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Original Article

Circulating adipokines and risk of obesity related cancers: A systematic review and meta-analysis

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ABSTRACT

Background: Obesity can influence on carcinogenesis through alterations in adipokines and subsequent inflammatory changes. This meta-analysis was aimed to comprehensively assess the association between circulating adipokines and risk of obesity-related cancers.

Methods: Pubmed and Embase were searched up to October 2017 for observational studies investigating the relationship between adipokines and cancers. Pooled odds ratio and the corresponding 95% confidence interval was estimated through the meta-analysis using a random-effects model.

Findings A total of 93 observational studies (adiponectin = 60, high molecular weight adiponectin = 9, leptin = 39, IL-6 = 16, TNF-α = 10, and resistin = 17) were included. Adiponectin was significantly associated with decreased risk of cancer (pooled OR 0.70, 95% CI 0.60–0.80; $I^2 = 71.9\%$; $P_{heterogeneity} < 0.01$). Leptin was significantly associated with increased risk of cancer (1.26, 1.05–1.51; $I^2 = 65.7\%$; $P_{heterogeneity} < 0.01$). For each 5 μg/ml increase in adiponectin and 5 ng/ml increase in leptin, the pooled OR was 0.88 (0.83–0.93; $I^2 = 80.2\%$; $P_{heterogeneity} < 0.01$) and 1.05 (1.01–1.09; $I^2 = 67.9\%$; $P_{heterogeneity} < 0.01$)), respectively. There was nonlinear dose-response association ($P_{nonlinearity}$ for adiponectin = 0.01; $P_{nonlinearity}$ for leptin = 0.003).IL-6 (1.09, 0.94–1.25), TNF- α (1.65, 0.99–2.74), and resistin (1.28, 0.78–2.11) was not associated with risk of cancer. By cancer site and type, highest category of adiponectin was associated with decreased risk of breast (OR 0.74, 0.60-0.91), colorectal (0.74, 0.60–0.91), and endometrial cancer (0.49, 0.34–0.72). Higher leptin was associated with increased risk of endometrial (1.88, 1.24–2.87) and kidney cancer (2.07, 1.51–2.83).

Conclusion: Our study suggests that adiponectin and leptin may play a role in the etiology of cancer.

Introduction

Worldwide obesity has more than doubled since 1980 and about 13% of adult population (11% of men and 15% of women) in the world were obese in 2014 [1]. Noncommunicable diseases, such as cardiovascular diseases, diabetes, and some cancers, are common health consequences of overweight and obesity [1]. Excessive body fat is associated with increased risk of cancer, including endometrial cancer (EC), esophageal adenocarcinoma, gastric cardia cancer, liver cancer, kidney cancer (KC), multiple myeloma (MM), meningioma, pancreatic cancer (PaC), colorectal cancer (CRC), prostate cancer (PrC), gallbladder cancer, breast cancer (BC), ovarian cancer (OC), and thyroid cancer [2,3]. Despite the considerable epidemiological evidence linking adiposity and cancer [4,5], it is still not clear how it promotes cancer development. One explainable mechanism is the adipokine system, which is closely linked to chronic inflammation. Alterations in adipokines and subsequent changes in

Abbreviations: BC, breast cancer; BMI, body mass index; CC, colon cancer; CI, confidence interval; CLEIA, chemiluminescent enzyme immunoassay; CRC, colorectal cancer; DM, diabetes mellitus; EC, endometrial cancer; ECLIA, electrochemiluminescence immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; F, female; HMW, high molecular weight; HOMA, homeostasis model assessment score of insulin resistance; HRT, hormone replacement therapy; IL-6, interleukin-6; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; KC, kidney cancer; M, males; MM, multiple myeloma; No., number; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OC, ovarian cancer (for cancer site) or oral contraceptive (for variables adjusted for); PaC, pancreatic cancer; PrC, prostate cancer; PSA, prostate-specific antigen; RIA, radioimmuoassay; RCC, renal cell carcinoma; RR, relative risk; S, sensitivity analysis; SD, standard deviation; SHBG, sex hormone binding globulin; TC, thyroid cancer; TNF-α, tumor necrosis factor-α; WC, waist circumference; WHR, waist-to-hip ratio; yrs, years.

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inflammatory markers can affect carcinogenesis by engaging in cell differentiation, growth, and apoptosis through various signalling pathways [6].

Adiponectin and leptin were the most studied, while interleukin-6 (IL-6), tumor necrosis factor-alfa (TNF-α), and resistin were relatively less studied. Most observational studies have shown that levels of adiponectin were low and that levels of leptin, IL-6, TNF-α, and resistin were high in obesity related cancers mentioned above. Previous meta-analysis showed inverse association between adiponectin and BC [7], CRC [8], and EC [9] and positive association between leptin and EC [10]. On the other hand, in the meta-analysis implementing Mendelian randomisation, the increase in adiponectin was significantly associated with the increased risk of CRC [11]. Meta-analysis investigating the association between adipokines and OC, KC, PrC, and PaC was rare [12] and epidemiologic studies showed conflicting results [13–30]. Moreover, previous meta-analyses of the relationship between adipokine and cancer has limitations that failed to take into account potential effect modifiers or confounding factors (e.g., age, ethnicity, adiposity, menopausal status, geographic area, etc.).

Thus, this meta-analysis was aimed to comprehensively assess the association between various circulating adipokines and risk of cancers, to obtain more precise estimates of risk of overall as well as each cancer type through dose-response meta-analysis, and to identify the factors affecting the relationship between adipokine and cancer.

Methods

The design, analysis, and reporting of this study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline (Supplementary Table S1) [31]. Literature search and selection of study was independently performed by two investigators (YKL and ARK).

Search strategy and study selection

PubMed and EMBASE databases were searched and detailed search terms were shown in the Supplementary Table S2. The last search update was on October 2017. We restricted our search to observational and human study. The references of selected articles, reviews, and meta-analyses were also checked for further additional studies. Inclusion criteria were as follows: (1) an observational study (e.g. cross-sectional, case-control, or cohort study); (2) investigating the relationship between circulating adiponectin, leptin, IL-6, TNF-α, and resistin and obesity related cancers; and (3) presenting the fully adjusted odds ratio (OR) or relative risk (RR) comparing the highest vs. lowest category and the corresponding 95% confidence interval (CI). Abstracts, case reports, comments, reviews, editorials, letters, and unpublished results were excluded. When more than one study was published including overlapping patients, we retained the latest study or the study with the larger sample to avoid duplication of information.

Data extraction and quality assessment

Two independent authors (YSY and ARK) reviewed the full text of selected eligible studies, and extracted the following data: study characteristics (name of first author, year of publication, study design, study period, and duration of follow-up), study population characteristics (sample size, country, sex, and age at enrolment), the fully adjusted ORs or RRs with corresponding 95% CIs, category-specific or total number of cases and non-cases, assessment method of adipokines, and adjustment variables. For dose-response meta-analysis, the midpoint (or range) of each category was also extracted. The quality of studies was assessed using the Newcastle–Ottawa scale.

Statistical analysis

We used random-effects models to calculate pooled ORs and 95% CIs of obesity related cancers for the highest vs. lowest category of adiponectin, leptin, IL-6, TNF-α, and resistin. Statistical heterogeneity was tested by Cochran's Q test [32] and quantified by I^2, the percentage of total variation across studies that was attributable to true heterogeneity rather than to chance [33]. Publication bias was investigated visually with funnel plots and Egger's test [34]. To check the robustness of our findings, an influence analysis was conducted by repeating the meta-analyses excluding one study at a time.

Linear and nonlinear dose-response meta-analyses were also conducted. For linear dose-response analysis, we used the method described by Greenland and Longnecker [35]. A potential nonlinear association was examined using the restricted cubic spline model [36]. For each study, cubic splines were modelled with three knots at fixed percentiles (10%, 50%, and 90%) of exposure distribution contributed by included studies [36]. Then, the derived curves were combined using multivariate random-effects meta-analysis. The p value for nonlinearity was obtained from the test of the null hypothesis that the regression coefficient of the second spline transformation was equal to zero.

We further conducted subgroup analyses to explore sources of heterogeneity. Meta-regression was used to identify etiologic heterogeneity (site and stage at diagnosis for CRC), potential effect modifiers (age at baseline, sex, geographical location, or menopausal status), and methodological characteristics (number of total cases, follow-up duration, and adjustment for confounders) according to priori selected variables.

For all analyses we used Stata14 (Stata Corp, College Station, TX). The p value <0.05 was considered statistically significant.

Results

The detailed procedure of study selection was provided in Fig. 1. Among total 13,255 articles identified from the initial search, 7786 articles were screened based on title and abstract for relevance to study topic after removing 5469 duplicates. Of these, 379 studies were fully reviewed, including bibliographic review to identify additional studies. We found only one available study for thyroid cancer [37], one study for hepatocellular carcinoma [38] and no available study for esophageal adenocarcinoma, gastric cardiac cancer, and cholangiocarcinoma in the relation with adipokines. Finally, a total of 93 studies were selected for this meta-analysis of obesity related adipokines (adiponectin = 60, high molecular weight adiponectin = 9, leptin = 39, IL-6 = 16, TNF-α = 10, and resistin = 17 studies) and risk of cancers (BC = 30, CRC = 22, EC = 15, OC = 6, KC = 7, PrC = 7, PaC = 8, and MM = 4 studies).

Study characteristics

The characteristics of included studies were summarised in Supplementary Table S3. We included five cohort, 42 case-control, and 46 nested case-control studies. Thirty-four studies were conducted in Europe, 32 in USA and Canada, 24 in Asia, and two in others country. In fifty-one studies, blood samples were taken before cancer diagnosis.

Adiponectin

Forty-nine studies with 15,476 cases and 22,131 controls [15–27,30,39–73] and 47 studies with 13,478 cases and 18,115 con-

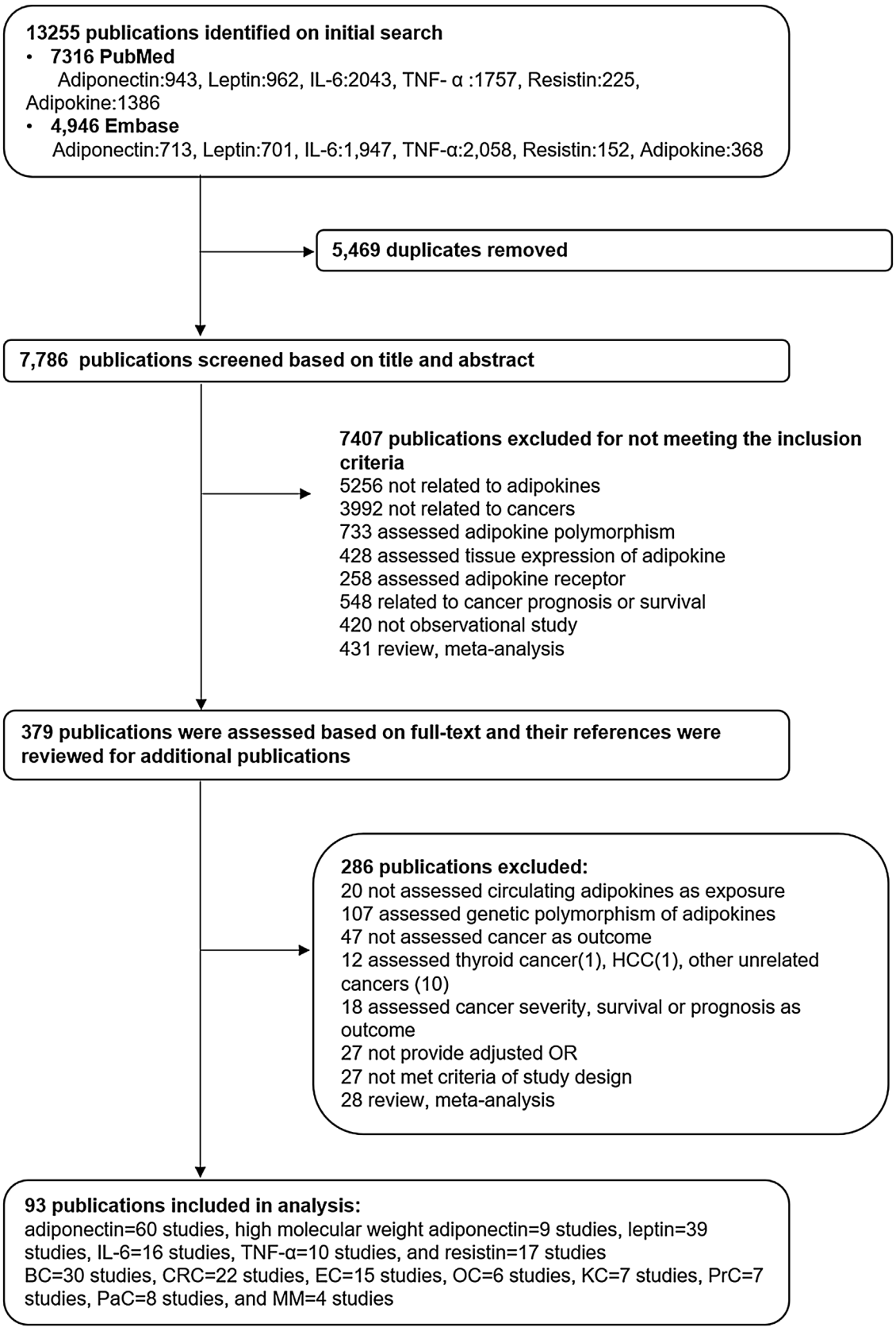

Fig. 1. Flowchart for study selection. BC = breast cancer; CRC = colorectal cancer; EC = endometrial cancer; HMW = high molecular weight; IL-6=interleukin-6; KC = kidney cancer; MM = multiple myeloma; OC = ovarian cancer; PaC = pancreatic cancer; PrC = prostate cancer; TC = thyroid cancer; TNF-α = tumor necrosis factor-alfa.

Table 1
Circulating adipokines and risk of cancer.

	Highest vs. lowest category meta-analysis				Dose-response meta-analysis				
	No. of studies	OR (95% CI)	I^2(%)	$P_{heterogeneity}$	Dose (unit)	No. of studies	OR (95% CI)	I^2(%)	$P_{heterogeneity}$
Adiponectin					5 μg/ml				
Breast cancer	14	0.74(0.60–0.91)	57.6	0.004		14	0.85 (0.75–0.95)	82.2	<0.001
Colorectal cancer	13	0.74(0.60–0.91)	32.7	0.12		10	0.89 (0.79–0.99)	41.2	0.08
Endometrial cancer	12	0.49(0.33–0.72)	71.0	<0.001		9	0.82 (0.74–0.91)	44.1	0.07
Kidney cancer	4	1.17(0.58–2.39)	87.2	<0.001		7	1.07 (0.80–1.42)	81.2	<0.001
Multiple myeloma	2	0.22(0.02–2.25)	87.5	0.005		2	0.74 (0.56–0.98)	80	0.02
Ovarian cancer	2	0.29(0.11–0.74)	0.0	0.89		1	0.72 (0.40–1.29)	–	–
Pancreatic cancer	7	0.98(0.67–1.43)	76.2	<0.001		6	0.97 (0.85–1.11)	81.6	<0.001
Prostate cancer	4	0.73(0.47–1.15)	34.8	0.20		3	0.88 (0.65–1.19)	68.9	0.04
Overall	58	0.70(0.60–0.80)	72.0	<0.001		52	0.88 (0.83–0.94)	78.6	<0.001
Leptin					5 ng/ml				
Breast cancer	9	1.03 (0.77–1.38)	65.5	0.003		13	1.04 (0.97–1.12)	74.6	<0.001
Colorectal cancer	9	1.11 (0.67–1.86)	73.7	<0.001		9	1.05 (0.92–1.21)	62.0	0.01
Endometrial cancer	6	1.88 (1.24–2.87)	55	0.05		4	1.10 (0.94–1.28)	73.2	0.01
Kidney cancer	3	2.07 (1.51–2.83)	10	0.33		5	1.04 (0.89–1.22)	77.8	0.001
Multiple myeloma	2	1.45 (0.85–2.45)	0	0.38		2	1.05 (0.98–1.12)	0	0.62
Ovarian cancer	1	11.83 (1.40–100.03)	–	–		–	–	–	
Pancreatic cancer	5	0.92 (0.44–1.91)	72.1	0.01		2	1.11(0.83–1.48)	79.5	0.03
Prostate cancer	4	1.11 (0.78–1.56)	0	0.53		3	1.01(0.93–1.08)	0	0.79
Overall	39	1.26 (1.05–1.52)	65.7	<0.001		38	1.05 (1.01–1.09)	68.0	<0.001
IL-6					1 pg/ml				
Breast cancer	2	0.98 (0.66–1.46)	60.8	0.11		3	1.07 (0.92–1.23)	0	0.79
Colorectal cancer	5	1.10 (0.79–1.51)	43.7	0.13		7	1.06 (0.95–1.19)	15.2	0.31
Endometrial cancer	1	0.70 (0.29–1.68)	–	–		1	0.81 (0.55–1.20)	–	–
Ovarian cancer	5	1.19 (0.91–1.57)	33.4	0.20		3	1.08 (1.01–1.16)	0	0.51
Prostate cancer	2	1.09 (0.72–1.64)	0	0.66		2	0.74 (0.52–1.06)	32.6	0.22
Overall	15	1.09 (0.94–1.25)	20.5	0.22		16	1.04 (0.98–1.11)	16.8	0.26
TNF-α					1 pg/ml				
Breast cancer	2	0.75 (0.58–0.97)	0	0.39		3	0.94 (0.84–1.05)	0	0.59
Colorectal cancer	2	5.41 (0.11–266.77)	97.4	0.01		2	0.92 (0.80–1.06)	0	0.95
Endometrial cancer	2	1.71 (1.15–2.53)	0	0.92		2	0.88 (0.50–1.57)	71.3	0.06
Ovarian cancer	3	1.78 (0.91–3.47)	40.6	0.19		3	1.25 (1.06–1.49)	0	0.56
Prostate cancer	0	–	–	–		1	1.10 (0.61–1.98)	–	
Overall	9	1.65 (0.99–2.74)	86.3	0.01		11	1.03 (0.92–1.15)	33.2	0.13
Resistin					1 ng/ml				
Breast cancer	5	1.66 (0.98–2.81)	73.7	0.01		8	1.09 (1.01–1.18)	82.7	0.001
Colorectal cancer	2	2.40 (0.40–14.33)	95.8	0.01		3	1.24 (0.90–1.70)	77.8	0.01
Kidney cancer	1	1.27 (0.75–2.15)	–	–		1	1.03 (0.94–1.12)	–	
Multiple myeloma	2	0.16 (0.01–3.84)	94.1	0.001		2	0.87 (0.79–0.95)	0.55	0.01
Overall	10	1.28 (0.78–2.11)	87.1	0.01		14	1.04 (0.98–1.11)	85.4	0.001

The P values for the within-subgroup heterogeneity were calculated from the Cochran's Q test. CI = confidence interval; No. = number; OR = Odds ratio.

trols [15–27,30,39,41,43,45,47,49,50,52,53,57–65,67–69,71–84] were included in the highest vs. lowest and dose-response meta-analysis of adiponectin, respectively. The highest category of adiponectin had a significantly decreased risk of cancer than lowest category (pooled OR 0.70, 95% CI 0.60-0.80; I^2 = 71.9%; $P_{heterogeneity}$ <0.001) (Table 1, Supplementary Fig. S1). In the linear dose-response analysis, each 5 μg/ml increment in adiponectin was associated with decreased risk of cancers (0.88, 0.83–0.94; I^2 = 78.6%; $P_{heterogeneity}$ <0.001) (Table 1, Supplementary Fig. S2). A significant non-linear dose–response relationship was observed between adiponectin levels and cancers ($P_{nonlinearity}$ = 0.02) (Fig. 2A). In the highest compared with lowest analysis, visual inspection of funnel plot showed asymmetrical appearance and the Egger test indicated evidence of publication bias (P_{Egger} = 0.01) (Supplementary Fig. S11A). In sensitivity analyses omitting one study at a time, remaining studies yielded consistent results in pooling ORs in both highest compared lowest analysis (OR range 0.68–0.72) and dose-response analysis (OR range 0.87–0.90).

By cancer site and type, highest category of adiponectin was associated with decreased risk of BC (pooled OR 0.74, 95% CI 0.60-0.91; I^2 = 57.6%; $P_{heterogeneity}$ = 0.004), CRC (0.74, 0.60–0.91; I^2 = 32.7%, $P_{heterogeneity}$ = 0.12), EC (0.49, 0.34–0.72; I^2 = 70.4%; $P_{heterogeneity}$ <0.01), and OC (0.29, 0.11-0.74; I^2 = 0%; $P_{heterogeneity}$ = 0.89) (Table 1). Each 5 μg/ml increment in adiponectin was associated with decreased risk of BC (0.85, 0.75–0.95; I^2 = 82.2%; $P_{heterogeneity}$<0.01), CRC (0.89, 0.79–0.99; I^2 = 41.2%; $P_{heterogeneity}$ = 0.08), and EC (0.81, 0.68–0.96; I^2 = 76.9%; $P_{heterogeneity}$ <0.01) in the linear dose-response meta-analysis (Table 1). There was no evidence of nonlinear association between adiponectin and BC, EC, KC, and PaC (all $P_{nonlinearity}$ ≥0.06). However, potential non-linear relationship between adiponectin and CRC risk was observed ($P_{nonlinearity}$ = 0.03) (Fig. 3B).

Leptin

Eligible studies for highest vs. lowest and dose-response meta-analysis of leptin were 31 studies (39 results, BC = 9, CRC = 9, EC = 6, KC = 3, MM = 2, OC = 1, PaC = 5, PrC = 4; 10,477 cases with 15,234 controls) [14,16,17,21,23,25,26,28–30,41,47,51,53,56,58–60,63,65,66,68,72,85–92] and 33 studies (38 results, BC = 13, CRC = 9, EC = 4, KC = 5, MM = 2, PaC = 2, PrC = 3; 9644 cases and 13,101 controls) [14,16,21,25,26,29,30,41,47,53,58–60,63,65,68,72,74,76,78–80,84–94], respectively. The highest category of leptin had a significantly increased risk of cancer than lowest category (pooled OR 1.26, 95% CI 1.05–1.52, I^2 = 5.7%, $P_{heterogeneity}$ <0.001) (Table 1, Supplementary Fig. S3). In the linear dose-response analysis, each 5 ng/ml increment in leptin was associated with increased risk of cancers (1.05, 1.01–1.09; I^2 = 67.9%; $P_{heterogeneity}$<0.01)

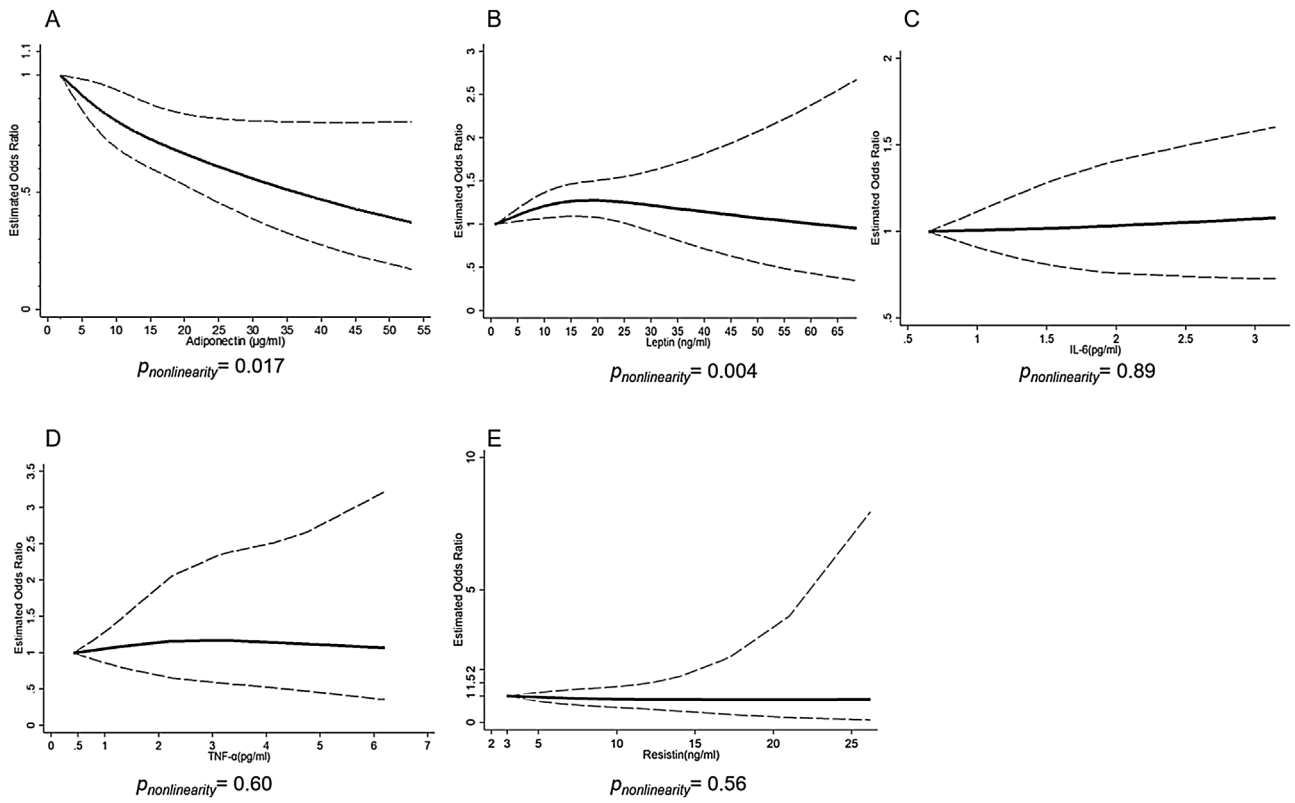

Fig. 2. Dose-response associations of circulating adipokines and risk of cancer. (A) Adiponectin, (B) leptin, (C) IL-6, (D) TNF-α, and (E) resistin.

(Table 1, Supplementary Fig. S4). A dose-response meta-analysis suggested a reverse J-shaped association ($P_{nonlinearity}$ = 0.003) (Fig. 2B). There was no evidence of publication bias by visual inspection of funnel plot and by the Egger test in the highest vs. lowest (P_{Egger} = 0.31) (Supplementary Fig. S11B) and dose-response analysis (P_{Egger} = 0.57). The association of leptin with cancer was not sensitive to any single study in the sensitivity analyses (OR range 1.23–1.30 in highest vs. lowest meta-analysis; 1.04–1.05 in dose-response meta-analysis).

For each cancer outcomes, highest category of leptin was found to be associated with increased risk of EC (1.88, 1.24–2.87; I^2 = 55.0%; $P_{heterogeneity}$ = 0.049) and KC (2.07, 1.51–2.83; I^2 = 72.1%; $P_{heterogeneity}$ = 0.01). In the linear dose-response analysis by cancer type, each 5 ng/ml increase in leptin was not significantly associated with BC, CRC, EC, KC, MM, PaC, or PrC. In addition, potential nonlinear relationship between leptin and BC risk was observed ($P_{nonlinearity}$ = 0.02) (Fig. 4A).

Il-6

IL-6 was not associated with overall cancer risk (pooled OR 1.09, 95% CI 0.94–1.25; I^2 = 20.5; $P_{heterogeneity}$ = 0.22) when all eligible 14 studies (15 results, BC = 3, CRC = 5, EC = 1, PrC = 3, OC = 6, 4359 cases with 6941 controls) [13,17,56,58,59,95–103] were pooled into the highest vs. lowest category of meta-analysis (Table 1, Supplementary Fig. S5). No publication bias (P_{Egger} = 0.77) was observed (Supplementary Fig. S11C). Sensitive analysis showed that no individual study affected the overall OR, since omission of any single study made no material difference (OR range 1.07–1.12).

A dose-response meta-analysis of 11 studies [58,59,95,96,98–101,103–105], which included a total of 4192 cases and 9759 controls, was performed to evaluate IL-6 and cancer association. The pooled OR of cancer per 1 pg/ml increment in IL-6 was 1.04 (0.98–1.11; I^2 = 16.8%, $P_{heterogeneity}$ = 0.26) without evidence of a potential nonlinear association ($P_{nonlinearity}$ = 0.89) (Fig. 2C). We found a significant publication bias (P_{Egger} = 0.02) and asymmetrical appearance of funnel plot. The sensitivity analyses after excluding one study for PrC by Heikkilä et al. [104] showed maximal pooled OR with significance (1.06, 1.01–1.12).

TNF-α

Eight studies with 2616 cases and 3982 controls were available to evaluate for highest vs. lowest meta-analysis of TNF-α and risk of cancer [56,58,59,96,97,102,103,106]. The highest category of TNF-α showed marginally increased risk of cancer than lowest category (pooled OR 1.65, 95% CI 0.99–2.74) with high heterogeneity (I^2 = 86.3%, $P_{heterogeneity}$ <0.001) (Table 1, Supplementary Fig. S7). Both funnel plot and Egger's test suggested obvious evidences of publication bias (P_{Egger} = 0.03) (Supplementary Fig. S11D). In addition, in the sensitivity analysis, removing study by Dias et al. [97] (1.92, 1.09–3.39), Gunter et al. [59] (1.90, 1.03–3.50), or Ho et al. [58] (1.89 1.05–3.41) at a time made significant differences in overall OR, respectively. Dose-response meta-analysis for TNF-α included eight studies with 2265 cases and 5213 controls [58,59,74,96,102,103,105,106]. The pooled OR of cancer per 1 pg/ml increment in TNF-α was 1.03 (0.92–1.15; I^2 = 33.2%; $P_{heterogeneity}$ = 0.13). Visual inspection of funnel plot did not show major asymmetrical appearance and the Egger test (P_{Egger} = 0.47) indicated no evidence of publication bias. The association of TNF-α with cancers was not sensitive to any single study in the sensitivity analyses (OR range 1.00–1.07).

Resistin

All ten studies with 2683 cases and 3558 controls [21,25,55,56,58,59,62,107–109] and 14 studies with 2740 cases and 3067 controls [21,25,58,59,62,74–76,79,80,107,108,110,111] were

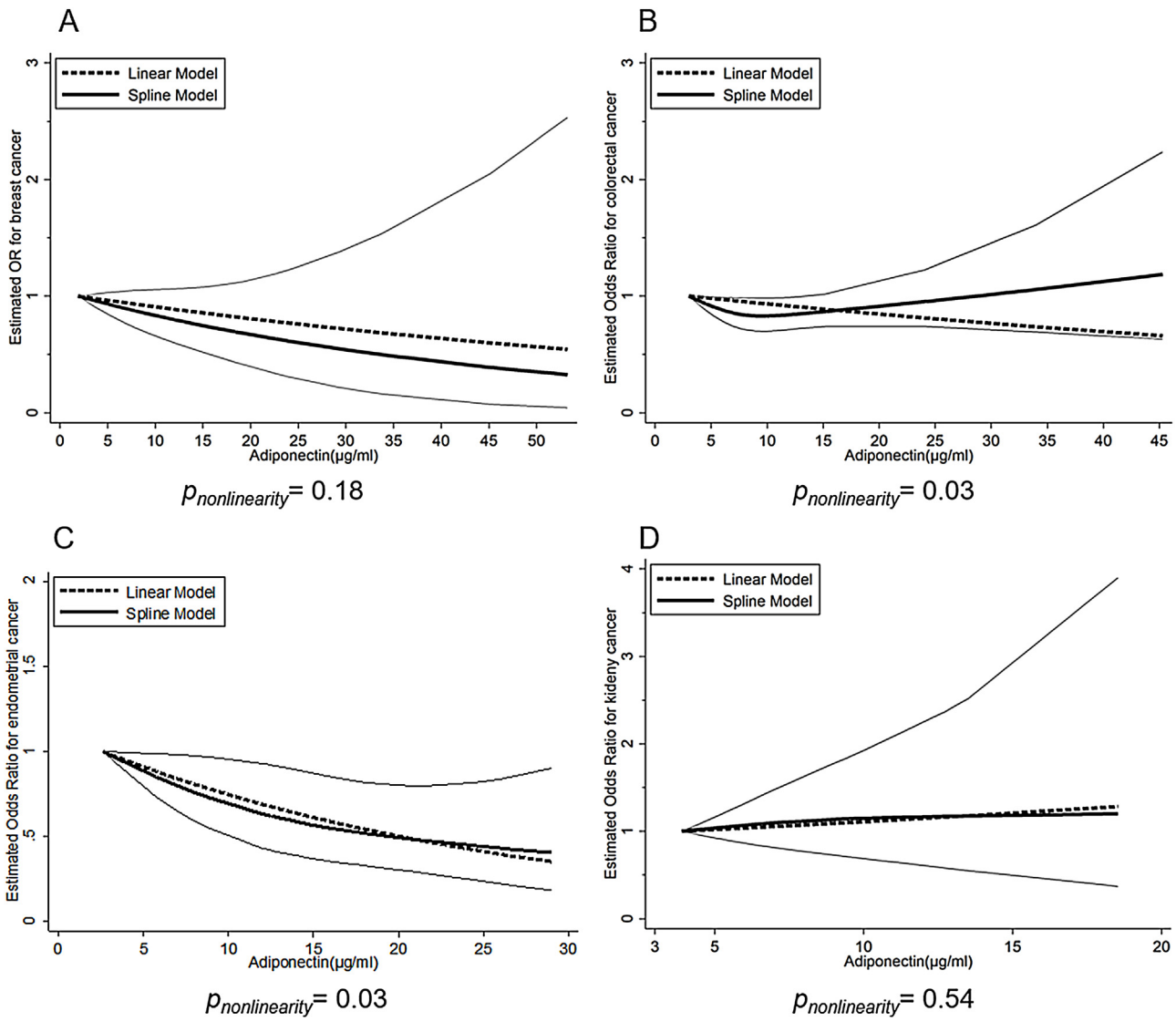

Fig. 3. Dose-response associations of circulating adiponectin and risk of breast, colorectal, endometrial and kidney cancer. (A) Breast cancer, (B) colorectal cancer, (C) endometrial cancer, and (D) kidney cancer.

pooled for highest vs. lowest and dose-response meta-analysis of resistin for cancer risk, respectively. The highest vs. lowest meta-analysis showed no relationship between resistin and cancer risk (pooled OR 1.28, 95% CI 0.78–2.11; I^2 = 87.1%; $P_{heterogeneity}$ <0.001) with high heterogeneity. In the linear dose-response analysis, each 1 ng/ml increase in resistin was not associated with risk of cancers (Pooled OR 1.04, 95% CI 0.98–1.11; I^2 = 85.4%; $P_{heterogeneity}$ <0.01) (Table1). In the sensitivity analyses, excluding a study by Dalamaga et al. [21] resulted in maximal pooled OR with significance in the highest vs. lowest meta-alaysis (pooled OR 1.59, 95% CI 1.05–2.43) and in the dose response meta-analysis (pooled OR 1.06, 95% CI 1.01–1.12). No publication biases were found in both highest vs. lowest and dose-response meta-analyses (all P_{Egger} >0.05) (Supplementary Fig. S11E).

Subgroup analysis

Subgroup analyses were performed based on highest vs. lowest meta-analysis. Supplementary table S4-S8 presents detailed results of subgroup analyses. A stratified analysis by study design and geographical area showed between-subgroup heterogeneity in relation between adiponectin and cancer (all $P_{heterogeneity}$ <0.05, Supplementary Table S4). For adiponectin and BC, the stratified analysis by menopausal status indicated a significant decreased risk for BC (pooled OR 0.70, 95% CI 0.54–0.90) in postmenopausal women but not in premenopausal women (0.74, 0.37–1.47). However, there was no evidence of between-subgroup heterogeneity ($P_{heterogeneity}$ = 0.42). A stratified analysis by study design showed between-subgroup heterogeneity in relation between adiponectin and BC (pooled OR for case control study 0.37, 95% CI 0.17–0.78 vs. pooled OR for cohort study 0.87, 0.76–0.99; $P_{heterogeneity}$ = 0.04) and adiponectin and KC (pooled OR for case control study 2.12, 1.54–2.92 vs. pooled OR for cohort study 0.61, 0.41–0.91, $P_{heterogeneity}$ = 0.04) (Supplementary Table S4).

When analysis was limited to studies controlling for adiposity (measure of body fatness), adiponectin and leptin are associated with cancer even after adjustment of anthropometric markers (Table 2). The adiposity adjusted pooled ORs of adiponectin and leptin were 0.70 (95% CI 0.59–0.81; I^2 = 74.0%) and 1.31 (1.06–1.61; I^2 = 65.3%), respectively.

There was no evidence of between-subgroup heterogeneity when stratified by leptin, IL-6, TNF-α, and resistin related to etiologic heterogeneity, potential effect modifiers, and methodological characteristics (all $P_{heterogeneity}$ ≥0.05).

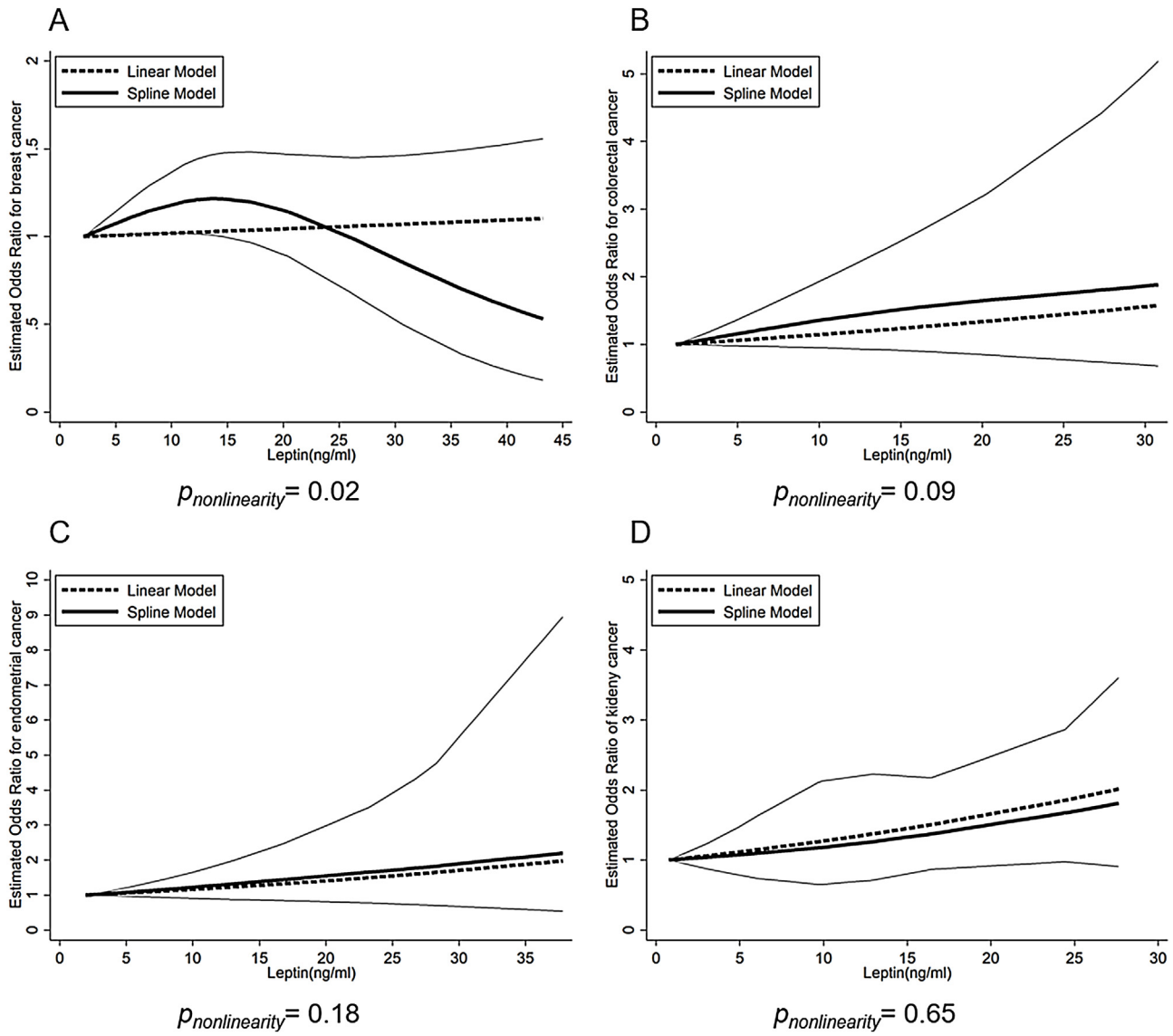

Fig. 4. Dose-response associations of circulating leptin and risk of breast, colorectal, endometrial and kidney cancer (A) breast cancer, (B) colorectal cancer, (C) endometrial cancer, and (D) kidney cancer.

Table 2
Meta-analysis comparing highest and lowest level of adiponectin, leptin, interleukin-6, TNF-α, and resistin and the risk of cancers by adjustment for adiposity.

Subgroups	No. of studies	OR (95% CI)	I^2 (%)	$P_{heterogeneity}$	
				Within Subgroup (Q, df)	Between subgroups
Adiponectin					
Yes	51	0.70 (0.60, 0.82)	74.0	0.001 (192.5, 50)	0.83
No	7	0.65 (0.53, 0.81)	0	0.53 (5.1, 6)	
Leptin					
Yes	30	1.31 (1.06, 1.62)	65.3	0.001 (83.6, 29)	0.61
No	9	1.15 (0.81, 1.63)	67.4	0.002 (24.5, 8)	
IL-6					
Yes	13	1.11 (0.96, 1.28)	19.2	0.25 (14.8, 11)	0.20
No	2	0.72 (0.41, 1.28)	0	0.37 (0.8, 1)	
TNF-α					
Yes	8	1.14 (0.82, 1.59)	66.9	0.01 (21.1, 7)	0.01
No	1	41.2 (12.6, 134.2)	–	–	
Resistin					
Yes	8	1.06 (0.64, 1.75)	83.5	0.001 (42.4, 7)	0.36
No	2	2.75 (0.59, 12.8)	92.8	0.001 (13.9, 1)	

Discussion

According to GLOBOCAN 2012 data [112], 3.9% of all new cancers in adults were attributable to high body mass index (BMI). Adipokine and related subclinical inflammation is one of hypotheses that explain a biological mechanism linking adiposity and risk of cancer. Low levels of adiponectin can disrupt the AMP-activated protein kinase (AMPK) and insulin-signal pathways contributing to promoting cancer cell proliferation. High levels of leptin may be involved in promotion of cancer cell proliferation, migration, and angiogenesis and inhibition of apoptosis. This is accomplished through activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT), AMPK, phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) signalling pathways [113]. Our results support the role of adiponectin and leptin in tumor growth.

Findings from this meta-analysis indicate an inverse association between adiponectin and cancer risk. Among cancers, BC, CRC, and EC were inversely related with adiponectin. Noteworthy results have been the nonlinear association between adiponectin and CRC (Fig. 3B). In this non-linear dose-response curve, a high adiponectin levels above a certain threshold appeared to be associated with an increased risk of CRC. Previous meta-analysis by Pei et al. [11] have shown that the specific polymorphisms of adiponectin gene were related with an excessive increase in circulating adiponectin level and a significantly increased risk of CRC. This suggests that high levels of adiponectin due to genetic polymorphism may be associated with an increased risk of CRC. Our meta-analysis showed that inverse association between adiponectin and risk of CRC. However, as shown in the non-linear dose response curve (Fig. 3B), risk of CRC seemed to be increased at very high levels of adiponectin (>30 μg/ml), although these were not statistically significant. This might be related to genetic polymorphism, but it is difficult to argue conclusively because we did not perform the analysis regarding genetic polymorphism. More research is needed to identify specific groups or related factors that increase CRC risk at extreme high adiponectin concentrations.

Another important consideration is that the association with cancer may appear different depending on the molecular type of adiponectin. HMW adiponectin has been known to decreased risk of cancer, and in this study HMW adiponectin was associated with a significantly decreased risk of cancers (Pooled OR 0.54, 95% CI 0.40–0.73, $I^2 = 67.3\%$, $P_{heterogeneity} < 0.01$) when all eligible nine studies [27,48,54,65,70,73,87,114,115] were pooled into the meta-analysis (Supplementary Fig. S12). Further research is needed on the mechanism in which the risk of CRC varies with the concentration of adiponectin.

We confirmed that high leptin was associated with significantly increased risk of cancers. The risk of EC and KC are increased in the highest vs. lowest meta-analysis, but not in the dose-response meta-analysis. Positive association between leptin and EC observed in this meta-analysis was consistent with results of meta-analysis by Wang et al. [116]. A noteworthy finding was nonlinear relationship between leptin and BC. Since most previous meta-analysis of the association between leptin and each cancer investigated the difference between the levels of leptin [116–118], it is difficult to directly compare to our results. Further studies on whether the association of leptin and BC really shows reverse J-shaped association and the mechanism to explain this association are needed.

Resistin can play a potential role in the carcinogenesis by stimulating several signalling pathways operating downstream of resistin interaction with toll like receptor 4 (TLR4) [119]. TNF-α and IL-6 play an important role in promoting carcinogenesis though the activation of various transcription factors and multiple oncogenic pathways [120]. However, no significant associations between these three markers and risk of cancers was observed in the current meta-analysis. Previous meta-analysis by Gong et al. [121] showed that higher resistin levels were found to be associated with increased obesity-related cancer risk (pooled OR 1.20, 95% CI 1.10–1.30). Unlike studies by Gong et al., we included more studies of MM. When these studies were excluded, a significant increase in pooled OR (1.77, 1.12–2.79) was observed. Additionally, in the sensitivity analysis, exclusion of a study by Dalamaga et al. [21] resulted in a maximal pooled OR with significance. This study had a limit of a small sample size based on the hospital.

Previous meta-analysis regarding IL-6 and TNF-α were relatively infrequent. Zhou et al. found no association between IL-6 and CRC in the meta-analysis using a total of 1068 CRC cases [122]. In the meta-analysis investigating the association OC and inflammatory marker, no significant association was observed for IL-6 and TNF-α [12]. However, elevated expression of IL-6 or TNF-α in tumor tissue of patients have been reported and this might be associated with grade of tumor, histologic type of cancer, lymph node or distant metastasis, and poor survival [123]. The biological effects of circulating vs. local inflammatory makers may differ and circulating levels could underestimate local effects of inflammatory marker. However, we could not consider the local effects of inflammatory markers.

Heterogeneity is a serious issue that limits interpretation of effect estimates and requires careful exploration. We further performed stratified analysis to identify the sources of heterogeneity.

In the stratified analysis by study design, a strong consistent association between adiponectin and risk of cancers with reduced heterogeneity was found in cohort study. When we analysed cohort studies by each cancer type, the pooled ORs of BC and KC for adiponectin were consistently significant without heterogeneity. In the cohort study, blood samples are generally drawn before diagnosis of cancer, suggesting that adiponectin may play a role in early stages of carcinogenesis. But, duration of follow-up did not change the relationships materially.

Recent evidences suggested that obesity and weight gain were linked to increased risk of cancer [124,125]. Given that excess adiposity is the primary determinant of adipokines, it is not surprising that adiponectin and leptin are also associated with cancers. Importantly, we show that adiponectin and leptin are associated with cancer even after adjustment of anthropometric markers (Table 2). This suggests that adipokines offer further predictive information on cancer risk beyond traditional anthropometric measures.

Hormone is the main factor that should be considered in the association between adipokines and hormone related cancers. In the subgroup analysis by menopausal status, the relationship between adiponectin and BC was more prominent in postmenopausal women (pooled OR 0.70, 95% CI 0.54–0.90) and analysis limited to studies adjusting for HRT or OC use yielded significant association between adiponectin and risk of BC (0.6, 0.4–0.9) without heterogeneity, although there was no evidence of between-subgroup heterogeneity. No further stratified analyses regarding EC and OC by menopausal status was conducted due to the limited number of eligible studies.

The strength of our research is that this study presents a relatively comprehensive review of the existing evidence on the association of various adipokines and obesity-related cancers. In particular, stratified analysis using a variety of selected variables could make our results more robust against the influence of confounding. Nevertheless, this meta-analysis has several limitations as well. First, residual or unknown confounding cannot be completely excluded, although we included researches having matched or adjusted for various potential confounding factors and providing fully adjusted ORs. Second, we could not analyse adipokine-cancer relationship by biologic characteristics of cancer (i.e., stage, histologic type, metastasis of cancer, etc.) due to the limited number of eligible studies. Therefore, more convincing evidence is needed to

identify the role of adipokine in different cancer types or stages of development.

In conclusion, we found that lower level of adiponectin and higher level of leptin are significantly associated with higher risk of cancers. In addition, our results suggested that the association between adiponectin and leptin and risk of cancer could be independent of adiposity. Our findings could be used to find high risk cancer patients. Further well-designed prospective cohort studies are needed to evaluate the association between adipokines and cancers along with considering features of cancers unanalysed in this study.

Authors' contributions

YSY and SWO planned study design; YKL, YSY, and ARK collected data; SWO and YSY performed statistical analysis. YSY wrote manuscript. SWO, YKL, and ARK provided critical revision of the manuscript. All authors contributed to the data interpretation and editing and reviewing manuscript.

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Declaration of interests

The authors declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.orcp.2019.03.006.

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