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Serum adiponectin in breast cancer

A meta-analysis

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Abstract

Background: Accumulating data have found that adiponectin is involved in development of breast cancer (BC). However, these results were inconsistent.

Method: A systematic search in PubMed, Embase, ISI Web of Science, and Chinese National Knowledge Infrastructure databases were conducted up to October 1, 2017. The standardized mean difference (SMD) with 95% confidence interval was applied to pool the effect size.

Results: Finally, 31 eligible studies were included in this meta-analysis. The overall results indicated that serum adiponectin levels in BC cases were significantly lower than the controls (SMD = −0.33, $P < 0.0001$). As for the subgroup analysis of menstrual status, serum adiponectin levels were significantly lower in pre- and postmenopausal BC cases. Moreover, the subgroup analysis by ethnicity in pre- and postmenopausal group indicated an inverse association between adiponectin levels and BC risk in Asian population, but not in Caucasian population.

Conclusion: The present meta-analysis suggests that low serum adiponectin concentration may be associated with an increased BC risk in premenopausal and postmenopausal women, especially among Asians. Adiponectin may serve as a biomarker of BC risk and help to identify subjects at high risk for BC development.

Abbreviations: BC = breast cancer, CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, FEM = fixed-effects model, LN = lymph node invasion, NOS = Newcastle–Ottawa scale, REM = random-effects model, SMD = standardized mean difference, VEGF = vascular endothelial growth factor.

Keywords: adiponectin, breast cancer, meta-analysis

1. Introduction

Breast cancer (BC) is the most common cancer diagnosed and the leading cause of cancer-related death in women worldwide.[1] It was estimated that there were 1.67 million new BC cases and 521,900 deaths due to BC globally based on the data from International Agency for Research on Cancer in 2012.[2] Although great advancements in cancer diagnosis and treatment recently, the 5-year relative survival of BC is still less than 20%.[1] Thus, it is urgent to identify new prognostic biomarkers involved in BC, which help to make early diagnosis, monitor tumor progression, and optimize medical management. Recent evidence has indicated that obesity was a well-recognized risk factor for BC development and recurrence, which is also linked to late-stage disease and poor prognosis.[3,4] The precise mechanism linking obesity and BC risk remains unclear, but it has been noted that adipose tissue can produce a group of polypeptide growth factors and cytokines including adiponectin and leptin, which may underlie such association and serve as potential biomarkers and therapeutic targets for the management of this aggressive disease.[5–7]

Adiponectin, a 244-amino acid polypeptide protein, is encoded on chromosome 3q27.[8] It is an insulin-sensitizing hormone secreted mainly by adipocytes of white adipose tissue, which play pivotal roles in regulation of energy homeostasis, inflammation, insulin sensitivity, and cell proliferation.[9] The published studies have suggested that the low serum adiponectin concentration was associated with hyperinsulinemia and increased vascular endothelial growth factor (VEGF) and insulin-like growth factor levels, which have been demonstrated to increase the risk of obesity-related malignancies, including BC.[10,11] However, some studies indicated no significant association between serum

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Table 1

Characteristics of included studies in this meta-analysis.

Author	Year	Ethnicity	Country	Age	Sample size	Control source	Cancer type	Treatment status	Stage I/II/II/IV
Ozmen et al	2017	Caucasian	Turkish	42±5/47±4	88	Population	BC	N	0/39/19/0
Georgiou et al	2017	Caucasian	Greece	57±11/56±18	209	Hospital	IDC/DCIS/LN	N	NR
Crisostomo et al	2017	Caucasian	Portugal	38–60/28–40	154	Hospital	BC	N	NR
Minatoya et al	2015	Asian	Japan	32–74/31–70	139	Hospital	BC	Y	NR
Guo et al	2015	Asian	China	47±9/47±9	2434	Hospital	BC	N	NR
Gunter et al	2015	Mix	America	59–69/57–69	1696	Population	BC	N	NR
Assiri et al	2015	Asian	Saudi	53±13/52±16	150	NR	BC	N	NR
Ahmed et al	2015	Asian	Pakistan	46±1/45±1	250	Hospital	BC	N	NR
Touvier et al	2014	Caucasian	France	49±6/51±6	1242	Population	BC	N	NR
Santillan-Benitez et al	2014	Caucasian	Mexico	40–50/40–50	88	Hospital	BC	N	4/9/11/7
Ollberding et al	2013	Mix	America	67±7/68±7	1412	Population	BC	N	NR
Gross et al	2013	Caucasian	America	62±9/63±9	544	Population	BC	NR	NR
Dalamaga et al	2013	Caucasian	Athens	62±8/62±9	204	Hospital	BC	NR	NR
Alokail et al	2013	Asian	Saudi	43±8/46±11	109	NR	BC	NR	NR
Wang et al	2013	Asian	China	48–69/47–69	152	Hospital	Breast carcinoma	N	35/28/19
Zhang et al	2012	Asian	China	25–70/25–70	86	Population	BC	NR	NR
Gulcelik et al	2012	Caucasian	Turkish	51±12/52±10	123	Hospital	BC	Y	22/35/26
Al Awadhi et al	2012	Asian	Kuwait	50±12/51±12	221	Population	BC	N	NR
Al Khaldi et al	2011	Asian	Kuwait	49±2/60±5	120	Hospital	BC	NR	NR
Fan et al	2010	Asian	China	38–77/	140	NR	BC	N	15/48/27
Shahar et al	2010	Asian	Malaysia	47±8/46±6	208	Population	BC	N	NR
Hancke et al	2010	Caucasian	German	59±1/49±1	200	NR	BC	Y	NR
Cust et al	2009	Caucasian	Australia	50–69/50–69	1122	Population	IBC	N	263/256/21/14
Tworoger et al (1)	2007	Caucasian	America	57-7/58-7	2741	NR	BC	N	NR
Tworoger et al (2)	2007	Caucasian	America	45-4/45-4	932	NR	BC	N	NR
Korner et al	2007	Caucasian	German	38–82/30–82	150	Population	Breast carcinoma	N	19/32/14/9
Kang et al	2007	Asian	Korea	47±9/48±6	84	Hospital	BC	NR	NR
Hou et al	2007	Asian	China	19-87/38–63	130	Hospital	Breast carcinoma	N	13/43/24
Chen et al	2006	Asian	Taiwan	50-1/49-2	200	Hospital	BC	N	37/39/24
Mantzoros et al	2004	Caucasian	America	45–75/45–75	341	Hospital	BC	NR	NR
Miyoshi et al	2003	Asian	Japan	54±1/53±1	202	Population	BC	N	NR

BC = breast cancer, DCIS = in-situ ductal carcinoma, IDC = infiltrating duct carcinoma, ILC = invasive lobular carcinoma, NR = not report, N, non-treatment.

adiponectin levels and risk of BC.[12,13] In addition, several studies have demonstrated significant low serum concentration of adiponectin in postmenopausal BC cases,[14,15] while other studies reported controversial findings in premenopausal women with BC.[16,17] This profile may be correlated with menstrual status and the observed association between adiponectin and BC in these studies were inconsistent.

Up to now, several meta-analyses based on different strategies tried to investigate the relationship between adiponectin levels and BC risk.[18–21] Unfortunately, the sample size in these studies was not large enough to reveal a reliable relationship. Furthermore, growing evidence suggests that different populations living in different areas might have different genetic backgrounds, different homeostasis model assessment (HOMA) indexes, and different sex-hormone-binding globulin and high-density lipoprotein cholesterol levels, which were associated with adiponectin concentration and had an effect on the results.[22–26] In addition, different populations may have different living and diet habits, which may also substantially affect serum adiponectin levels.[11,26] Thus, the ethnicity may be an important factor affecting the results. However, no such subgroup analyses were conducted based on ethnicity.[19–21]

Moreover, obviously high heterogeneity was identified, but no meta-regression analysis was performed to investigate confounding factors.[18,19,21] The eligible studies in these meta-analyses have different quality scores and the low-quality study may affect the overall results. However, no subgroup analyses were performed in the high-quality group to confirm the stability of the overall results, which may result in bias.[18–21] Henceforth, some new studies were performed to investigate the link between adiponectin and BC on multiple ethnic populations.[12,16,17,22,23,27–34] However, the results remain inconclusive. Therefore, the data need to be updated, and more reliable association of serum adiponectin levels with the risk of BC is warranted.

Due to the critical role of adiponectin in the pathogenesis of BC and the inconsistency of these studies, an updated meta-analysis was conducted to assess the association between serum adiponectin concentration and BC risk by precise results.

2. Materials and methods

2.1. Literature search

The preferred reporting items for systematic reviews and meta-analyses protocol was prospectively conducted. Ethical approval was unnecessary in this study because it was a meta-analysis analyzing existing articles and did not need handle individual patient data. Two independent reviewers conducted a systematic literature search in the PubMed, Embase, ISI Web of Science, and Chinese National Knowledge Infrastructure databases to identify relevant studies from inception to October 1, 2017. The search terms were as follows: “adiponectin” AND “breast neoplasms” or “breast neoplasm” or “breast tumor” or “breast tumors” or “breast cancer” or “human mammary neoplasm” or “human mammary neoplasm” or “human mammary carcinoma.” No

Table 2

The levels of serum adiponectin in each eligible study.

		Cases			Control					
Author	Year	Mean	SD	N	Mean	SD	N	Unit	Method	Quality score
Ozmen et al	2017	1.32	0.26	58	1.24	0.21	30	μg/mL	ELISA	7
Georgiou et al	2017	12.53	8.23	157	12.71	4.94	52	μg/mL	ELISA	8
Crisostomo et al	2017	8.45	5.19	77	8.63	5.99	77	μg/mL	ELISA	8
Minatoya et al	2015	5	3.2	63	8.1	5.7	76	μg/mL	CLEIA	8
Guo et al	2015	6.34	3.54	1167	6.56	3.72	1167	μg/mL	ELISA	6
Gunter et al	2015	28.59	14.79	875	29.32	14.39	821	μg/mL	MHAP	8
Assiri et al	2015	8.44	2.12	82	10.96	1.6	68	μg/mL	ELISA	7
Ahmed et al	2015	6.63	1.45	175	10.17	5.29	175	μg/mL	ELISA	6
Touvier et al	2014	13.8	9	218	11	8.7	1024	μg/mL	RIA	6
Santillan-Benitez et al	2014	14.6	6	40	13.5	7.5	48	μg/mL	ELISA	7
Ollberding et al	2013	8.9	7.18	706	10	7.77	706	μg/mL	ELISA	7
Gross et al	2013	7.99	3.83	272	8.7	4.04	272	μg/mL	ELISA	7
Dalamaga et al	2013	16.9	9.8	102	19.8	10.1	102	μg/mL	ELISA	8
Alokail et al	2013	14.8	1	56	19.1	1.2	53	μg/mL	ELISA	6
Wang et al	2013	8.12	2.87	82	10.52	2.76	70	μg/mL	CLEIA	6
Zhang et al	2012	4.54	2.6	43	6.48	4.66	43	μg/mL	ELISA	7
Gulcelik et al	2012	8.58	2.09	83	13.91	3.26	40	μg/mL	ELISA	8
Al Awadhi et al	2012	8	4	144	6.3	3	77	μg/mL	ELISA	8
Al Khaldi et al	2011	8.45	4	60	4.1	2	68	μg/mL	ELISA	7
Fan et al	2010	8.6	2.92	90	10.37	2.81	50	μg/mL	ELISA	7
Shahar et al	2010	11.9	4.8	70	15.2	7.3	138	μg/mL	ELISA	7
Hancke et al	2010	18.53	7.56	159	17.77	6.4	41	μg/mL	ELISA	6
Cust et al	2009	6.9	4.15	561	6.6	4.81	561	μg/mL	RIA	8
Tworoger et al (1)	2007	14.4	9.11	1166	14.8	9.33	1575	μg/mL	RIA	7
Tworoger et al (2)	2007	16.7	8.47	311	15.6	8.14	621	μg/mL	RIA	7
Korner et al	2007	9.1	4	74	11.3	4.7	76	μg/mL	RIA	6
Kang et al	2007	6.93	3.2	41	7.6	3.5	43	μg/mL	ELISA	6
Hou et al	2007	8.6	2.92	80	10.37	2.81	50	μg/mL	ELISA	7
Chen et al	2006	10.24	5.8	100	19.17	12.4	100	μg/mL	RIA	8
Mantzoros et al	2004	16.7	10	174	17.4	10.5	167	μg/mL	RIA	8
Miyoshi et al	2003	7.57	3.13	102	8.83	3.8	100	μg/mL	ELISA	7
			LN+			LN−				
Wang et al	2013	7.05	2.65	44	10.42	2.27	38	μg/mL	CLEIA	6
Fan et al	2010	6.98	2.6	46	10.3	2.22	34	μg/mL	ELISA	7
Chen et al	2006	10.28	0.84	59	10.19	0.75	41	μg/mL	RIA	8

CLEIA = chemiluminescence enzyme immunoassay, ELISA = enzyme-linked immunosorbent assay, LN = lymph node invasion, RIA = radioimmunoassy.

publication date or languages restrictions were imposed. Ethical approval was not necessary, because available data were collected from the previous published studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: a study designed as case–control study; a study evaluating the association between serum/plasma adiponectin levels and BC; sufficient data available for calculating standardized mean difference (SMD) with 95% confidence interval (CI); the participants of the study should be human; all patients were pathologically diagnosed as BC.

Exclusion criteria: duplicative or overlapping publications; a study with incomplete data; abstracts, conferences, letters, or case reports. Only the study with the largest number of subjects was included when multiple studies were based on the same case series. Two independent investigators reviewed the references list of previous meta-analyses for potentially relevant publications.

2.3. Data extraction

The information of included studies was collected independently by 2 investigators with use of a predesigned data extraction form. Items were collected as follows: first author, publication date, country, age, ethnicity, sample size, control source, sample size, cancer type, serum adiponectin levels (mean and standard deviation), test method, menstrual status, lymph node invasion (LN), and treatment status. The third author would further recheck these publications if there was any discrepancy. The information is shown in Tables 1 and 2.

2.4. Quality assessment

The quality of each eligible study was evaluated according to Newcastle–Ottawa scale. A "*" rating system was used to assess quality based on 3 broad perspectives, including selection, comparability, exposure in the primary study.[35] The total scores ranged 0 to 9. A study with scores of 7 to 9 points was considered as a high-quality study (Table 2).

2.5. Statistical analysis

All collected data were calculated as the SMD with 95% CI to evaluate the association between serum adiponectin levels and BC. Heterogeneity was examined with use of Chi-squared-based Q test and I^2 statistics and P value < 0.10 was considered

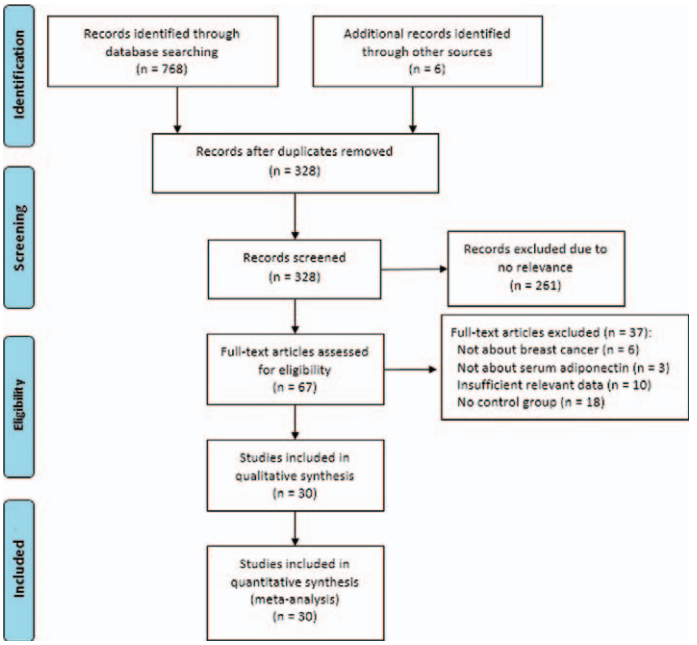

Figure 1. Flow diagram of literature selection for meta-analysis.

statistically significant. The pooled SMD would be computed by the fixed-effects model (FEM) if there was no or low heterogeneity ($I^2 > 50\%$ and $P < 0.10$). If not, the random-effects model (REM) was applied. Subgroup analyses based on ethnicity (Asian and Caucasian), control source (hospital-based [HB] and population-based [PB] population), menstrual status, and study quality-specific effects were conducted to investigate the potential origin of heterogeneity. Moreover, sensitivity analyses and multivariate meta-regression analysis were also performed to evaluate the stability of the results.

Potential publication bias was tested by Egger' linear regression and Begg's test and $P < 0.05$ indicated statistically significant publication bias. Visual inspection of asymmetry in funnel plots was conducted to detect publication bias. All data analyses were performed with STATA 12.0 software (Stata Corp LP, College Station, TX).

Table 3

The levels of serum adiponectin in pre- and postmenopausal breast cancer cases and controls.

			Cases			Control			
Author	**Year**	**Menstrual status**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Unit**
Georgiou et al	2017	Pre	10.82	3.6	44	11.39	4.8	17	μg/mL
Georgiou et al	2017	Post	13.19	9.37	113	13.35	4.94	35	μg/mL
Minatoya et al	2015	Pre	4.6	2.3	22	7.1	5.2	31	μg/mL
Minatoya et al	2015	Post	5.2	3.6	41	8.8	5.9	45	μg/mL
Guo et al	2015	Pre	6.24	3.46	745	6.44	3.57	785	μg/mL
Guo et al	2015	Post	6.58	3.74	396	6.95	4.08	339	μg/mL
Gunter et al	2015	Post	28.59	14.79	875	29.32	14.39	821	ng/mL
Assiri et al	2015	Pre	9.92	0.62	44	10.86	1.67	27	ng/mL
Assiri et al	2015	Post	6.74	1.92	38	11.01	1.58	41	ng/mL
Ahmed et al	2015	Pre	6.63	1.45	175	10.17	5.29	175	μg/mL
Gross et al	2013	Post	7.99	3.83	272	8.7	4.04	272	μg/mL
Dalamaga et al	2013	Post	16.9	9.8	102	19.8	10.1	102	μg/mL
Gulcelik et al	2012	Pre	8.44	2.02	41	13.7	3.12	20	μg/mL
Gulcelik et al	2012	Post	8.72	2.17	42	14.13	3.4	20	μg/mL
Fan et al	2010	Pre	9.31	2.34	48	10.06	2.86	26	μg/mL
Fan et al	2010	Post	7.74	3.33	42	10.43	2.81	24	μg/mL
Hancke et al	2010	Pre	15.78	6	40	17.14	6	25	μg/mL
Hancke et al	2010	Post	19.45	7.63	119	18.77	6.8	16	μg/mL
Cust et al	2009	Post	6.9	4.15	561	6.6	4.81	561	μg/mL
Hou et al	2007	Pre	9.31	2.34	43	10.06	2.86	26	μg/mL
Hou et al	2007	Post	7.74	3.33	37	10.43	2.81	24	μg/mL
Mantzoros et al	2004	Pre	14.5	7.8	49	13	7.1	44	μg/mL
Mantzoros et al	2004	Post	17.6	10.6	125	19	11.1	123	μg/mL

Post = postmenopausal women, Pre, premenopausal women.

Table 4

The pooled and subgroup results of the serum adiponectin levels in breast cancer compared with controls.

Indication	N	Cases	Control	SMD	95% CI	*P*	I^2 (%)	Model
Overall	31	7388	8491	−0.33	−0.48–−0.18	<0.0001	94.4	Random
Ethnicity								
Asian	15	2355	2278	−0.61	−0.96–−0.25	0.001	96.1	Random
Caucasian	14	3452	4686	−0.12	−0.27–0.05	0.168	89.7	Random
Mix	2	1581	1527	−0.09	−0.19–−0.001	0.047	44.8	Fixed
Method								
ELISA	21	3764	3400	−0.41	−0.64–−0.17	0.001	95	Random
RIA	7	2640	4124	−0.11	−0.30–0.09	0.288	91.7	Random
Control source								
Population	11	3123	3848	−0.41	−0.65–−0.17	0.001	95.1	Random
Hospital	14	3123	2235	−0.31	−0.53–−0.09	0.006	94.1	Random
Treatment status								
N	21	6335	7586	−0.25	−0.38–−0,11	<0.0001	92.2	Random
NR	7	748	748	−0.49	−1.14–0.16	0.137	96.9	Random
Menstrual status								
Premenstrual								
Overall	10	1251	1176	−0.50	−0.85–−0.15	0.005	90.3	Random
Ethnicity								
Asian	6	1077	1070	−0.49	−0.90–−0.08	0.020	91.0	Random
Caucasian	4	174	106	−0.56	−1.48–0.35	0.229	91.8	Random
Postmenstrual								
Overall	13	2763	2423	−0.46	−0.68–−0.25	<0.0001	90.9	Random
Ethnicity								
Asian	5	544	473	−0.97	−1.72–−0.22	0.011	94.3	Random
Caucasian	7	1344	1129	−0.26	−0.53–0.01	0.056	87.0	Random
Quality score								
High quality (≥7)	23	5416	5842	−0.24	−0.39–−0.09	0.002	92.5	Random
Low quality (<7)	8	1972	2649	−0.68	−1.14–−0.22	0.004	97.1	Random
High-quality group								
Ethnicity								
Asian	9	834	770	−0.46	−0.90–−0.02	0.041	93.5	Random
Caucasian	11	3001	3545	−0.15	−0.32–−0.04	0.115	89.6	Random
Menstrual status								
Premenstrual	7	291	191	−0.56	−1.06–−0.06	0.028	85	Random
Postmenstrual	11	2248	2068	−0.57	−0.83–−0.31	<0.0001	92.4	Random
Method								
ELISA	16	2166	1921	−0.27	−0.53–−0.002	0.048	93.1	Random
RIA	5	2312	3024	−0.13	−0.33–0.08	0.232	98.9	Random
Control source								
Population	8	2687	2671	−0.15	−0.28–−0.02	0.022	75.1	Random
Hospital	11	1048	830	−0.58	−0.91–−0.24	0.001	91.7	Random
Treatment status								
N	16	4619	5074	−0.20	−0.34–−0.06	0.006	89.6	Random
NR	4	651	652	0.06	−0.41–0.53	0.80	93.6	Random
BMI								
<25	4	846	881	−0.25	−4.05–−0.90	0.002	99.2	Random
>25	2	623	598	−0.02	−0.23–0.19	0.888	33	Fixed
LN								
LN+/LN−	3	149	113	−0.86	−1.88–0.16	0.098	93.3	Random

BMI = body mass index, CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, N, non-treatment, NR = not report, RIA = radioimmunoassy, SMD = standardized mean difference.

3. Results

3.1. Search results and study characteristics

As showed in Fig. 1, 774 articles were identified with our search strategy. A total of 707 studies were excluded after removing duplications and scanning titles and abstracts. A total of 37 articles were removed due to various reasons by further and full-view screening. In addition, the publications by Tworoger et al[36] investigated the association of serum adiponectin levels with BC in 2 individual cohorts. Therefore, a total of 30 articles (31 case–control studies) meeting inclusion–exclusion criteria were eligible in this meta-analysis, which contained 15,879 subjects (7388 cases and 8491 controls) (Fig. 1).[12,13,16,17,22,23,27–34,36–51]

Of the 31 included studies, 15 studies (4633 subjects) reported on Asians and 14 studies (8138 subjects) on Caucasians. Moreover, 11 studies employed PB control, while 14 studies applied HB control. As for measurement method, 21 studies were conducted with use of enzyme-linked immunosorbent assay (ELISA) and 7 studies with use of radioimmunoassay. For menstrual status, 10 studies included premenstrual women with BC, while 13 studies with postmenstrual women with BC. In addition, the estimated quality of each included study ranged

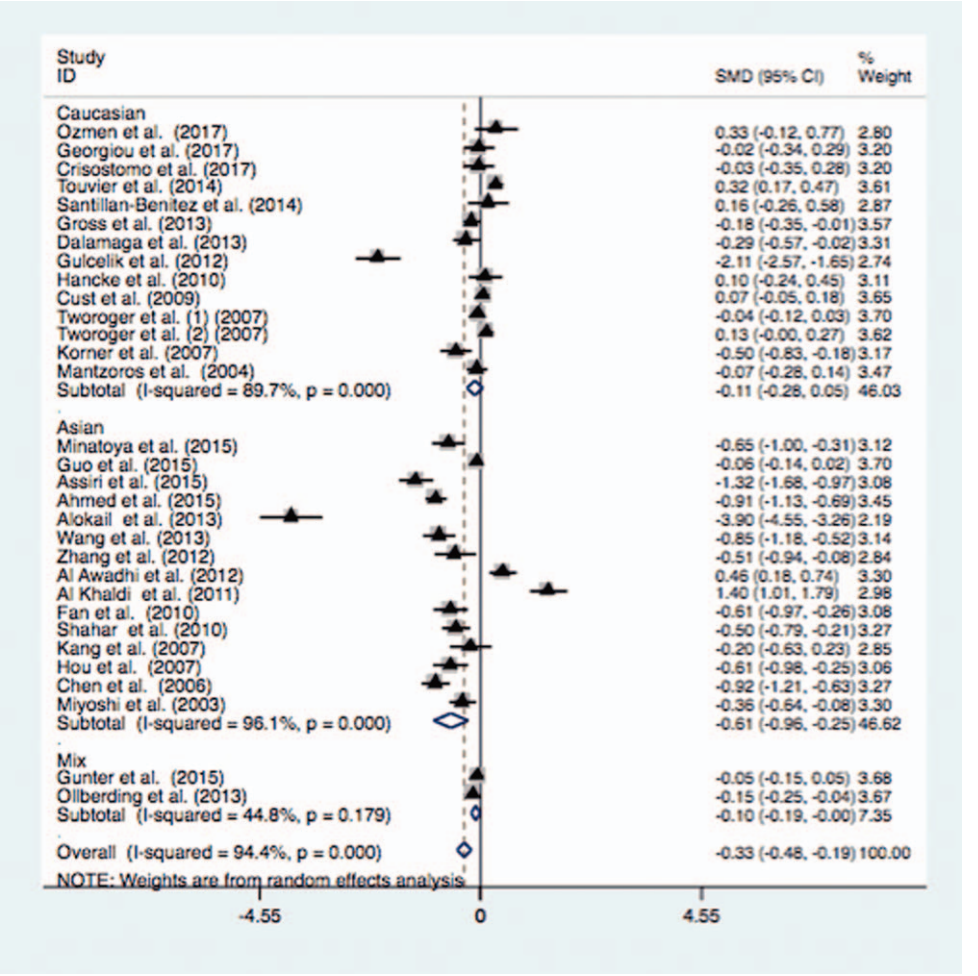

Figure 2. Forest plot of breast cancer risk associated with serum adiponectin levels for the subgroup analysis by ethnicity (Caucasian, Asian, and mixed).

from 6 to 8 points. The main characteristics of included studies were presented in Tables 1–3.

3.2. Overall meta-analysis

As showed in Table 4, the results using the REM indicated that serum adiponectin levels in BC cases were significantly lower than controls (SMD = −0.33, 95% CI = −0.48 to −0.18, $P < 0.0001$). However, a nonignorable heterogeneity was observed among studies ($I^2 = 94.4\%$). Therefore, subgroup analyses of different specific effects were performed to investigate the origin of significant heterogeneity.

3.3. Subgroup meta-analysis

In the subgroup analysis of ethnicity, lower serum adiponectin levels were detected in patients with BC in Asian population (SMD = −0.61, 95% CI = −0.96 to −0.25, $P = 0.001$), while no significant difference between serum adiponectin levels, and BC was identified in Caucasian population (Fig. 2). As for stratification by measurement method, serum adiponectin levels were significantly lower in cases with BC in ELISA group (SMD = −0.41, 95% CI = −0.67 to −0.17, $P = 0.001$) (Fig. 3). However, there was no significant association in radioimmunoassay group. We further conducted subgroup analysis by control source, and the results showed that significantly lower serum adiponectin concentration was observed in PB group and HB group. Moreover, the subgroup analysis of treatment status indicated lower serum adiponectin concentration in nontreatment group (Table 4).

As for the subgroup analysis of menstrual status, the results demonstrated that serum adiponectin levels were significantly lower in pre- and postmenopausal BC cases independently when compared with healthy controls (Fig. 4). We further conducted subgroup analysis by ethnicity; significantly lower serum adiponectin concentration was identified in premenopausal BC patients for Asian population (SMD = −0.49, 95% CI = −0.90 to −0.08, $P = 0.02$). However, no significant association was observed in Caucasian population (SMD = −0.56, 95% CI = −1.48 to 0.35, $P = 0.229$) (Table 4). Similarly, significantly lower serum adiponectin concentration was identified in postmenopausal BC cases for Asian population (SMD = −0.97, 95% CI = −1.72 to −0.22, $P = 0.011$), but not for Caucasian population (SMD = −0.26, 95% CI = −0.53 to 0.01, $P = 0.056$) (Table 4).

The serum adiponectin concentration of the cases was significantly lower in low- and high-quality group when compared with the controls (Fig. 5). As for the high-quality group, significantly lower adiponectin concentration was seen in BC cases for Asian population, but not in Caucasian population (Fig. 6). Similarly, such significant association was also identified

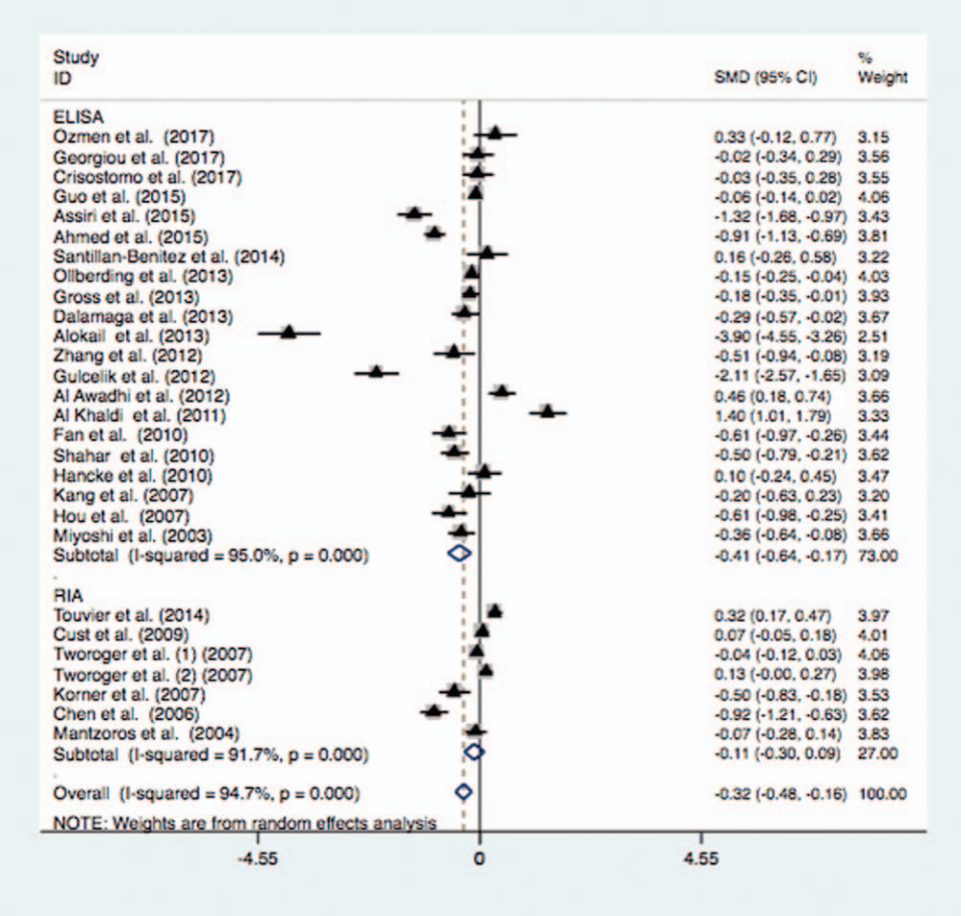

Figure 3. Forest plot of breast cancer risk associated with serum adiponectin levels for the subgroup analysis by ethnicity (enzyme-linked immunosorbent assay and radioimmunoassay).

between serum adiponectin levels and BC in pre- and postmenopausal women. In addition, the subgroup analyses by measurement method, control source, and treatment status in the high-quality group indicated similar results (Table 4).

3.4. Association of serum adiponectin levels and clinicopathological features in BC

In the subgroup analysis of body mass index (BMI), the results indicated that serum adiponectin concentration was lower in BMI <25 group. However, there was no association between serum adiponectin levels and BC in BMI >25 group (Table 4). In addition, no significant difference was identified in serum adiponectin levels in BC cases with LN and without LN (SMD $=-0.86$, 95% CI $=-1.88$ to 0.16, $P=0.098$) (Fig. 7).

3.5. Sensitivity analysis and meta-regression analysis

Although stringent protocols were applied in this meta-analysis, some of studies may affect the results of pooled analysis. Thus, sensitivity analyses were conducted to evaluate the stability of these results.[12,13,16,17,22,23,27–34,36–51] First, sensitivity analysis was conducted by sequentially excluding each study to evaluate the effect of any individual study on the obtained conclusions. Moreover, the corresponding pooled SMDs were not significantly altered. Second, the REM was compared with the FEM, and the conclusions were not materially changed, which suggested the stability of our meta-analysis.

A multivariate meta-regression analysis was conducted to assess the potential confounding factors. The results indicated that the publish year, publish language, control source, and study quality as confounding factors did not substantially affect heterogeneity (adjusted P value is 0.099, 0.832, 0.332, and 0.486, respectively).[12,13,16,17,22,23,27–34,36–51]

3.6. Publication bias

Publication bias was evaluated by the Begg's funnel plot and Egger's regression intercept tests. Egger's test indicated that no significant publication bias was identified (data not shown). Moreover, the shape of the Begg's funnel plot presented basically symmetric distribution (Fig. 8).

4. Discussion

BC is the most common malignancy among women worldwide.[1,2] Although the targeted therapy of BC makes great progress, the amount of cancer-related deaths is still large due to ineffective treatment, the large population with advanced-stage BC at diagnosis, and poor prognosis of advanced BC. Thus, it is crucial to identify new specific biomarkers and therapeutic targets for BC to make early diagnosis and monitor tumor progression. Many studies have indicated the pivotal roles played by

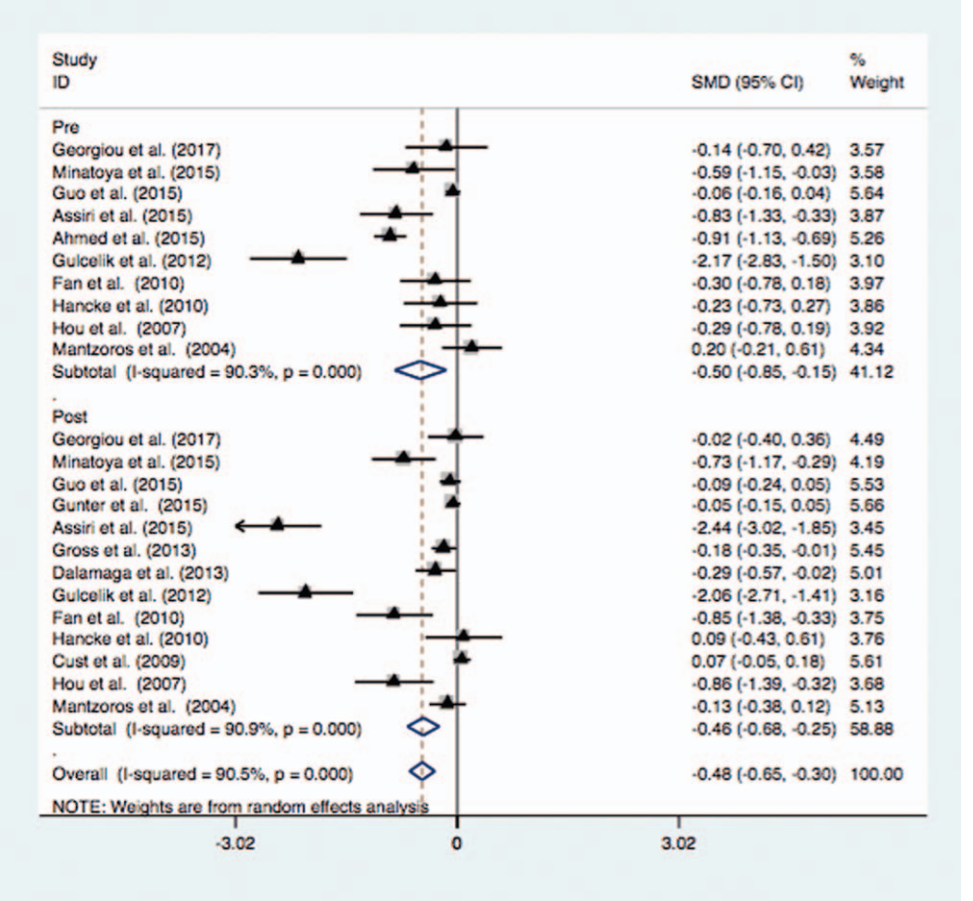

Figure 4. Forest plot of breast cancer risk associated with serum adiponectin levels for the subgroup analysis by menstrual status (premenopausal and postmenopausal).

adiponectin in BC development, progression, and recurrence.[52–55] However, these results remain inconsistent. Thus, a meta-analysis was conducted to determine the value of serum adiponectin levels in BC.

In the current meta-analysis, there were 31 studies investigating the association between serum adiponectin levels and BC risk. The overall results suggested significantly decreased serum adiponectin levels in the patients with BC compared with the controls. However, we must treat these results cautiously when referring to these findings due to a nonignorable heterogeneity, which may be contributed to the following variability: different populations (Caucasian and Asian populations) with different environments might have different genetic backgrounds and demographic characteristics; the results from the PB controls can represent the exposure situation of overall population; the patients in these studies has different tumor stages, size, molecular subtypes, lymph node metastasis status, and types of BC; different analytic methods were applied to measure the concentrations of serum adiponectin; the quality of these included studies was different; these BC cases had different menstrual; different treatment statuses were identified in patients with BC; the included participants had different demographic characteristics and clinicopathological features. The abovementioned study features may have a substantial effect on the results.

First, a multivariate meta-regression analysis was conducted to evaluate confounding factors, and the results suggested that no significant differences among all the analyzed factors (the publish year, publish language, control source, and study quality) were identified. Furthermore, sensitivity analyses were conducted by sequentially excluding individual study and the corresponding pooled SMDs were similar, which indicated the stability of this study. Moreover, the summary estimates were calculated with REM to be more conservative, and the similar results were obtained. Therefore, we further evaluated the influence of several study features including ethnicity, control source, study quality, menstrual status, treatment status, and clinicopathological features of BC on between-study heterogeneity through subgroup analyses.

When subgroup analysis was restricted to menstrual status, our results revealed an inverse association in both premenopausal and postmenopausal women. When subgroup analysis by menstrual status was conducted in high-quality study group, the similar result was obtained. In addition, the result was consistent with previous study by Macis et al, which compared "highest" and "lowest" serum adiponectin concentration and reported an indication of a weak inverse relationship in postmenopausal women. Nevertheless, the association between adiponectin and premenopausal BC risk was just in the same direction, but not significant due to limited sample size analyzed.[20] Interestingly, Ye et al[19] included 8 studies to investigated the association between circulating adiponectin levels and BC. The pooled data indicated no association of adiponectin levels with risk of BC in premenopausal women. Moreover, Liu et al[21] reported that there was no significant

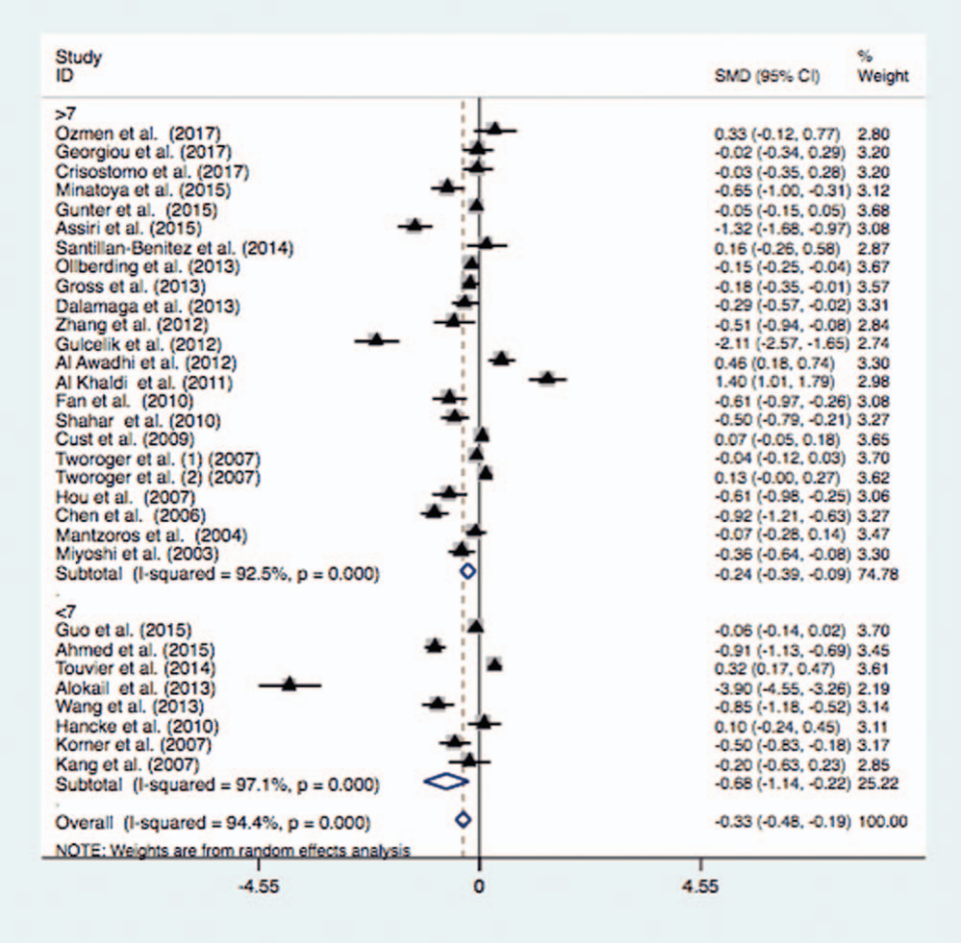

Figure 5. Forest plot of breast cancer risk associated with serum adiponectin levels for the subgroup analysis by study quality (Newcastle–Ottawa scale <7 and ≥7).

increased BC risk when comparing "highest" and "lowest" serum adiponectin levels. In addition, there was significantly high adiponectin levels in postmenopausal BC women, but not in premenopausal women with BC. In addition, Gui et al[18] demonstrated that there was no significant difference in premenopausal and postmenopausal BC women. Surprisingly, our results were contrary to the results of the 3 previous meta-analyses.[18,19,21] The result can be explained by the following reasons: we included larger sample size (31 case–control studies) regarding the relationship between serum adiponectin concentration and BC risk, which may be closer to the real value; the study by Ye et al[19] reported estimates that was not adjusted for confounders. Moreover, the study by Liu et al[21] were conducted with odds ratios calculated with different adjustment, which could bias the results and lead to an exaggerated effect size; the sensitivity analysis was performed by 2 different methods, and the corresponding pooled SMDs were similar; a multivariate meta-regression analysis was conducted to assess the potential confounding factors. Therefore, our results were more stable and credible; no subgroup analysis by menstrual status was conducted in the high-quality group to confirm the stability of the overall results, which may result in bias.

The above-mentioned meta-analyses did not conduct subgroup analysis by ethnicity.[19–21] In our study, the subgroup analysis by ethnicity in premenopausal and postmenopausal group indicated that the patients with BC showed significantly lower adiponectin levels than the healthy controls for Asian population, but not for Caucasian population. This discrepancy between Caucasians and Asians could be attributed to the genetic background, nongenetic risk factors, and different environments and life styles. Growing evidence suggests that different populations living in different areas might have different genetic backgrounds, different HOMA indexes, and different sex-hormone-binding globulin and high-density lipoprotein cholesterol levels, which is associated with adiponectin concentration and affect the results. In addition, different living and diet habits may also have a substantial effect on serum adiponectin levels. A low-calorie diet, regularly physical exercise, daily intake of fish, and medical interventions for weight loss may induced an increase in adiponectin levels.[26,56] Moreover, some pharmacological interventions, such as antihypertensive and anti-inflammatory, may also affect the secretion of adiponectin in adipose tissue.[56] In addition, in the subgroup analyses of treatment status, serum adiponectin in BC cases were found significantly lower in nontreatment group.

In the subgroup analysis of BMI and lymph node metastasis status, the results indicated a direction of an inverse association between serum adiponectin levels and BC in BMI > 25 group or in LN+ group. However, such relationship was not significant because of the relatively small numbers of studies (2 studies in BMI > 25 group and 3 in lymph node metastasis status group),

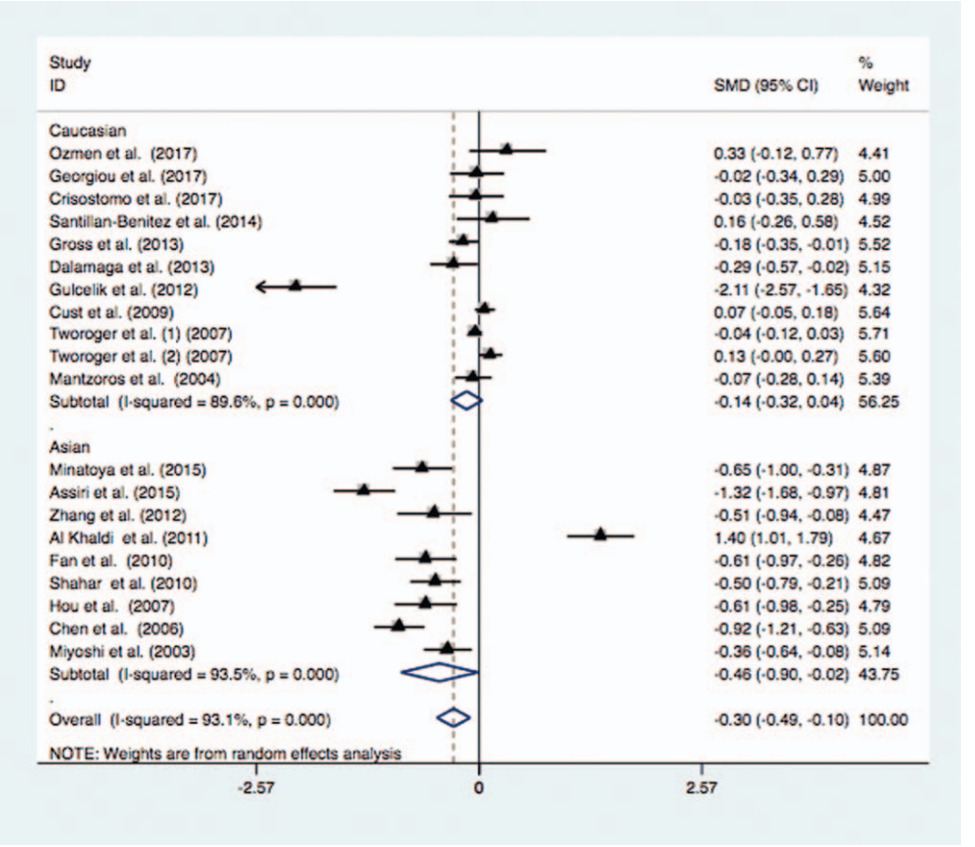

Figure 6. Forest plot of breast cancer risk associated with serum adiponectin levels for the subgroup analysis by ethnicity in high-quality study group (Caucasian and Asian).

which reduce the power to detect such small difference and to reveal a reliable relationship. The clinicopathological features of BC were varied by tumor stage or grade, size, and molecular subtypes, but no subgroup analyses were conducted due to insufficient data to calculate the pooled SMDs. Nevertheless, some studies have demonstrated that there was a significant association between lower adiponectin levels and increased risk of BC with high tumor grade, or stage.[40,48]

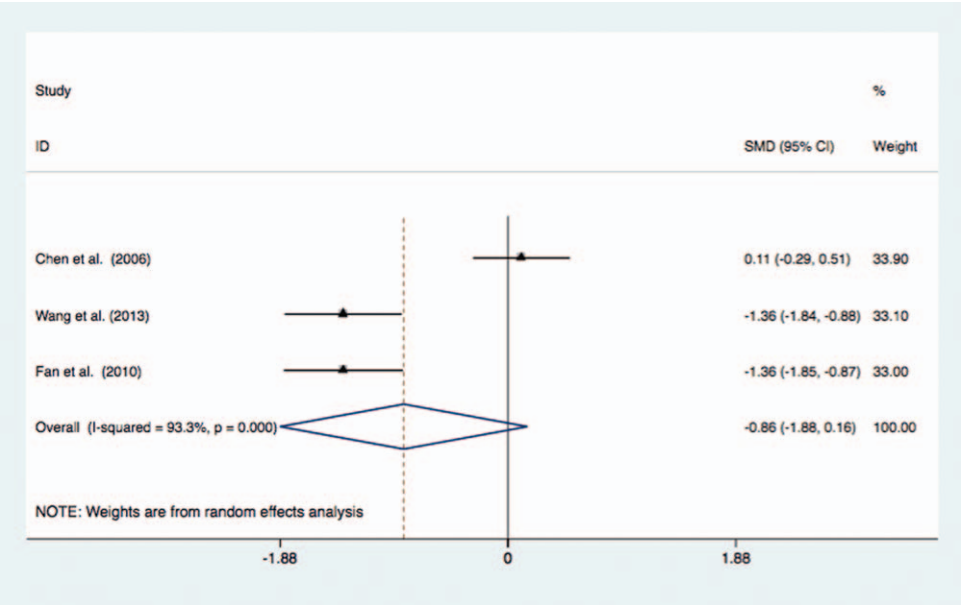

Figure 7. Comparison of differences of the serum adiponectin concentration in breast cancer cases with or without lymph node invasion.

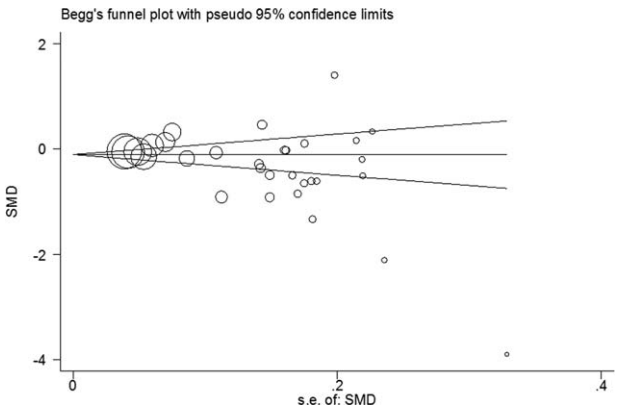

Figure 8. Funnel plot for evaluating publication bias on association between serum adiponectin levels and breast cancer.

Although the mechanism remains unclear, there were several investigations with various propositions of molecular mechanisms, by which elevated serum adiponectin levels played a protective role in reducing the risk of BC development. These included decreased serum insulin levels and insulin resistance resulting in proliferation decrease of BC cells, downregulation of the expression of VEGF, decrease of estrogen levels, and the enhancement of cell differentiation.[8,9,22] In addition, the main functions of adiponectin in our body are its regulation of insulin sensitivity, inflammation, cell proliferation, energy homeostasis, and vascular reactivity, which serves as a key factor for molecular study and a therapeutic target for various human cancers, such as cervical cancer, ovarian cancer, and endometrial cancer.[2,57–60] Studies reported that serum adiponectin concentration affected the pathogenesis of cervical cancers by an inverse association with obesity, which may play an important role in inhibiting proliferation and activating apoptosis.[58] Moreover, low adiponectin levels increase the risk of developing ovarian cancer and ovarian hormones may affect the regulation of adiponectin receptor expression.[57] In addition, high adiponectin levels are involved in a decreased risk of developing endometrial cancer through the insulin resistance and hypothyroidism that cause obesity.[10]

We note several potential limitations in this study. First, further analyses were not conducted to detect other aggressive clinicopathological features (tumor stages and histological grade) and different types of BC (estrogen receptor/progesterone receptor, human epidermal growth factor receptor 2+ and Triple negative) due to insufficient original data. Second, the included studies were observational studies, which may have not been completely controlled for confounders. Despite these limitations, we created a strict protocol and conducted study selection and data identification to reduce potential bias through the whole process. Thus, the objectivity and reliability of the results are guaranteed.

In summary, this study indicated an intriguing association between low serum adiponectin levels and increased risk of BC. Further investigation is needed to explore a threshold of adiponectin which could can have a protective effect against BC. Moreover, adiponectin may serve as a biomarker of BC risk and help to identify subjects at high risk for BC development. More rigorous and uniform case–control is necessary to confirm these results.

Author contributions

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Resources: Li Gu, Qian Li.
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Writing – original draft: Li Gu, Jing Fu, Chang Cao, Qian Li.
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Conceptualization: De-Hua Li.
Project administration: De-Hua Li, Ming-Yao Chen.
Supervision: De-Hua Li, Ming-Yao Chen.

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