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Association of serum leptin with breast cancer

A meta-analysis

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Abstract

Background: Accumulating evidence has demonstrated that leptin is associated to the tumorigenesis and progression of breast cancer (BC). However, these studies remain inconsistent. Thus, a meta-analysis was conducted to investigate the role of leptin in the patients with BC.

Method: A systematic search in PubMed, Embase, ISI Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases was conducted up to September 1, 2017. The standardized mean difference (SMD) with 95% confidence interval (CI) was applied to pool the effect size. A funnel plot and Egger test were used to evaluate publication bias.

Results: Finally, 43 eligible studies were included in the current meta-analysis. Overall, serum leptin levels in BC cases were significantly higher compared with the controls (SMD = 0.61, $P < .0001$). When subgroup analyses were restricted to ethnicity and menstrual status, higher serum leptin concentration was also detected in patients with BC. Moreover, BC cases with body mass index (BMI) >25 indicated significantly higher serum leptin levels (SMD = 1.48, $P = .034$). Furthermore, the BC cases with lymph node metastases showed significantly higher serum leptin concentration (SMD = 0.53, $P = .015$).

Conclusion: The present meta-analysis suggests that the serum leptin may profiles as a pivotal role in the pathogenesis and metastasis of BC. In addition, leptin will provide useful information for a therapeutic target to treat BC.

Abbreviations: BC = breast cancer, CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ER = estrogen receptor, FEM = fixed-effects model, LN = lymph node invasion, PR = progesterone receptor, REM = random-effects model, RIA = radioimmunoassay, SMD = standardized mean difference.

Keywords: breast cancer, leptin, meta-analysis, serum

1. Introduction

Breast cancer (BC) is one of the commonest causes of cancer-related death and is the most frequently diagnosed cancer in women worldwide.[1,2] The incidence of BC has increased dramatically because of the prolonged life-span and the increased exposure to risk factors including hormone replacement therapy, alcohol consumption, family history of BC, and obesity.[3,4] Although the targeted treatment of BC has made important progress, the 5-year relative survival for this kind of tumor is still less than 17% due to the difficulties of making early diagnosis, large population with advanced-stage BC at diagnosis, and ineffectual treatment.[5,6] Thus, it is crucial to identify new prognostic factors and therapeutic targets for BC to stratify cancer patients, monitor tumor progression, and make early diagnosis. Growing evidence has indicated several potential predictive biomarkers and therapeutic targets for BC, such as insulin-like growth factor, intercellular adhesion molecule 1 (ICAM-1), visfatin, adiponectin, and resistin.[7–13]

Leptin is a circulating satiety hormone produced mainly by white adipose tissue and is expressed in normal breast epithelium and BC cell lines. Several experimental studies have indicated the crucial role played by leptin in regulating energy expenditure and metabolism and provoking proliferation. In addition, leptin can activate leptin receptor, different signaling pathways, and enzyme aromatase and exert its proliferative effects on malignant epithelial cells, which may induce carcinogenesis of breast tissue and promote the proliferation and angiogenesis of BC cells. In addition, elevated leptin expression in BC was reported to be involved in higher tumor grade and size.[14–16]

Some studies have provided strong evidence that leptin is over-expressed in the majority of BC patients and is also involved in tumorigenesis and the progression of BC.[17–20] However, other studies have reported no association between serum leptin levels and BC development.[10,21] Furthermore, a few studies have indicated an inverse association between circulating concentration of leptin and the risk of BC in premenopausal women.[22,23] Nevertheless, some authors found a negative correlation between serum leptin and BC development in the premenopausal women, but a positive correlation in postmenopausal women.[24] The current data available investigating the association between leptin and BC remains inconsistent due to different measurement methods, inhomogeneous

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study designs, and small sample sizes, which result in insufficient power to detect such possible small effect.

Due to the critical role of leptin in prospective molecular target for cancer prediction, prevention, and therapeutics and the inconsistency of previous studies, a comprehensive meta-analysis was conducted to evaluate the reliable association between serum leptin levels and BC risk by precise results.

2. Materials and methods

2.1. Literature search

The PRISMA 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 systematically searched PubMed, Embase, ISI Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases to identify relevant studies from inception to September 1, 2017, using the following search terms: "leptin" 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". There were no publication date or languages restrictions on trial eligibility. References from the retrieved articles were also screened for potentially relevant publications. For multiple studies based on the same case series, only the study with largest sample size was eligible.

2.2. Study selection

The inclusion criteria were as follows:

(1) a case-control study;
(2) a study investigating the association between serum leptin levels and BC;

Table 1

Characteristics of included studies involving association between the serum leptin levels and breast cancer.

								Menstrual status (pre/post)		Stage
Author	Year	Ethnicity	Country	Age	BMI	Sample size	Control source	Cases	Control	I/II/II/IV
Rodrigo et al	2017	Asian	Sri Lanka	48±11/47±2	NR	160	population	42/42	38/38	NR
Li et al	2017	Asian	China	63±8/62±7	NR	112	hospital	0/0	56/56	NR
El-Hussiny et al	2017	Other	Egypt	47±7/43±9	NR	96	population	NR	NR	12/12/12/12
Georgiou et al	2016	Caucasian	Greece	56±11/56±17	NR	216	hospital	44	113	NR
Crisostomo et al	2016	Caucasian	Portugal	54±6/54±9	25±3/37±4	154	hospital	30/32	47/45	NR
Assiri et al	2016	Asian	Saudi	67±5/66±7	28±3/23±6	199	hospital	NR	NR	32/78
Gunter et al	2015	Caucasian	America	64±3/63±3	25±1/26±2	1696	population	NR	875/821	NR
Mohammadzadeh et al	2015	Asian	Iran	48±10/49±7	27±3/28±5	200	hospital	57/60	43/40	NR
Santillan-Benitez et al	2013	Caucasian	Mexico	54±11/41±13	28±3/25±5	88	hospital	NR	NR	NR
Romero et al	2013	Caucasian	Mexico	53±10/46±10	33±3/33±3	152	hospital	NR	NR	4/39/20/10/5
Ollberding et al	2013	Caucasian	America	67±7/67±7	26±5/26±5	1412	population	NR	NR	156/275/177
Gross et al	2013	Caucasian	America	62±9/62±9	27±1/25±1	544	population	NR	NR	NR
Dalamaga et al	2013	Caucasian	Greece	61±8/62±8	28±4/26±5	204	hospital	NR	NR	NR
Alokail et al	2013	Asian	Saudi	46±11/43±7	31±5/31±7	109	hospital	NR	NR	NR
Touvier et al	2013	Caucasian	France	49±6/51±6	NR	784	population	NR	NR	NR
Guo et al	2012	Asian	China	32–74/30–64	21±2/22±2	78	hospital	22/16	20/20	12/25/5/0
Zhang et al	2012	Asian	China	25–70/25–70	NR	86	population	18/22	25/21	NR
Chen et al	2012	Asian	China	50±10/51±6	NR	132	hospital	NR	NR	NR
Gu et al	2012	Caucasian	America	46±5/NR	25±5/25±5	1215	hospital	405/810	NR	NR
AL Awadhi et al	2012	Caucasian	America	50±12/51±12	30±7/27±5	221	hospital	87/50	57/27	NR
Harris et al	2011	Caucasian	America	44±4/43±3	24±4/25±5	966	population	330/636	NR	NR
Hancke et al	2010	Caucasian	Germany	59±1/49±2	26±1/24±1	200	hospital	40/25	119/16	NR
Aliustaoglu M	2010	Caucasian	Turkey	53±12/40±13	27±4/27±5	60	population	10/NR	20NR	NR
Fan et al	2010	Asian	China	50±8/47±9	NR	140	hospital	48/26	42/24	15/48/27
Maccio et al	2010	Caucasian	Italy	50.6/52.3	NR	401	population	82/105	98/116	27/23/20/12
Cust et al	2009	Caucasian	Australia	52.5/NR	25±1/24±1	1122	hospital	NR	NR	263/255/21/14
Han et al	2008	Asian	China	45±14/44±13	25±3/23±3	740	hospital	NR	NR	NR
Pazaitou et al	2007	Caucasian	Greece	63±11/55±11	29±5/29±6	150	hospital	13/22	61/54	19/32/14/9
Liu et al	2007	Asian	China	50±11/47±12	23±3/22±3	88	population	28/NR	19/NR	NR
Hou et al	2007	Asian	China	48±17/49±6	24±2/24±1	130	hospital	43/NR	37/NR	13/43/24/0
Geisler et al	2007	Caucasian	Norway	69±3/65±0.5	25±2/25±1	158	hospital	0	44	NR
Huang et al	2006	Asian	China	53±3/58±6	<23/<23	92	population	0/0	36/56	NR
Li et al	2006	Asian	China	51±7/NR	>25/>25	88	population	NR	NR	13/25/10
Woo et al	2006	Asian	Korea	NR	NR	90	hospital	30/26	15/19	38/6/1
Chen et al	2006	Asian	China	49±1/49±1	22±1/24±1	200	hospital	NR	NR	37/39/24
Jen et al (1)	2005	Caucasian	America	57±0.7/55±0.7	29±1/28±1	157	hospital	39/30	118/123	NR
Jen et al (2)	2005	Black	America	52±0.3/54±0.2	30±1/28±1	163	hospital	39/30	118/123	NR
Stattin et al	2004	Caucasian	France	59±4/60±4.8	26±3/26±3	407	hospital	NR	NR	NR
Mantzoros et al	2004	Caucasian	Greece	NR	NR	341	hospital	49/44	125/123	NR
Coskun et al (1)	2003	Caucasian	Turkey	51±11/44±11	25±3/26±3	80	hospital	NR	NR	NR
Coskun et al (2)	2003	Caucasian	Turkey	48±13/44±11	26±3/26±3	55	hospital	NR	NR	NR
Ozet et al	2001	Caucasian	Turkey	52±1/52±1	27±1/25±1	116	population	15/NR	43/NR	28/30
Petridou et al	2000	Caucasian	Greece	NR	NR	150	hospital	14/15	61/60	NR

BMI = body mass index, NR = not report, Post = postmenstrual, Pre = premenstrual.

(3) a study involving available data for estimating available data for calculating standardized mean difference (SMD) with 95% confidence interval (CI);
(4) the participants in study should be pathological diagnosed with BC.

Exclusion criteria:

(1) duplicative or overlapping study;
(2) the study without control subjects or other essential information;
(3) abstracts, conferences, letters, or non-human studies.

2.3. Data extraction

The detail information of each included study was collected in a predesigned data extraction form independently by 2 reviewers. Items were collected as follows: first author, publication date, country, ethnicity, control source, sample size, age of participant, body mass index (BMI), BC type, serum leptin levels (mean and standard deviation), measurement method, estrogen receptor (ER) status, progesterone receptor (PR) status, lymph node invasion (LN), and treatment and menstrual status. Any discrepancy was resolved by consensus. The information was shown in Tables 1 and 2.

2.4. Assessment of quality

The quality of included eligible studies regarding the role of serum leptin levels in BC was assessed based on Newcastle–Ottawa Scale (NOS), which included the selection, the comparability of the groups, and the ascertainment of the exposure or outcome of interest with use of a "-" rating system.[11,25,26] The total scores ranged 0 to 9. A study with

Table 2

The levels of serum leptin in each eligible study.

		Cases			Control						Treatment	
Author	Year	Mean	SD	N	Mean	SD	N	Unit	Method	Cancer type	Y/N	Quality score
Rodrigo et al	2017	19.23	1.87	80	17.57	1.47	80	ng/mL	ELISA	BC	N	7
Li et al	2017	19.89	5.53	56	15.02	4.84	56	ng/mL	ELISA	BC	N	6
El-Hussiny et al	2017	121.3	43.13	48	54.14	9.275	48	ng/mL	ELISA	IDC/ILC	N	5
Georgiou et al	2016	22.02	16.68	157	21.9	15.6	52	ng/mL	ELISA	IDC/DCIS/LN	N	6
Crisostomo et al	2016	22.89	11.63	77	24.03	13.34	77	ng/mL	ELISA	BC	N	6
Assiri et al	2016	24.59	5.57	110	19.62	2.03	89	ng/mL	ELISA	BC	N	7
Gunter et al	2015	15.07	4.4	875	15.11	4.9	821	ng/mL	ELISA	BC	N	7
Mohammadzadeh et al	2015	67.9	32.55	100	28.3	31.38	100	ng/mL	ELISA	BC	N	7
Santillan-Benitez et al	2013	22.6	15.2	40	18.5	11.6	48	ng/mL	ELISA	Breast carcinoma	N	5
Romero et al	2013	90.3	27.5	76	37.1	32.6	76	ng/mL	ELISA	BC	N	7
Ollberding et al	2013	22.9	6.25	706	19	6.15	706	ng/mL	ELISA	BC	N	6
Gross et al	2013	32.9	36.1	272	27.4	27.4	272	ng/mL	ELISA	BC	N	5
Dalamaga et al	2013	28.8	17.2	102	27.8	17.5	102	ng/mL	ELISA	BC	N	8
Alokail et al	2013	25.6	1.7	56	16	2.2	53	ng/mL	ELISA	BC	N	6
Touvier et al	2013	13	12	218	9.8	10.3	1024	ng/mL	ELISA	BC	N	6
Guo et al	2012	15.48	6.52	42	12.52	6.09	36	ng/mL	ELISA	BC	N	7
Zhang et al	2012	8.35	5.57	43	5.31	3.39	43	ng/mL	ELISA	BC	N	7
Chen et al	2012	18.1	10.3	82	10.8	4.58	50	ng/mL	ELISA	BC	N	6
Gu et al	2012	14.18	6	405	14.18	6	810	ng/mL	ELISA	BC	N	7
AL Awadhi et al	2012	27.5	2	144	20.7	11.1	77	ng/mL	ELISA	BC	N	7
Harris et al	2011	15.5	6.82	330	16.2	9	636	ng/mL	ELISA	BC	N	7
Hancke et al	2010	20.87	15.13	159	14.9	12.81	41	ng/mL	ELISA	BC	NR	6
Aliustaoglu M	2010	2.86	1.97	30	2.64	1.9	30	ng/mL	ELISA	BC	N	6
Fan et al	2010	1.35	0.42	90	1.06	0.39	50	ng/mL	ELISA	MIX	N	7
Maccio et al	2010	25.91	13.54	180	18.84	13.58	221	ng/mL	ELISA	BC	N	7
Cust et al	2009	14.1	3.03	561	14.5	3.38	561	ng/mL	ELISA	ICD	N	8
Han et al	2008	18.97	9.97	240	13.31	7.81	500	ng/mL	ELISA	BC	N	7
Pazaitou et al	2007	10.9	5.16	74	11.4	5.23	76	ng/mL	ELISA	BC	N	7
Liu et al	2007	10.43	7.55	47	8.13	2.56	41	ng/mL	ELISA	Breast carcinoma	N	7
Hou et al	2007	1.31	0.4	80	1.1	0.28	50	ng/mL	ELISA	MIX	N	6
Geisler et al	2007	27.9	17	44	25	15	114	ng/mL	RIA	BC	N	6
Huang et al	2006	30. 51	3.02	36	12. 63	2.26	56	ng/mL	ELISA	BC	N	6
Li et al	2006	12. 02	1. 23	48	9. 79	1.16	40	ng/mL	RIA	BC	N	6
Woo et al	2006	13.42	11.93	45	9.81	6.65	45	ng/mL	RIA	BC	N	7
Chen et al	2006	13.64	11.8	100	10.07	5.5	100	ng/mL	RIA	BC	N	6
Jen et al (1)	2005	18.7	12.67	82	18.1	9.52	75	ng/mL	RIA	BC	N	7
Jen et al (2)	2005	24.5	14.57	83	21.9	13.41	80	ng/mL	RIA	BC	N	7
Stattin et al	2004	16.7	10.63	149	17.1	11.7	258	ng/mL	RIA	BC	N	7
Mantzoros et al	2004	24.2	16.1	174	24.1	18.4	167	ng/mL	RIA	BC	N	7
Coskun et al (1)	2003	38.1	19.5	55	35.6	13.9	25	ng/mL	ELISA	Non-metastasis BC	NR	7
Coskun et al (2)	2003	39.6	16.3	30	35.6	13.9	25	ng/mL	ELISA	Metastasis BC	NR	7
Ozet et al	2001	27	20.64	58	17.65	7.38	58	ng/mL	RIA	IDC	N	6
Petridou et al	2000	23.6	15.58	75	24.5	20.78	75	ng/mL	RIA	MIX	N	7

BC = breast cancer, DCIS = in-situ ductal carcinoma, ELISA = enzyme-linked immunosorbent assay, IDC = infiltrating duct carcinoma, ILC = invasive lobular carcinoma, N = non-treatment, NR = not report, RIA = radioimmunoassy, SD = standard deviation.

scores of ≥7 points was viewed as a high-quality study (Table 2). Any disagreement was settled through discussion.

2.5. Statistical analysis

All of the data were calculated as SMD with 95% CI to compare the serum levels of leptin in BC cases with that in healthy controls. Heterogeneity was examined by Chi-squared-based Q test and I squared (I^2) statistics test (P value <.10 indicated significance). The pooled effect size was calculated by the random-effects model (REM) if significant heterogeneity existed (I^2 >50% and P <.10). Otherwise, the fixed-effects model (FEM) was applied. To investigate the potential origin of heterogeneity, stratification was employed for subgroup analyses based on ethnicity, test method, control source, study quality, menstrual status, and clinical characteristics. In addition, sensitivity analyses were also conducted by sequentially excluding individual study to assess the stability of the results.[25,27]

Egger linear regression and Begg test were used to test potential publication bias. Visual inspection of asymmetry in funnel plots was carried out to further detect publication bias. All data analyses were conducted with STATA 12.0 software (Stata Corp LP, College Station, TX).

3. Results

3.1. Study characteristics

The flowchart of the study selection is presented in Figure 1. Based on our search strategy, 1278 publications were identified. 1164 publications were excluded due to duplications (682 studies) and irrelevant studies (482 studies). After reading the full-text, 71 publications were excluded due to various reasons. Moreover, the publications by Jen et al investigated the association of serum leptin levels with BC in different ethnicities (Caucasian and black) and BC types (Non-metastasis and metastasis BC), respectively.[28,29] Thus, the 2 publications can be view as 4 individual studies. Finally, 41 publications (43 studies) following our strict inclusion-exclusion criteria were eligible, which involved 14,403 subjects (6459 cases and 7944 controls)[7–10,14,17–22,24,28–56] (Fig. 1).

The main characteristics of included studies are shown in Tables 1 and 2. Of the 43 included studies, 16 studies involving 2644 subjects reported on Asians and 25 studies involving 11,500 subjects on Caucasians. For measurement method, 33 studies were conducted using enzyme-linked immunosorbent assay (ELISA) and 10 studies using radioimmunoassay (RIA). As for menstrual status, 16 studies included premenstrual women,

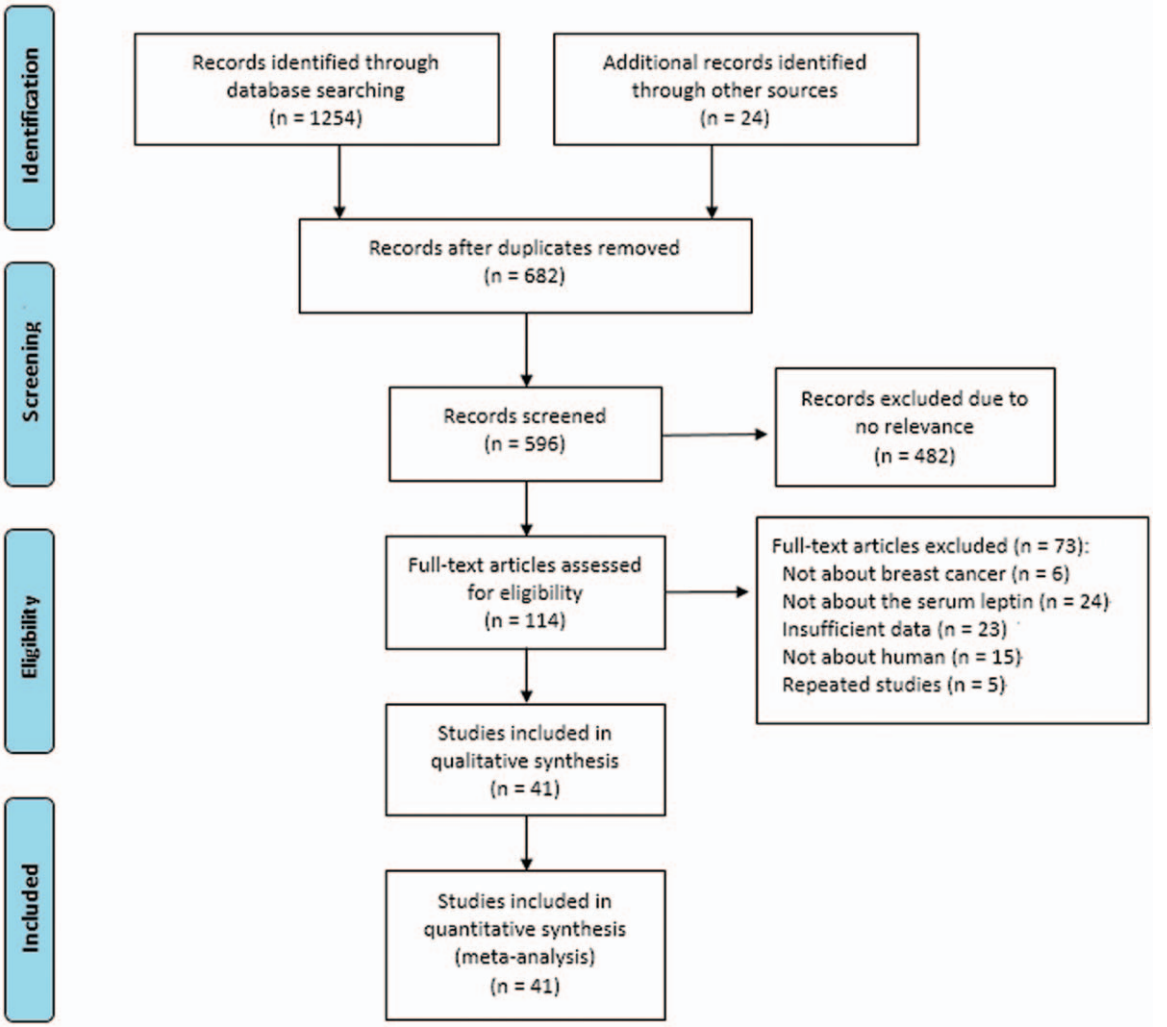

Figure 1. Flow diagram of literature selection for meta-analysis.

while 20 studies with postmenstrual women. In addition, there were 6 studies investigating the association of the serum leptin levels with BC with LN+, ER+, and PR+, respectively (Table 3). Moreover, the estimated quality of each eligible study ranged from 5 to 8 points. All the cases were histologically confirmed.

3.2. Overall meta-analysis

The overall results with the REM suggested that serum leptin levels in BC cases were significantly higher than the controls (SMD = 0.61, 95% CI = 0.45–0.77, $P < .0001$). However, there was a non-ignorable heterogeneity among studies ($I^2 = 94.9\%$). Thus, subgroup analyses of different specific effects were conducted to explore the origin of significant heterogeneity in our dataset (Table 4).

3.3. Subgroup meta-analysis

In the subgroup analysis of ethnicity, the mean leptin levels were significantly higher in patients with BC in Asian population (SMD = 1.29, 95% CI = 0.91–1.68, $P < .0001$) or Caucasian population (SMD = 0.23, 95% CI = 0.09–0.37, $P = .001$) (Fig. 2). Similarly, the subgroup analysis by test method suggested significantly higher serum leptin levels in BC cases than the controls in ELISA (SMD = 0.71, 95% CI = 0.51–0.91, $P < .0001$) or RIA (SMD = 0.32, 95% CI = 0.07–0.57, $P = .012$) (Fig. 3). When stratified by language, significantly higher serum leptin concentrations were identified in cases with BC whether the studies were published in English (SMD = 0.49, 95% CI = 0.33–0.64, $P < .0001$) or in Chinese (SMD = 1.77, 95% CI = 0.80–2.74, $P < .0001$). In addition, the subgroup analysis of control source indicated that there were significantly higher serum leptin levels in BC cases in hospital-based control (SMD = 0.51, 95% CI = 0.31–0.71, $P < .0001$) or population-based control (SMD = 0.85, 95% CI = 0.55–1.14, $P < .0001$) (Fig. 4). Moreover, significantly higher serum leptin concentration was observed in BC cases in the non-treatment group (SMD = 0.64, 95% CI = 0.47–0.81, $P < .0001$) (Table 4).

The mean leptin levels were significantly higher in the pre-menopausal BC cases (SMD = 0.28, 95% CI = 0.07–0.48, $P = .008$) or post-menopausal BC cases (SMD = 0.63, 95% CI = 0.38–0.88, $P < .0001$) than these in controls (Fig. 5). When stratified by ethnicity, the pre-menopausal BC cases indicated significantly higher serum leptin levels than the controls in Asian population (SMD = 0.68, 95% CI = 0.47–0.89, $P < .0001$) or Caucasian population (SMD = 0.12, 95% CI = 0.09–0.44, $P = .014$). When the subgroup analysis by ethnicity was conducted in post-menopausal women, such significant association was identified in Asian population (SMD = 1.41, 95% CI = 0.57–2.25, $P = .001$) or Caucasian population (SMD = 0.33, 95% CI = 0.10–0.56, $P = .006$) (Table 4).

Based on stratification analysis by study quality, the mean leptin levels were significantly different between BC cases and controls in high-quality study or low-quality study group. In the high-quality study group, further subgroup analyses of ethnicity suggested significantly higher serum leptin levels in BC cases in Asian population (SMD = 0.76, 95% CI = 0.56–0.96, $P < .0001$) or Caucasian population (SMD = 0.2, 95% CI = 0.03–0.37, $P = .021$). When stratified by menstrual status, similar significant association was identified between the pre-menopausal BC cases (SMD = 0.24, 95% CI = 0.01–0.47, $P = .039$) or post-menopausal BC cases (SMD = 0.30, 95% CI = 0.11–0.49, $P = .002$) and the controls (Table 4).

Additionally, BC cases with BMI>25 (SMD = 1.48, 95% CI = 0.11–2.85, $P = .034$) indicated significantly higher serum leptin levels than those in controls. However, no significant association was identified regarding serum leptin levels between the BC cases and the controls with BMI<25 (Table 4).

Table 3

The levels of serum leptin in breast cancer cases with different clinicopathological features.

Author	Year	LN (+) Mean	LN (+) SD	LN (+) N	LN (−) Mean	LN (−) SD	LN (−) N	Unit	Method	Quality score
Assiri et al	2016	25.64	2.44	89	21.84	3.55	21	ng/mL	ELISA	7
Guo et al	2012	1.46	0.58	22	1.24	0.65	20	ng/mL	ELISA	7
Fan et al	2010	1.26	0.48	20	1.04	0.45	70	ng/mL	ELISA	7
Maccio et al	2010	20.5	10.3	35	19	6.8	21	ng/mL	ELISA	7
Huang et al	2006	36.70	24.16	21	21.84	12.98	15	ng/mL	ELISA	6
Chen et al	2006	11.23	6.45	59	10.81	7.49	41	ng/mL	RIA	6
		ER (+)			ER (−)					
Assiri et al	2016	24.73	3.47	84	25.69	2.37	26	ng/mL	ELISA	7
Mohammadzadeh et al	2015	68.45	42.68	64	59.1	45.39	36	ng/mL	ELISA	7
Santillan-Benitez et al	2013	18.7	15.2	27	10.9	4.78	4	ng/mL	ELISA	5
Guo et al	2012	8.23	6.02	12	7.18	4.17	30	ng/mL	ELISA	7
Liu et al	2007	9.71	8.13	28	11.8	6.27	19	ng/mL	ELISA	7
Chen et al	2006	11.33	6.27	60	10.67	5.55	28	ng/mL	RIA	6
		PR (+)			PR (−)					
Assiri et al	2016	27.12	3.64	67	26.3	2.87	43	ng/mL	ELISA	7
Mohammadzadeh et al	2015	73.43	40.84	72	36	40.65	28	ng/mL	ELISA	7
Santillan-Benitez et al	2013	21.4	15.2	25	13.9	4.78	6	ng/mL	ELISA	5
Guo et al	2012	5.05	20.7	14	6.93	5.59	28	ng/mL	ELISA	7
Liu et al	2007	9.15	5.62	31	11.65	8.98	16	ng/mL	ELISA	7
Chen et al	2006	11.73	6.65	48	10.54	5.35	37	ng/mL	RIA	6

ER = estrogen receptor, LN = lymph node invasion, PR = progesterone receptor.

Table 4

The pooled and sub-group results of the serum leptin levels in breast cancer compared with the controls.

Indication	N	Cases	Control	SMD	95% CI	P_z	I^2 (%)	P_{Het}	Model
Overall	43	6459	7944	0.61	0.45–0.77	<.0001	94.9	<.001	Random
Ethnicity									
Caucasian	25	5073	6427	0.23	0.09–0.37	.001	91.1	<.001	Random
Asian	16	1255	1389	1.29	0.91–1.68	<.0001	94.8	<.001	Random
Method									
ELISA	33	5610	6932	0.71	0.51–0.91	<.0001	95.8	<.001	Random
RIA	10	858	1012	0.32	0.07–0.57	.012	85.1	<.001	Random
Control source									
Population	14	2971	4076	0.85	0.55–1.14	<.0001	96.5	<.001	Random
Hospital	29	3488	3868	0.51	0.31–0.71	<.0001	93.9	<.001	Random
Publish language									
In-English	37	6118	7669	0.49	0.33–0.64	<.0001	94.2	<.001	Random
In-Chinese	6	341	275	1.77	0.80–2.74	<.0001	96.3	<.001	Random
Treatment status									
N	40	6215	7853	0.64	0.47–0.81	<.0001	95.3	<.001	Random
NR	3	244	91	0.30	0.06–0.55	.017	0	.882	Fixed
Menstrual status									
Premenstrual									
Overall	16	1310	2006	0.28	0.07–0.48	.008	81.9	<.001	Random
Ethnicity									
Asian	7	292	266	0.68	0.47–0.89	<.0001	29.5	.203	Fixed
Caucasian	8	979	1710	0.12	0.09–0.44	.014	58.5	.018	Random
Postmenstrual									
Overall	20	2736	2582	0.63	0.38–0.88	<.0001	93.4	<.001	Random
Ethnicity									
Asian	8	271	254	1.41	0.57–2.25	.001	89.9	<.001	Random
Caucasian	11	2347	2205	0.33	0.10–0.56	.006	91.1	<.001	Random
Quality score									
High quality (≥ 7)	25	4192	5069	0.37	0.22–0.57	<.0001	93.1	<.001	Random
Low quality (< 7)	18	2267	2875	1.00	0.68–1.32	<.0001	95.7	<.001	Random
High-quality group									
Ethnicity									
Caucasian	15	3312	4005	0.20	0.03–0.37	.021	91.3	<.001	Random
Asian	9	797	984	0.76	0.56–0.96	<.0001	70.4	<.001	Random
Menstrual status									
Premenstrual	11	1113	1820	0.24	0.01–0.47	.039	82.8	<.001	Random
Postmenstrual	12	1593	1533	0.30	0.11–0.49	.002	78.9	<.001	Random
BMI									
<25	5	213	269	0.61	−0.01–1.19	.058	94.1	<.001	Random
>25	7	419	425	1.48	0.11–2.85	.034	97.9	<.001	Random
ER									
ER+/ER-	6	275	143	0.02	−0.19–0.23	.852	4.9	.395	Fixed
PR									
PR+/PR-	6	257	158	0.24	−0.12–0.69	.194	64.3	.015	Random
LN									
LN+/LN-	6	246	188	0.53	0.10–0.95	.015	73.9	.002	Random

BMI = body mass index, ELISA = enzyme-linked immunosorbent assay, LN = lymph node invasion, PR = progesterone receptor, RIA = radioimmunoassay, SMD = standardized mean difference.

3.4. Correlation of serum leptin and clinicopathological features of BC

There was no significant difference in leptin levels in BC cases with positive ER and negative ER (SMD = 0.02, 95% CI = −0.19–0.23, P = .852) (Fig. 6). Similarly, no significant difference was identified in serum leptin levels in BC cases with positive PR and negative PR (SMD = 0.24, 95% CI = −0.12–0.69, P = .194). In addition, the BC cases with lymph node metastases indicated significantly higher serum leptin levels than those with no lymph node metastases (SMD = 0.53, 95% CI = 0.10–0.95, P = .015) (Fig. 6) (Table 4).

3.5. Publication bias

The Begg funnel plot and Egger regression intercept tests were used to assess publication bias. The result of Egger test indicated no significant publication bias. Moreover, the shape of the Begg funnel plot presented basically symmetric distribution (Fig. 7).

3.6. Sensitivity analysis and meta-regression analysis

Although stringent protocols were applied to carry out all studies, some of studies may affect the pooled results. Thus, sensitivity analyses were used to evaluate the stability of these results. The sensitivity analysis was conducted by sequentially excluding each

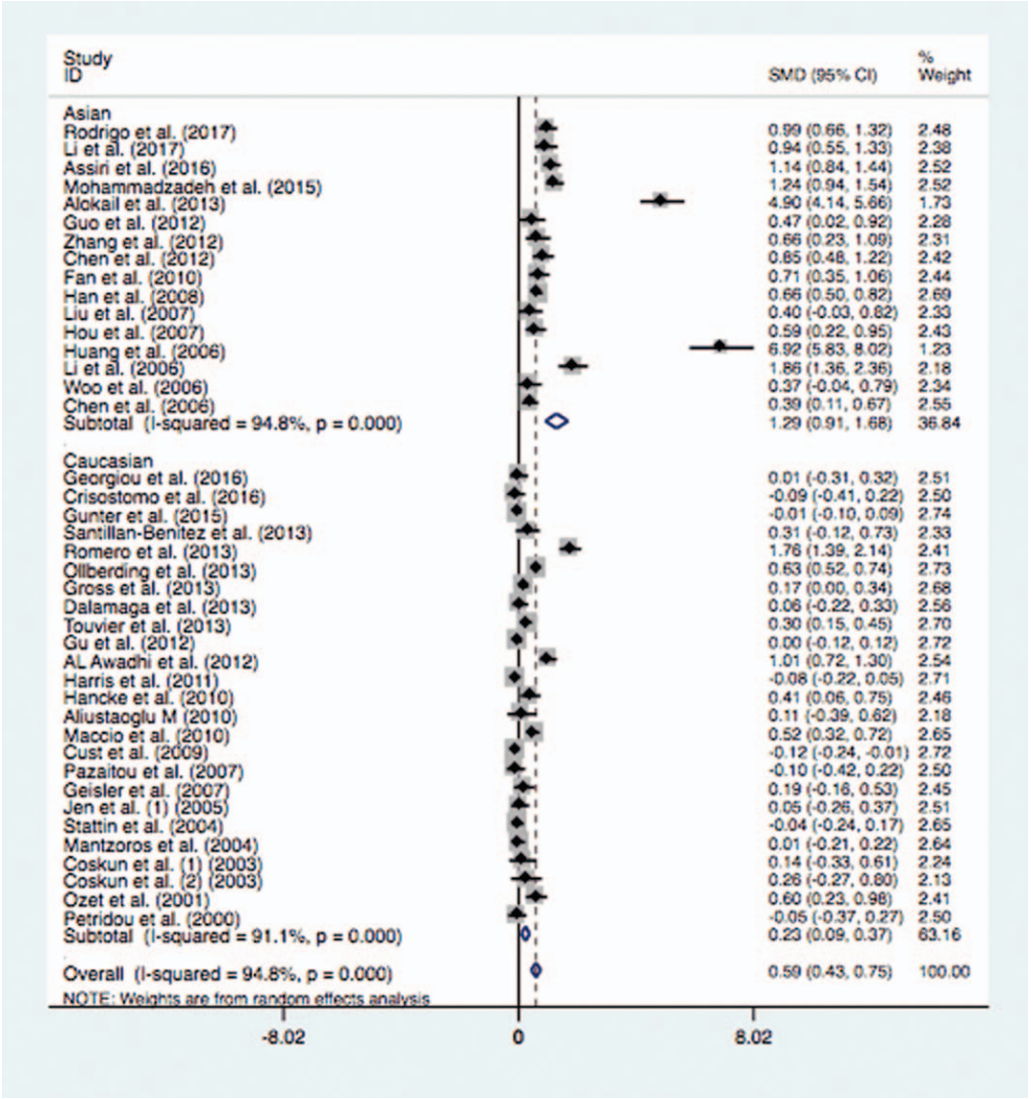

Figure 2. Forest plot of breast cancer risk associated with serum leptin levels for the subgroup analysis by ethnicity (Caucasian and Asian).

study to evaluate the influence of any individual study on the pooled results. The corresponding pooled results were not significantly altered. In addition, we noticed that some publications in forest plots were far apart from the results of other publications, which may be the root cause of the moderate heterogeneity. Thus, further sensitivity analyses excluding these publications did not change our results, which indicated the robust of the analysis. Therefore, we also included these publications in our meta-analysis. Moreover, the REM was compared with the FEM, and the conclusions were not changed, which suggested the stability of our meta-analysis.

Furthermore, a multivariate meta-regression analysis was conducted to assess the potential confounding factors. The results showed that the publish year, ethnicity, study quality, and test method did not have a substantial effect on heterogeneity (adjusted *P* value is .819, .416, .098, and .386, respectively).

4. Discussion

BC is the most frequently diagnosed cancer in women worldwide. It has been well-established that the postoperative metastasis and recurrence result in limited therapeutic options, poor prognosis, and cancer-related death. Thus, it is urgent for these researchers to investigate the molecular mechanisms of such malignancy and to identify specific biomarkers, which may be helpful in improving the rate of early diagnose, predicting prognosis, and guiding surveillance of BC. To our knowledge, of these well-established reliable biomarkers, leptin serves as a key molecular target for cancer prediction, prevention, and therapeutics. However, the issue regarding serum leptin levels and risk of BC remains controversial. Therefore, a meta-analysis was conducted to determine the value of serum leptin levels in BC.

In this meta-analysis, the overall results suggested that the serum leptin levels significantly increased in the BC patients compared with those in the controls. However, we must treat these results cautiously when referring to these findings. Because a non-ignorable heterogeneity between studies was identified, this may be contributed to the following factors:

(1) different populations (Caucasian and Asian populations) living in different areas with different environments might have different genetic backgrounds;

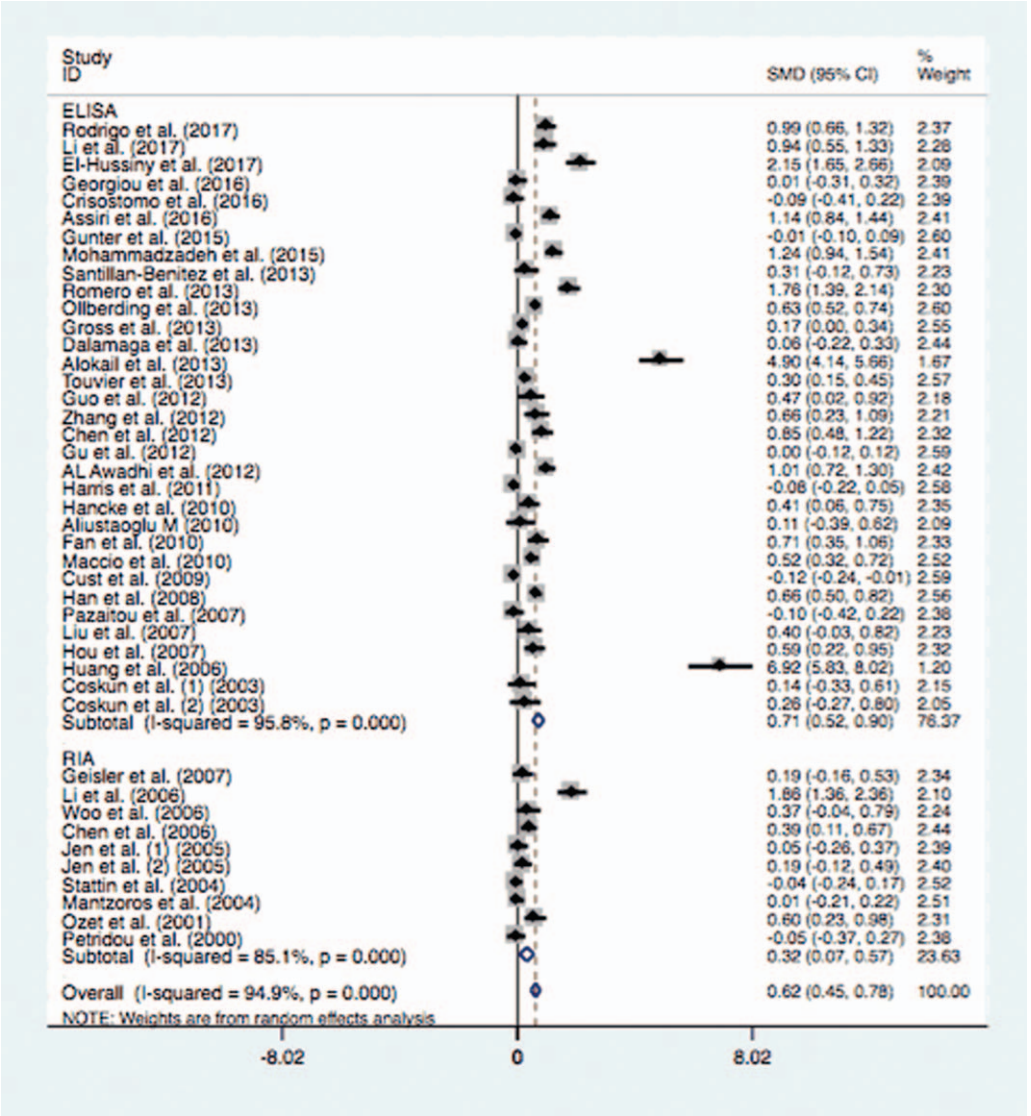

Figure 3. Forest plot of breast cancer risk associated with serum leptin levels for the subgroup analysis by measurement method (ELISA and RIA). ELISA = enzyme-linked immunosorbent assay, RIA = radioimmunoassay.

(2) the results from the population-based controls can represent the exposure situation of overall population;
(3) the patients in these studies have different stages and types of BC, which indicated different pathways in the pathogenesis of BC;
(4) these studies applied different analytic methods to measure the levels of serum leptin;
(5) the quality of these eligible studies was different;
(6) these patients with BC had different menstrual and treatment statuses;
(7) the included cases and controls had different demographic characteristics and clinical information.

First, we conducted the sensitivity analysis by sequentially excluding each study. The corresponding pooled SMDs were similar, which indicated the stability of this meta-analysis. In addition, we noticed that some publications in forest plots were far apart from the results of other publications,[17,37,50,52] further sensitivity analyses were conducted, which did not change our conclusion. The between-heterogeneity decreased from 94.9% to 91.5%, which indicated that these studies might contribute to heterogeneity but not be the root cause of the moderate heterogeneity. Thus, we still included these publications in our meta-analysis. Moreover, the similar results were obtained after the REM was compared with the FEM. Furthermore, a multivariate meta-regression analysis was conducted to further evaluate, and the results indicated no substantial effect of publish year, ethnicity, study quality, and test method on heterogeneity. Therefore, we conducted subgroup analyses to investigate the origin of heterogeneity through these above-mentioned factors.

When subgroup analyses were restricted to ethnicity, measurement method, publish language, and control source, our results revealed higher serum leptin concentrations in the patients with BC. Furthermore, the subgroup analysis by ethnicity also indicated in the high-quality group that the patients with BC

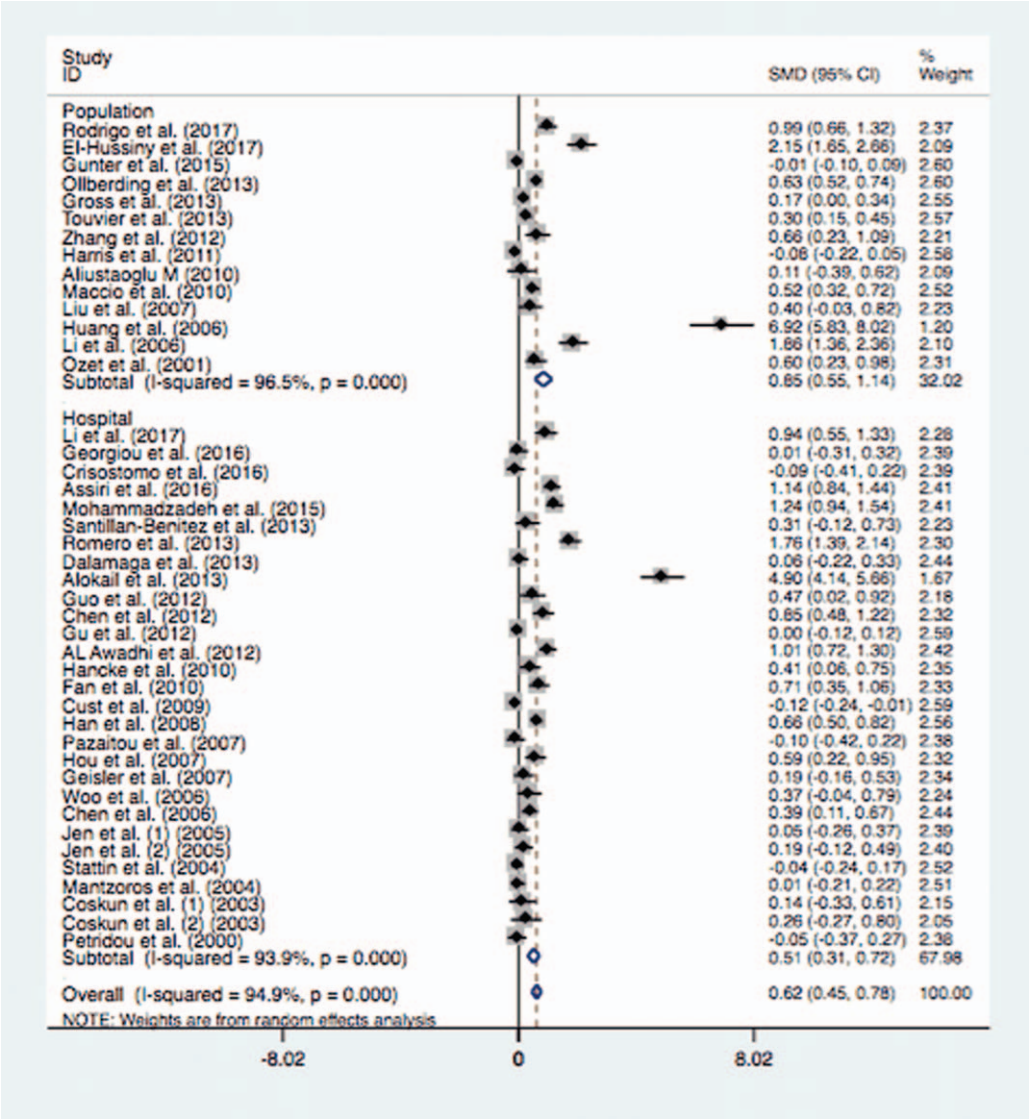

Figure 4. Forest plot of breast cancer risk associated with serum leptin levels for the subgroup analysis by control source (Population and Hospital).

showed higher serum leptin levels than the healthy controls. The above-mentioned results were consistent with the previous studies that there were significant higher serum leptin levels identified in cases with colorectal and prostate cancer compared with the controls.[57,58] Previous studies indicated significant association between serum leptin levels and risk of cancer in postmenopausal women but suggested discrepant results when the premenopausal women were included to analysis due to inherent biological differences.[59,60] However, we found a significant difference of serum leptin levels between cases and controls according to both premenopausal and postmenopausal status. Furthermore, such similar results were obtained in the subgroup analysis by menstrual status in the high-quality group.

Of the well-established risk factors for the development BC, obesity is considered as an important risk factor, especially in postmenopausal women. Leptin was one of the classical adipokines secreted by adipose tissue that was associated with insulin sensitivity, angiogenesis, and energy metabolism.[61] Previous studies reported that higher circulating levels of leptin were associated to increased body fat mass and were involved in cancer development and progression. Furthermore, several authors showed serum leptin concentration was higher in obese patients with BC than that in obese patients without cancer.[19,50] Thus, obesity may be related to leptin production in overweight/obese person with or without BC. However, many studies did not isolate the BMI in the experimental design, which may reduce the power to reveal a reliable relationship. We conducted a meta-analysis to investigate the role of serum leptin expression in BC according to BMI. The result indicated that serum leptin levels significantly increased independently in BC cases for BMI >25. Although the mechanism remains unclear, we speculated that the elevated levels of leptin were consistent with the amount of body fat in overweight/obese groups, which could positively correlate with hyperleptinemia, insulin-sensitizing, and synthesis and activity of insulin-growth factor (IGF)-I and II. The IGF-I and II and leptin could have substantial effect on tumorigenesis

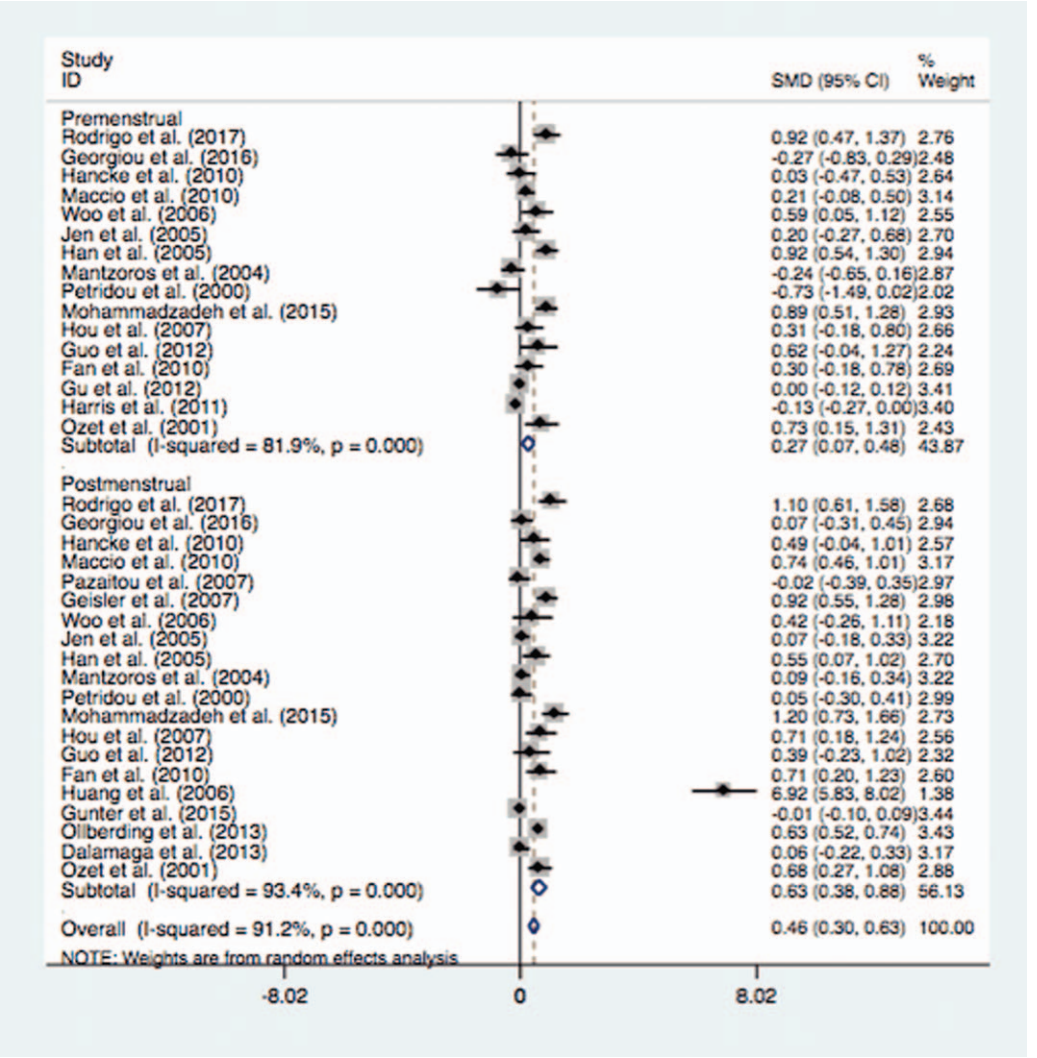

Figure 5. Forest plot of breast cancer risk associated with serum leptin levels for the subgroup analysis by menstrual status (Premenstrual and Postmenstrual).

through various intracellular pathways, which may synergize with other growth factors to enhance their mitogenic effects in obese hyperinsulinemic patients.[19,62]

Leptin is regulated by transcriptional control with sex steroid hormones such as progesterone and estrogen. Thus, amplified signals though progesterone or estrogen were associated with increased leptin levels. However, no significant differences were identified regarding serum leptin levels in BC cases with and without PR or ER. We must treat these results cautiously. First, studies in premenopausal BC cases indicated some association between serum levels of leptin and increased tissue PR concentration from BC cancer tissue. It may demonstrate that menstrual status may serve as an important factor affecting the production of leptin. Second, such association may be affected by different analytic methods, ethnicity, and influencing aspects. There were only 6 studies for analysis, which decreased the statistical power. Thus, diet and other known risk factors will remain a key area of research for understanding the BC risk and complex interactions of lifestyle. In addition, leptin was significantly higher in advanced BC with LN invasion, which demonstrated that it might play a role in the tumor metastasis.

It is known that leptin interacts with pathways in the central nervous system and direct peripheral mechanisms.[63] Moreover, the hyperactive leptin signaling network in central and peripheral system has a substantial effect on various steps in BC development and progression, and it can interact with breast epithelial tumor cells and with the different components within the BC microenvironment.[15,63,64] The higher serum leptin levels can increase the risk of BC. Therapeutic strategies to decrease leptin concentration, such as downregulation of its serum levels, decreased expression of leptin receptors, inhibition of leptin signaling by a short peptide or other leptin receptor agonists, as well as pharmacological interventions with antidiabetic drugs, should be proposed with the goal of enhancing the pharmacological effects for treating BC in the near future. In addition, all women can change their lifestyles (low-fat diet and physical exercise) to achieve healthy weight for BC prevention and treatment efforts.

We note several potential limitations in this study. First, further analyses were not performed to detect other aggressive clinicopathological features due insufficient original data, such as tumor stages, tumor differentiation (inflammatory vs non-

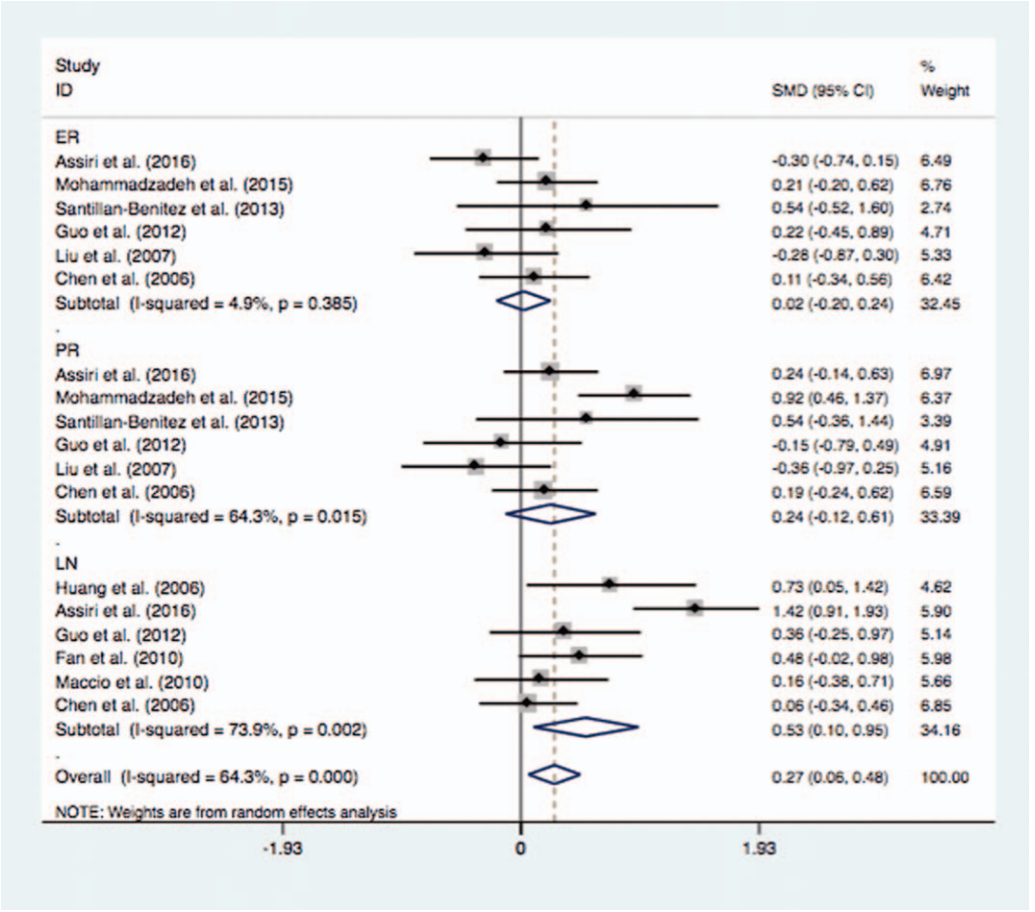

Figure 6. Comparison of differences of the serum leptin concentration in breast cancer cases with or without ER, PR, and LN. ER = estrogen receptor, LN = lymph node invasion, PR = progesterone receptor.

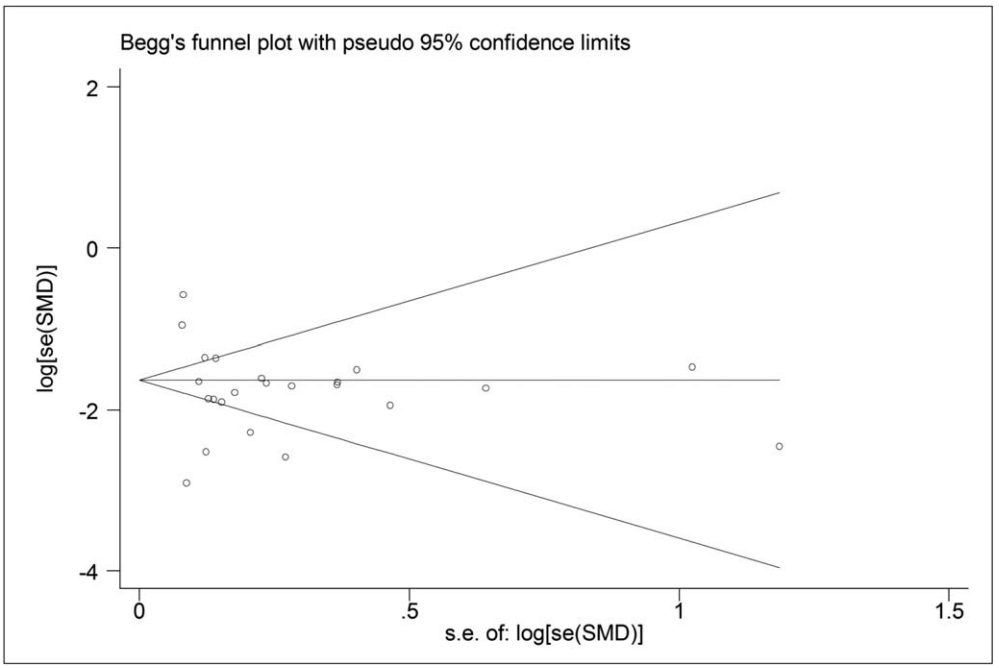

Figure 7. Funnel plot for evaluating publication bias on association between serum leptin levels and breast cancer.

inflammatory BC; triple negative vs other types), and histological grade. Second, subgroup analysis showed that disease type and ethnicity might be the source of heterogeneity. Nevertheless, there may be other inexplicable heterogeneity affecting the results. Third, a majority of studies eligible in this meta-analysis were conducted in Asian and Caucasian populations. Thus, the results are possibly mainly applicable to the Asians and Caucasians. 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 suggests that the serum leptin may profiles as a pivotal role in the pathogenesis, development, and metastasis of BC. Further investigation is needed to explore a threshold of leptin which could stimulate the development of cancer. Moreover, leptin will provide useful information for a therapeutic target to treat BC. More rigorous and uniform case-control is necessary to confirm these results.

Author contributions

Conceptualization: Li Gu, Cheng-Di Wang, Chang Cao, Lin-Rui Cai, De-Hua Li, Yuzhen Zheng.
Data curation: Li Gu, Cheng-Di Wang, Chang Cao, De-Hua Li, Yuzhen Zheng.
Investigation: Li Gu.
Project administration: Lin-Rui Cai, Yuzhen Zheng.
Software: Chang Cao, Lin-Rui Cai, De-Hua Li, Yuzhen Zheng.
Supervision: Chang Cao, Lin-Rui Cai, De-Hua Li, Yuzhen Zheng.

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