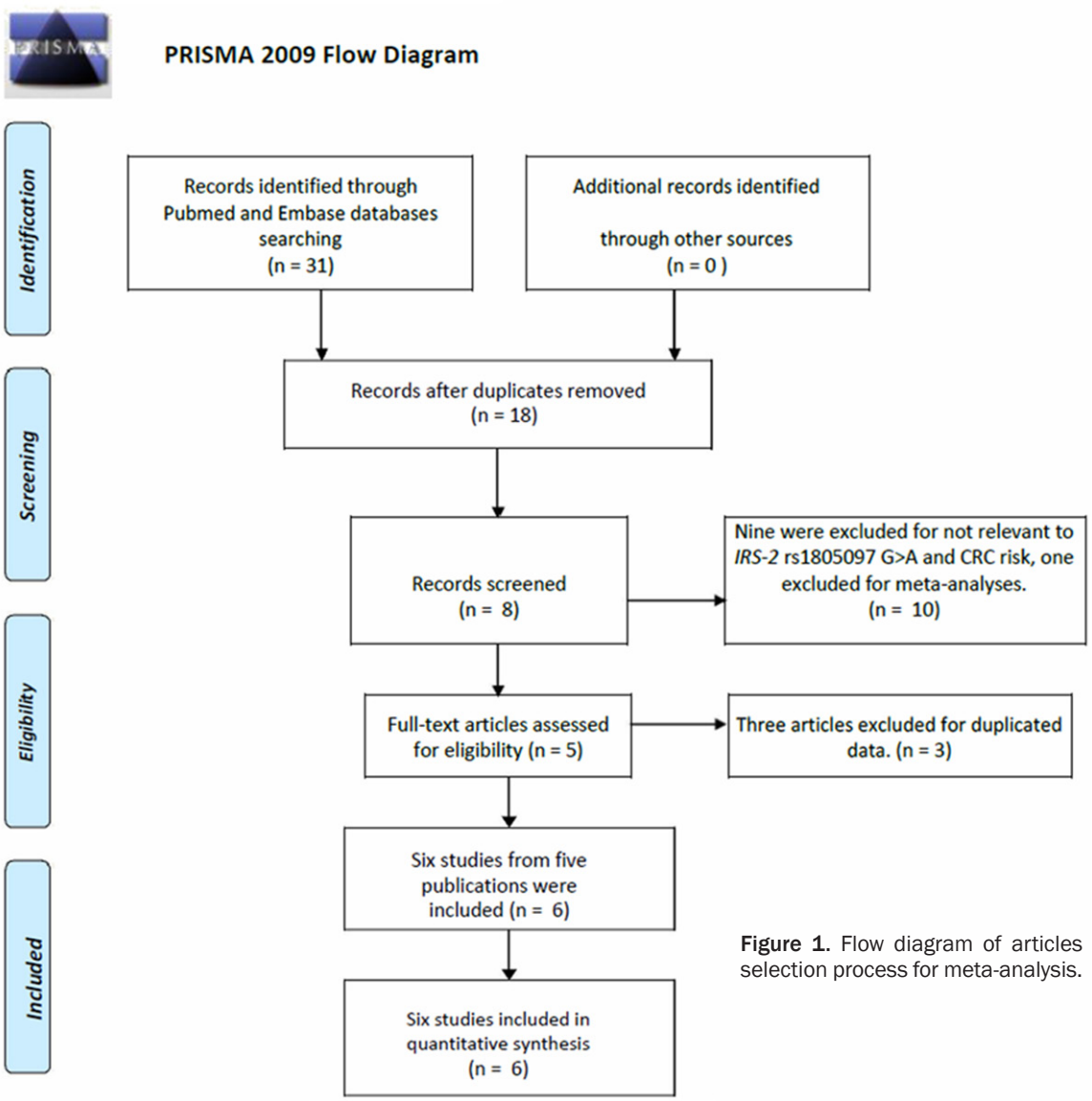

Figure 1. Flow diagram of articles selection process for meta-analysis.

out to check the effects of confounding factors: CRC region and ethnicities. Sensitivity analysis was performed to examine the reliability of our findings. Chi-square based Q test and I^2 test were used to assess the statistical heterogeneity across the included studies, and the heterogeneity was considered significant when I^2> 50% or P<0.10 [25]. The fixed-effects model was applied when there was no significant heterogeneity [26]; otherwise, the random-effects modelwas harnessed [27]. Publication bias was assessed by Begg's funnel plot and the Egger' linear regression test [28], and a P<0.10 was considered significant. All statistical analyses were conducted with STATA software (version 12.0; Stata Corporation, College Station, Texas USA). And all P values were defined as two-side.

Results

Characteristics

A total of thirty-one relevant publications were retrieved. **Figure 1** showed the major selecting process. Finally, there were five publications [15-19] (including six case-control studies) focused on the association between the *IRS-2* rs1805097 G>A polymorphism and CRC risk. Of these articles, three investigated mixed colorectal cancer [15-17], two investigated colon cancer [18, 19] and one investigated rectal cancer [18]. Among these case-control stud-

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

Study	Year	Country	Ethnicity	Source of control	Region	No. of cases/ controls	Adjusted factors	Quality score	Genotype Method	HWE
Mahmoudi et al	2014	Iran	Caucasians	Hospital-based	Colorectal cancer	261/339	Sex, ethnic background, and geographic origin	6.5	PCR-RFLP	0.638
Yukseloglu et al	2014	Turkey	Caucasians	Hospital-based	Colorectal cancer	161/197	Age, sex, ethnic background, and geographic origin	7	PCR-RFLP	0.621
Pechlivanis et al	2007	Czech Republic	Caucasians	Hospital-based	Colorectal cancer	712/748	Sex, ethnic background, and geographic origin	7.5	Taq-Man	0.281
Samowitz et al	2006	American	American population	Hospital-based	Colon cancer	1788/1981	Age, sex and geographic origin	8	PCR-RFLP	0.436
Slattery et al	2004	American	American population	Mixed	Colon cancer	1346/1544	Sex, ethnic background, and geographic origin	6.5	TaqMan	0.197
Slattery et al	2004	American	American population	Mixed	Rectal cancer	952/1205	Sex, ethnic background, and geographic origin	6.5	TaqMan	0.051

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Distribution of *IRS-2* rs1805097 G>A polymorphism genotype and allele

Study	Year	Case			Control			Case		Control	
		GG	GA	AA	GG	GA	AA	A	G	A	G
Mahmoudi et al	2014	109	118	34	139	153	47	186	336	247	431
Yukseloglu et al	2014	79	58	24	88	85	24	106	216	133	261
Pechlivanis et al	2007	211	277	81	268	309	106	439	699	521	845
Samowitz et al	2006	718	657	197	829	906	229	1051	2093	1364	2564
Slattery et al	2004	467	409	128	481	552	134	665	1343	820	1514
Slattery et al	2004	325	343	98	421	423	139	539	993	701	1265

HWE: Hardy-Weinberg equilibrium.

ies, three were from Caucasians [15-17] and three were from American populations [18, 19]. The characteristics of the included studies and the distribution of *IRS-2* rs1805097 G>A variants as well as their alleles are summarized in **Tables 1** and **2**, respectively. Results of quality scores were presented in **Table 1**.

Quantitative synthesis

There were five papers met the inclusion criteria with 5,220 CRC cases and 6,014 controls, one article (Slattery *et al.*) provided two independent groups, thus, we treated them separately [18]. A total of six case-control studies were eligible in the present meta-analysis. Overall, *IRS-2* rs1805097 G>A polymorphism associated with the decreased risk of overall CRC risk in dominant genetic model (OR, 0.91; 95% CI, 0.84-0.99; *P*=0.022, **Table 3** and **Figure 2**). In a subgroup analysis by the region of CRC, *IRS-2* rs1805097 G>A polymorphism was associated with a significantly decreased risk of colon cancer in dominant genetic model (OR, 0.84; 95% CI, 0.76-0.94; *P*=0.002, **Table 3** and **Figure 3**), but not mixed colorectal cancer and rectal cancer. In a subgroup analysis by ethnicity, a significant decreased CRC risk was identified among American populations in dominant genetic model (OR, 0.88; 95% CI, 0.80-0.97; *P*=0.007, **Table 3** and **Figure 2**), but not Caucasians. Other results of comparison are listed in **Table 3**.

Tests for publication bias, sensitivity analyses, and heterogeneity

Begg's funnel plot used to check potential publication biases indicated nearly symmetrical pattern, suggesting that there was no significant bias (A vs. G: Begg's test *P*=0.707; AA vs. GG: Begg's test *P*=1.000; AA+GA vs. GG: Begg's test *P*=0.707; AA vs. GA+GG: Begg's test *P*=1.000; **Figure 4**). In addition, Egger's test harnessed to quantitatively examine the publication bias, also found no evidence of bias (A vs. G: Egger's test *P*=0.467; AA vs. GG: Egger's test *P*=0.835; AA+GA vs. GG: Egger's test *P*=0.540; AA vs. GA+GG: Egger's test *P*=0.841).

Sensitivity analyses were performed by eliding an individual study at a time for each case-con-

Table 3. Meta-analysis of the *IRS-2* rs1805097 G>A polymorphism and colorectal cancer risk

	No. of study	A vs. G			AA vs. GG			AA+GA vs. GG			AA vs. GA+GG		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	6	0.96 (0.90-1.01)	0.132	0.939	0.97 (0.86-1.10)	0.669	0.994	0.91 (0.84-0.99)	0.022	0.260	1.02 (0.91-1.15)	0.721	0.695
Ethnicity													
Caucasians	3	1.00 (0.88-1.13)	0.943	0.913	0.98 (0.76-1.27)	0.875	0.900	1.01 (0.85-1.20)	0.884	0.519	0.96 (0.75-1.22)	0.732	0.625
American populations	3	0.94 (0.88-1.01)	0.093	0.772	0.97 (0.84-1.12)	0.687	0.898	0.88 (0.80-0.97)	0.007	0.198	1.04 (0.91-1.20)	0.541	0.422
Cancer type													
Mixed	3	1.00 (0.88-1.13)	0.943	0.913	0.98 (0.76-1.27)	0.875	0.900	1.01 (0.85-1.20)	0.884	0.519	0.96 (0.75-1.22)	0.732	0.625
Colon cancer	2	0.93 (0.86-1.00)	0.078	0.696	0.99 (0.84-1.17)	0.904	0.957	0.84 (0.76-0.94)	0.002	0.499	1.10 (0.94-1.29)	0.238	0.825
Rectal cancer	1	0.98 (0.85-1.13)	0.772	N/A	0.91 (0.68-1.23)	0.549	N/A	1.02 (0.84-1.23)	0.867	N/A	0.89 (0.67-1.18)	0.414	N/A

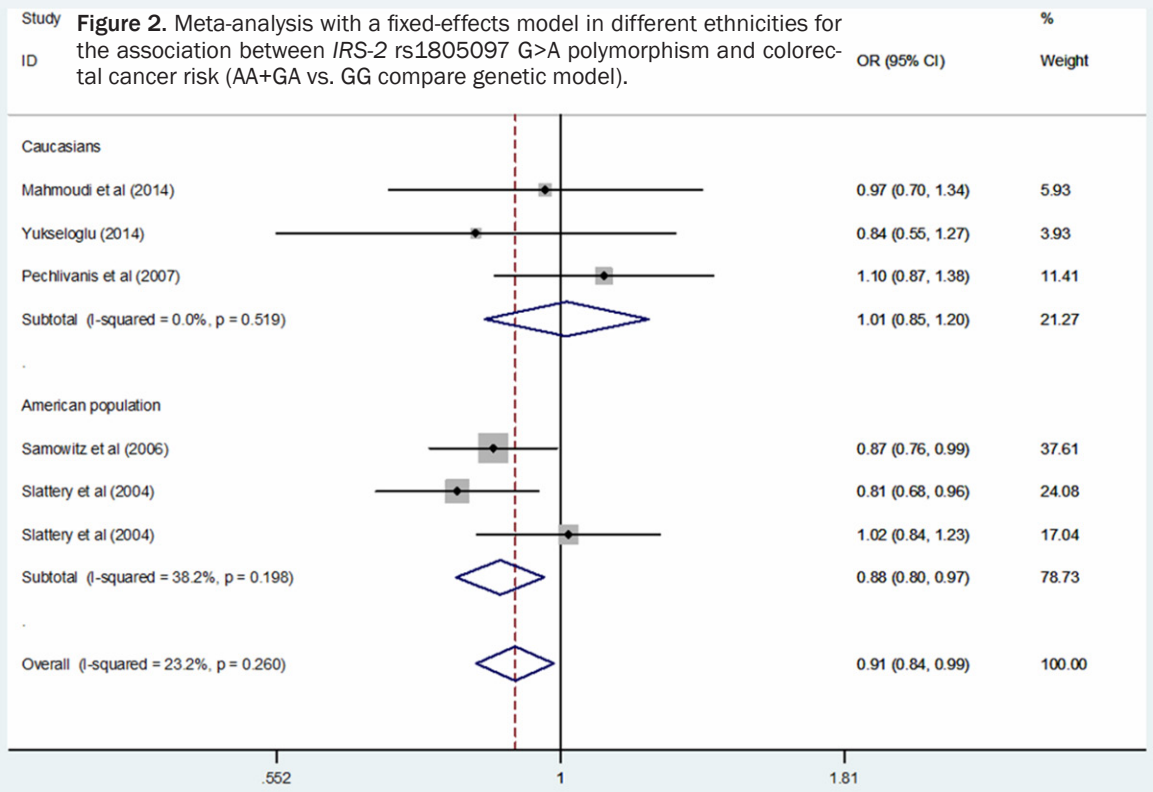

Figure 2. Meta-analysis with a fixed-effects model in different ethnicities for the association between *IRS-2* rs1805097 G>A polymorphism and colorectal cancer risk (AA+GA vs. GG compare genetic model).

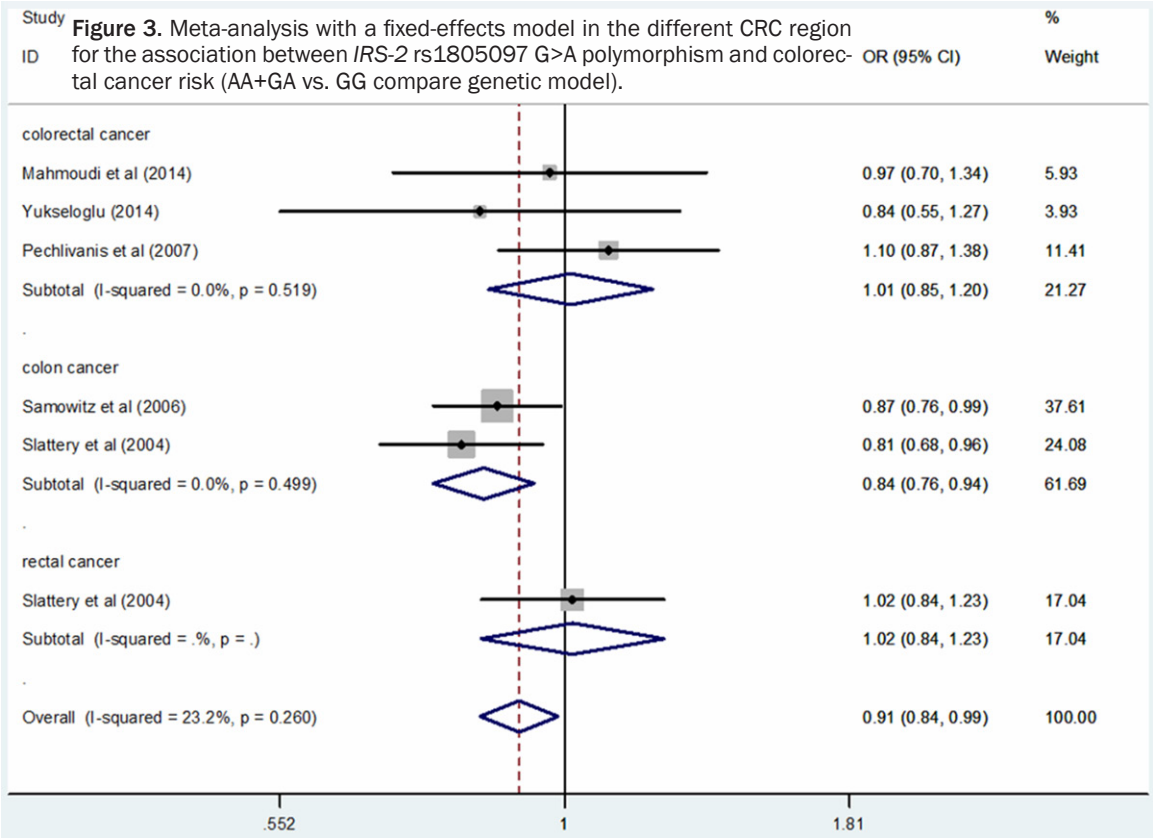

Figure 3. Meta-analysis with a fixed-effects model in the different CRC region for the association between *IRS-2* rs1805097 G>A polymorphism and colorectal cancer risk (AA+GA vs. GG compare genetic model).

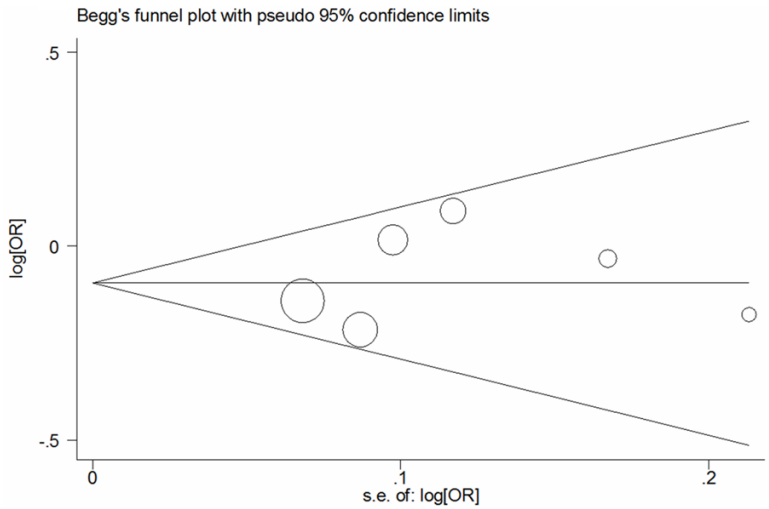

Figure 4. Begg's funnel plot of meta-analysis of the association between the *IRS-2* rs1805097 G>A polymorphism and the risk of colorectal cancer (AA+GA vs. GG compare genetic model).

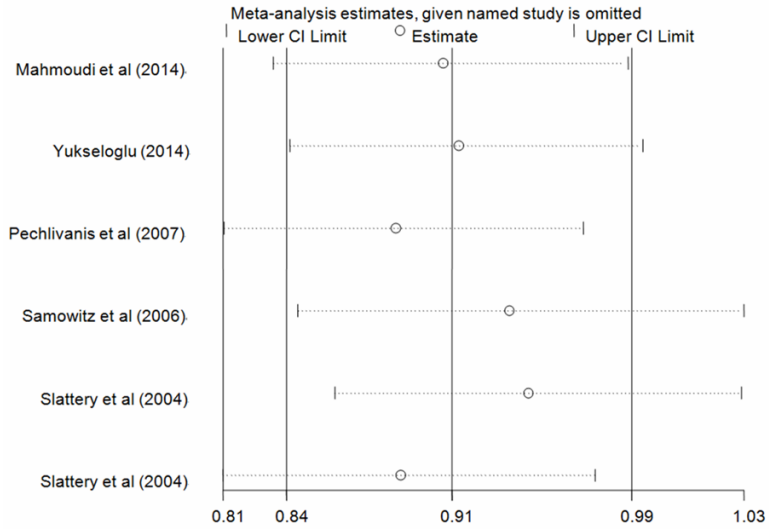

Figure 5. Sensitivity analysis of the influence of AA+GA vs. GG compare genetic model in overall colorectal cancer meta-analysis (random-effects estimates for *IRS-2* rs1805097 G>A polymorphism).

trol study. These corresponding pooled ORs were not materially changed (**Figure 5**, data not shown). The results of sensitivity analyses highlighted the stability of the results in our study.

As shown in **Table 3**, heterogeneity was not significant in all genetic comparison models, suggesting the stability of our findings.

Discussion

IRS2 express in various cells and modulate the function of metabolism, proliferation, and antiapoptosis [10, 11]. IRS-2, one of the typical signaling adaptors, was involved in several pathways, such as the extracellular signal-regulated kinase pathways and the phosphatidylinositol 3'-kinase pathways, despite the fact it has no intrinsic kinase activity and requires upstream activators [11]. Owing to its implication in multiple cancer-related pathways, IRS-2 was considered to play an important role in accelerating the progression and metastasis of malignancy [11, 29-31].

Of late, several epidemiologic investigations focused on the relationship of polymorphismsin *IRS-2* gene with CRC risk. The most prevalent *IRS-2* gene variants, rs1805097 G>A, has been most extensively studied. An amino acid substitution (Gly to Asp) at codon 1057 in *IRS2* gene by transversion of rs1805097 G>A polymorphism was located close to two putative tyrosine phosphorylation sites (positions 1042 and 1072), and might alter the tertiary structure and function of IRS2 [32]. Recently, Slattery *et al.* and Samowitz *et al.* reported that a nonsynonymous mutation (G→A) in *IRS-2* (rs1805097 G>A polymorphism) decreased the susceptibility of colon cancer [18, 19]. Nevertheless, these studies may have insufficient power to obtain a conclusive result, probably due to certain limitations such as small sample size. Meta-analysis is considered a powerful way for pooling the conflicting findings from different studies with more statistical power; thus, it can get more reliable results than a single study [33]. In this pooled-analysis, we found that *IRS-2* rs1805097 G>A polymorphism was correlated with the decreased susceptibility of CRC (**Table 3**). Our findings suggest the presence of the A allele, which is correlated with affecting IRS2 structure and activ-

ity, might decrease the risk of CRC. A stratified analysis was also performed regarding different ethnicities and the region of CRC for this SNP. This polymorphism may be associated with the decreased susceptibility of CRC among American populations, but not Caucasians. We also found that *IRS-2* rs1805097 G>A polymorphism was associated with a significantly decreased risk of colon cancer, but not mixed colorectal cancer and rectal cancer. This pooled-analysis indicated the influence of *IRS-2* rs1805097 G>A variants and diversity in different populations and different region to the risk of CRC. To the best of our knowledge, numerous genetic and environmental factors can influence the susceptibility of CRC on different levels. Due to lack of sufficient data of environmental factors and life style, these important factors were not considered. Future studies are needed to validate our results, particularly with regard to environmental factors and the interactions of gene-gene and gene-environment.

Certain merits in our study should be addressed. Firstly, the present meta-analysis was the most extensive synthesis exploring the relationship of *IRS-2* rs1805097 G>A polymorphism with CRC susceptibility. Secondly, our findings suggested the correlation between *IRS-2* rs1805097 G>A polymorphism and CRC risk. Thirdly, all included studies were high quality (the quality score ≥ 6), suggesting our results were relatively reliable.

However, in the present meta-analysis, there are some limitations inherited from the published studies. First of all, only six published case-control studies were recruited, and certain negative and/or non-significant studies maybe remain unpublished, therefore the bias might inevitably occur. Secondly, the findings were based on crude ORs and CIs. Although the participants were matched on sex, age and residence in all included studies, these factors might only slightly affect the effective evaluations and further precise assessment should be adjusted by other potentially suspected factors, such as alcohol consumption, smoking status, glucose level and body mass index *et al*. Due to lack of these detailed background data in the included studies, an adjusted estimates was not conducted. Finally, the *IRS-2* rs1805097 G>A polymorphism and other SNPs may locate on the same exon, given this polymorphism might involve in the development of CRC by altering the spatial structure and function of IRS-2 protein, thus, other important SNPs in *IRS-2* gene should not be ignored.

In conclusion, our findings indicate that the *IRS-2* rs1805097 G>A polymorphism is correlated with the decreased susceptibility of CRC, especially in American populations and colon cancer subgroups. Nevertheless, for practical reasons, larger epidemiologic studies assessing different populations (e.g., Asians and Africans) and incorporating with detailed functional comprehensive assessment are warranted to validate these findings.

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Disclosure of conflict of interest

None.

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