REVIEW

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Association between *rs1862513* and *rs3745367* Genetic Polymorphisms of Resistin and Risk of Cancer: A Meta-Analysis

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Abstract

The present study aimed to assess any associations between resistin gene (*RETN*) polymorphisms and cancer susceptibility by conducting a meta-analysis. A comprehensive literature search was performed with PubMed, Web of Science, Scopus and Google Scholar for relevant studies published before April 2018. For the *rs1862513* polymorphism, data from 9 studies covering 1,951 cancer patients and 2,295 healthy controls were included in this meta-analysis. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Our meta-analysis revealed that this *RETN* polymorphism significantly increased the risk of cancer in codominant (OR=1.23, 95% CI= 1.01-1.50, p=0.04, CG vs CC; and OR=1.25, 95% CI= 1.03-1.53, p=0.03, GG vs CC), dominant (OR=1.19, 95% CI= 1.05-1.35, p=0.006, CG+GG vs CC), and allele (OR=1.14, 95% CI= 1.00-1.30, p=0.04, G vs C) inheritance genetic models. Stratification analysis by cancer type revealed that the *rs1862513* variant significantly increased the risk of colorectal and breast cancer, and that cancer overall in Caucasians (OR=1.22, 95% CI= 1.04-1.43, p=0.02, CG+GG vs CC; OR=1.18, 95% CI= 1.04-1.34, p=0.01, G vs C). The data revealed no correlation between the *rs3745367* polymorphism and cancer risk. Further well-designed studies with larger sample sizes and different ethnicities are warranted to validate the present findings.

Keywords: Resistin- *RETN*- cancer- polymorphism- meta-analysis

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Introduction

Cancer, a major public health issue, is a leading cause of death worldwide. It has been estimated that more than 14.1 million new cases and 8.2 million cancer-related deaths happened annually (Siegel et al., 2016). Cancer is recognized as a multifactorial disease resulting from the integration between genetic and environmental factors (Lichtenstein et al., 2000). Single-nucleotide polymorphisms (SNPs) and small insertions or deletions (indels) are the most common genetic variations in human genome (Hashemi et al., 2018). Several studies showing the association between functional SNPs in various genes and the risk of developing cancer.

Adipokines, such as resistin, leptin, adiponectin and visfatin, are mainly synthesized in white adipose tissue and have been related to the pathogenesis of autoimmune disease, inflammatory diseases and cancer (John et al., 2006; Salageanu et al., 2010; Riondino et al., 2014; Muppala et al., 2017; Li and Han, 2018).

Resistin is a 12.5-kDa cysteine-rich polypeptide that upregulates the expression of proinflammatory cytokines and helps expand the population of regulatory T cells (Steppan et al., 2001; Bokarewa et al., 2005). The *RETN* gene encode resistin is mapped to chromosome 9 (19p13.2). Resistin is increased in type 2 diabetes and is closely correlated with insulin resistance and obesity (Shuldiner et al., 2001; Steppan et al., 2001; John et al., 2006). Obesity is well recognized as a risk factor for colorectal cancer development (Joshi et al., 2014; Joshi and Lee, 2014). Resistin may also be involved in the pathogenesis of cancer (Gonullu et al., 2010; Danese et al., 2012; Riondino et al., 2014). The serum levels of resistin have been shown to be higher in colorectal cancer (CRC) (Kumor et al., 2009; Gonullu et al., 2010; Nakajima et al., 2010; Danese et al., 2012; Slomian et al., 2017), and breast cancer (Dalamaga et al., 2013; Assiri et al., 2015; Deshmukh et al., 2015; Assiri and Kamel, 2016; Zeidan et al., 2018) than controls subjects.

Previous studies also demonstrated that the *RETN* gene variants were associated with the regulation of *RETN* gene expression and serum levels of resistin

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(Cho et al., 2004; Osawa et al., 2004).

In the last few years, a number of studies on the association between REST gene polymorphisms and risk of cancer have been published, with controversial results (Wagsater et al., 2008; Pechlivanis et al., 2009; Al-Harithy and Al-Ghafari, 2010; Alharithy, 2014; Mahmoudi et al., 2014; Duzkoylu et al., 2015; Mahmoudi et al., 2016; Hu et al., 2017; Kohan, 2017; Munoz-Palomeque et al., 2018). Therefore, we conducted a meta-analysis to exactly establish the association between *RETN* rs1862513 C>G (-420 C<G) and rs3745367 (+299 G>A gene polymorphisms and the risk of cancer.

Literature search

Literature searching in the databases such as PubMed, Web of Science, Scopus, and Google Scholar was performed for all articles describing an association between resistin polymorphisms and cancer risk published up to April 2018. Comprehensive search strategies involved the Mesh term and Keywords: ('resistin' or '*RETN*'), ('polymorphism' or 'variant' or 'genotype' or 'SNP' or 'mutations'), ('cancer' or 'tumor'). Relevant studies which were eligible for the meta-analysis must meet the following criteria: 1) Original case-control studies of the correlation between the *RETN* polymorphisms and cancer 2) studies provided sufficient information of the genotype frequencies of *RETN* polymorphisms in both cases and controls. The criteria for exclusion were: 1) the articles have described case reports, reviews, overlapped data, animal or mechanism studies for *RETN* polymorphisms and cancer; 2) no genotype frequency or genotype information were provided for *RETN* polymorphism and cancer.

Data extraction

The papers were reviewed by two independent researchers. The following data were collected from each study such as the first author's last name, publication year, ethnicity, the sample size, and the genotype and allele frequencies of cases and controls.

Statistical analysis

Meta-analysis was carried out using Revman 5.3 software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA 14.1 software (Stata Corporation, College Station, TX, USA). Hardy-Weinberg Equilibrium (HWE) in the control group was tested by χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled using forest-plots graphs to evaluate the association between *RETN* polymorphisms and cancer. The significance of the pooled OR was determined with the Z-test, and P-values < 0.05 were considered statistically significant. Heterogeneity among studies was assessed using the I^2 statistic and the χ^2 test-based Q statistic. A $p < 0.10$ and an $I^2 > 50\%$ indicated significant heterogeneity. Once heterogeneity existed among studies, a random-effect model was applied; otherwise a fixed-effect model was used.

Publication bias was assessed by funnel plot. The degree of asymmetry was measured using Egger's linear regression test; $p < 0.05$ was considered significant publication bias.

Sensitivity analysis

Sensitivity analysis was achieved using the method of eliminating studies one by one to verify whether our results were influenced by each included study or not.

Results

Study characteristics

10 studies met all the inclusion criteria and were included in this meta-analysis. Characteristics of the eligible studies are summarized in Table 1.

For *rs1862513* polymorphism, data from 9 studies including 1951 cancer patients and 2,295 healthy controls were included in this meta-analysis. Regarding *rs3745367* polymorphism, data from 3 studies containing 603 cases and 701 controls were included in this meta-analysis.

Quantitative synthesis

All the calculated results were summarized in Table 2. Our meta-analysis revealed that *rs1862513* polymorphism of *RETN* significantly increased the risk of cancer in codominant (OR=1.23, 95%CI= 1.01-1.50, p=0.04, CG vs CC; and OR=1.25, 95%CI= 1.03-1.53, p=0.03, GG vs CC), dominant (OR=1.19, 95%CI= 1.05-1.35, p=0.006, CG+GG vs CC), and allele (OR=1.14, 95%CI= 1.00-1.30, p=0.04, G vs C) inheritance genetic models (Figure 1 and Table 2).

Stratification analysis by cancer type showed that *rs1862513* variant significantly increased the risk of colorectal cancer as well as breast cancer (Table 2).

As shown in Table 2, the *rs1862513* variant significantly increased the risk of cancer in Caucasian in dominant (OR=1.22, 95% CI= 1.04-1.43, p=0.02, CG+GG vs CC) and allele (OR=1.18, 95% CI= 1.04-1.34, p=0.01, G vs C) genetics model.

Regarding *rs3745367* variant, the finding showed no significant association between the variant and cancer risk (Table 2).

Publication bias

The potential publication bias was assessed using a Begg's funnel plot (Figure 2) and Egger's test (Table 2). Begg's and Egger's tests proposed no evident publication bias in codominant, dominant recessive, overdominant, and allele inheritance models.

Sensitivity analysis

To verify the outcome of our analyses, we conducted a sensitivity analysis by excluding studies one by one, and then calculating the pooled estimate for the remaining studies (Figure 3). The sensitivity analysis proposed that certain studies significantly affect the association between *RETN* polymorphism and risk of cancer. We believe that the small number of studies included in our meta-analysis may contribute to the influence of the abovementioned studies; if more studies had been included, the influence of any one study would be decreased.

Table 1. Characteristics of the Included Studies on RETN rs1862513 and rs3745367 Polymorphisms and Risk of Cancer

First Author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping Method	Case/ controls	Genotype and allele distribution of cases and controls										HWE (p)
								Cases					controls					
rs1862513								CC	CG	GG	C	G	CC	CG	GG	C	G	
Al-Harithy	2010	Saudi Arabia	Asian	Colon cancer	HB	PCR-RFLP	60/6	16	33	11	65	55	24	20	16	68	52	0.013
Alharithy	2014	Saudi Arabia	Asian	Colon cancer	HB	PCR-RFLP	60/6	15	33	12	63	57	24	20	16	68	52	0.013
Duzkoylu	2015	Turkey	Caucasian	Colorectal cancer	HB	PCR-RFLP	123/79	53	61	9	167	79	31	36	12	98	60	0.771
Hu	2017	China	Asian	Lung cancer	HB	Real-time PCR	371/451	164	157	50	485	257	182	203	66	567	335	0.444
Kohan	2017	Iran	Asian	Breast cancer	HB	PCR-RFLP	150/15	50	63	37	163	137	63	63	24	189	111	0.225
Mahmoudi	2014	Iran	Asian	Colorectal cancer	HB	PCR-RFLP	197/217	38	83	76	159	235	56	85	76	197	237	0.002
Munoz- Palomeque	2018	Mexico	Caucasian	Breast cancer	PB	PCR-RFLP	100/308	53	42	5	148	52	199	102	7	500	116	0.144
Pechlivanis	2009	Czech Republic	Caucasian	Colorectal cancer	HB	PCR-RFLP	642/714	317	262	63	896	388	393	265	56	1051	377	0.230
Wagsater	2008	Sweden	Caucasian	Colorectal cancer	HB	Taqman	248/256	127	95	26	349	147	137	103	16	377	135	0.563
rs3745367								GG	GA	AA	G	A	GG	AG	AA	G	A	HWE (p)
Alharithy	2014	Saudi Arabia	Asian	Colon cancer	HB	PCR-RFLP	60/6	3	51	6	57	63	15	39	6	69	51	0.011
Hu	2017	China	Asian	Lung cancer	HB	Real-timePCR	371/451	164	164	43	492	250	190	194	67	574	328	0.134
Mahmoudi	2016	Iran	Asian	Colorectal cancer	HB	PCR-RFLP	312/438	65	72	35	202	142	78	86	26	242	138	0.767

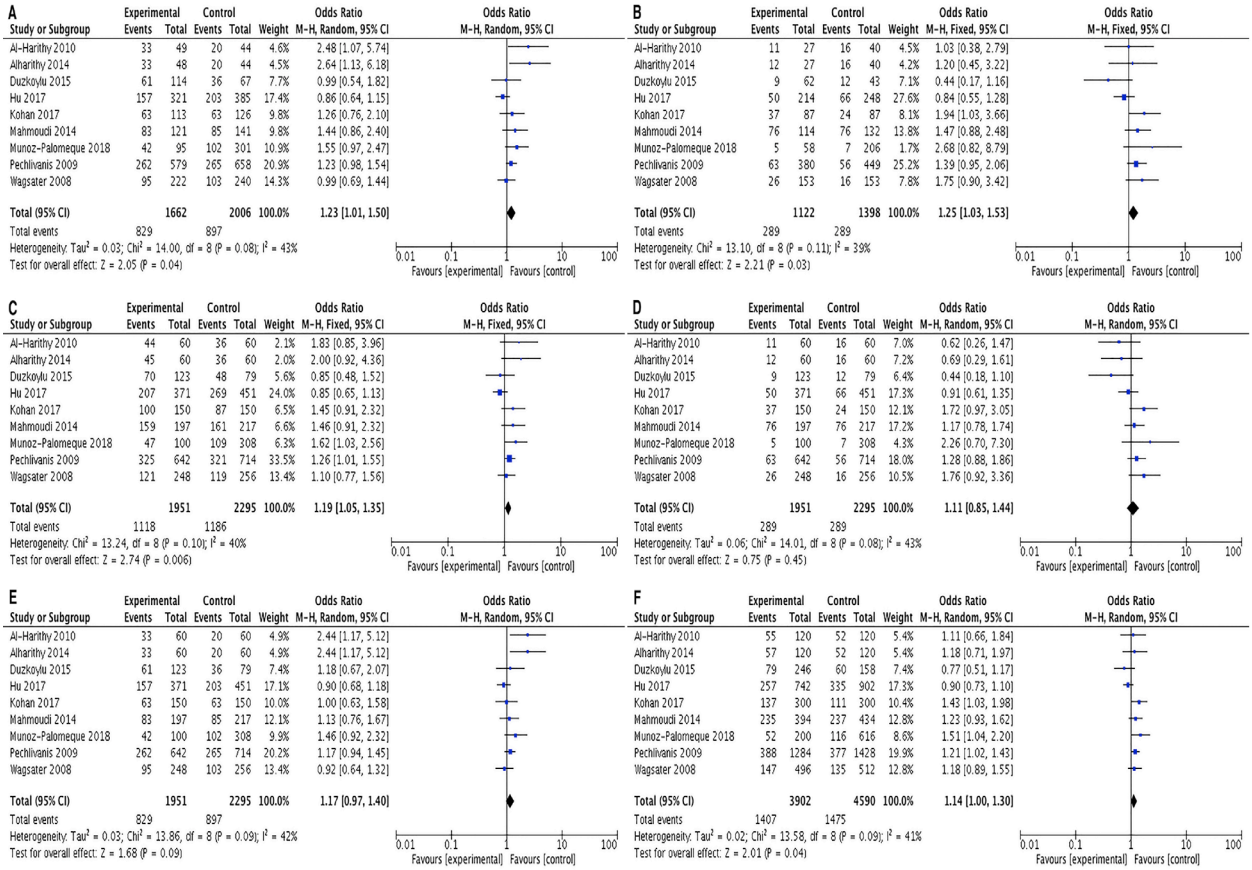

Figure 1. Forest Plot of the Risk of Cancer Associated with RETN rs1862513 Polymorphism under Codominant Heterozygous Model (A), Codominant Homozygous Model (B), Dominant Model (C), Reccesive Model (D), Ovedominanat Model (E), and Allelic Model (F).

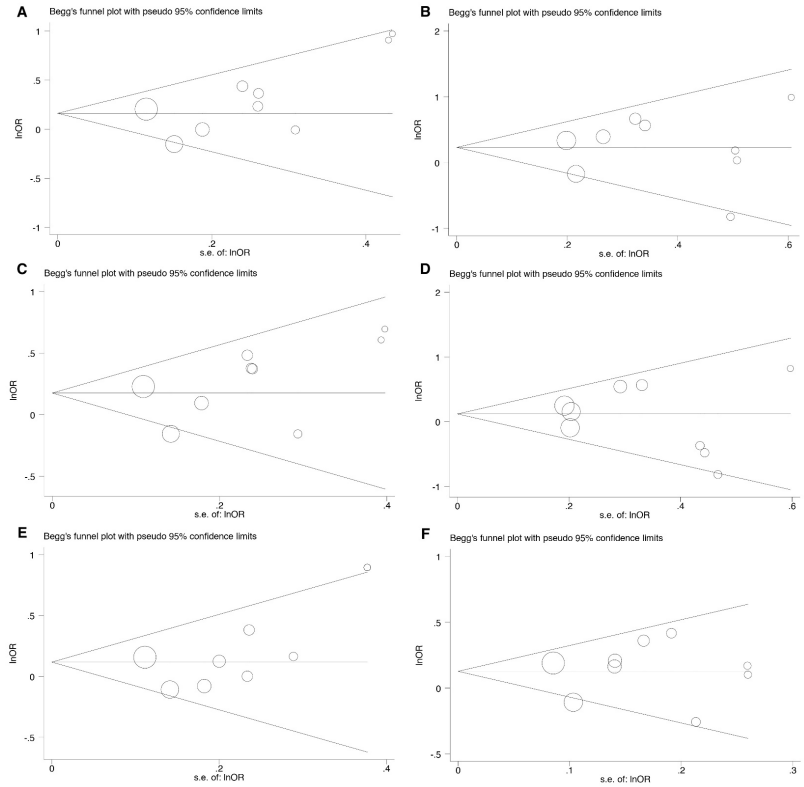

Figure 2. Begg's Funnel Plot for Publication Bias Test for RETN rs1862513 Polymorphism. Each point represents a separate study for the indicated association. (A), heterozygous model; (B), codominant homozygous model; (C), dominant model; (D), reccesive model; (E), ovedominanat model; (F), allelic model.

Table 2. The Pooled ORs and 95%CIs for the Association between RETN Polymorphisms and Cancer Susceptibility

Polymorphism	Association test			Heterogeneity test			Egger's test P	Begg's test P
	OR (95%CI)	Z	p	$\chi 2$	I^2 (%)	p		
rs1862513 C>G								
CG vs CC	1.23 (1.01-1.50)	2.05	0.04	14.00	43	0.08	0.891	0.532
GG vs CC	1.25 (1.03-1.53)	2.21	0.03	13.10	39	0.11	0.607	0.621
CG+GG vs CC	1.19 (1.05-1.35)	2.74	0.006	13.24	40	0.10	0.451	0.211
GG vs CG+CC	1.11 (0.85-1.35)	0.75	0.45	14.01	43	0.08	0.926	0.118
CG vs GG+CC	1.17 (0.97-1.40	1.68	0.09	13.86	42	0.09	0.153	0.466
G vs C	1.14 (1.00-1.30)	2.01	0.04	13.58	41	0.09	0.520	0.532
rs3745367 G>A								
AG vs GG	1.32 (0.72-2.45)	0.90	0.37	7.80	74	0.002	0.407	0.602
AA vs GG	1.38 (0.60-3.17)	0.76	0.44	7.67	74	0.02	0.883	0.117
AG+GG vs AA	1.34 (0.73-2.46)	0.96	0.34	8.43	76	0.01	0.368	0.602
AA vs AG+GG	1.05 (0.60-1.84)	0.18	0.92	4.69	57	0.10	0.193	0.117
AG vs AA+GG	1.19 (0.74-1.93)	0.73	0.47	6.34	68	0.04	0.679	0.602
A vs G	1.11 (0.83-1.50)	0.71	0.48	5.43	63	0.07	0.187	0.117

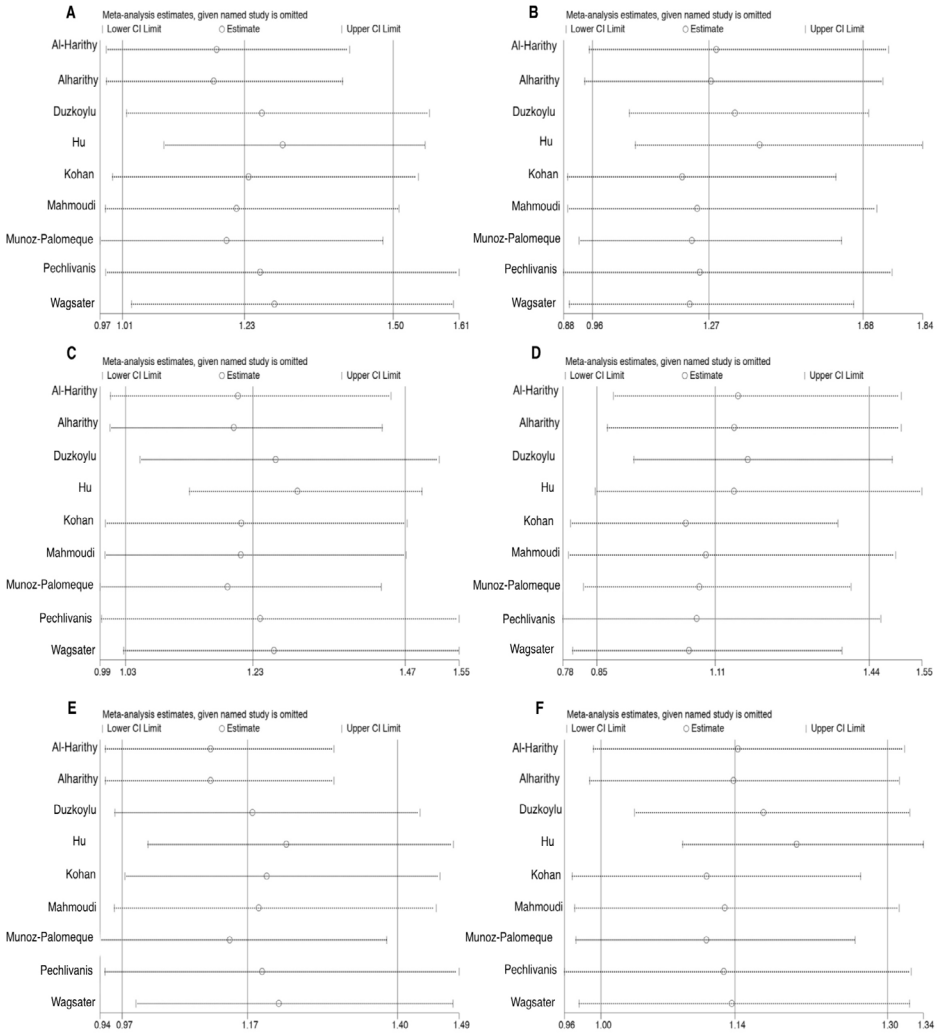

Figure 3. Results of Sensitivity Analysis of the Entire Database under Codominant Heterozygous Model (A), Codominant Homozygous Model (B), Dominant Model (C), Reccesive Model (D), Ovedominanat Model (E), and Allelic Model (F).

Table 3. Stratified Analysis of RETN rs1862513 C>G Polymorphism on Cancer Susceptibility

Type of cancer	NO.	CG vs CC		GG vs CC		CG+GG vs CC		GG vs CG+CC		CG vs GG+CC		G vs C	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Cancer type													
Colorectal cancer	6	1.25 (1.06-1.47)	0.009	1.31 (1.02-1.68)	0.04	1.25 (1.07-1.46)	0.005	1.01 (0.72-1.43)	0.93	1.19 (1.02-1.39)	0.03	1.16 (1.03-1.30)	0.01
Breast cancer	2	1.41 (0.99-1.99)	0.05	2.07 (1.18-3.63)	0.01	1.53 (1.10-2.13)	0.01	1.80 (1.07-3.02)	0.03	1.20 (0.87-1.67)	0.26	1.47 (1.15-1.87)	0.002
Lung cancer	1	0.86 (0.64-1.15)	0.31	0.84 (0.55-1.28)	0.42	0.85 (0.65-1.13)	0.27	0.91 (0.61-1.35)	0.64	0.90 (0.68-1.7)	0.44	0.90 (0.73-1.10)	0.29
Ethnicities													
Asian	5	1.42 (0.94-2.14)	0.10	1.19 (0.91-1.55)	0.21	1.33 (0.94-1.89)	0.11	1.05 (0.83-1.32)	0.70	1.27 (0.89-1.81)	0.81	1.09 (0.95-1.24)	0.24
Caucasian	4	1.19 (1.00-1.41)	0.05	1.31 (0.75-2.30)	0.35	1.22 (1.04-1.43)	0.02	1.23 (0.71-2.11)	0.46	1.14 (0.97-1.35)	0.11	1.18 (1.04-1.34)	0.01

Discussion

Cancer is a complex disease and it has been proposed that individual genetic variants may only have a modest independent effect on the disease. Adipokines, secreted by the adipose tissue, are convincing candidates for the relationship between obesity and cancer risk (Guadagni et al., 2009; Li et al., 2017; Zhang et al., 2017; Malvi et al., 2018). Obesity leads to insulin resistance and hyperinsulinemia, and insulin levels are positively correlated with colorectal cancer risk (Schoen et al., 1999; Giovannucci, 2007).

Up to now, a number of studies have been carefully designed and investigated the effect of genetic polymorphisms of *RETN* gene on the risk of cancer. Most of these studies were based on a small sample size and the findings were inconsistent (Wagsater et al., 2008; Pechlivanis et al., 2009; Al-Harithy and Al-Ghafari, 2010; Alharithy, 2014; Mahmoudi et al., 2014; Duzkoylu et al., 2015; Mahmoudi et al., 2016; Hu et al., 2017; Kohan, 2017; Munoz-Palomeque et al., 2018). This is the first meta-analysis conducted to specify the effect of *RETN rs1862513* and *rs3745367* polymorphisms on susceptibility to cancer. Data from 9 studies indicated that *RETN rs1862513* variant significantly increased the risk of cancer in codominant, dominant, and allele inheritance genetic models. We did not find any publication bias, which shows the reliability of the pooled results. Heterogeneity across studies suggests that there is a variation among the outcomes of studies than expected by chance. Sensitivity analysis also revealed an evidence of heterogeneity.

Stratified analyses based on cancer type showed that the *rs1862513* variant significantly increased the risk of colorectal cancer as well as breast cancer.

The *rs1862513* (-420 C>G) polymorphism is located in the promoter region of *RETN* and has been shown to be associated with *RETN* protein expression (Cho et al., 2004; Osawa et al., 2004).

The *RETN* is a polymorphic and a functional polymorphism at -420 (*rs186513*) affects promoter activity and increases the expression of resistin. The molecular mechanism by which resistin affect cancer risk is not fully understood.

Regarding *rs3745367* variant, data from 3 studies did not support an association between variant and risk of cancer.

A significant deviation from HWE was found in 3 studies included the meta-analysis (Al-Harithy and Al-Ghafari, 2010; Alharithy, 2014). There is no clear clarification for deviation from HWE. The possible cause may be due to genetic drift.

In summary, our metanalysis investigation showed that rs1862513 polymorphism of *RETN* is a risk factor for cancer development. More studies with larger sample sizes are necessary to clarify the possible roles of *RETN* polymorphisms in cancer.

Conflict of interest

The Authors declare that there is no conflict of interest to disclose.

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