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META-ANALYSIS

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The first combined meta-analytic approach for elucidating the relationship of circulating resistin levels and *RETN* gene polymorphisms with colorectal and breast cancer

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Abstract

Background: Evidence suggests that circulating resistin levels are altered in colorectal cancer (CRC) and breast cancer (BC). Again, polymorphisms in resistin-encoding gene *RETN* have been evaluated in CRC and BC. However, there is a scarcity of data establishing the relationship of resistin and *RETN* polymorphisms (rs1862513 and rs3745367) with these cancers. This study aimed to analyze the relationship of resistin levels and *RETN* polymorphisms with CRC and BC in a combined meta-analytic approach.

Main body of the abstract: After a comprehensive online literature search, screening and eligibility check, 41 articles (31 with resistin level and 10 with *RETN* polymorphisms) were retrieved for meta-analyses. The mean difference (MD) of resistin was calculated and pooled to investigate the effect sizes with a 95% confidence interval (CI), and the connection of genetic polymorphisms was analyzed with an odds ratio (OR) and 95% CI. The analysis showed that resistin level is significantly higher in CRC (MD = 3.39) and BC (MD = 3.91) patients. Subgroup analysis in CRC showed significantly higher resistin in serum (MD = 4.61) and plasma (MD = 0.34), and in BC, a significantly elevated resistin level was reported in premenopausal (MD = 7.82) and postmenopausal (MD = 0.37) patients. Again, *RETN* rs1862513 showed a significantly strong association with CRC (codominant 1—OR 1.24, codominant 2—OR 1.31, dominant model—OR 1.25, and allele model—OR 1.16) and with BC (codominant 2—OR 1.51, codominant 3—OR 1.51, recessive model—OR 1.51, and allele model—OR 1.21). *RETN* rs3745367 did not show any association with these cancers.

Short conclusion: Overall, our analysis indicates that higher circulating resistin levels are associated with an elevated risk of CRC and premenopausal and postmenopausal BC. Besides, rs1862513 in *RETN* gene is significantly connected with both CRC and BC.

Keywords: Resistin, *RETN*, Breast cancer, Colorectal cancer, Meta-analysis

Background

Colorectal cancer (CRC) is a frequently occurred malignancy throughout the world. It is consistently placed among the top three cancers based on morbidity and mortality rates [1, 2]. It is a public health concern worldwide, particularly in developed countries, where the incidence rate (about 18%) is higher than the developing or under-developed countries. In the past few decades, the percentage of CRC cases are rapidly increasing in developing regions. This is considered a complex multi-pathway malignancy associated with a chronic inflammatory reaction, metabolic syndrome, obesity, and insulin resistance. Recent evidence suggests that adipocyte-secreted factors such as resistin, adiponectin, visfatin, leptin, and various cytokines (IL-6, IL-10, TNF-α,

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etc.) may play the key role to correlate obesity with CRC [3, 4].

In terms of incidence, breast cancer (BC) has been the leading malignancy among women worldwide. It is also one of the commonest causes of mortality, comprising almost 6.6% of all cancer-related deaths. Statistics showed that about 2.1 million BC cases were recorded in 2018, leading to the death of 626,679 patients [5, 6]. BC is a heterogeneous and polygenic multifactorial disease that occurs due to the combined effect of multiple factors, including genetic and epigenetic abnormalities, unhealthy lifestyle, and environmental pollutants [7]. Taking high-fat diets, physical inactivity, early menstrual cycle, late menopause, denser breast tissues, age, hormonal imbalance or exogenous hormone therapy, radiation therapy, high mental stress, and exposure to environmental pollutants are the common causes of BC [8].

Resistin, also known as an adipocyte-secreted factor, is a 12.5 kDa cysteine-rich 108-amino-acid peptide adipocytokine secreted by adipocytes and monocytes [9]. This inflammatory protein was first identified in mice adipose tissue and subsequently named resistin due to its role in insulin resistance [10]. Translational studies revealed that human resistin is primarily secreted from macrophages rather than from adipocytes [11]. The adipokine resistin belongs to the family of resistin-like molecules (RELM) and is commonly localized in inflammatory zone 3 [10, 12]. Resistin is one of the most common candidate molecules that play a significant role in numerous physiological and pathological processes in human body. Accumulating evidence suggests that this cytokine exhibits inflammatory, autoimmune, metabolic, proliferative, angiogenic, and metastatic properties via multiple cellular and molecular pathways [1, 13].

Although resistin was initially investigated for a functional role in insulin resistance and obesity, its diverse role in different diseases has drawn the concentration of researchers, making it one of the most studied biomarkers. Serum levels of resistin have been implicated in the occurrence and progression of various inflammatory processes, such as atherosclerosis, diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, inflammatory bowel disease, rheumatic arthritis, and malignant tumors [1, 13, 14]. Elevated concentration of resistin in plasma acts as a prognostic biomarker in the progression and metastasis of breast, colorectal, ovarian, pancreatic, lung, endometrial, prostate, and other obesity-related cancers in human. High serum resistin level was also found to be strongly associated with tumor stage and poor survival [15, 16]. Previous studies reported a significantly higher concentration of serum resistin in BC patients. Moreover, enhanced expression of serum resistin in BC tissues was found to be correlated with postmenopausal BC and poor tumor prognosis [17]. Again, increased circulating resistin levels in CRC have also been documented by previous studies. However, there is a gap in the consistency of previously published results on the association of serum resistin level with BC and CRC risk, which should be clarified.

Resistin is encoded by *RETN*, an important adipocytokine gene located on chromosome 9 (19p13.3) and mainly expressed in adipocytes [18, 19]. Previous investigations on *RETN* genetic polymorphisms reported their strong correlation with circulating resistin levels, *RETN* expression, and body mass index (BMI) [20, 21]. Single nucleotide polymorphisms (SNPs) are generally spotted in the promoter region and 3'-untranslated region of *RETN* [22]. Common SNPs in the *RETN* gene, including promoter rs1862513 (C-180G/ C-420G) and rs3745367 (G + 299A), have been previously analyzed for their contribution to the progression of several diseases, including CRC [19, 21, 23–25] and BC [18, 22]. However, the outcomes of these studies remained conflicting and need to be re-evaluated.

To date, numerous case–control studies have been carried out in different ethnic groups to examine the correlation of resistin levels and *RETN* gene polymorphisms with multiple cancers, especially with CRC and BC. However, these findings remained inconclusive and inconsistent. To our knowledge, no previous systemic review and meta-analysis was conducted to evaluate the relationship between both circulatory resistin and *RETN* gene polymorphisms and these cancers. Therefore, we performed the first combined meta-analyses to establish a comprehensive relationship of resistin levels in serum or plasma and *RETN* genetic polymorphisms with CRC and BC.

Results

Description of the included studies

Our literature search generated a total of 2674 publications in PubMed, ScienceDirect, BMC, EMBASE, Cochrane Library, Web of Science, and Google Scholar databases for both meta-analyses shown in Fig. 1. Following the removal of duplicates and studies analyzing biomarkers other than resistin and polymorphisms other than *RETN*, 579 records remained for the title and abstract screening. Due to the lack of full-text access and excluding reviews, commentaries, or studies with inadequate data, 41 articles remained for both qualitative and quantitative analysis (meta-analysis) among which 31 for resistin level and 10 for *RETN* genetic association.

Of 31 articles with resistin levels, a total of 16 studies were on CRC [11, 25–39], and 15 studies were on BC [18, 40–53]. Among the 16 studies on CRC, 9 studies [25–33] analyzed the serum resistin in 382 CRC cases

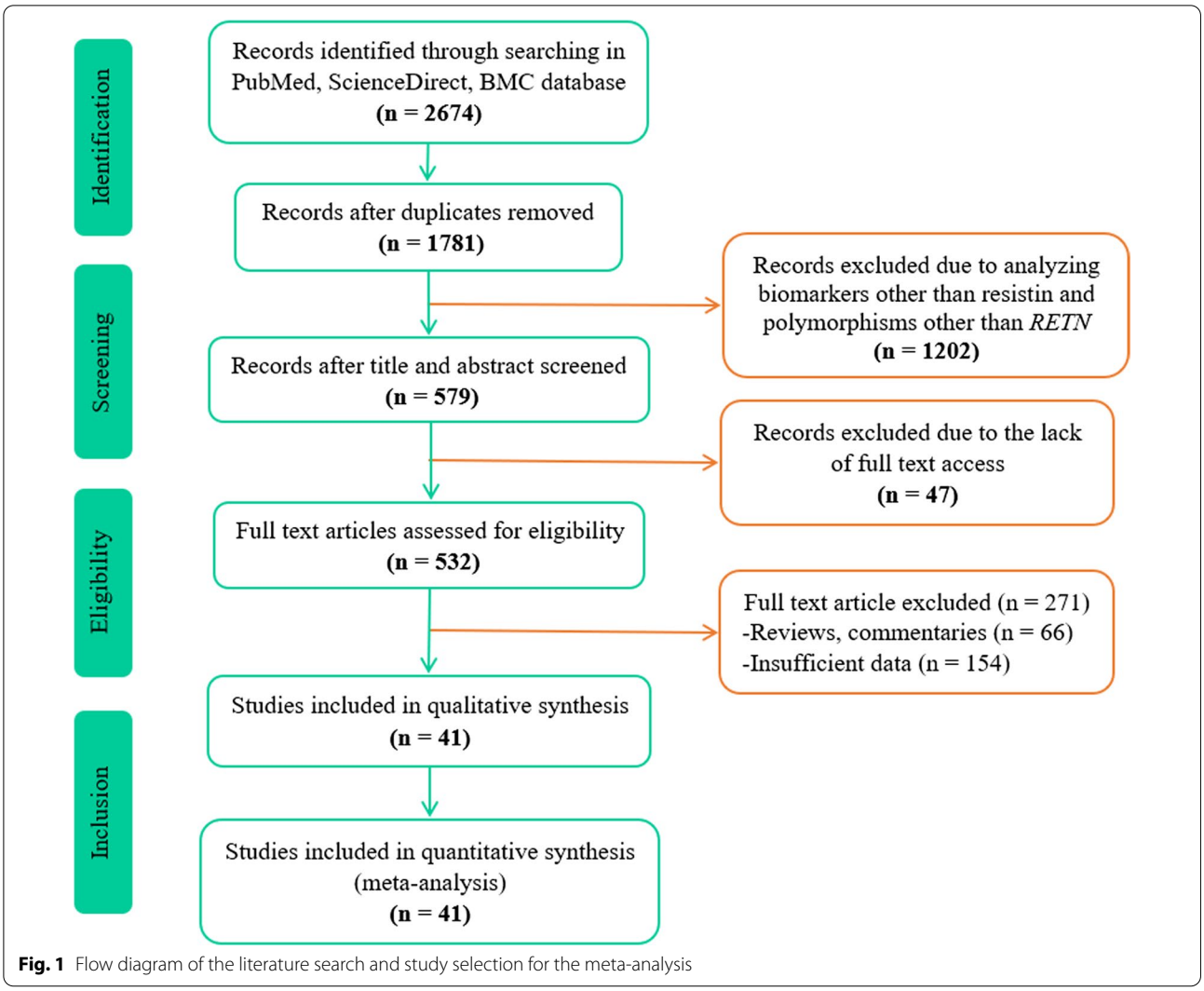

Fig. 1 Flow diagram of the literature search and study selection for the meta-analysis

and 367 controls, whereas 7 studies [11, 34–39] analyzed the plasma resistin in 1199 CRC cases and 1492 controls. Again, among 15 studies in analyzing resistin level in 2132 BC patients and 1780 controls, only two studies [24, 51] analyzed the plasma resistin level in 916 cases and 864 controls, while 13 studies [18, 40–48, 50, 52, 53] analyzed serum resistin level in 1216 cases and 916 controls. The characteristics of the selected studies evaluating resistin level with CRC and BC are summarized in Tables 1 and 2, respectively.

Again, of 41 studies, 10 studies evaluated the association of *RETN* gene polymorphisms with CRC and BC. Six studies examined the association of rs1862513 on CRC [19, 21, 24, 25, 38, 54] and 3 studies examined the correlation of rs1862513 on BC [18, 22, 55] that included a total of 2095 cases and 2385 controls. For rs3745367, only three eligible studies were found with 747 cases and 791 controls, among which two studies were on CRC [21, 23] and one with BC [22]. Table 3 represents the characteristics of selected studies evaluating *RETN* gene polymorphisms.

Meta-analysis of resistin levels and link with CRC and BC

According to our meta-analysis of 31 studies, the levels of resistin in both CRC and BC patients are significantly higher than those in the control groups, as illustrated in Figs. 2 and 3, respectively. The results of the meta-analysis revealed that the resistin level was significantly higher in CRC patients than in controls when using a random effect model (MD = 3.39, 95% CI = 2.23–4.54, $p < 0.00001$). Again, in terms of BC, patients had a significantly higher level of resistin than controls (MD = 3.91, 95% CI = 1.12–6.71, $p = 0.006$) and the difference was statistically significant.

Table 1 Characteristics of the selected studies evaluating resistin level with colorectal cancer in the meta-analysis

Study ID	Country	Cases/controls	Assay type	Kit provider	Mean resistin level (ng/ml) ± SD		NOS score
					Cases	Controls	
Serum							
Al-Harithy et al. [25]	KSA	60/60	ELISA kit	ALPCO Diagnostic	19.44 ± 8.46	5.45 ± 2.73	7
Danese et al. [26]	Italy	40/40	ELISA kit	Mediagnost	9.99 ± 15.76	4.98 ± 4.92	8
Gonullu et al. [27]	Turkey	36/37	ELISA kit	BioSource	6.1 ± 3.3	4.5 ± 1.5	8
Joshi et al. [28]	South Korea	100/100	ELISA kit	Adipogen	4.9 ± 2.3	2.8 ± 1.7	8
Kosova et al. [29]	Turkey	20/20	ELISA kit	Millipore Corporation	4.92 ± 2.2	3.39 ± 1.1	7
Kumor et al. [30]	Poland	36/25	ELISA kit	R&D Systems	6.79 ± 2.41	3.6 ± 1.08	7
Lu et al. [31]	China	30/30	ELISA kit	ADL	7.72 ± 2.6	7.42 ± 3.72	7
Shafik et al. [32]	Egypt	30/25	ELISA kit	AssayMax™	18.86 ± 2.6	9.55 ± 1.4	7
Tulubas et al. [33]	Turkey	30/30	ELISA kit	AssayMax™	18.77 ± 5.09	13.36 ± 6.36	8
Total		382/367					
Plasma							
Farahani et al. [34]	Iran	82/88	ELISA kit	ZellBio	5.7 ± 1.2	5.4 ± 1.3	8
Hillenbrand et al. [35]	Germany	67/60	Multiplex Assay	Millipore	19.53 ± 29.58	13.63 ± 14.96	7
Ho et al. [36]	USA	456/834	Multiplex Assay	Millipore	13.03 ± 4.83	12.57 ± 4.31	8
Mihajlovic et al. [11]	Serbia	86/75	ELISA kit	R&D Systems	20.72 ± 10.62	12.08 ± 7.58	7
Nakajima et al. [37]	Japan	115/115	ELISA kit	BioVender	4.67 ± 2.48	3.33 ± 1.88	8
Wägsäter et al. [38]	Sweden	35/34	ELISA kit	R&D Systems	2.62 ± 0.70	3.42 ± 0.77	7
Zhao et al. [39]	China	358/286	ELISA kit	Biovision Inc	8.03 ± 4.99	5.69 ± 3.18	8
Total		1199/1492					

NOS, Newcastle–Ottawa Scale

When we stratified the studies on CRC by the sample sources (serum and plasma), 9 studies offered relevant data for serum resistin level, and 7 studies offered relevant data for plasma resistin level, shown in Fig. 2. Subgroup analysis in CRC revealed that the serum resistin level was significantly higher in patients compared to controls (MD = 4.61, 95% CI = 2.32–6.91, $p < 0.0001$), whereas a higher level of plasma resistin was also found in patients compared to controls (MD = 0.34, 95% CI = 0.13–0.54, $p = 0.001$). In CRC patients, the mean difference of resistin is higher in serum samples than in plasma samples (serum vs. plasma: MD = 4.61 vs. MD = 0.34).

Again, when the studies on BC studies were stratified by menopausal status, 5 studies offered relevant data for premenopausal women, and 9 studies offered relevant data for postmenopausal women, depicted in Fig. 3. The mean difference in resistin level found for premenopausal women was significantly higher compared to premenopausal controls (MD = 7.82, 95% CI = 7.46–8.19, $p < 0.00001$), and for postmenopausal women the level of resistin was also higher in comparison with postmenopausal controls (MD = 0.37, 95% CI = 0.21–0.54, $p < 0.00001$). The mean difference of resistin is higher in premenopausal women than in postmenopausal women (premenopausal vs. postmenopausal: MD = 7.82 vs. MD = 0.37). From the funnel plot analysis for detecting the association of resistin (Fig. 7), we did not find any notable asymmetry for CRC and BC.

Meta-analysis of RETN polymorphisms and link with CRC and BC

Table 4 shows the association of *RETN* genetic polymorphisms with CRC and BC. Analysis of *RETN* rs1862513 polymorphism in CRC revealed that four genetic association models including codominant 1 (GC vs. CC), codominant 2 (GG vs. CC), dominant model (GG + GC vs. CC), and allele contrast (G vs. C) are associated with significantly enhanced risk of CRC (OR 1.24, 95% CI 1.05–1.47, $p = 0.010$; OR 1.31, 95% CI 1.018–1.69, $p = 0.036$; OR 1.25, 95% CI 1.07–1.46, $p = 0.005$; and OR 1.16, 95% CI 1.03–1.30, $p = 0.012$, respectively) (Fig. 4). Again, analysis of rs1862513 polymorphism in BC also showed significantly strong association in codominant 2 (GG vs. CC), codominant 3 (GG vs. GC), recessive (GG vs. GC + CC), and allele (G vs. C) models (OR 1.51, 95% CI 1.12–2.03, $p = 0.007$; OR 1.51, 95% CI 1.12–2.04, $p = 0.007$; OR 1.51, 95% CI 1.15–1.99, $p = 0.004$; and OR 1.21, 95% CI 1.05–1.40, $p = 0.008$, respectively) (Fig. 5).

Table 2 Characteristics of the selected studies evaluating resistin level with breast cancer in the meta-analysis

Study ID	Country	Sample source	Sample type	Cases/controls	Assay type	Kit provider	Mean resistin level (ng/ml) ± SD		NOS score
							Cases	Controls	
Ahmed [40]	Iraq	Serum	Premenopausal	90/90	ELISA kit	Bio-Rad Laboratories	18.32 ± 2.4	3.5 ± 0.5	7
Alokail et al. [41]	KSA	Serum	Both	56/53	ELISA kit	Immunodiagnoztik	18.9 ± 1.2	15.2 ± 1	7
Aly et al. [42]	KSA	Serum	UD	35/40	ELISA kit	Invitrogen	4.42 ± 4.74	1.84 ± 2.35	7
Assiri & Kamel [43]	KSA	Serum	Postmenopausal	110/89	ELISA kit	R&D systems	26.24 ± 1.95	22.63 ± 3.99	8
Assiri et al. [44]	KSA	Serum	Both	82/68	ELISA kit	R&D systems	26.24 ± 1.59	22.69 ± 2.58	8
Crisóstomo et al. [45]	Portugal	Serum	Both	77/77	ELISA kit	Duo Set ELISA	14.58 ± 10	10.86 ± 8.55	8
Dalamaga et al. [46]	Greece	Serum	Postmenopausal	102/102	ELISA kit	Avibion	11.2 ± 6.4	7.7 ± 4.85	8
Dalamaga et al. [47]	Greece	Serum	Postmenopausal	103/103	ELISA kit	Avibion	11.24 ± 6.44	7.73 ± 4.85	8
Georgiou et al. [48]	Greece	Serum	Both	157/52	ELISA kit	BioVendor	6.09 ± 3.08	6.16 ± 1.85	7
Gunter et al. [49]	USA	Plasma	Postmenopausal	875/821	ELISA kit	EMD Millipore	12.1 ± 1.8	12.3 ± 1.933	8
Hou et al. [50]	China	Serum	Both	80/50	ELISA kit	R&D systems	26.35 ± 5.36	23.32 ± 4.75	7
Kang et al. [51]	Korea	Plasma	Both	41/43	ELISA kit	AdipoGen	5.23 ± 6.9	1.46 ± 2	8
Muñoz-Palomeque et al. [18]	Mexico	Serum	Postmenopausal	20/40	ELISA kit	Preprotech Kit	10.60 ± 2.08	8.26 ± 2.38	7
Patrício et al. [52]	Portugal	Serum	Both	64/52	ELISA kit	Duo Set ELISA	17.30 ± 12.6	11.60 ± 11.4	8
Wang et al. [53]	Taiwan	Serum	UD	240/100	ELISA kit	eBioscience	32.72 ± 13.42	27.36 ± 5.49	7
Total				2132/1780					

The meta-analysis of the RETN rs3745367 polymorphism in CRC and BC, on the other hand, found no statistically significant link in any genetic model (Figs. 6, 7). Funnel plots for detecting the link of *RETN* rs1862513 and rs3745367 polymorphisms with CRC and BC are depicted in Fig. 8. However, no significant asymmetry was found.

Publication bias, heterogeneity, and sensitivity analysis

We also analyzed the publication bias for both CRC and BC with resistin level, as shown in Table 5. In the case of CRC, Egger's *p*-value was found to be significant (0.044), but the Begg-Mazumdar *p*-value was statistically not significant (0.280) for the overall sample (serum and plasma). However, no significant publication bias was found in subgroup analysis for serum and plasma resistin levels ($p > 0.05$ for both). Again, a significant publication bias was observed in overall BC samples (Egger's *p*-value: 0.0005 and Begg-Mazumdar *p*-value: 0.015), but in terms of premenopausal BC patients, neither Egger's test ($p = 0.075$) nor Begg-Mazumdar's test ($p = 0.624$) showed a statistically significant publication bias. However, for postmenopausal women, Egger's *p*-value was significant (0.005) though the significance was not observed with Begg-Mazumdar *p*-value (0.532). We also found a significant heterogeneity ($p < 0.00001$) across the overall analysis of studies with resistin level in both CRC and BC as well as subgroup analysis according to the menopausal status of subjects (premenopausal and postmenopausal) in BC and sources of the sample (serum or plasma) in CRC (Figs. 2 and 3).

In terms of *RETN* polymorphisms with the risk of CRC and BC, negligible publication bias was reported (Table 4). Begg-Mazumdar's *p*-value in the recessive model (0.039) and Egger's *p*-value in allele model (0.033) were significant in CRC and BC, respectively, for rs1862513 polymorphism. Only Egger's *p*-value in allele model (0.042) for rs3745367 was found to be significant. No other publication bias was found. Again, heterogeneity analysis showed that for rs1862513, only codominant model 3 (0.038) with CRC and for rs3745367 codominant 1 (0.029), dominant (0.041), and overdominant model

Table 3 Characteristics of selected studies evaluating *RETN* gene polymorphisms included in the meta-analysis

Study ID	Year	Country	Cancer type	Genotyping method	Cases	Controls	Cases			Controls			HWE *p*-value	NOS score
							GG	GC	CC	GG	GC	CC		
RETN rs1862513														
Al-Harithy et al	2010	KSA	CRC	PCR–RFLP	60	60	11	33	16	16	20	24	0.013	7
Alharithy et al	2014	KSA	CRC	PCR–RFLP	60	60	12	33	15	16	20	24	0.013	8
Duzkoylu et al	2015	Turkey	CRC	PCR–RFLP	123	79	9	61	53	12	36	31	0.772	7
Mahmoudi et al	2014	Iran	CRC	PCR–RFLP	197	217	76	83	38	76	85	56	0.002	8
Pechlivanis et al	2009	Czech Republic	CRC	PCR–RFLP	642	714	63	262	317	56	265	393	0.230	6
Wågsater et al	2008	Sweden	CRC	TaqMan	248	256	26	95	127	16	103	137	0.563	7
Kohan et al	2017	Iran	BC	PCR–RFLP	150	150	37	63	50	24	63	63	0.225	7
Munoz-Palomeque et al	2018	Mexico	BC	PCR–RFLP	100	308	5	42	53	7	102	199	0.144	8
Wang et al	2020	China	BC	TaqMan	515	541	96	205	214	76	241	224	0.390	8
Total			2095	2385	335	877	883	299	935	1151				
Study ID	**Year**	**Country**	**Cancer type**	**Genotyping method**	**Cases**	**Controls**	**Cases**			**Controls**			**HWE *p*-value**	**NOS score**
							AA	**GA**	**GG**	**AA**	**GA**	**GG**		
RETN rs3745367														
Alharithy et al	2014	KSA	CRC	PCR–RFLP	60	60	6	51	3	6	39	15	0.011	7
Mahmoudi et al	2016	Iran	CRC	PCR–RFLP	172	190	35	72	65	26	86	78	0.768	8
Wang et al	2020	China	BC	TaqMan	515	541	72	259	184	77	252	212	0.879	7
Total					747	791	113	382	252	109	377	305		

BC, breast cancer; CRC, colorectal cancer; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa Scale

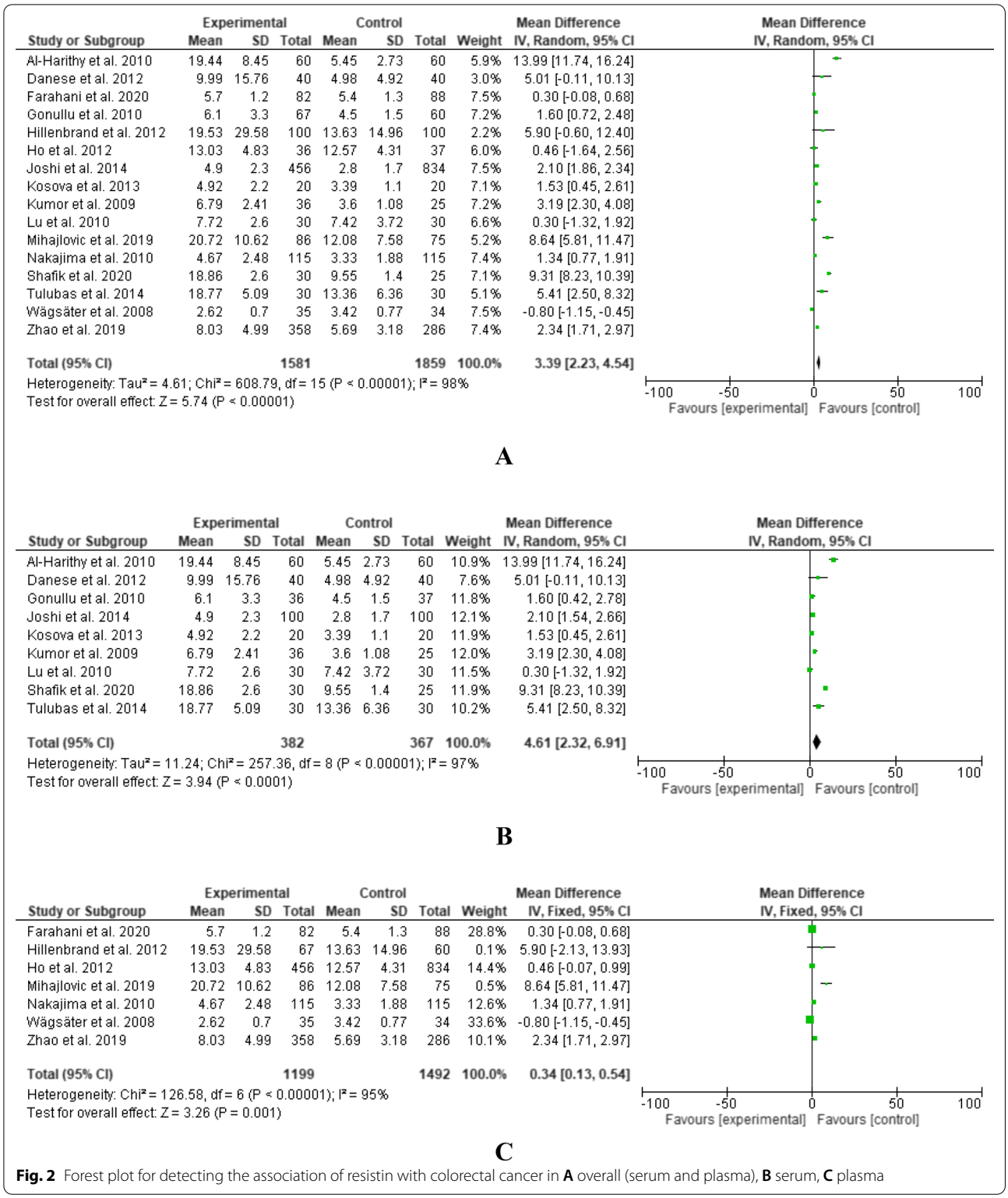

Fig. 2 Forest plot for detecting the association of resistin with colorectal cancer in **A** overall (serum and plasma), **B** serum, **C** plasma

(0.041) showed significant heterogeneity (Table 4). Sensitivity analysis for detecting the link of *RETN* rs1862513 and rs3745367 polymorphisms with CRC and BC suggests the reliability and stability of our analysis, as shown in Additional file 1: Fig. S1.

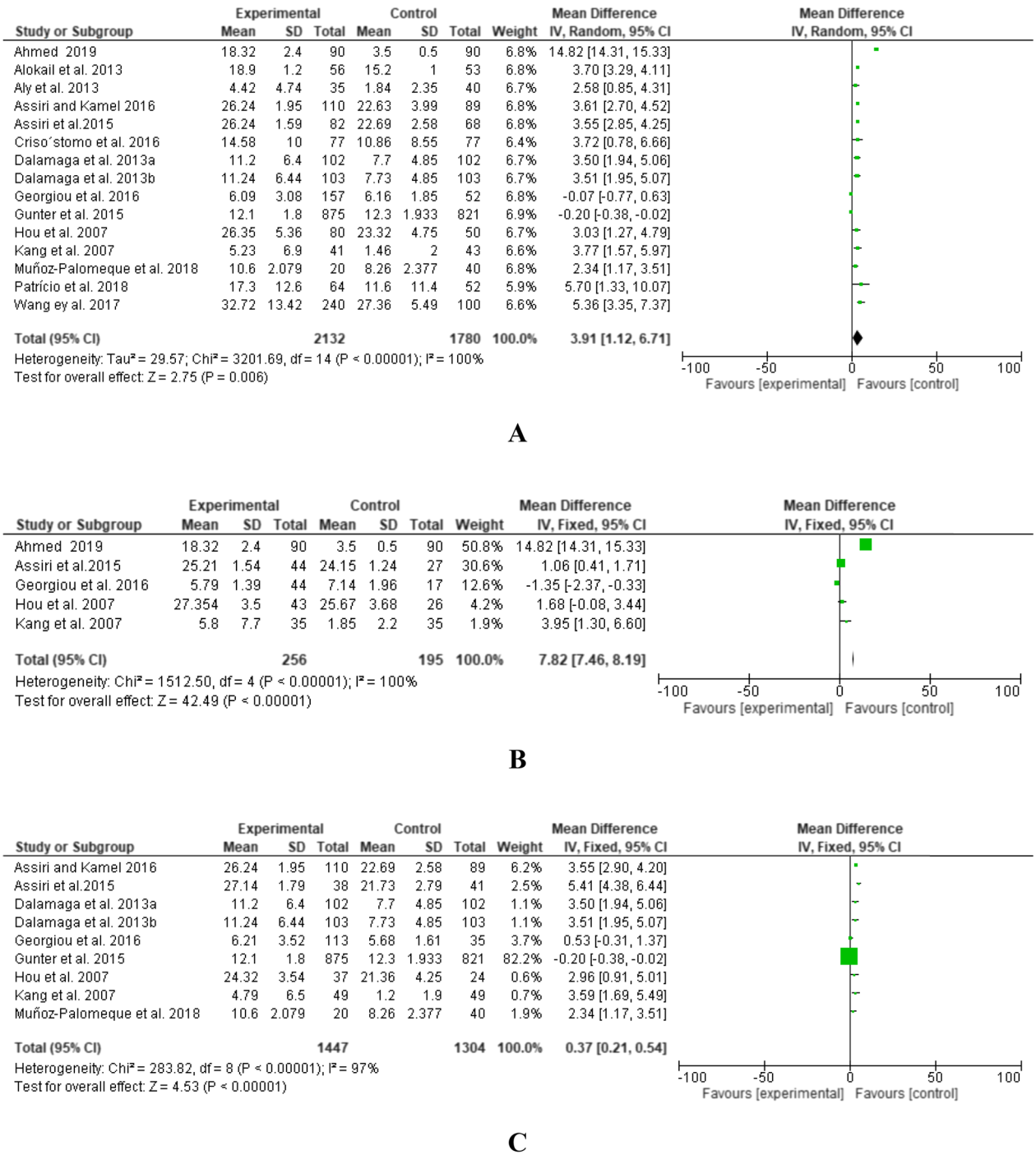

Fig. 3 Forest plot for detecting the association of resistin with breast cancer in **A** overall (premenopausal and postmenopausal), **B** premenopausal women, **C** postmenopausal women

Discussion

Resistin, an adipocytokine secreted by monocytes and macrophages, has been extensively studied due to its numerous roles in different physiological and pathological processes. It has been found that resistin is associated with inflammatory, metabolic, autoimmune processes in the human body as well as several cancers, including colorectal, breast, lung, endometrial, gastric, pancreatic, and liver cancers [53, 56, 57]. Again, *RETN* gene, which encodes resistin, has also been investigated for its role in

Table 4 Meta-analysis and subgroup analysis of selected studies evaluating the association of *RETN* gene polymorphisms with colorectal and breast cancer

Genetic model	Test of association			Test of heterogeneity			Publication bias (*p*-value)	
	OR	95% CI	*p*-value	Model	*p*-value	I^2 (%)	Egger's test	Begg-Mazumdar's test
RETN rs1862513 (CRC)								
Codominant 1 (GC vs. CC)	1.24	1.05–1.47	**0.010**	Fixed	0.165	36.28	0.226	0.091
Codominant 2 (GG vs. CC)	1.31	1.018–1.69	**0.036**	Fixed	0.292	18.74	0.236	0.348
Codominant 3 (GG vs. GC)	0.85	0.56–1.29	0.444	Random	0.038	57.58	0.125	0.091
Dominant model (GG + GC vs. CC)	1.25	1.07–1.46	**0.005**	Fixed	0.418	0	0.526	0.188
Recessive model (GG vs. GC + CC)	1.01	0.72–1.43	0.934	Random	0.095	46.74	0.120	0.039
Over dominant (GC vs. GG + CC)	1.25	0.98–1.60	0.070	Random	0.097	46.37	0.168	0.060
Allele contrast (G vs. C)	1.16	1.03–1.30	**0.012**	Fixed	0.541	0	0.297	0.091
RETN rs1862513 (BC)								
Codominant 1 (GC vs. CC)	1.05	0.86–1.30	0.622	Fixed	0.101	56.43	0.244	0.602
Codominant 2 (GG vs. CC)	1.51	1.12–2.03	**0.007**	Fixed	0.360	2.23	0.166	0.117
Codominant 3 (GG vs. GC)	1.51	1.12–2.04	**0.007**	Fixed	0.969	0	0.074	0.117
Dominant model (GG + GC vs. CC)	1.16	0.95–1.41	0.135	Fixed	0.109	54.89	0.124	0.602
Recessive model (GG vs. GC + CC)	1.51	1.15–1.99	**0.004**	Fixed	0.653	0	0.125	0.117
Over dominant (GC vs. GG + CC)	1.02	0.73–1.43	0.912	Random	0.095	57.48	0.346	0.117
Allele contrast (G vs. C)	1.21	1.05–1.40	**0.008**	Fixed	0.172	43.23	0.033	0.117
RETN rs3745367 (CRC + BC)								
Codominant 1 (AG vs. GG)	1.41	0.80–2.48	0.239	Random	0.029	71.64	0.436	0.602
Codominant 2 (AA vs. GG)	1.27	0.93–1.74	0.138	Fixed	0.142	48.71	0.117	0.117
Codominant 3 (AA vs. AG)	1.04	0.77–1.40	0.794	Fixed	0.245	28.99	0.890	0.602
Dominant model (AA + AG vs. GG)	1.42	0.85–2.36	0.182	Random	0.041	68.78	0.287	0.117
Recessive model (AA vs. AG + GG)	1.12	0.84–1.49	0.443	Fixed	0.324	11.32	0.786	0.602
Over dominant (AG vs. AA + GG)	1.24	0.78–1.98	0.359	Random	0.041	68.66	0.627	0.602
Allele contrast (A vs. G)	1.14	0.98–1.31	0.083	Fixed	0.397	0	0.042	0.117

Bold values indicate statistically significant ($p < 0.05$)

BC, breast cancer; CRC, colorectal cancer; OR, odds ratio; 95% CI, 95% confidence interval

different diseases, including CRC and BC. Two common SNPs in RETN gene, namely, rs1862513 and rs3745367, have been evaluated for the risk link with BC and CRC [18, 21–23]. This combined meta-analytic approach summarized that serum and plasma resistin levels are positively connected with an increased risk of CRC and BC. Again, *RETN* rs1862513 is also linked with the risk of CRC. Regardless of the inconsistent outcomes of the previous analyses, this is the first study evaluating the relationship of resistin levels and *RETN* gene polymorphisms at a time in both BC and CRC patients.

Accumulating evidence suggests that there is a significant correlation between attenuation in circulatory resistin levels and different diseases. It has been proposed that resistin plays a key role in cancer progression and cell cycle regulation. Resistin also has a potential link between inflammation, atherosclerosis, obesity, cardiovascular pathology, non-alcoholic fatty liver disease, and rheumatic diseases [34, 48]. Studies revealed that circulating resistin could promote several processes, including metastasis, proliferation, and angiogenesis associated with cancer development through stimulating different signaling mechanisms such as p38 MAPK/NF-κB and PI3K/Akt pathways [58]. Although multiple studies with resistin found that higher resistin levels are linked to an increased risk of carcinogenesis, a few studies found no or an insignificant association.

The connection of resistin with CRC risk has been studied extensively in a wide variety of populations. The potential effect of resistin in CRC can be elucidated via different mechanisms. Several in vitro studies have demonstrated that the increased levels of resistin have proinflammatory effects controlled by the stimulation of TLR4 receptor and NF-κB signaling pathways. Besides, some studies also reported that resistin regulates matrix metalloproteinases (MMPs) production and modulates vascular endothelial growth factor (VEGF) secretion, which is linked with tumor invasiveness [4]. We found that high

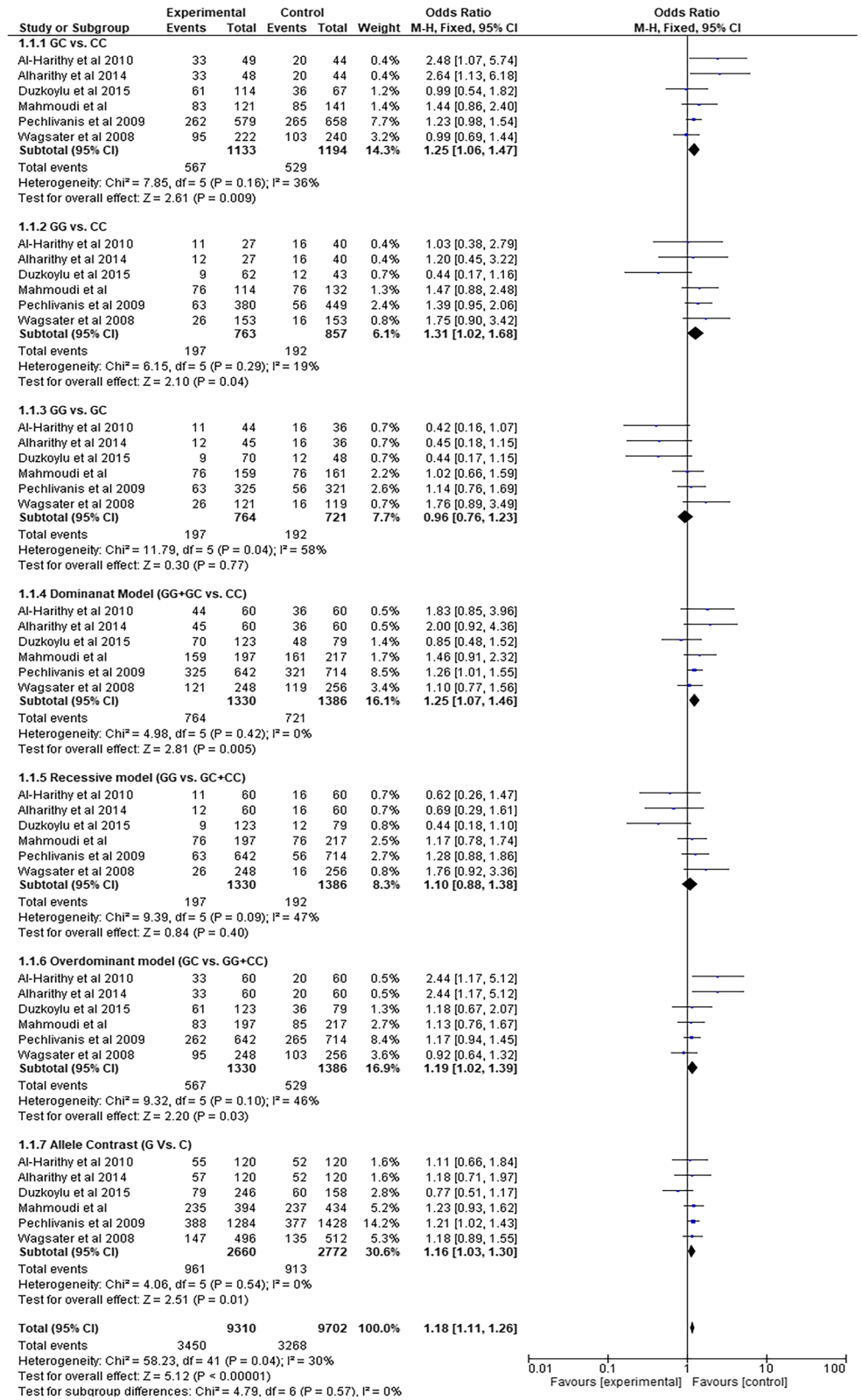

Fig. 4 Forest plot for detecting the association between *RETN* rs1862513 polymorphism and colorectal cancer

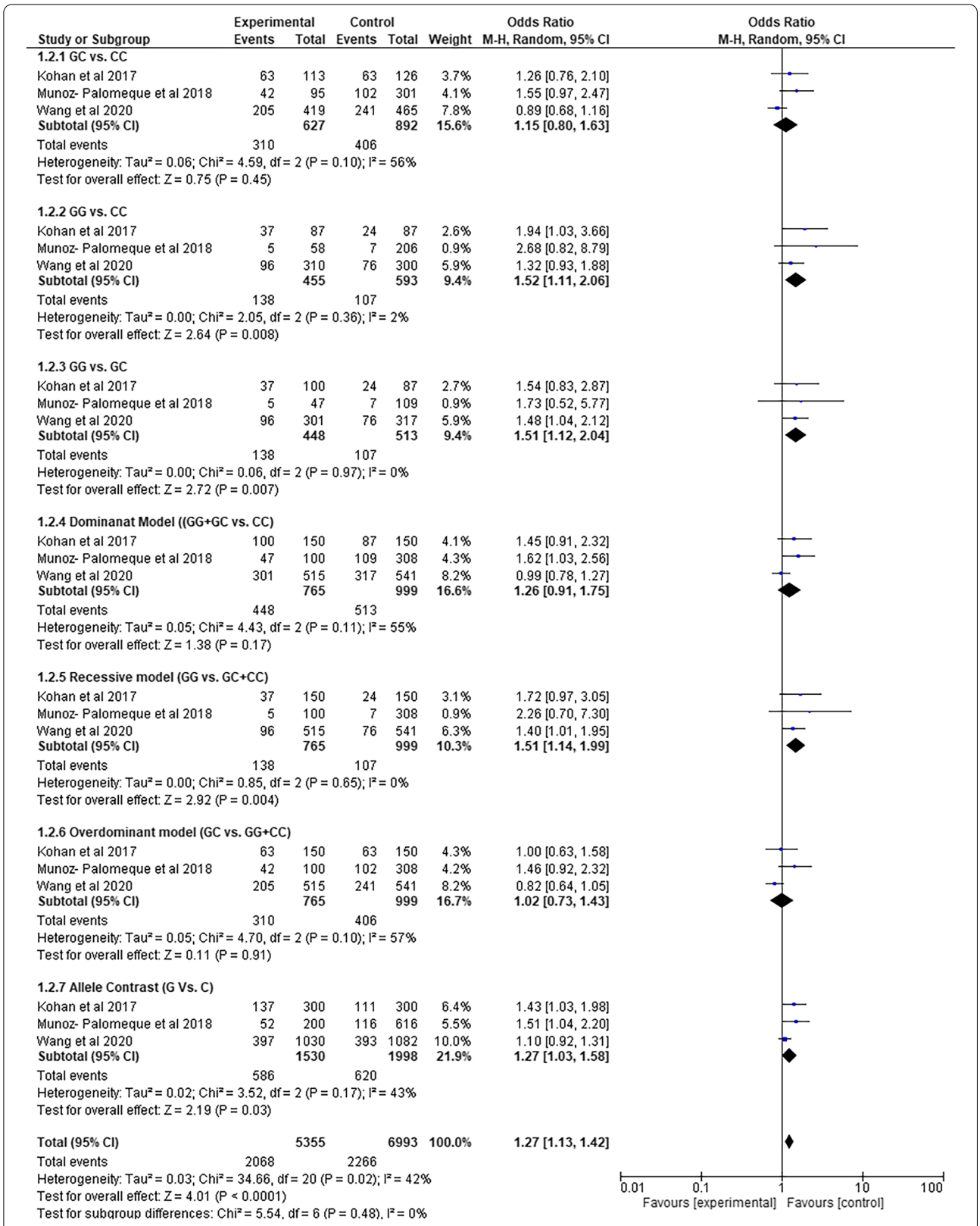

Fig. 5 Forest plot for detecting the association between *RETN* rs1862513 polymorphism and breast cancer

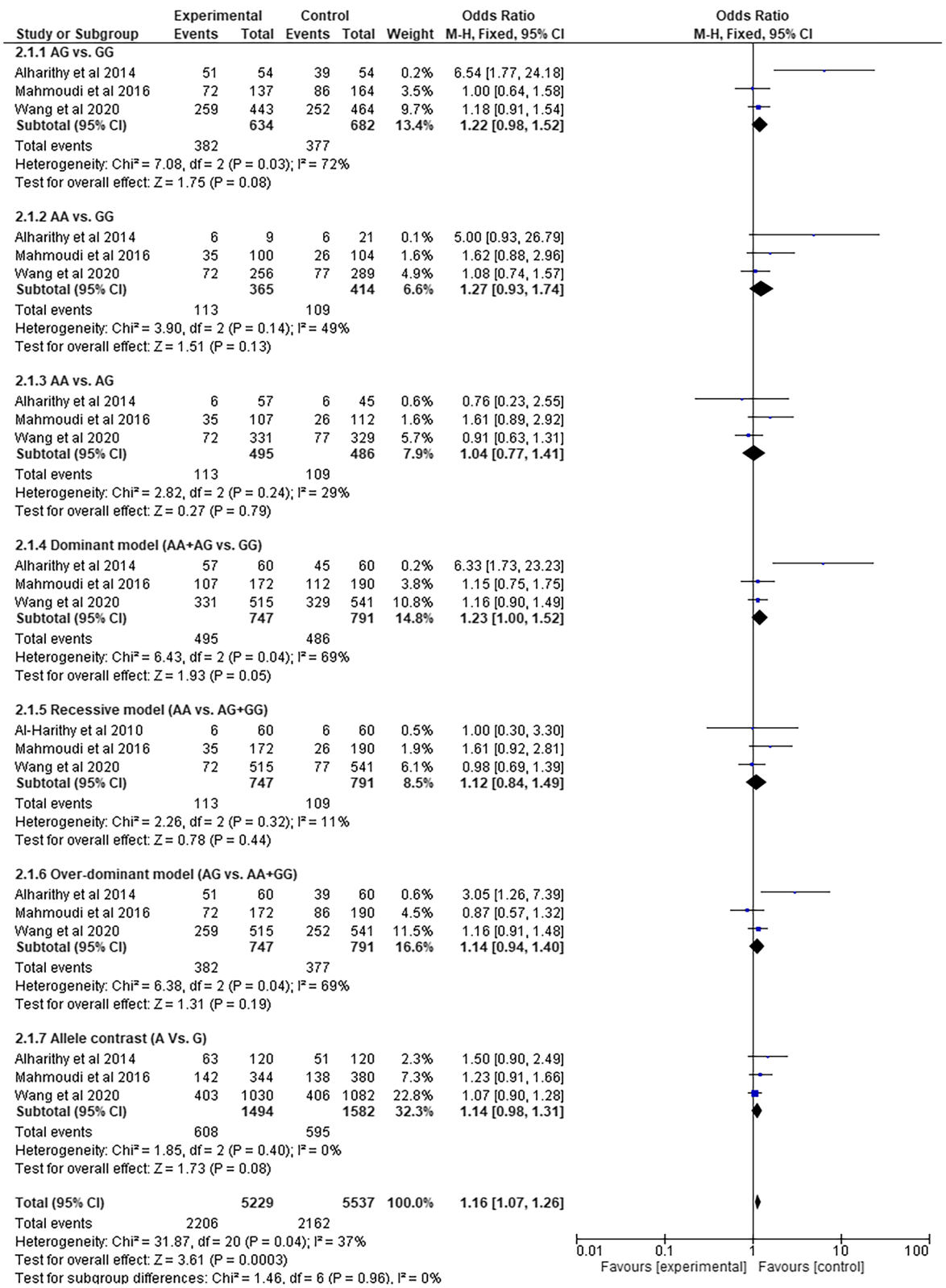

Fig. 6 Forest plot for detecting the association of *RETN* rs3745367 polymorphisms with colorectal and breast cancer

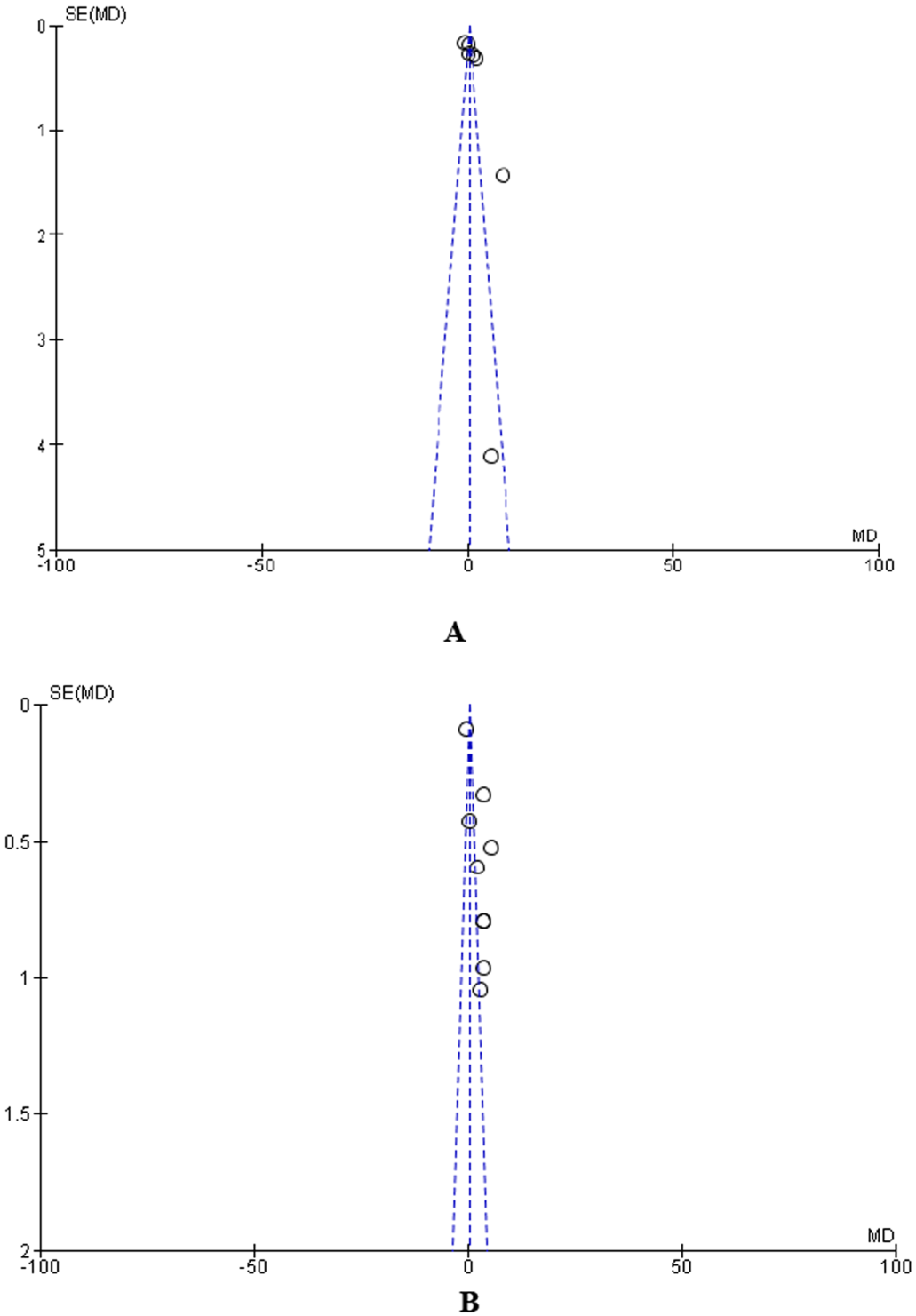

Fig. 7 Funnel plot for detecting the association of resistin in **A** colorectal cancer, **B** breast cancer

resistin levels are associated with CRC. According to our findings, patients with CRC have significantly higher resistin concentration than that of the control group (MD = 3.39). Our analysis is consistent with the previous findings in different populations, including population from the Kingdom of Saudi Arabia [25], Italy [26], Turkey [27, 29, 33], South Korea [28], Poland [30], China [31, 39],

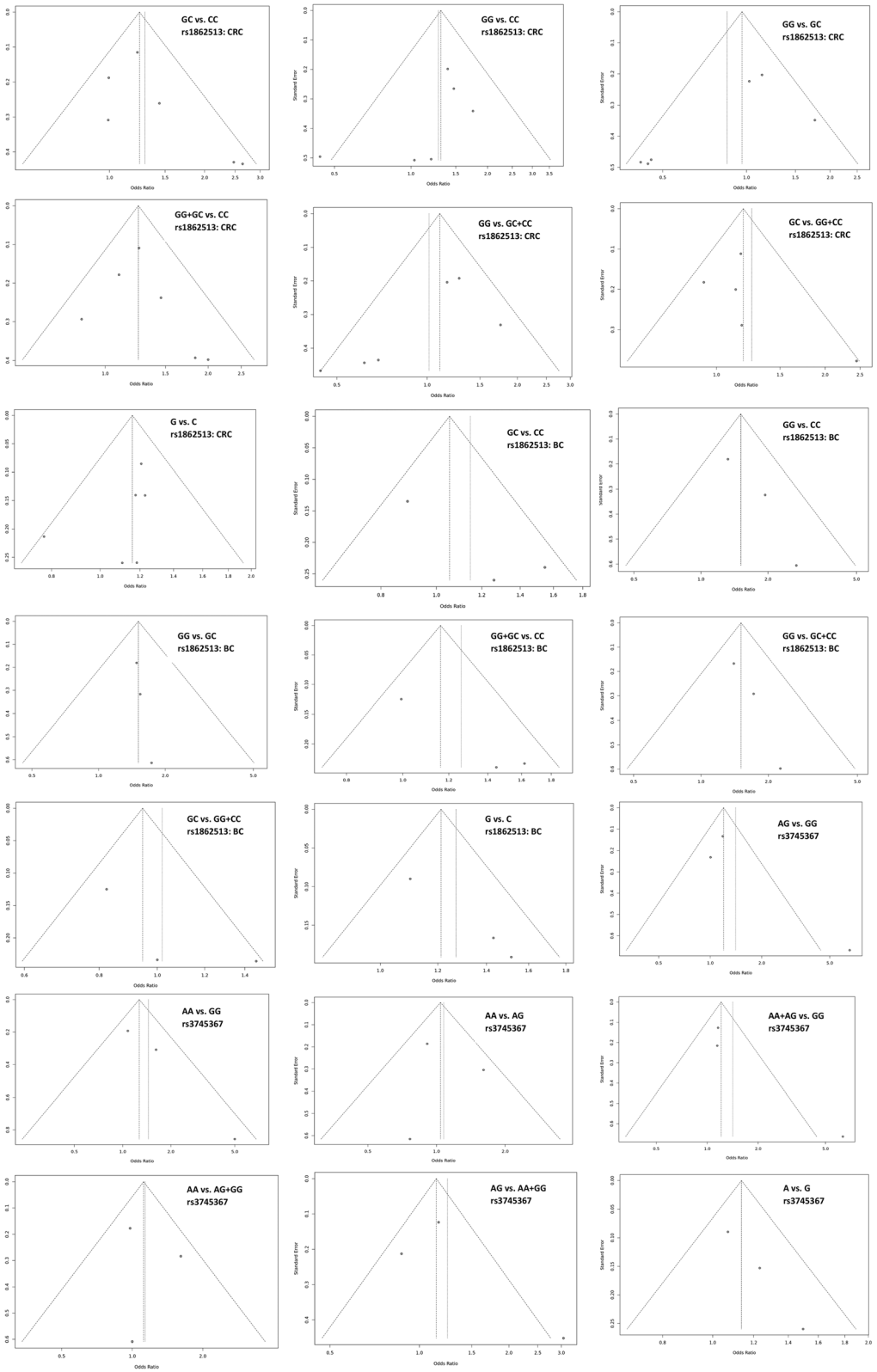

Fig. 8 Funnel plots for detecting the association of *RETN* rs1862513 and rs3745367 polymorphisms with colorectal and breast cancer

Table 5 Analysis of publication bias in selected studies evaluating resistin level with colorectal and breast cancer

Cancer type	Sample type	Egger's *p*-value	Begg-Mazumdar's *p*-value
Colorectal cancer	Overall	0.044	0.280
	Serum	0.284	0.404
	Plasma	0.968	0.652
Breast cancer	Overall	0.0005	0.015
	Premenopausal	0.075	0.624
	Postmenopausal	0.005	0.532

*$p < 0.05$ considered as statistically significant

Egypt [32], Iran [34], Germany [35], America [36], Serbia [11], and Japan [37].

Again, based on CRC subgroup analysis, we uncovered that serum resistin levels were significantly higher in CRC patients compared to controls (MD = 4.61). Our findings are consistent with previous findings in Saudi Arabian [25], Italian [26], Turkish [27, 29, 33], South Korean [28], Polish [30], Chinese [31], and Egyptian [32] population. We found an elevated plasma resistin level in CRC patients compared to healthy controls (MD = 0.34). Our results are in concordance with the previous findings reported in Iranian [34], German [35], American [36], Serbian [11], Japanese [37], and Chinese [39] populations. We also did not observe any notable asymmetry in the funnel plot for CRC. However, in terms of plasma resistin level, our findings are inconsistent with a case–control study in the Swedish population (35 cases and 34 controls) where Wägsäter et al. [38] reported a decreased plasma resistin level (2.62 ± 0.70 ng/ml) in CRC patients in compared to the controls (3.42 ± 0.77 ng/ml).

Elevated resistin levels in serum or plasma have been found to be correlated with an increased risk of BC [59]. A higher expression of resistin in BC tissues was also found to be significantly linked with the tumor size, tumor stage, estrogen receptor status, lymph node metastasis, and poor survival [60]. Previous studies have demonstrated that increased resistin expression in BC tissues is linked with cancer progression, premenopausal BC, postmenopausal BC, and poor prognosis of cancer [17]. Recent epidemiologic studies also correlated resistin levels with BC and proved that this association is not dependent on age, BMI, menopausal status, and other biomarkers such as glucose adiponectin levels in patients [44].

Our present meta-analysis reported that the levels of resistin in fifteen studies that included 2132 BC patients and 1780 controls, and the resistin level were significantly higher in BC patients (MD = 3.91). Our findings are consistent with previous reports in different ethnicities, including Iraqi [40], Arabians [41–44], Portuguese [45, 52], Greek [46, 47], Chinese [50], Korean [51], Mexican [18], and Taiwanese [53] populations. However, two studies included in the analysis did not show consistency with our findings. A large case–control study in the USA with 875 BC cases and 821 controls showed that the mean resistin level in patients was slightly lower (12.1 ± 1.8 ng/ml) than that of the controls (12.3 ± 1.933 ng/ml) [49]. Another case–control study in 157 cases of BC and 52 healthy controls from Greece reported the negative relationship between higher resistin level and BC risk. They found that the resistin level was 6.09 ± 3.08 ng/ml in BC patients and 6.16 ± 1.85 ng/ml in the control subjects, depicting a very low difference between the two groups [48].

Again, we found a substantially higher level of resistin in premenopausal and postmenopausal patients relative to controls when the studies on BC were stratified by menopausal status (premenopausal vs. postmenopausal: MD = 7.82 vs. MD = 0.37). Our findings are consistent with previous studies with premenopausal women [40, 44, 50, 51]. However, a study by Georgiou et al. [48] reported an inverse relationship where premenopausal patients had lower resistin levels than premenopausal controls. Our findings with postmenopausal women are consistent with our other studies [18, 43, 44, 46, 47, 50, 51]. However, one previous study by Gunter et al. [49] depicted inconsistency with our finding. From the funnel plot analysis for detecting the association of resistin, we did not find any significant asymmetry for the risk of BC.

The association of *RETN* polymorphisms with CRC and BC has been previously investigated in multiple populations. In our study, the meta-analysis of *RETN* gene rs1862513 polymorphism in CRC demonstrated that codominant 1 (OR 1.24), codominant 2 (OR 1.31), dominant (OR 1.25), and allele model (OR 1.16) are significantly connected with enhanced risk of CRC. Our results are in conformation with the previous results [19]. However, no association with CRC was observed in some previous studies [11, 21, 25, 38]. Again, rs1862513 polymorphism in BC also showed a significantly strong correlation in codominant 2 (OR 1.51), codominant 3 (OR 1.51), recessive (OR 1.51), and allele (OR 1.21) models. Muñoz-Palomeque et al. [18] also showed a significantly increased risk of BC with this SNP. However, no statistically strong correlation was observed in previous analysis by Wang et al. [22].

The meta-analysis of the RETN rs3745367 polymorphism in CRC and BC, on the other hand, found no statistically significant risk association in any genetic model. Our results are consistent with those of Wang et al. [22] in BC, Mahmoudi et al. [23] in CRC. However, Alharithy

et al. [24] showed a significantly increased association of rs3745367 variant with the risk of CRC.

We should point out some limitations of our meta-analysis. Firstly, although we have followed a perfect strategy for literature search, there might be a possibility of missing some eligible studies. Furthermore, we only included studies that were published in English. Secondly, there appeared some sort of publication bias. Thirdly, we found significant heterogeneity across the studies. Study design, quality, and sample type may account for this heterogeneity. Fourthly, present meta-analyses are based on case–control studies, and the inherent lacking's of which may influence our outcomes to some extent. Finally, we could not discuss some potential confounders that may be associated with the alteration of resistin levels and *RETN* polymorphisms such as obesity, smoking, dietary habits, sex, alcohol, lack of exercise, and clinicopathological characteristics, including tumor stage, distant metastasis, and type of cancers. However, keeping in mind the potential role of circulating resistin and *RETN* genetic polymorphisms in both CRC and BC risk and the inconsistent published evidence based on the effect of resistin, the present study is the first combined effort with both cancers and is of greater importance.

Conclusion

In conclusion, the present study indicates that serum and plasma resistin levels are positively associated with an elevated risk of CRC. Besides, elevated resistin level is positively associated with increased BC risk in premenopausal and postmenopausal women. Moreover, *RETN* rs1862513 polymorphism is connected with the risk of both CRC and BC. Our analysis will help enhance the understanding of cancer risks with resistin levels and *RETN* genetic variants. However, based on the limitations mentioned above, more randomized trials with a larger sample size are required to confirm the relationship of resistin and *RETN* polymorphisms with the development of CRC and BC.

Methods

Literature search

Both meta-analyses were carried out following the guidelines of PRISMA [61]. For collecting data of resistin, a comprehensive literature search was conducted in PubMed, ScienceDirect, BMC, EMBASE, Cochrane Library, Web of Science, and Google Scholar databases using the following search keywords: "resistin," "adipokines," "adipocytokines," "serum resistin," "plasma resistin," "resistin and colorectal cancer," "resistin and breast cancer." Again, for *RETN* genetic polymorphisms-related data, we searched on the same databases using the following keywords: "resistin," "*RETN*," "SNPs," "polymorphisms," "variants," "rs1862513," or "C-180G," or "C-420G," "rs3745367," or "G + 299A," "*RETN* and colorectal cancer," "*RETN* and breast cancer." In addition, we manually reviewed the list of bibliography from the retrieved articles to include relevant studies. Furthermore, we have added literature only written in English.

Study selection criteria

The following criteria were used to select studies for inclusion in both meta-analyses: (1) If the study evaluated the link of resistin level and *RETN* polymorphisms (rs1862513 and/or 3745367) with BC and CRC; (2) if it was a case–control, cross-sectional, or cohort study; (3) if the study provided appropriate data to calculate resistin level and in case of genetic meta-analysis if the studies provided useful genotypic data; and (4) if the study performed on human. Studies were excluded if they had the following criteria: (1) If the study was a review, editorial, or letter to the editor; (2) if there is no control cohort; (3) if the study had inadequate data; and (4) if the authors with incomplete study data did not reply to the requests from the authors.

Data extraction

Two authors (MAA and TA) independently assessed the eligibility of included studies and any disagreements were resolved by consensus with another author (MSI). From each article selected, we retrieved the following information: first author's name, publication year, study conducting country, cancer type, sources of the sample (plasma or serum) or SNP studied, type of sample, number of study cases and controls, assay type or genotyping method, name of the kit provider, mean resistin level (ng/ml) ± standard deviation (SD) in both cases and controls, and p-value of HWE of controls for genetic association study. Where median and range or interquartile range were given for resistin level, we calculated mean and SD using the method described by Wan et al. [62].

Quality score assessment

The quality of each selected study for our meta-analyses involving the correlation of serum or plasma resistin levels or the association of *RETN* polymorphisms in CRC and BC was assessed based on the Newcastle–Ottawa Scale (NOS) [63]. We evaluated the quality of each study following three aspects: (1) the study selection procedure, (2) literature comparability, and (3) the exposure determination in case–control studies. NOS total scores ranged from 0 to 9, with a score greater than 7 indicating a high-quality study.

Statistical analysis

All statistical analysis was performed using the Review Manager (RevMan) 5.4 software (Nordic Cochrane Center, Copenhagen, Denmark). We calculated all data as mean (ng/ml) ± SD to assess plasma or serum resistin relationship with CRC and BC. Again, for genetic association analysis, we calculated the association of RETN variants in seven genetic models, including codominant 1–3, dominant, overdominant, recessive, and allele model. The Q-statistic to test the heterogeneity between studies and the I^2-statistic to quantify the total differences resulting from heterogeneity was calculated. We selected the random effect model for calculating the pooled mean differences when $p < 50\%$. Our meta-analyses also assessed potential publication bias by applying Egger's regression test [64] and Begg's rank correlation test [65]. We stratified all collected data according to the menopausal status of subjects (premenopausal and postmenopausal) in BC and sources of the sample (serum or plasma) in CRC and employed in subgroup analyses (forest plot) to evaluate the source of heterogeneity for evaluating the association of resistin level. In all analyses, $p < 0.05$ was considered to be statistically significant.

Abbreviations

95% CI: 95% Confidence interval; BC: Breast cancer; BMI: Body mass index; CRC : Colorectal cancer; HWE: Hardy–Weinberg equilibrium; MD: Mean difference; MMP: Matrix metalloproteinase; NOS: Newcastle–Ottawa Scale; OR: Odds ratio; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RELM: Resistin-like molecule; *RETN*: Resistin; SNP: Single nucleotide polymorphism; VEGF: Vascular endothelial growth factor.

Supplementary Information

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Additional file 1. Supplementary material: Sensitivity analysis.

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Authors' contributions

MSI analyzed the data, developed the software and conceptualized the study, validated the data analysis, supervised the study, wrote the review and edited; MAA and TA helped in literature search; MAA wrote the original draft and helped in methodology; MSS was involved in analysis, writing—reviewing and editing. All authors have 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.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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