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Clinical significance of circulating omentin levels in various malignant tumors: Evidence from a systematic review and meta-analysis

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ABSTRACT

Aberrant circulating level of omentin has been reported in various solid tumors. However, whether decreased or increased levels of omentin contribute in cancer risk is remained controversial in different epidemiological studies. This comprehensive meta-analysis of observational studies was conducted to investigate the association between circulating omentin level and human cancer risk. An electronic search of health-related databases, was performed to identify all eligible studies in English, up to July 2019. Combined standard mean difference (SMD) with 95%CI was computed to assess the correlation of omentin levels with human cancer risk in a random effect model. The risk of publication bias was also evaluated using Funnel plot and Egger regression tests. A total of 16 studies with 1106 cases and 3078 healthy controls were included. Pooled SMD analysis based on the cancer type, revealed a strong correlation of omentin level and cancer risk in patients with colorectal (SMD = 2.08, 95%CI: 1.67–2.50, P < 0.001), prostate (SMD = 1.38, 95%CI: 1.15–1.62, P < 0.001), and breast (SMD = −0.78, 95%CI: −1.1, −0.45, P < 0.001) cancers. Elevated circulating omentin levels was also found in cancer patients with BMI ≥ 25 (SMD = 1.33, 95%CI: 0.52–2.15, P = 0.001) indicating a potential role for omentin in development of some obesity-linked cancers. The findings of this meta-analysis indicated a significant association of omentin level with greater risk of colorectal, pancreas, and breast tumors. Circulating omentin level may represent a potential novel biomarker for early detection of colorectal, prostate, and breast cancers especially in overweight/obese subjects. Further prospective well-designed studies are warranted to confirm our findings.

1. Introduction

Cancer is a major cause of morbidity and mortality in various geographic regions around the world [1]. Beside the known risk factors including unhealthy lifestyle, genetic lesions and various environmental parameters as crucial cancer-causing agents, metabolic related disorders such as obesity and metabolic syndrome have also been associated with a significant increased risk of cancer [2]. It is clear that identifying the causes of cancer provides a basis for establishing possible strategies for cancer prevention. A growing body of evidence has indicated that obesity and its related metabolic changes have been linked to the higher risk and poor prognosis of many types of cancers including colorectal, post-menopausal breast, endometrial, esophageal, kidney, and pancreatic cancers. A higher incidence rate for cancer has also been reported in obese women compared to the normal weight individuals [3].

Overgrowth of the adipose tissue results in substantial changes in its cellular composition and deregulated expression of various bioactive substances. Subsequently, these dysmetabolic changes can promote a transition towards chronic subclinical inflammation, insulin resistance, and abnormal alterations in serum levels of adipocytokines [4,5]. Altered expression of adipocytokines may play a role as a vital link between obesity and cancer development [6]. As these bioactive compounds have a wide range of metabolic functions, aberrant circulating levels of some of them such as adiponectin, leptin, visfatin, and omentin have been reported in different cancers [7–9].

Omentin, also known as intelectin-1, intestinal lactoferrin receptor, or galactofuranose-binding lectin, is a new highly expressed adipokine that is mostly secreted from the visceral compared to the subcutaneous adipose tissue [10,11]. The circulating levels of omentin have been inversely correlated with insulin resistance, BMI, and fasting blood sugar while is directly correlated with serum high density lipoprotein

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(HDL), adiponectin, and endothelial function [12,13]. Different studies have showed that serum level of omentin is decreased in obesity-related disorders like type-II diabetes mellitus [14–16]. Deregulated circulating levels of omentin have also been reported in various solid tumor malignancies including colorectal, prostate, and breast cancer [17–19]. Almost, the majority of relevant studies have reported aberrant circulating levels of omentin in all cancer patients compared to the healthy controls, indicating a relationship between omentin and the risk of cancer. However, the conclusions regarding whether decreased or increased levels of omentin contribute in cancer risk remain controversial in different epidemiological studies. Given to the fact that, each individual study may only provide conclusions with limited statistical power due to the small sample size and methodological limitations, we have conducted this systematic review and meta-analysis of the existing data to comprehensively evaluate the relationship between the circulating omentin level and cancer risk.

2. Methods

2.1. Literature search strategy and study selection

The present systematic review was carried out in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) [20]. A systematic electronic literature search of databases including: PubMed, EMBASE, Web of Sciences, and Scopus was performed to identify the relevant studies in English up to July 2019. All searches were performed using individual or/and different combinations of Mesh terms including: “Omentin”, “Intelectin”, “Omentin/intelectin”, “intestinal lactoferrin receptor”, “galactofuranose binding”, “cancer”, “carcinoma”, “neoplasm”, and “tumor”. Additionally, the reference lists of all selected articles was checked to identify additional eligible publications.

2.2. Inclusion and exclusion criteria

Studies were qualified for inclusion if they met the following criteria: (1) being original or nested case-control study; (2) reporting omentin serum/plasma levels in healthy controls and patients with any types of cancer; (3) providing enough data to determine standardized mean difference (SMD) with corresponding 95% confidence intervals (CI). Studies were excluded if they were (1) conducted on animals, cells, or tissues, (2) reviews, letters, case reports, editorials, or comments, (3) studies with no control group or original data; (4) studies that only refer to the mechanism or prognosis or survival.

2.3. Data extraction and quality assessment

Two reviewers (MHA & HMM) independently reviewed all eligible studies to extract data using a pre-defined database. Any discordance was resolved through a consensus discussion with a third reviewer. Briefly, the following information and data were extracted from each included study: the first author’s surname and year of publication, country of origin, study design, cancer type, omentin detection assay, sample size, number of cases and controls, age, gender, BMI, and omentin mean ± SD. Newcastle-OTTAWA Scales (NOS) with a star rating system (a score of 0–9) was applied to assess the quality of each study included [21]. Each study with the score ≥ 5 was considered as high-quality.

2.4. Statistical analysis

All statistical analyses were conducted with Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ) and the statistical significance was defined as a p-value less than 0.05. Weighted standardized mean difference (SMDs) and corresponding 95% confidence interval were calculated based on the sample size, mean, and SD reported for omentin in each eligible study to measure the strength of relationship between the circulating omentin levels and risk of cancer development. In the case of studies with reported median, range, and/or interquartile range (IQR), the mean and SD were estimated based on a method described by Wan et al. [22]. The Cochran Q statistic and inconsistency index (I^2) were used to measure the level of heterogeneity among the included studies. If $I^2 > 50\%$, and $p < 0.05$, the heterogeneity was considered as statistically significant and the random effects model was used, otherwise, the fixed effect model was applied. Sensitivity analyses were conducted by omitting one study at a time to assess the stability of the results. Besides, subgroup analysis based on study sample size, geographical area, study quality, cancer type, mean BMI, age, and BMI-match was performed to explore the potential sources of heterogeneity. Meta-regression and Galbraith plot analyses were also used to further explore which study or variables contribute to substantial heterogeneity [23,24]. Egger’s linear regression test and visual inspection of Funnel plots were applied to evaluate the potential publication bias.

3. Result

3.1. Literature search

The flow diagram of selection strategy is shown in Fig. 1. In our initial search a total of 172 articles were retrieved and checked for relevance, out of which 129 duplicates, irrelevant, and/or non-original studies were omitted. Another 27 studies were also deleted due to insufficient data to calculate SMD, non-serum measurements, and lack of healthy controls. Consequently, 16 articles presenting the data on the association between omentin and cancer risk were eligible for further quantitative analysis.

3.2. Study characteristics

General characteristics of the eligible studies are presented in Table 1. All studies were in English and published between 2013 and 2019. Overally, a total of 1106 cases and 3078 controls were included in the analyses. Eleven studies were conducted in Asia [17–19,25–31], three in Europe [32–34], and two in the USA [35,36]. The circulating level of omentin was reported to be measured by ELISA method in 15 studies and EIA in one study [33]. A total of 9 different types of cancer were evaluated as follows; three colorectal cancers, three prostate cancers, two breast cancers, two ovarian cancers, two endometrial cancers, one bladder cancer, one pancreas cancer, one lung cancer, and one renal cell carcinoma.

3.3. Quantitative analysis

Data regarding the mean and SD of circulating omentin levels of 14 included studies were pooled to calculate the summery SMD as an estimate of the association between the circulating omentin and risk of cancer. These analyses were considered either in overall or in subgroups based on different cancer types, study quality, sample size, mean age, mean BMI, and BMI-match. Due to the considerable level of heterogeneity ($I^2 = 98.86\%$ and $P < 0.001$) a random effect model was applied. In overall, our meta-results revealed no significant difference in the circulating omentin levels between the cancer patients and control group, indicating no correlation between omentin and cancer risk (SMD = −0.05 and 95%CI = −0.87 to 0.77) (Fig. 2). However, stratified analysis by various cancer types showed a significant relationship between the circulating omentin level and cancer risk in patients with colorectal (SMD = 2.08, 95%CI: 1.67–2.50, $P < 0.001$), prostate (SMD = 1.38, 95%CI: 1.15–1.62, $P < 0.001$), and breast (SMD = −0.78, 95%CI: −1.1, −0.45, $P < 0.001$) cancers (Fig. 3a). Moreover, in subgroup analysis based on the mean BMI, an elevated circulating omentin level was also found for cancer patients with

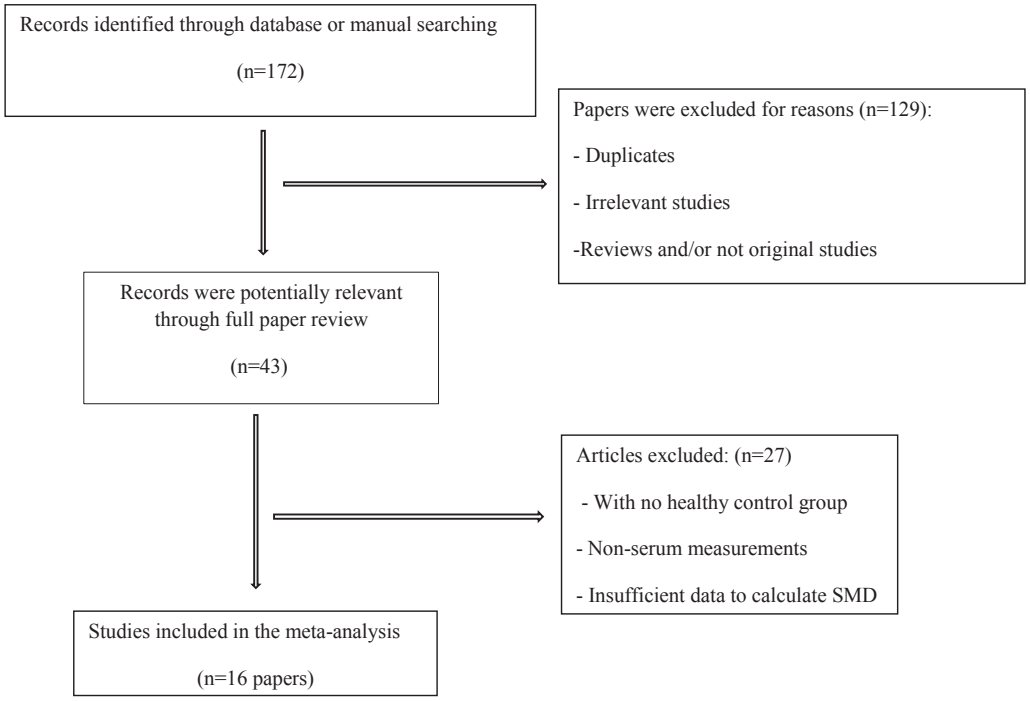


Fig. 1. Flow diagram of the article selection.

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

Author & year	Region	Cancer type	Study design	Assay method	Age case/control	Female/male (case/control)	BMI case/control	Sample size case/control	Omentin level (Mean ± SD)		Quality
									Case	Control	
Fazeli, 2013	Iran	CRC	Case/Control	EIA	56.72 ± 9.25 53.03 ± 6.14	23/16 15/15	26.07 ± 4.58 27.15 ± 3.69	39/30	203.23 ± 125.00	9.120 ± 2.50	6
Uyeturk Ug, 2014	Turkey	PC	Case/Control	EIA	65.00 ± 7.750 66.00 ± 7.00	Male	28.00 ± 2.75 25.00 ± 2.50	50/30	546.80 ± 144.58	373.00 ± 143.36	6
Karabulut, 2016	Turkey	PAC	Case/Control	EIA	59.00 ± 13.00 NR	20/13 NR	NR	33/30	9.57 ± 53.97	1.61 ± 1.05	6
Cymbaluk-Płoska, 2018	Poland	EC	Case/Control	EIA	NR	Female	NR	92/76	610.10 ± 492.55	1338.4 ± 468.58	6
Zhang, 2016	China	BLC	Case/Control	EIA	63.52 ± 12.27 62.90 ± 10.34	14/28 14/28	22.79 ± 2.44 24.04 ± 3.40	42/42	1.825 ± 2.29	5.21 ± 2.48	5
Alaee, 2016	Iran	BC	Case/Control	EIA	54.3 ± 8.30 50.3 ± 3.20	NR	24.40 ± 0.6 23.40 ± 1.5	30/30	73.100 ± 29.70	108.80 ± 65.40	6
Onstad, 2014	USA	OC	Case/Control	EIA	NR	NR	NR	148/148	416.60 ± NR	756.40 ± NR	6
Shen, 2015	China	RCC	Case/Control	EIA	59.12 ± 2.03 56.07 ± 1.56	14/27 14/28	24.13 ± 0.50 25.25 ± 0.50	41/42	3.620 ± 0.760	9.860 ± 1.44	6
Holman, 2014	USA	EC	Case/Control	EIA	60.00 ± 11.44 59.00 ± 11.69	Female	NR	74/74	575.76 ± 229.47	673.77 ± 324.87	6
Yildiz, 2017	Turkey	OC	Case/Control	EIA	57.00 ± 10.50 55.00 ± 8.00	Female	30.70 ± 1.0 29.00 ± 1.0	41/41	43.800 ± 19.10	37.400 ± 12.00	5
Nourbakhsh, 2018	Iran	BC	Case/Control	EIA	39.00 ± 11.00 35.00 ± 7.00	Female	26 ± 3.40 24.2 ± 6.0	45/45	157.00 ± 66.00	217.00 ± 75.00	6
Fryczkowsk, 2015	Poland	PC	Case/Control	EIA	70.00 ± 2.25 67.00 ± 1.50	Male	26.40 ± 1.0 26.40 ± 1.0	40/40	478.80 ± 46.63	408.30 ± 51.20	5
Uyeturk Um, 2014	Turkey	CRC	Case/Control	EIA	62.00 ± 3.00 56.00 ± 7.00	19/26 17/18	27.00 ± 4.5 27.00 ± 4.5	45/35	618.0 ± 151.75	376.00 ± 126.75	6
Aleksandrov, 2016	German	CRC	Cohort Study	EIA	56.30 ± 7.30 50.20 ± 9.00	106/145 1386/909	27.70 ± 4.9 26.10 ± 4.2	251/2295	458.60 ± 32.00	395.60 ± 26.33	6
Khadem Ansari 2018	Iran	LC	Case/Control	EIA	65.13 ± 9.32 58.65 ± 7.82	Male	23.82 ± 4.28 24.10 ± 2.93	45/30	3.63 ± 0.70	5.43 ± 1.95	6
Zhou 2019	China	PCa	Case/Control	EIA	72.07 ± 7.29 71.34 ± 6.29	Male	25.64 ± 2.73 24.76 ± 3.00	90/90	12.94 ± 6.15	4.96 ± 4.71	7

CRC: Colorectal cancer, PCa: Prostate cancer, PAC: Pancreatic cancer, BLC: Bladder cancer, BC: Breast cancer, EC: Endometrial cancer, OC: Ovarian cancer, RCC: Renal cell carcinoma, LC: Lung Cancer, NR: not reported.

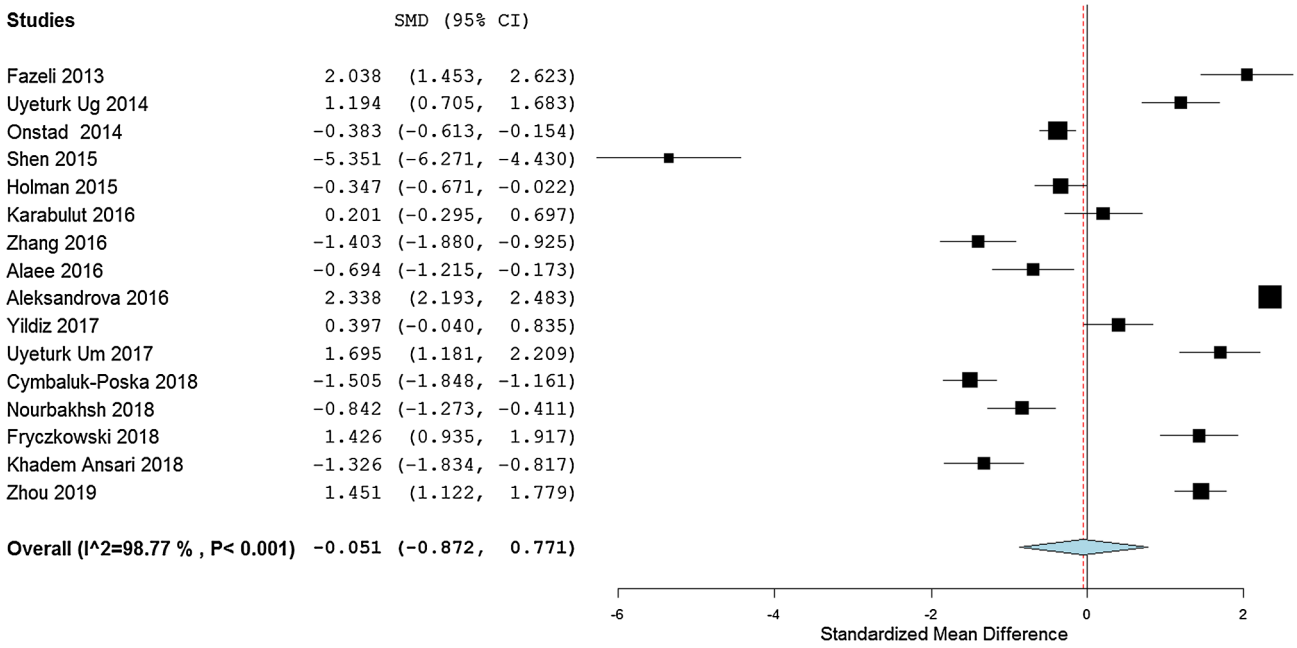


Fig. 2. Forest plot showing the association of circulating omentin level and cancer risk in pooling SMD analysis.

BMI ≥ 25 (SMD = 1.33, 95%CI: 0.52–2.15, P = 0.001) indicating a potential role for omentin in development of obesity-linked cancers (Fig. 3b). However, no significant association was found between the high omentin level and cancer risk in other subgroups based on BMI (Table 2).

3.4. Heterogeneity analysis

In order to explore the potential sources of heterogeneity, in addition to subgroup analysis, meta-regression, Galbraith plot, and sensitivity analysis were also carried out to evaluate the influence of single study or other factors that may affect the pooled SMD. Exploratory univariate meta-regression analysis for potential covariates including ethnicity, cancer type, study quality, sample size, mean age, BMI match, and mean BMI for summary SMD analysis revealed that cancer type (P = 0.011), and mean BMI (P < 0.001), may significantly contribute in between-study variance (Table 2).

Galbraith plot analysis was also performed to facilitate examinations of heterogeneity through the detection of outlier studies. In our results, the study by Shen et al. [27] was detected as outlier and might be responsible for the existence of such a high heterogeneity (Fig. 4). However, pooled SMD analysis in the absence of this study did not lead to a significant decrease in heterogeneity (I^2 = 98.76), while, led to nominally shift of overall SMD toward the positive values at the same time (SMD = 0.282 and 95% CI = −0.51 to 1.07). Furthermore, during the sensitivity analysis assessing the effect of each single study on the overall results of the meta-analysis through omitting one study at a time, the SMDs ranged between −0.20 (−0.86 to 0.47) after excluding the Aleksandrovaet al. study and 0.28 (−0.51 to 1.07) after excluding the Shen et al. study with no change in the overall estimate direction. This means that no single study significantly affected the overall SMD, indicating the stability and robustness of the results (Fig. 5).

3.5. Publication bias

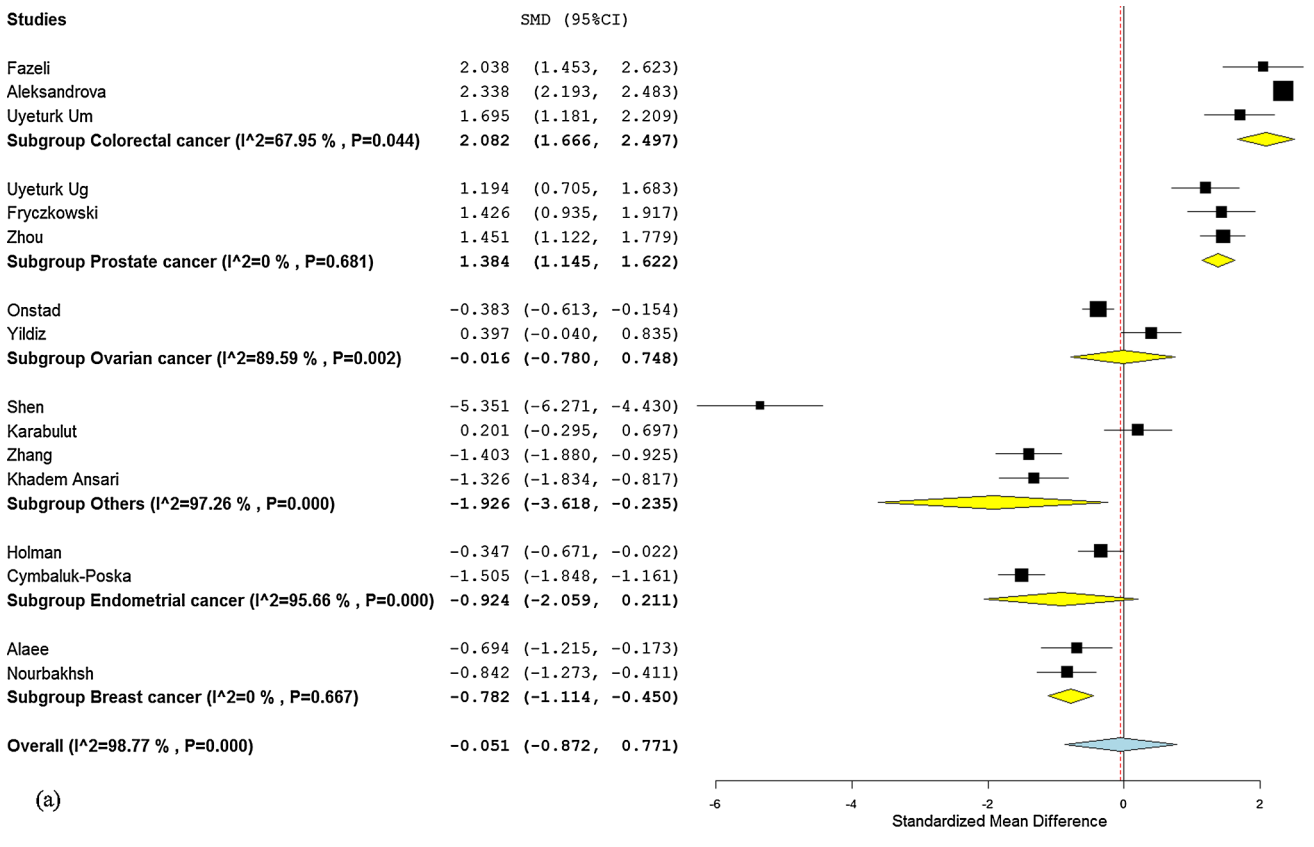
Based on the visual inspection of Begg's funnel plot (Fig. 6) and the results of Egger's regression test, the publication bias was found across the included studies (P = 0.015).

4. Discussion

The relationship between the circulating omentin level and risk of cancer has been investigated in various malignant tumors [17,25,34]. Although, altered circulating levels of omentin were found in some different cancers, whether its decreased or increased level is associated with cancer risk remains controversial in different epidemiological studies. Besides, the result of single study may not have sufficient generalizability due to lower statistical power resulting from limitations in sample size and methodological design. Therefore, pooling the results of all relevant studies is often the best way to achieve the real decision-making conclusions. To the best of our knowledge, this is the first meta-analysis to quantitatively evaluate the relationship between the circulating omentin levels and risk of cancer in patients with malignant solid tumors.

The present comprehensive meta-analysis assessed the association between serum omentin level and risk of solid tumor malignancies by pooling SMDs of 16 eligible case-control studies. The outcomes of this meta-analysis indicates a significant association between the altered omentin levels with a greater risk of cancer in patients with colorectal, prostate, and breast cancers compared to the healthy controls. An elevated circulating omentin level was also found for cancer patients with mean BMI ≥ 25. These results suggest that omentin levels may positively correlate with the risk of obesity-linked cancers. Moreover, the results of Galbraith plot and sensitivity analysis confirmed the stability and robustness of pooled result. Considering the role of omentin in linking the obesity to cancer development [37] and the findings of this meta-analysis as well as the inconsistency in published results, it can be concluded that the altered levels of omentin may represent a potential novel biomarker for early detection of colorectal, prostate, and breast cancers especially in overweight subjects who may benefit from preventive medicine.

There are controversial results about the expression level of omentin in different types of cancer. In our results, based on pooled SMD analysis, the omentin level was higher in colorectal and prostate cancers [17,18,25,29,34]. Although the exact clinicopathological effects of omentin in cancer remains to be clarified, it is proposed that omentin may be involved in cancer progression through stimulating the angiogenesis by activating the PI3K/AKT signaling pathway. Thus, up-regulation of AKT signaling can lead to development of carcinogenesis



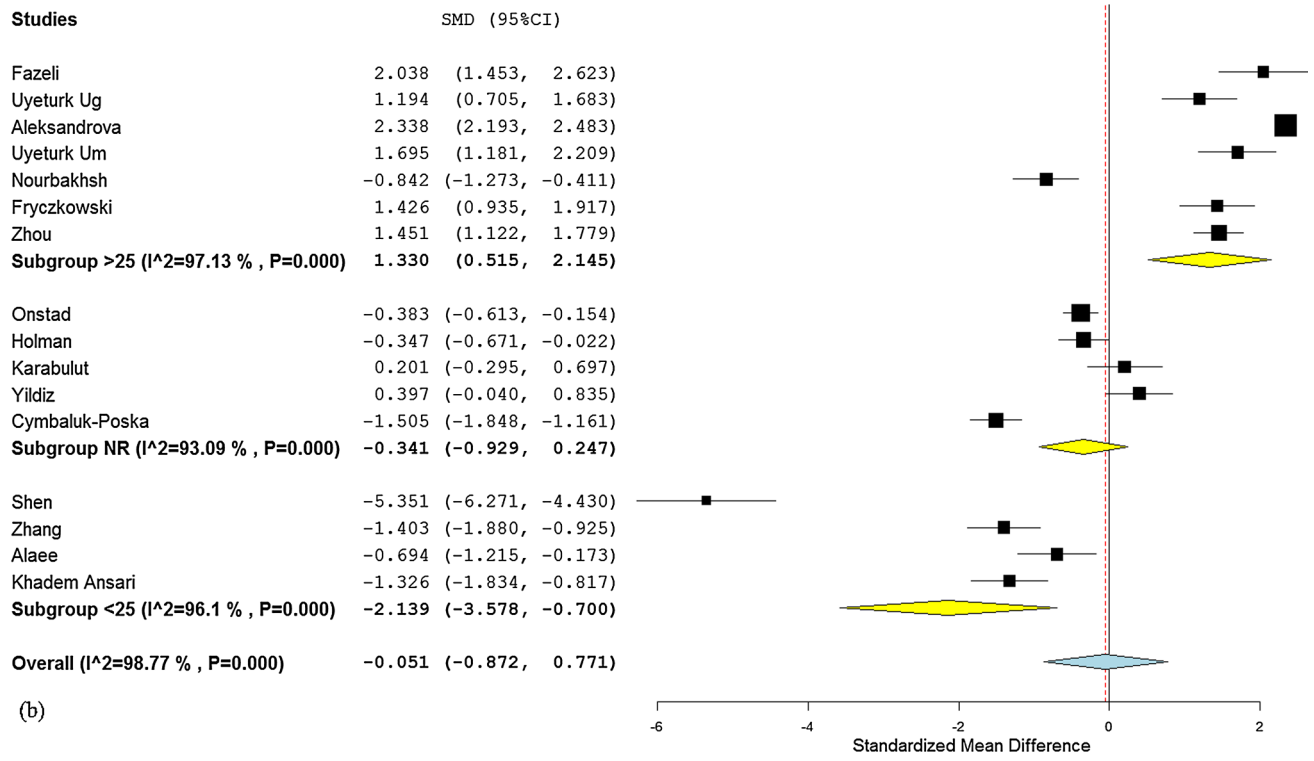


Fig. 3. Forest plot of pooled SMD for the association of circulating omentin level and cancer risk in subgroup analysis according to the tumor type (a) and BMI (b).

[17,38,39]. It has also been suggested that elevated levels of omentin in cancerous tissues facilitate the glucose uptake, provide sufficient energy supplies and consequently increase the level of insulin sensitivity for cancer cell development [33].

A growing body of evidence suggests obesity as a risk factor for multiple cancers. Obesity is believed to potentially lead to a new wave of the development of more than 13 different obesity-linked cancer such as esophagus, stomach, colon, liver, kidney, gallbladder, pancreas,

Table 2
Stratified analyses of pooled SMD of circulating omentin-1 levels and cancer risk.

Subgroups		Number of studies	Pooled SMD (95% CI)	P- value	Heterogeneity			P-value[b]
					I^2 (%)	P-value[a]	Model	
Total		16	−0.05 (−0.87–0.77)	0.904	98.77	< 0.001	Random	0.001
Cancer types	CRC	3	2.08 (1.67–2.50)	< 0.001	67.95	0.044	Random	
	BC	2	−0.78 (−1.11, −0.45)	< 0.001	0	0.667	Fixed	
	PCa	3	1.38 (1.15–1.62)	< 0.001	0	0.681	Fixed	
	OC	2	−0.02 (−0.78 to 0.75)	0.967	89.59	0.002	Random	
	EC	2	−0.92 (−2.06 to 0.21)	0.110	95.66	< 0.001	Random	
	Others	4	−1.93 (−3.62, −0.24)	0.026	97.26	< 0.001	Random	
Sample size	< 70	11	−0.10 (−1.07 to 0.86)	0.645	97.21	< 0.001	Random	0.576
	≥70	5	0.31 (−1.22 to 1.85)	0.689	98.77	< 0.001	Random	
Ethnicity	Caucasian	13	0.32 (−0.55 to 1.19)	0.315	98.74	< 0.001	Random	0.056
	Asian	3	−1.74 (−4.96 to 1.48)	0.089	99.16	< 0.001	Random	
Study quality	NOS score ≤ 5	4	0.52 (−0.82 to 1.88)	0.445	96.86	< 0.001	Random	0.449
	NOS score > 5	12	−0.25 (−1.25 to 0.76)	0.630	99.02	< 0.001	Random	
Mean age, years	< 60	7	−0.24 (−1.75 to 1.26)	0.752	98.96	< 0.001	Random	0.594
	≥ 60	7	0.36 (−0.58 to 1.35)	0.433	97.14	< 0.001	Random	
	NR	2	−0.93 (−2.03 to 0.16)	0.095	99.46	< 0.001	Random	
Mean BMI, kg/m^2	< 25	4	−2.14 (−3.58, −0.70)	0.004	96.10	< 0.001	Random	< 0.001
	≥ 25	7	1.33 (0.52–2.15)	0.001	97.13	< 0.001	Random	
	NR	5	−0.34 (−0.93 to 0.25)	0.255	93.09	< 0.001	Random	
BMI matched	Yes	4	−0.359 (−1.54 to 0.82)	0.552	95.78	< 0.001	Random	0.693
	No	12	−0.05 (−0.92 to 1.02)	0918	98.96	< 0.001	Random	

Abbreviations: NOS: Newcastle-Ottawa Scale, SMD: Standardized Mean Difference, CI: Confidence Interval, BMI: Body Mass Index, CRC: Colorectal cancer, BC: Breast cancer, PCa: Prostate cancer, OC: Ovarian cancer, EC: Endometrial cancer, RCC: Renal cell carcinoma, PAC: Pancreatic cancer, BLC: Bladder cancer, LC: Lung cancer, NR: not reported.

[a] P-value for heterogeneity within each subgroup.

[b] P-value for heterogeneity between subgroups with meta-regression analysis.

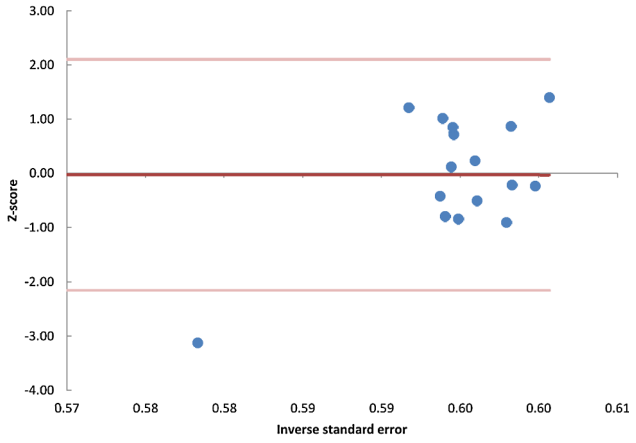


Fig. 4. Galbraith plots of the association between circulating omentin level and cancer risk in pooling SMD analysis.

ovary, endometrium, postmenopausal breast, prostate, meningioma, thyroid, multiple myeloma, and non-Hodgkin lymphoma [40]. It is widely believed that adipose tissue with its endocrine role in secreting different molecules and probably accumulation of various compounds can affect body physiology. Excessive adipose tissue may lead to a malproduction of adipocytokines in obesity condition. This process has been associated with various obesity -related comorbidities such as carcinogenesis. In fact, elevated levels of omentin in obesity has been proposed to exert a pro-carcinogenic role. This process may occur due to the involvement in cancer cells proliferation and inducing the immune and inflammatory responses [41]. Taken together, these roles may support the notion that high circulating omentin level is positively associated with increased risk of cancer development in overweight or obese patients.

Along with the presence of some strengths including a well-designed methodological issue, enrolling all relevant eligible studies and a wide variety of ethnicity in this meta-analysis, several important limitations should also be pointed out when interpreting the results. First, only English published studies were enrolled in this meta-analysis that probably influenced the pooled results. Second, existence of different potential biases and uncontrolled confounding factors as main inherent limitation in enrolled observational case-control studies that probably introduced bias. Third, age, BMI, and cut-off values of omentin level were inconsistent across the included studies that may also contribute in creating bias and heterogeneity. Forth, inadequate consideration of the potential confounding factors and discrepancy in various adjustments may also introduce a degree of heterogeneity. Additionally, the possibility of publication bias in favor of published articles with positive results may also exist.

5. Conclusions

In conclusion, our meta-results indicated a significant association between altered circulating omentin levels and increased risk of colorectal, prostate and breast cancers. The omentin level can also be suggested to serve as a risk assessment biomarker in overweight/obese patients who may benefit from preventive medicine. However, defining an optimal cut-off value for circulating omentin level based on the tumor type and BMI categories may be of high importance to identify subjects at high risk for different types of cancer. Further well-designed studies carefully controlled for potential confounding factors are necessary to clarify the more subtle roles of omentin in cancer development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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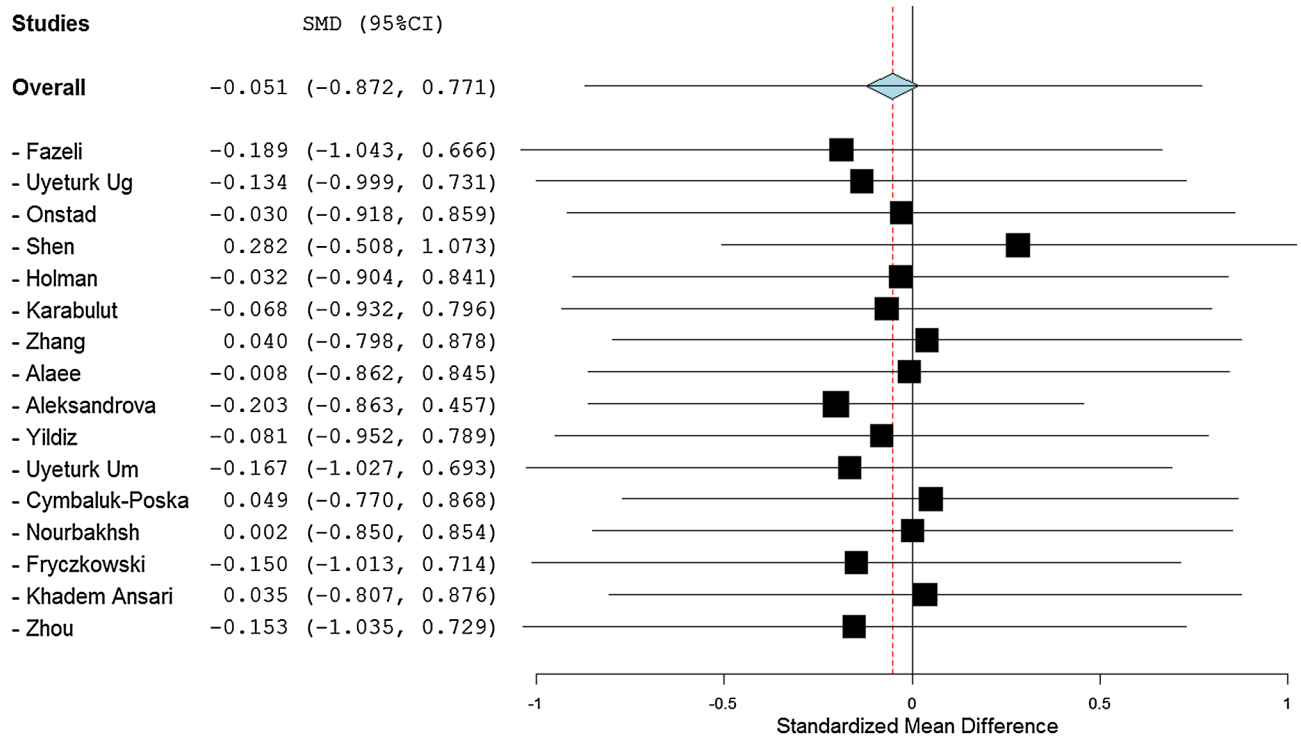

Fig. 5. Sensitivity analysis on the relationship between circulating omentin level and cancer risk.

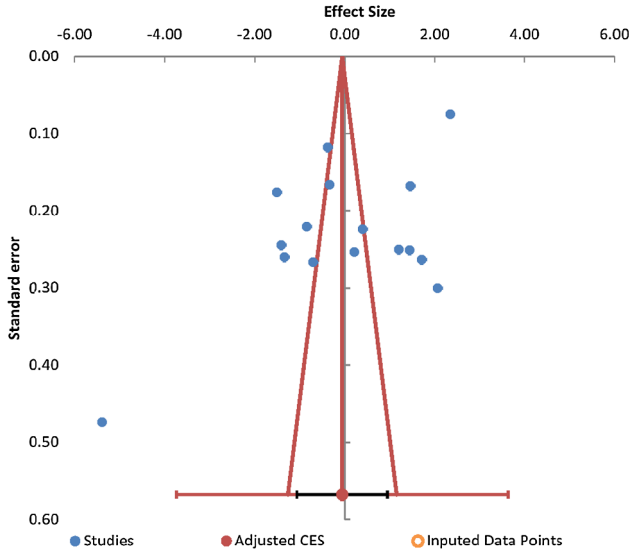

Fig. 6. Funnel plot of the publication bias on the association of circulating omentin and cancer risk in pooling SMD analysis.

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