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Circulating visfatin levels and cancers risk: A systematic review and meta-analysis

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Abstract

Visfatin levels have been reported to be abnormal in many types of cancers. However, epidemiological studies yielded inconsistent results. Therefore, a meta-analysis was performed to assess the association between circulating visfatin levels and cancer risk. A systematic search was conducted for relevant studies in health-related electronic databases up to March 2018. Data related to standard mean difference (SMD) and overall odds ratio (ORS) were collected and analyzed. Summary SMD and pooled OR with 95% CIs were calculated using a random-effect model. Funnel plot and Egger's linear regression test were conducted to examine the risk of publication bias. A total of 27 studies with 2,693 cases and 3,040 healthy controls were included in meta-analysis for pooling SMD analysis. The results of the meta-analysis showed a significant higher visfatin levels in patients with various cancers than in controls, with a pooled SMD of 0.88, 95% CI = 0.56–1.20, $p = 0.000$. In subgroup, metaregression, Galbraith plot, and sensitivity analysis showed no substantial difference among all the analyzed factors. Data from 14 studies were also used for pooling ORs analysis. Metaresults revealed that high visfatin levels were associated with cancer risk (OR = 1.24, 95% CI: 1.14–1.34, $p = 0.000$). No evidence of publication bias was observed for pooling ORs and SMD analysis. This meta-analysis indicated a significant association between high circulating visfatin levels and increased risk of various cancers. Visfatin may represent a potential biomarker for early detection of cancers who may benefit from preventive treatment.Note.

KEYWORDS

cancer, circulating visfatin levels, meta-analysis

1 | INTRODUCTION

Cancer represents an important public health problem in most regions worldwide. Beyond the established cancer predisposing factors such as genetic lesions, environmental parameters, and unhealthy lifestyle, as crucial causes of cancer, overweight, obesity, and metabolic syndrome are also associated with the risk of cancer. Literature have revealed that metabolic changes related to obesity is associated with an increased risk of cancer. It was proposed that cancer incidence rate in obese women is much more than those in normal weight women (Calle & Kaaks, 2004). In the process of obesity, adipose tissue undergoes some dysmetabolic changes that can lead to chronic subclinical inflammation, insulin resistance, and abnormal circulating concentrations of adipocytokines (Basen-Engquist & Chang, 2011). It is hypothesized that abnormalities in adipocytokines production are key regulators for the vital link between obesity and cancer (Lohmann et al., 2016).

Adipocytokines as a group of small peptide hormonal growth factors, secreted by adipocytes, play important regulatory role in a wide range of biological and physiological processes, such as appetite, inflammation, insulin sensitivity, immune system, hematopoietic function, and vascular homostasis (Cao, 2014). Among them aberrant

circulating level of adiponectin, leptin, resistin, and visfatin have been extensively studied in cancer (Dalamaga & Christodoulatos, 2017).

Visfatin or nicotinamide phosphorybosiltransferase (NAMPT) or pre-B-cell-enhancing factor has enzyme activity in the synthesis of cellular nicotinamide adenine dinucleotide (NAD^+) and plays an important role in the regulation of cellular growth, angiogenesis, and apoptosis in mammalian cells (Bowlby, Thomas, D'Agostino, & Kridel, 2012; Mohammadi et al., 2015). Visfatin overexpression has been recently found in various cancers including colorectal, gastric, breast, prostatic, pancreas, and esophageal cancers (Bi & Che, 2010; Dalamaga, 2012). The downregulation of visfatin promotes apoptosis in cancer cells and attenuates tumor growth. Therefore, specific NAMPT inhibitors might be adjuvant therapeutic modalities (Tan et al., 2013). Although many studies provided evidence that high visfatin levels were associated with the risk of obesity-related cancers, some studies observed different results. Many studies showed visfatin levels were similar or lower in patients with cancer compared with the normal healthy controls. Therefore, understanding the exact role of visfatin in cancer may offer a novel target in tumor diagnosis and therapeutic strategy.

To the best of our knowledge, no systematic review and/or meta-analysis has been conducted to evaluate the association between circulating visfatin levels and the risk of cancer. Conducting a comprehensive meta-analysis may lead to an evidence-based quantitative assessment of the association. Hence, despite the contradiction in the existing data from current available studies, the current study summarized available data to gain a more explicit and evidence-based conclusion on the association between visfatin levels and the risk of cancer.

2 | METHODS

2.1 | Literature Search strategy and study selection

An electronic literature search of databases including PubMed, Medline, Web of Sciences, Embase, and Scopus was conducted for publications, in English, up to May 2018. The search terms included "visfatin," "NAMPT," "PBEF," "Visfatin/NAMPT," "Visfatin/PBEF," "cancer," "carcinoma," "neoplasm," and "tumor" or their equivalents were used individually or/and in various combinations to retrieve the relevant literatures. In addition, the reference lists of all identified literature were also checked to identify additional relevant articles. This systematic literature search and subsequent meta-analysis were planned and conducted according to the standards for reporting meta-analysis of observational studies.

Two investigators (MM and HMM) independently reviewed the titles and abstracts of all studies for relevance and eligibility. Ecological studies, abstracts, unpublished reports, duplicate publications, reviews, letters, case report, editorials, or comments were not considered eligible. In the case of duplicate studies, the most recent or informative study was included. Studies were considered eligible if they met the following criteria: (a) case-control or nested case-control studies published as original article; (b) must be reported the visfatin serum/plasma levels in patients with any types of cancer and healthy controls; (c) provided sufficient data to calculate standardized mean difference (SMD) and/or odds ratio (OR) with corresponding 95% CI. Studies were excluded, if they did not refer to cancer, serum/plasma visfatin, and healthy controls. Also, investigations performed on animals, cells or tissues were not included in the analysis.

2.2 | Data extraction and quality assessment

Two authors (MM and FM) were independently extracted data from all eligible publications using a piloted data extraction sheet. Any discordance was resolved through discussion and team consensus. Briefly, the following information was extracted from each eligible study: first author's surname and year of publication, country of origin, cancer type, study design, visfatin detection assay, number of cases and controls, age, gender, body mass index (BMI), visfatin mean (SD), adjusted OR (95% CI) for the risk of cancer incidence, and confounders adjusted in multivariate analysis. Quality assessment for each study included was done using the Newcastle-OTTAWA Scales (NOS) which uses a star rating system (a score of 0–9; Stang, 2010). Studies with the score ≥ 5 considered good quality.

2.3 | Statistical analysis

The standardized mean differences (SMDs) and corresponding 95% CIs were calculated based on the sample size, mean, and SD extracted from eligible studies to measure the strength of the association between circulating visfatin levels and cancer risk. If a study only provided the median, range and/or interquartile range (IQR), mean, and SD were estimated, as described by Wan, Wang, Liu, and Tong (2014). The pooled ORs and 95%CIs were also calculated. The statistical significance of the pooled OR and pooled SMD was determined by the Z-test and considered significant for $p < 0.05$.

The Cochran Q statistic and inconsistency index (I^2) were used to assess the heterogeneity of effect size among different studies.

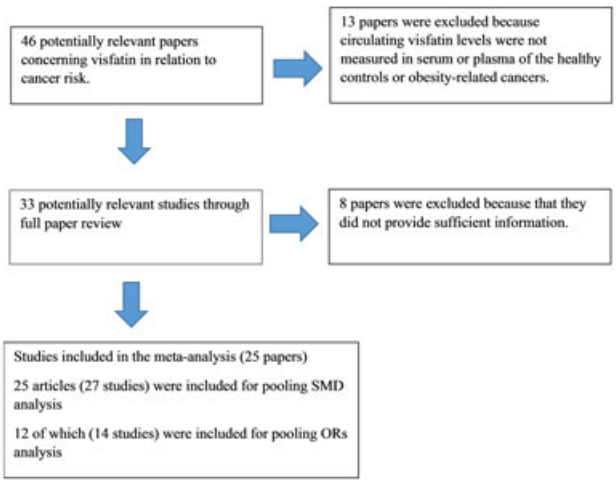

FIGURE 1 Procedure of article selection [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of studies included in the meta-analysis

Author, year	Country	Cancer	Study design	Detection assay	Sample size case/control	Age case/control	Female/male (case/control)	BMI case/control	Visfatin (Mean ± SD)		Adjusted OR (95% CI)	Adjustments	NOS score
									Cases	Controls			
Fazeli et al., 2013	Iran	CRC	Retrospective matched case-control	ELISA	39/30	56.72 ± 9.25/ 53.03 ± 6.14	23/16 15/15	26.07 ± 4.58 27.15 ± 3.69	4.10 ± 1.72	1.99 ± 2.18	NR	–	6
Tsai et al., 2017	Taiwan	HCC + HB-V	Retrospective case-control	ELISA	36/92	62.0 ± 10.9/ 51.8 ± 5.9	10/26 24/68	23.4 ± 4.0/ 23.8 ± 3.1	25.20 ± 9.80	7.50 ± 5.20	1.17 (1.00–1.37)	Age, gender,diabetes mellitus, and obesity	4
Tsai et al., 2017	Taiwan	HCC + HC-V	Retrospective case-control	ELISA	39/92	69.4 ± 9.7/ 51.8 ± 5.9	18/21 24/68	23.5 ± 4.1/ 23.8 ± 3.1	29.50 ± 7.60	7.50 ± 5.20	1.17 (1.00–1.37)	Age, gender,diabetes mellitus, and obesity	4
Rodrigo et al., 2017	Sri Lanka	BC	Matched case-control	ELISA	80/80	48.69 ± 11.40/ 47.55 ± 10.39	80/0 80/0	NR	0.35 ± 0.15	0.14 ± 0.08	1.70 (0.83–3.49)	Age, BMI, and menopausal status	4
Fazeli et al., 2016	Iran	CRA	Case-control	ELISA	34/35	48.3 ± 10.96/ 51.6 ± 12.52	16/18 17/18	26.14 ± 1.29/ 26.22 ± 1.31	6.70 ± 3.01	6.80 ± 2.49	NR	-	4
Nakajima et al., 2010a, 2010b	Japan	CRC	Matched case-control	ELISA	115/115	63.7 ± 10.3/ 63.5 ± 10.5	46/69 46/69	22.9 ± 2.9/ 23.1 ± 2.7	3.90 ± 4.30	1.40 ± 1.10	2.99 (1.86–4.79)	Age, BMI, and menopausal status	7
Nergiz Avcioglu, 2014	Turkey	EC	Case-control	ELISA	46/44	61.4 ± 9.1/ 50.7 ± 11.1	46/0 44/0	NR	9.7 ± 43.3	5.90 ± 3.85	NR	–	5
Zhang et al., 2014	China	Bladder C	Case-control	ELISA	131/109	63.49 ± 12.96/ 63.12 ± 10.28	24/107 NR	NR	16.02 ± 7.95	6.46 ± 2.08	NR	–	5
Lu, Wang, Xia, and Qian, 2014	China	GC	Case-control	ELISA	262/262	NR	106/156 106/156	NR	78.4 ± 20	41.5 ± 12	NR	–	5
Li et al., 2014	China	BC	Case-control	ELISA	248/100	NR	Only female	NR	65.6 ± 16.9	37.2 ± 9.6	NR	–	5
Yu-Duan et al., 2013	Taiwan	OSCC	Matched case-control	ELISA	51/57	52.6 ± 10.1/ 53.1 ± 7.0	Only male	24.3 ± 3.9/ 24.8 ± 2.7	7.0 ± 4.5	4.80 ± 1.90	1.37 (1.03–1.81)	Age, BMI, SBP, DBP, total cholesterol, triglyceride, betel-quid chewing, drinking, and smoking status	5
Tian et al., 2013	China	EC	Case-control	ELISA	120/120	56.7 ± 8.9/ 55.8 ± 10.7	Only female	27.35 ± 4.91/ 25.37 ± 4.10	19.65 ± 4.08	15.02 ± 5.38	1.05 (1.02–1.09)	BMI, WHR, diabetes, hypertension, and family history of cancer	5
Luhn et al., 2013a	California	EC	Nested case-control	ELISA	94/189	66.4 ± 5.7/NR	Only female	NR	0.84 ± 1.65	0.76 ± 1.07	1.29 (0.55–3.01)	Family history of breast or endometrial cancer, education level, parity, history of diabetes diagnosis, oral contraceptive use, and current smoking status	5

(Continues)

TABLE 1 (Continued)

Author, year	Country	Cancer	Study design	Detection assay	Sample size case/control	Age case/control	Female/male (case/control)	BMI case/control	Visfatin (Mean ± SD)		Adjusted OR (95% CI)	Adjustments	NOS score
									Cases	Controls			
Dalamaga, 2012	Greece	BC	Matched case-control	ELISA	103/103	61.5 ± 8.2/62.3 ± 8.8	Only female	27.7 ± 4.14/25.9 ± 5.4	57.9 ± 31.2	43.6 ± 28.1	NR	–	6
Assiri, Kamel, and Hassanien, 2015	Saudi Arabia	BC	Matched case-control	ELISA	82/68	53.68 ± 13.98/52.25 ± 16.62	Only females	24.59 ± 1.48/24.84 ± 1.35	18.36 ± 3.92	15.57 ± 2.41	1.09 (1.06–1.12)	Age and BMI	6
Ilhan et al., 2015	Turkey	EC	Case-control	ELISA	42/42	60/NR	Only females	NR	14.9 ± 10.6	8.1 ± 6.9	NR	–	5
Tulubas, 2014	Turkey	CC	Case-control	ELISA	30/30	61.4 ± 1.5/54.7 ± 10.0	15/15 17/13	26.4 ± 4.0/28.6 ± 5.4	222.2 ± 38.3	171.8 ± 32.0	NR	–	4
El-Benhawy, El Moneim, and Ebeid, 2015	Egypt	BC	Matched case-control	ELISA	70/20	NR	Only female	NR	5.0 ± 46.5	0.5 ± 2.96	28.86 (5.18–160.83)	Age, BMI, menopausal status, and serum resistin	5
Nakajima et al., 2009	Japan	GC	Matched case-control	ELISA	156/156	61.0 ± 11.8/60.8 ± 11.5	65/91 65/91	20.7 ± 1.63/23.3 ± 3.7	4.1 ± 5.7	1.4 ± 1.3	1.95 (1.301–2.934)	NR	7
Chen et al., 2016	China	Early CRC	Case-control	ELISA	161/286	59.3 ± 11.5/58.8 ± 12.9	67/90 117/169	23.7 ± 1.3/23.1 ± 0.8	5.14 ± 1.14	3.94 ± 1.13	3.37 (1.93–8.37)	Age, BMI, WHR, SBP,TG, HOMA-IR, lifestyle characteristics, medications, family history of CRC, and diabetes	4
Chen et al., 2016	China	Advanced CRC	Case-control	ELISA	197/286	62.4 ± 12.3/58.8 ± 12.9	89/112 117/169	22.8 ± 1.5/23.1 ± 0.8	6.21 ± 1.22	3.94 ± 1.13	2.38 (1.82–8.35)	Age, BMI, WHR, SBP,TG, HOMA-IR, lifestyle characteristics, medications, family history of CRC, and diabetes	4
Nakajima et al., 2009	Japan	SCC	Case-control	ELISA	117/117	63.6 ± 8.7/63.6 ± 8.8	30/87 30/87	NR	2.6 ± 4.15	1.4 ± 1.3	0.99 (0.71–1.38)	NR	8
Gasiorowska et al., 2013	Poland	PC	Case-control	ELISA	45/13	65.6 ± 11.5/Matched age	27/18	21.8 ± 3.4/Matched BMI	2.8 ± 1.8	3.8 ± 1.1	NR	–	5
Suga et al., 2013	Japan	CTCL	Case-control	ELISA	39/42	57.6 ± 12.3/42.6 ± 17.3	17/22 23/19	NR	1.89 ± 1.26	1.75 ± 0.92	NR	–	4
Sun et al., 2017	China	HCC	Case-control	ELISA	135/149	49.93 ± 11.72/46.34 ± 7.12	17/118 68/81	22.06 ± 3.31/22.34 ± 3.55	1.113 ± 1.03	0.759 ± 0.10	NR	–	4

(Continues)

TABLE 1 (Continued)

Author, year	Country	Cancer	Study design	Detection assay	Sample size case/control	Age case/control	Female/male (case/control)	BMI case/control	Visfatin (Mean ± SD)		Adjusted OR (95% CI)	Adjustments	NOS score
									Cases	Controls			
Zekri, Bakr, Ezzat, Zakaria, and Elbaz, 2015	Egypt	CRC	Case-control	ELISA	34/29	41.27 ± 1.73/ 43.07 ± 2.79	14/20 11/16	NR	5.12 ± 1.17	6.58 ± 1.35	NR	–	4
Chen et al., 2014	Taiwan	HCC	Nested case-control	ELISA	187/374	52.38 ± 8.27/ 52.17 ± 8.14	31/154 62/311	NR	11.10 ± 15.5	12.30 ± 17.3	0.99 (0.98–1.01)	Age, gender, and residence area	5

Note. BC: breast cancer; CC: colon cancer; CRA: colorectal adenoma; CRC: colorectal cancer; CTCL: cutaneous T-cell lymphoma; EC: endometrial cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; NR: Not reported; OSCC: oral squamous cell carcinoma; PC: pancreatic cancer; SCC: squamous cell carcinoma.

If $I^2 > 50\%$, and $p < 0.05$, heterogeneity was statistically significant, and the random effects model was used, otherwise, the fixed effect model was applied. Sensitivity analyses was performed to assess the stability of the results by sequential omitting of individual studies in the meta-analysis. To explore the potential sources of heterogeneity, subgroup analysis, based on study size, geographical area, study quality, risk estimate adjustment, mean age, mean BMI, and BMI matched status was performed. Galbraith plot and metaregression analysis were also used to further explore which study or variables contribute substantial heterogeneity (Galbraith, 1988; Stanley & Jarrell, 1989). Potential publication bias was evaluated by using funnel plots and Egger's linear regression test. Statistical analysis were performed using Comprehensive Meta-Analysis (CMA) computer program (Biostat, Englewood, NJ) and statistical significance was defined as a *p*-value <0.05.

3 | RESULTS

3.1 | Literature search

A summary of the literature selection is provided in Figure 1. In our initial searches a total of 46 potentially relevant papers concerning visfatin in relation to cancer risk were revealed. More detailed review, resulted in exclusion of 13 papers that did not measure the circulating visfatin levels in serum or plasma of the healthy controls or cancer patients. In subsequent screening steps for remained articles, eight papers were excluded due to insufficient information. Consequently, 25 articles with 27 studies including 2,693 patients with cancer and 3,040 healthy controls were included in meta-analysis for pooling SMD analysis (Assiri, Kamel, & Hassanien, 2015; Chen et al., 2014; Chen et al., 2016;; Dalamaga et al., 2012; El-Benhawy, El Moneim, & Ebeid, 2015; Fazeli et al., 2013, 2016; Gąsiorowska et al., 2013; Ilhan et al., 2015; Li et al., 2014; Lu, Wang, Xia, & Qian, 2014; Luhn et al., 2013a; Nakajima et al., 2009, 2010a, 2010b; Nergiz Avcioglu et al., 2015; Rodrigo et al., 2017; Suga et al., 2013; Sun et al., 2017; Tian et al., 2013; Tsai et al., 2017; Tulubas, Mete, Oznur, & Topcu, 2013; Yu-Duan et al., 2013; Zekri, Bakr, Ezzat, Zakaria, & Elbaz, 2015; Zhang et al., 2014). Of these, 12 publications with 14 studies, provided data for ORs, were also included in our secondary meta-analysis to estimate pooled ORs with 95% CIs (Assiri et al., 2015; Chen et al., 2014; Chen et al., 2016; El-Benhawy et al., 2015; Luhn et al., 2013b; Nakajima et al., 2009, 2010a, 2010b; Rodrigo et al., 2017; Tian et al., 2013; Tsai et al., 2017; Yu-Duan et al., 2013). Two articles comprised two different groups of patients and were thus counted as two studies (Chen et al., 2016; Tsai et al., 2017). The general characteristics of the selected studies are summarized in Table 1. All articles were published between 2009 and 2017. With regard to the ethnicity, 16 studies had been conducted on Asian populations, two on African and nine on Caucasians cases. A total of nine different types of cancer including; six colorectal cancer (CRC), four hepatocellular carcinoma (HCC), two gastric cancer (GC), four endometrial cancer (EC), six breast cancer (BC), two squamous cell carcinoma (SCC), one pancreatic

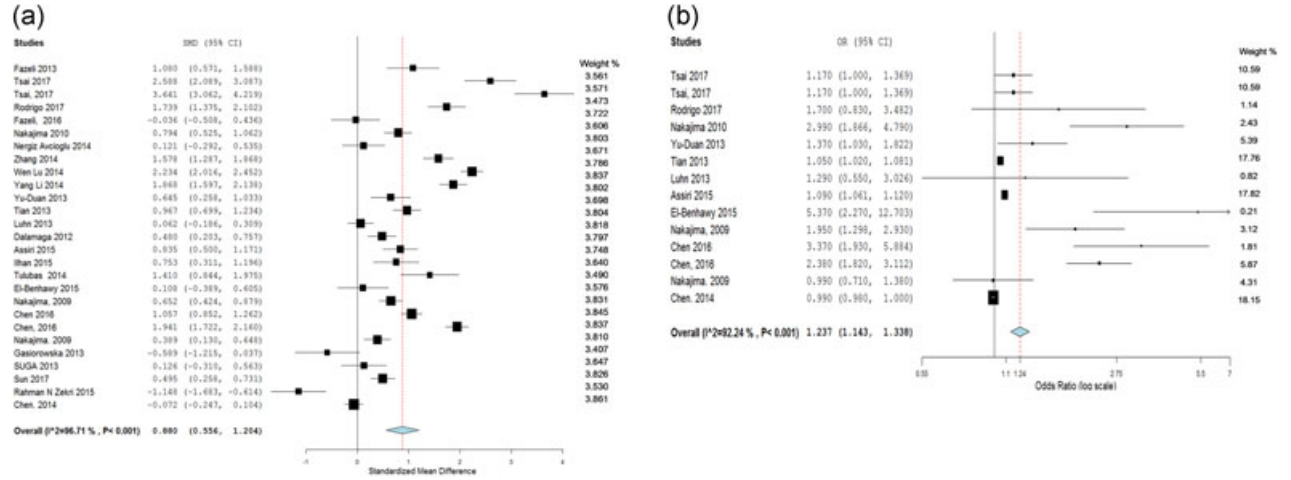

FIGURE 2 Forest plot showing the association of circulating levels of visfatin and cancer risk in pooling SMD (a) and ORs (b) analysis [Color figure can be viewed at wileyonlinelibrary.com]

cancer, one cutaneous T-cell lymphoma (CTCL), and one bladder cancer (BC) were evaluated in studies included. Circulating visfatin levels were measured in all studies using enzyme-linked immunosorbent assay (ELISA). Most research provided the mean and SD for visfatin serum levels. Mean and SDs for six articles were calculated using median, range and/or IQR (El-Benhawy et al., 2015; Nakajima et al., 2009, 2010a, 2010b; Nergiz Avcioglu et al., 2015; Sun et al., 2017). The ORs of most studies were adjusted for age, gender, and BMI. According to the NOS scoring system, 17 studies that awarded five stars or more were considered high-quality studies, whereas the rest 10 studies awarded lower than five stars were defined as low quality.

3.2 | Circulating visfatin levels and carcinogenesis

Data from 27 studies were pooled to evaluate the SMD of circulating visfatin with different cancers risk. Due to a significant amount of heterogeneity (I^2 = 96.71%; p = 0.000), a random-effects model was applied. Metaresults showed a significant higher level of visfatin in patients with cancer than in the controls (*SMD* = 0.88, 95% CI = 0.56–1.20; Figure 2a). Further, in subgroup analysis by sample size, ethnicity, study quality, risk estimate adjustment, cancer type, mean age, mean BMI, and BMI matched were also showed that visfatin levels were higher in cancer cases (Table 2).

Data form 14 studies were analyzed to calculate the combined OR. The multivariate adjusted ORs for each study and the combined OR are presented in Figure 2b. Metaresults based on random-effects models revealed that the high visfatin levels were associated with cancer risk (OR = 1.24, 95% CI: 1.14–1.34, p = 0.000). Reflecting a statistically significant amount of heterogeneity subgroup analysis was carried out next (I^2 = 92.24%, p < 0.0001). In subgroup analysis, the pooled OR of visfatin levels comparing cancer cases with healthy controls was not changed substantially (Table 3). However, in stratified analysis based on risk estimate adjustment, no significant difference was found for two studies with no risk adjustment (OR = 1.38, 95% CI: 0.71–2.67, p = 0.347).

3.3 | Heterogeneity analysis

To assess the potential sources of heterogeneity in the results, subgroup, metaregression, Galbraith plot, and sensitivity analysis were carry out. In stratified subgroup analysis, both the summary SMD and pooled OR of visfatin levels did not differ substantially according to sample size, ethnicity, study quality, risk estimate adjustment, cancer type, mean age, mean BMI, and BMI matched (Tables 2 and 3). Higher levels of circulating visfatin were observed in the patients compared with controls across all subgroups. To further investigate the potential sources of heterogeneity in the results, exploratory univariate metaregression analyses was performed by considering all the possible factors including sample size, ethnicity, study quality, risk estimate adjustment, cancer type, mean age, mean BMI, and BMI matched. Metaregression analysis revealed that ethnicity (p = 0.003) for summary SMD analysis, and ethnicity (p = 0.041) and mean age (p = 0.039) for pooled OR analysis were found to be significant contributing factors for between-study variance (Tables 2 and 3).

Galbraith plot analysis was also performed to detect the outliers as the potential sources of heterogeneity. For the pooling SMD analysis, two studies (Tsai et al., 2017; Zekri et al., 2015), and for the pooling ORs analysis, one study (Tsai et al., 2017) were detected as the outliers and possible major contributors to high heterogeneity (Figure 3a,b). Although excluding those studies, did not significantly change the level of heterogeneity, but high visfatin levels were still found in patients with cancer. Further, sensitivity analysis assessing the effect of each study on the overall results of meta-analysis, revealed no significant change in the direction of the ORs and SMD effects, indicating the stability and robustness of the results (Figure 4a,b).

TABLE 2 Stratified analyses of summary SMD of circulating visfatin levels and cancer risk

Subgroups		Number of studies	Pooled SMD (95% CI)	*p*-Value	Heterogeneity			
					I^2 (%)	*p*-Value[a]	Model	*p*-Value[b]
Total		27	0.88 (0.56–1.20)	< 0.001	96.71	< 0.001	Random	–
Sample size	< 100	15	0.75 (0.23–1.28)	0.005	95.5	< 0.001	Random	0.458
	≥ 100	12	1.03 (0.59–1.47)	< 0.001	96.59	< 0.001	Random	
Ethnicity	Caucasian	9	0.46 (0.13–0.79)	0.006	84.03	< 0.001	Random	0.003
	Asian	16	1.28 (0.85–1.70)	< 0.001	97.46	< 0.001	Random	
	African	2	−0.52 (-1.75–0.72)	0.41	91.21	< 0.001	Random	
Study quality	NOS score < 5	10	1.17 (0.54–1.82)	< 0.001	97.10	< 0.001	Random	0.219
	NOS score ≥ 5	17	0.71 (0.34–1.08)	< 0.001	96.34	< 0.001	Random	
Risk estimate adjustment	Yes	12	1.17 (0.67–1.68)	< 0.001	97.34	< 0.001	Random	0.145
	No	15	0.64 (0.20–1.08)	0.004	96.28	< 0.001	Random	
Cancer type	Digestive system cancer	15	0.98 (0.48–1.48)	< 0.001	97.64	< 0.001	Random	0.553
	Others	12	0.76 (0.38–1.14)	< 0.001	94.22	< 0.001	Random	
Mean age, year	< 60	11	0.53 (0.14–0.92)	0.007	94.37	< 0.001	Random	0.208
	≥ 60	13	1.05 (0.53–1.53)	< 0.001	96.57	< 0.001	Random	
	Not mentioned	3	1.43 (0.49–2.38)	0.003	96.60	< 0.001	Random	
Mean BMI, kg/m^2	< 25	10	1.20 (0.70–1.69)	0.001	96.33	< 0.001	Random	0.398
	≥ 25	5	0.76 (0.34–1.18)	< 0.001	83.06	< 0.001	Random	
	Not mentioned	12	0.81 (0.238–1.39)	0.0.3	97.75	< 0.001	Random	
BMI matched	Yes	8	0.46 (−0.09–1.01)	0.104	93.15	< 0.001	Random	0.129
	No	19	1.06 (0.66–1.45)	< 0.001	97.34	< 0.001	Random	

Note. BMI, body mass index; CI, confidence interval; NOS, Newcastle-Ottawa Scale; SMD, standardized mean difference.

[a]*p*-Value for heterogeneity within each subgroup.

[b]*p*-Value for heterogeneity between subgroups with metaregression analysis.

TABLE 3 Subgroup analysis of pooling ORs of circulating visfatin and cancer risk

Subgroups		Number of studies	Pooled OR (95% CI)	*p*-Value	Heterogeneity			
					I^2 (%)	*p*-Value[a]	Model	*p*-Value[b]
Total		14	1.24 (1.14–1.34)	< 0.001	92.24	< 0.001	Random	–
Sample size	< 100	7	1.24 (1.07–1.43)	0.004	67.51	< 0.001	Random	0.520
	≥ 100	7	1.30 (1.16–1.47)	< 0.001	94.23	< 0.001	Random	
Ethnicity	Caucasian	2	1.09 (1.06–1.12)	< 0.001	0	< 0.001	Random	0.041
	Asian	11	1.28 (1.16–1.41)	< 0.001	91.57	< 0.001	Random	
	African	1	5.37 (2.27–12.70)	–	–	–	–	
Study quality	NOS score < 5	5	1.67 (1.20–2.40)	0.003	88.33	< 0.001	Random	0.455
	NOS score ≥ 5	9	1.12 (1.04–1.21)	0.003	92.14	< 0.001	Random	
Risk estimate adjustment	Yes	12	1.23 (1.13–1.34)	< 0.001	93.02	< 0.001	Random	0.702
	No	2	1.38 (0.71–2.67)	0.347	84.35	0.011	Random	
Cancer type	Digestive system cancer	8	1.63 (1.27–2.09)	< 0.001	93.29	< 0.001	Random	0.364
	Others	6	1.09 (1.01–1.17)	0.029	73.48	0.002	Random	
Mean age, years	< 60	6	1.08 (1.01–1.16)	0.037	93.43	< 0.001	Random	0.039
	≥ 60	7	1.55 (1.17–2.05)	0.002	85.35	< 0.001	Random	
	Not mentioned	1	5.37 (2.27–12.70)	–	–	–	–	
Mean BMI, kg/m^2	< 25	8	1.62 (1.30–2.02)	< 0.001	90.7	< 0.001	Random	0.427
	≥ 25	1	1.05 (1.02–1.08)	0.02	–	–	–	
	Not mentioned	5	1.39 (0.93–2.06)	0.20	76.96	< 0.001	Random	
BMI matched	Yes	5	1.88 (1.2–2.95)	0.006	88.38	< 0.001	Random	0.272
	No	9	1.21 (1.09–1.33)	< 0.001	91.25	< 0.001	Random	

Note. BMI, body mass index; CI, confidence interval; NOS, Newcastle-Ottawa Scale; OR, odds ratio.

[a]*p*-Value for heterogeneity within each subgroup.

[b]*p*-Value for heterogeneity between subgroups with metaregression analysis.

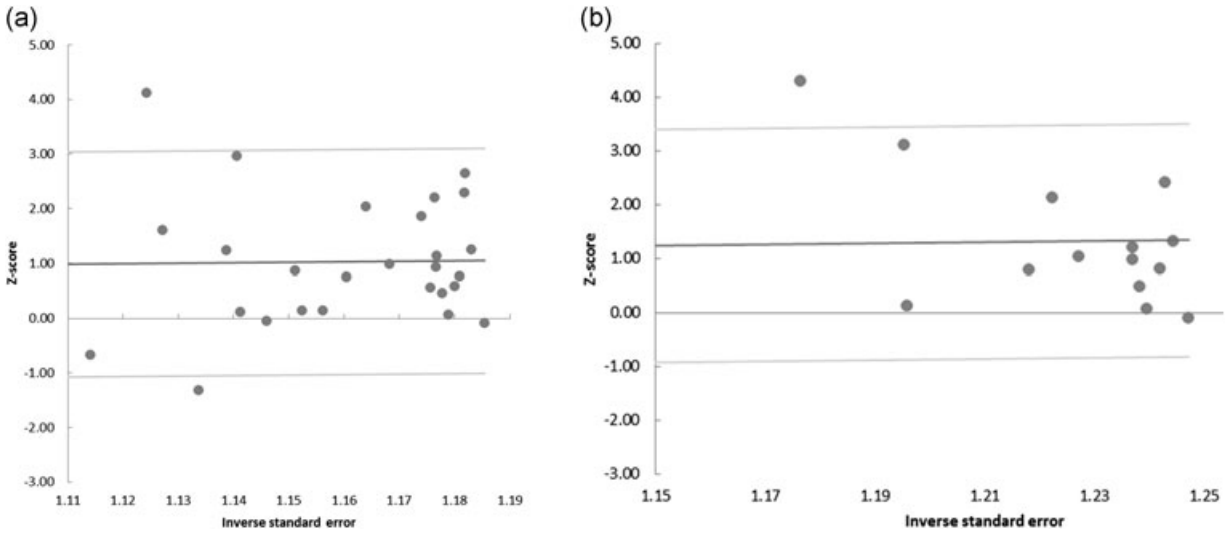

FIGURE 3 Galbraith plots for the association of circulating visfatin levels and cancer risk in summary SMD analysis (a) and summary ORs

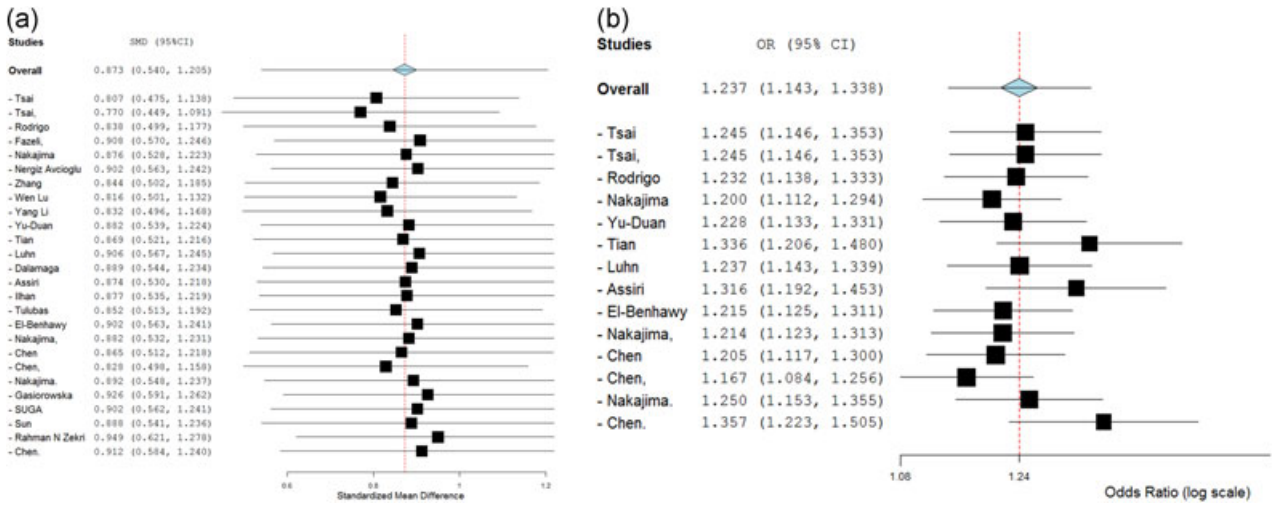

FIGURE 4 Sensitivity analysis on the relationship between circulating visfatin level and cancer risk. (a) For the pooled SMD; (b) For the pooled ORs [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Publication bias

Begg's funnel plot and Egger's regression asymmetry test were used to examine the publication bias of the meta-analysis regarding the association of visfatin with cancer. For both pooling SMD and ORs analysis, the visual inspection of funnel plots and Egger's test results provided no statistical evidence of publication bias across the included studies (Figure 5a,b).

4 | DISCUSSION

Currently, increasing evidence in the literature supports the association between adipocytokines and cancers risk. Several studies have shown the role of visfatin, as an adipokine, in different cancers. Whether circulating visfatin levels are higher in patients with cancer is inconsistent. Several studies have shown role of visfatin in different cancers (Bae et al., 2006; Kim et al., 2010; Patel et al., 2010; Wang et al., 2009). The results of this meta-analysis of 27 studies, revealed a direct association of higher circulating visfatin levels with the risk of cancers. Despite the existence of substantial heterogeneity across the studies included, metaresults indicated that elevated serum visfatin levels in malignant individuals comparing to the healthy controls can serve as a potential biomarker for early detection of cancers. Moreover, subgroup analysis based on different factors was also confirmed that visfatin levels independently are associated with different cancer risk. To investigate the influence of study features on significant between-study heterogeneity, exploratory analysis including Galbraith plots, metaregression, subgroup, and sensitivity analysis were also performed to identify potential sources. No substantial difference were observed among all the analyzed

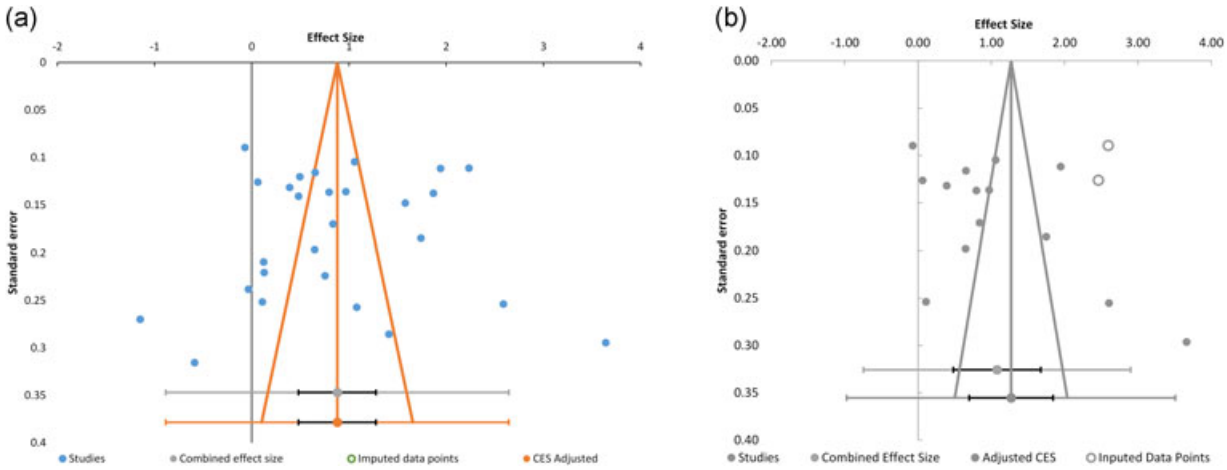

FIGURE 5 Funnel plot of the publication bias on the association of circulating visfatin and different cancers in pooling SMD analysis (a) and pooling ORs analysis (b) [Color figure can be viewed at wileyonlinelibrary.com]

factors. Due to nonsignificant alteration in heterogeneity among the analyzed factors, all summary estimates were calculated using random effect models to take into account between-study variations.

Increasing evidence has shown human visfatin could regulate angiogenesis and tumor growth. For example, recently has shown visfatin induces exogenously gastric cancer cell proliferation and increases hTERT (human telomerase catalytic subunit) gene expression (Mohammadi et al., 2015). In another study, in prostate cancer cells, has shown exogenous visfatin increases proliferation of these cells (Patel et al., 2010). Bae et al. reported in breast cancer cells, transcription of human Visfatin genes is regulated by hypoxia inducible factor-1, a key factor in malignant tumor progression (Bae et al., 2006). Also, Kim et al. (2010) reported that visfatin regulates proliferation of MCF-7 human breast cancer cells. Exogenous administration of recombinant visfatin increased cell proliferation and DNA synthesis rate in MCF-7 cells. Furthermore, visfatin activated G1-S phase cell cycle progression by upregulation of cyclin D1 and cdk2 expression. Visfatin also increased the expression of matrix metalloproteinases 2, matrix metalloproteinases 9, and vascular endothelial growth factor genes, suggesting that it may function in metastasis and angiogenesis of breast cancer (Kim et al., 2010). Visfatin stimulates vascular smooth muscle cell proliferation via NMN-mediated ERK1/2 and p38 signaling (Wang et al., 2009). Zhang et al. reported that APO866, a potent inhibitor of NAMPT, is a potent growth inhibitor against glioblastoma through targeting NAMPT (Zhang et al., 2012).

According to the results of several studies it seems plausible that visfatin levels may be associated with the incidence of obesity-related cancer. A meta-analysis was conducted by pooling both ORs and SMD. Higher visfatin levels were found to be associated with increased cancer risk. To our knowledge this is the first comprehensive meta-analysis considering the association between circulating visfatin levels and cancer risk. Despite the existence some advantages including a well-designed methodological issue and enrolling all available eligible studies, the present meta-analysis has some limitations which have to be pointed out when interpreting the results. First, all included studies were published in English which could have influenced the pooled results. Second, this meta-analysis is based on observational case-control studies, which vulnerability to the potential biases and uncontrolled confounding factors is their main inherent limitation. Third, the significant heterogeneity across the included studies may have reduced the reliability of the meta-analysis and thus the conclusion should be more conservative. Although stratified subgroup analysis was conducted, none of the included factors were confirmed to contributing factors. Inadequate considering of the potential confounding factors in the majority of included studies and discrepancy in various adjustment may also partially explain this heterogeneity. In addition, the possibility of publication bias in favor of published articles with positive results may also exist.

In conclusion, the present meta-analysis indicated a significant association between high circulating visfatin levels and increased risk of cancers. Visfatin may serve as a potential biomarker for early detection of cancers who may benefit from preventive treatment. However, this need to establish the optimal cut-off value for circulating visfatin level to identify those subjects at high risk for different types of cancer. This may be achieved by understanding the more subtle roles of visfatin in the progression of cancers through conducting further well-designed studies, carefully controlled for potential confounding factors in the future.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest regarding the publication of this article.

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