Original Paper

High Leptin Level is an Independent Risk Factor of Endometrial Cancer: A Meta-Analysis

Ping-Ping Wang^a Xiao-Yan He^b Robin Wang^{c,d} Zengfang Wang^a
Yan-Gang Wang^c

^aDepartment of Obstetrics, Maternal and Child Health Hospital of Weifang, Weifang, ^bDepartment of Oncology, People's Hospital of Ganzhou, Ganzhou, ^cDepartment of Endocrinology, the Affiliated Hospital of Medical College, Qingdao University, Qingdao, ^dDepartment of Internal Medicine, Maternal and Child Health Hospital of Weifang, Weifang, China

Key Words

Leptin • Endometrial cancer • Meta-analysis

Abstract

Background/Aims: Previous studies suggested that high leptin level might increase risk of endometrial cancer, but available data were conflicting and whether high leptin level was an independent risk factor of endometrial cancer was still unclear. Therefore, a meta-analysis was performed to assess whether high leptin level was an independent risk factor of endometrial cancer. **Methods:** PubMed, Web of Science, and Embase databases were searched for epidemiological studies published up to June 26, 2014. The pooled risk ratio (RR) with 95% confidence interval (95%CI) was used to assess the association between leptin level and risk of endometrial cancer. **Results:** Six studies with a total of 3136 individuals were finally included into the meta-analysis. Meta-analysis of total 6 studies showed that high leptin level was associated with increased risk of endometrial cancer (RR = 2.55, 95%CI 1.91-3.41, P < 0.001). After adjusting for confounding factors, high leptin level was also associated with increased risk of endometrial cancer (RR = 1.59, 95%CI 1.27-1.98, P < 0.001). Sensitivity analysis proved the stability of the pooled estimates. The RR of endometrial cancer was 1.10 (95%CI, 1.03-1.18, P = 0.005) per 5 ng/mL increment in leptin levels. There was no obvious risk of publication bias (P Egger = 0.54). **Conclusion:** Our findings suggest that high leptin level is an independent risk factor of endometrial cancer. More prospective studies are needed to further confirm the association in the future.

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Ping-Ping Wang

Department of Obstetrics, Maternal and Child Health Hospital of Weifang,
Weifang 261011 (China)
E-Mail wangppwf@yeah.net

Introduction

Endometrial cancer is a major cause of morbidity and mortality for women worldwide, with an estimated 287,100 new cases diagnosed every year [1, 2]. It is the sixth most common malignancy in women worldwide. It has been clear that obesity is strongly associated with increased risk of endometrial cancer [2, 3]. Interventions aiming to reducing obesity may provide an effective method for the prevention of endometrial cancer [4-6]. Considering the important role of obesity in the development of cancer, adipokines, such as adiponectin and leptin, are considered to have important roles in the link between obesity and endometrial cancer [7-9]. Leptin is a main kind cytokine produced by adipocytes, which has an important role in the regulation of energy balance and glucose metabolism [10-12]. Previous studies have suggested both hyperinsulinemia and obesity are associated with high leptin levels, and leptin can decrease tissues' sensitivity to insulin and lead to higher insulin levels [10, 12]. Numerous studies have assessed the role of leptin on risks of various cancers, but there are no studies with confirming conclusion [11, 12]. There were also several published studies investigating whether high leptin level could increase the risk of endometrial cancer; but they provided conflicting data and whether high leptin level is an independent risk factor of endometrial cancer is still unclear [13-17]. It's no doubt that more convincing evidence is needed to fully elucidate the exact role of leptin in the development of endometrial cancer, since identification of the connection between leptin and endometrial cancer can help us both get a better understanding of endometrial carcinogenesis and develop some preventive strategies against endometrial cancer. Therefore, a meta-analysis was performed in present study to assess whether high leptin level was an independent risk factor of endometrial cancer.

Materials and Methods

Search strategy

PubMed, Web of Science, and Embase databases were searched for epidemiological studies published up to June 26, 2014. The following search terms were used in combination to retrieve the relevant literatures in all these databases above: (leptin or adipokines) and (endometrial cancer or endometrial carcinoma). Reference lists of articles were scrutinized to identify additional articles. There was no language limitation in the literature search.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: (1) the study must be an original epidemiologic study of cohort, nested case-control, or case-control studies; (2) the exposure of interest was the (serum or plasma) leptin levels detecting in blood samples; (3) the outcome of interest was endometrial cancer incidence; (4) the article must report odds ratio (OR) or relative risk (RR), corresponding 95% confidence intervals (95%CI) to assess the effect of leptin levels on endometrial cancer risk.

Data extraction

Two investigators performed the data extraction independently. If there was any disagreement between the two investigators, it was resolved by consensus with a third investigator. The following data were extracted from each included study: first author's name, publication year, country, study design, number of subjects, OR or RR with 95%CI, and confounders adjusted for in multivariate analysis.

Statistical analysis

The pooled RR with 95%CI was used to assess the association between leptin level and risk of endometrial cancer. Heterogeneity of effect size among studies was assessed by the Cochran's Q-test and estimated the amount of variation due to heterogeneity by calculating the I^2 value [18, 19]. If I^2 was more than 50% and substantial heterogeneity existed, the random-effects model was used to pool the results

Table 1. Characteristics of those six studies assessing the association between leptin level and risk of endometrial cancer. (BMI, Body mass index; ELISA, Enzyme-linked immunosorbent assay; RIA, Radioimmunoassay)

Author, year (ref.)	Country	Participants (Case/Control)	Study design	Leptin assay	Adjusted confounding factors
Ma et al., 2013 [29]	China	206/310	Case-control	ELISA	BMI, glucose, cholesterol, triglycerides, highdensity lipoprotein cholesterol, age, insulin and leptin-to-adiponectin.
Luhn et al., 2013 [17]	USA	167/327	Nested case-control	RIA	Family history of breast or endometrial cancer, education level, parity, history of diabetes diagnosis, oral contraceptive use, and current smoking status, BMI, and estradiol
Dallal et al., 2013 [16]	USA	62/124	Nested case-control	ELISA	Age at baseline/blood drawG5 years, clinic site, time of blood drawG2 h, trial participation status, Estradiol, C-peptide, and BMI.
Friedenreich et al., 2012 [15]	Canada	514/	Case-control	ELISA	Age at reference, nulliparous, menopausal hormone use, hypertension, weight at reference date, and waist-to-hip ratio.
Ashizawa et al., 2010 [14]	Japan	146/150	Nested case-control	RIA	Age, BMI, hypertension, and diabetes mellitus.
Petridou et al., 2002 [13]	Greece	84/84	Case-control	RIA	Age, education, height, age at menarche, menopausal status, history of pregnancies by outcome, alcohol and coffee consumption, and smoking status, total energy intake, and BMI.

according to the DerSimonian-Laird method [20]; Otherwise, the fixed-effects model was adopted as the pooling method [18]. Sensitivity analysis by removal of individual studies by turns was performed to assess the robustness of the pooled results of meta-analysis. To assess the possible dose-response relationship between leptin levels and incidence of endometrial cancer, a multivariate random-effects meta-analysis taking into account the between-study heterogeneity was performed to compute the trend from the correlated RR estimates across categories of leptin levels [21]. Publication bias was tested by means of funnel plot and Egger's test [22, 23]. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). All reported P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

We identified 105 potentially relevant articles concerning the association between leptin level and endometrial cancer risk. After checking the abstracts, 94 articles were firstly excluded because they were obvious irrelevant studies, reviews, or case reports. The left 11 articles were further evaluated by full-text, and five studies were excluded including 4 studies without usable data [24-27] and one study without relevant exposure [28]. Finally, 6 articles with a total of 3136 individuals were finally included into the meta-analysis [13-17]. Those 6 studies included 3 nested case-control studies and 3 case-control studies. All studies provided adjusted estimates for the association between leptin level and risk of endometrial cancer. Table 1 shows the main characteristics of those six studies included into the meta-analysis (Table 1).

Meta-analysis

Meta-analysis of total 6 studies showed that high leptin level was associated with increased risk of endometrial cancer (RR = 2.55, 95%CI 1.91-3.41, $P < 0.001$) (Fig. 1A). After adjusting for confounding factors, high leptin level was also associated with increased risk of endometrial cancer (RR = 1.59, 95%CI 1.27-1.98, $P < 0.001$) (Fig. 1B). After adjusting for BMI and other factors, high leptin level was still associated with increased risk of endometrial cancer (RR = 1.67, 95%CI 1.28-2.17, $P < 0.001$) (Fig. 1C). Subgroup analysis by study design found similar findings ($P < 0.01$). Sensitivity analysis by removal of individual studies by turns showed no obvious influence of individual study on the pooled estimate, which proved

Fig. 1. The effect of leptin levels on endometrial cancer risk. (A) Unadjusted effect. (B) Adjusted for possible confounding factors. (C) Adjusted for BMI and all other possible confounding factors.

the stability of the pooled estimates. The dose-response meta-analysis showed that RR of endometrial cancer was 1.10 (95%CI, 1.03-1.18, P = 0.005) per 5 ng/mL increment in leptin level (Fig. 2).

Publication bias

The funnel plot showed no obvious evidence of publication bias (Fig. 3). In addition, Egger's regression test also showed that there was no obvious risk of publication bias (P_{Egger} = 0.54).

Fig. 2. The dose-response analysis between leptin level and risk of endometrial cancer with restricted cubic splines in a multivariate random-effects dose-response model. (The solid line and the long dash line represent the estimated relative risk and its 95% confidence interval of the nonlinear relationship. Short dash line represents the linear relationship.)

Fig. 3. Begg's funnel plot showed no obvious evidence of publication bias.

Discussion

Though several studies were performed to assess the role of leptin levels on risk of endometrial cancer, they provided conflicting results. In addition, whether high leptin level is an independent risk factor of endometrial cancer is still unclear. Therefore, we performed this meta-analysis to assess whether high leptin level was an independent risk factor of endometrial cancer. To the best of our knowledge, it is the first meta-analysis aiming to comprehensively assess the association between leptin levels and endometrial cancer risk. Our meta-analysis provides an appropriate approach to obtain a more definitive conclusion regarding the role of leptin in the development of endometrial cancer and allows a much bigger possibility of reaching reasonable conclusion.

Six studies with a total of 3136 individuals were finally included into the meta-analysis [13-17, 29]. Meta-analysis of total 6 studies showed that high leptin level was associated with increased risk of endometrial cancer (Fig. 1). After adjusting for BMI and other factors, high leptin level was still associated with increased risk of endometrial cancer (RR = 1.67, 95%CI 1.28-2.17, $P < 0.001$) (Fig. 1). Therefore, our findings suggest that high leptin level is an independent risk factor of endometrial cancer, and leptin indeed plays important roles in the carcinogenesis of endometrial cancer.

Though obesity has been identified as an important risk factor of endometrial cancer, the exact mechanism is still unclear. Adipokines, including leptin, are believed to play important roles in the link between obesity and endometrial cancer [30-32]. Our findings suggest that high leptin level is an independent risk factor of endometrial cancer, which further suggests a major role for leptin in endometrial carcinogenesis independent of obesity. In addition, the RR of developing endometrial cancer is 1.10 (95%CI, 1.03-1.18) per 5 ng/mL increment in the leptin level (Fig. 2), and there is an obvious dose-response relationship between leptin levels and risk of endometrial cancer, and individuals with high levels of leptin have higher risk of developing endometrial cancer.

Obesity is associated with increased endometrial cancer risk, and leptin is an important biomarker of obesity. But the findings from the meta-analysis shows that high leptin level

is an independent risk factor of endometrial cancer independent of BMI, which indicates that leptin may be involved in the endometrial carcinogenesis by other pathways. Previous studies have suggested that leptin plays a major role in the regulation of glucose, insulin-sensitizing activity, inflammation, lipid homeostasis, and other pathophysiology involved in carcinogenesis [33-35]. Previous studies also have suggested that leptin can stimulate cell growth, invasion, and angiogenesis via activating different signaling pathways [9, 36, 37], which may promote the development of endometrial cancer. However, the potential mechanisms underlying the association between leptin and endometrial cancer are complex, and it needs more future studies.

Some limitations should be considered when interpreting the results in the meta-analysis. Firstly, although three databases (PubMed, Web of Science, and Embase) were searched for possible studies, there was no obvious risk of publication bias, it was possible that some unpublished studies with negative findings were not indexed in those three databases and was impossible to be included into the meta-analysis. In addition, studies published in non-English language were also indexed in common databases, which could result in the risk of language bias in the meta-analysis. Secondly, the present meta-analysis included 6 studies, and three of them were case-control design. Since the case-control studies are easily subject to selection bias, the inherent limitations of such studies may influence the findings from the meta-analysis. To reduce the risk of bias, more studies with reasonable design and prospective design are needed to further assess the role of leptin in endometrial carcinogenesis. Finally, considering the small number of studies included in our meta-analysis, it is worth noting that the validity of pooled estimates needs further identification. Further studies with large number of participants are needed to identify the findings from the meta-analysis.

Despite these three limitations, our meta-analysis has several strengths. First, six studies with a total of 3136 individuals were included into the meta-analysis. The large sample size of pooled size allowed us to get a more precise assessment on the relation between leptin level and endometrial cancer, and obtain a more definitive conclusion regarding the role of leptin in the development of endometrial cancer. Second, the control of confounding factors, especially BMI, allowed us to decrease the risk of bias and get an exact assessment of the relation between leptin level and endometrial cancer. Finally, the multivariate random-effects meta-analysis in present study suggests that there is an obvious dose-response relationship between leptin levels and incidence of endometrial cancer, with a 1.10 (95%CI, 1.03-1.18) incensement of RR for endometrial cancer per 5 ng/mL increment in leptin level (Fig. 2). The dose-response relationship adds the strength for the obvious association between leptin levels and risk of endometrial cancer.

In conclusion, our findings suggest that high leptin level is an independent risk factor of endometrial cancer, and there an obvious dose-response relationship between leptin levels and incidence of endometrial cancer. In addition, more prospective studies are needed to further confirm the association in the future.

Disclosure Statement

We declare that we have no conflicts of interest.

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