Original Paper

Adiponectin and Endometrial Cancer: A Systematic Review and Meta-Analysis

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Key Words

Endometrial cancer • Obesity-related cancer • Adiponectin • Adipokines • Postmenopausal women

Abstract

Objective: This study evaluates the association between serum adiponectin concentrations and the risk of endometrial cancer through a comprehensive meta-analysis of currently available clinical data. **Methods:** PubMed, Embase, the Chinese Biomedical Literature Database and the Science Citation Index (ISI Web of Science) were searched for studies that examined the association between blood adiponectin concentrations and the risk of endometrial cancer. Data from studies that met the inclusion criteria were systematically reviewed, and pooled analyses were performed according to the guidelines of Meta-Analysis of Observational Studies in Epidemiology and PRIMSA. **Results:** Eight case-control studies (including 1257 endometrial cancer patients and 2008 controls) and four nested case-control studies (including 659 endometrial cancer patients and 1398 controls) were included. We found that serum adiponectin level was inversely correlated with the risk of endometrial cancer development after pooling the case-control studies (OR = 0.50, 95% CI: 0.39-0.60; $P < 0.001$). However, meta-analysis of nested case-control studies thus far did not support a broad linkage between serum adiponectin level and endometrial cancer, although a correlation may exist in the subgroup of postmenopausal women (OR=0.81, 95%CI: 0.65-1.00; $P=0.060$), particularly in postmenopausal women without current hormone replacement therapy (OR = 0.62, 95% CI: 0.44-0.86; $P = 0.004$). **Conclusions:** Meta-analysis of currently available clinical evidence supports the association between high serum adiponectin concentration and reduced risk of endometrial cancer development, particularly in the group of postmenopausal women without current hormone replacement therapy. However, additional studies with prospective design are required to fully support this linkage.

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Introduction

Obesity is known to increase the risks of certain types of cancers. Among which, obesity may account for 17–46% of the increased risk of endometrial cancer in postmenopausal women [1]. The mechanisms underlying such associations can be multitudes, which entail insulin resistance, chronic inflammation, and alterations in the concentrations of circulating adipokines [2–5].

Among all adipokines, adiponectin is the most abundant one in blood. Despite the fact that it is primarily produced in adipose tissue, serum concentrations of adiponectin are paradoxically reduced in obese patients [6]. Besides its intimate involvement in the regulation of metabolism, adiponectin has been shown in a series of *in vitro* studies that inhibits the proliferation of several cancer-derived cell-types such as breast cancer, endometrial cancer, prostate cancer and colorectal cancer [7–15]. The suppressive effects on these cancers may involve AMPK-mediated or non-AMPK-mediated modulation of mTOR-S6K, PI3K-AKT, JUN-STAT3 and MAPK signaling pathways, suggesting that adiponectin may play a direct role in tumor development and growth [3, 16–18].

Consistent with these *in vitro* observations, the results from some emerging epidemiological studies have shown that low levels of adiponectin are correlated with elevated risks of breast cancer [19], colon cancer [19, 20] and prostate cancer [19]. In 2003, Petridou et al. reported that plasma adiponectin concentration was inversely related to the risk of endometrial cancer [21]. Since then, other case-control or nested case-control studies have been published with occasional conflicting results [21–32]. The goal of this study is to further clarify the relationship between blood adiponectin and endometrial cancer. To this end, all currently available clinical studies in this area were comprehensively analyzed using meta-analysis, following the guidelines given in Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Materials and Methods

Search strategy

The databases of Medline (PubMed), Embase (Embase.com), the Science Citation Index (ISI Web of Science) and the Chinese Biomedical Literature Database (CBM via the Electronic Library of Sichuan University) were electronically searched to obtain all publications related to the association between adiponectin and endometrial cancer (up to September 1, 2014) without language restriction. "Adiponectin" and "Endometrial Neoplasms" and their related terms were used. To avoid missing any relevant studies, reference lists from highly related reviews were further retrieved. For studies published in languages other than English and Chinese, a foreign language teacher or a language translation company was consulted. Studies were compared to eliminate reports that potentially duplicated the results of the same patients, and when necessary, the authors were contacted.

Study selection

Studies were included if they satisfied the following criteria: 1) Reference levels (e.g. the lowest category of tertiles, quartiles or quintiles) and at-risk levels of adiponectin (e.g. the highest category of tertiles, quartiles or quintiles) were provided. 2) endometrial cancer was the outcome of interest; 3) estimate effect, such as hazard ratio (HR), relative risk (RR) or odds ratio (OR) with 95% confidence interval (CI), was provided.

Data extraction and assessment of quality

Two authors (Zeng, Fangxin and Chen, Tao) independently extracted information from the studies, and any disagreements were resolved through discussion to achieve consensus. The following data were extracted for each of the studies that met the selection criteria: the name of the first author, the year of publication, the country of origin of study, ethnicity, mean age and age range, the amounts of all participants

and endometrial cancer cases, the fully adjusted effect-estimates with the corresponding 95% CIs and study-specific adjusted confounding factors. The quality of included studies was evaluated according to the Newcastle-Ottawa scale [Table 4][33].

Statistical analysis

OR with 95% CI was chosen as the effect-estimate to assess the potential association between serum adiponectin and endometrial cancer. One study presented data in the form of RR, and it was deemed equivalent to OR for pooled analysis. We calculated the combined ORs with 95% CIs by comparing the highest category versus the lowest category of adiponectin levels and using the most adjusted effects-estimates. Due to the included studies had different cut-off values or different categories of adiponectin (e.g. tertiles or quartiles), which could lead to heterogeneity and weaken the pooled results, the present study further calculated the estimated effects and 95% CIs for an increment of 10 µg/ml of adiponectin with studies divided the levels of adiponectin into more than two categories (e.g. tertiles, quartiles, etc.). This dose-response analysis was performed according to the method provided by Greenland, Orsini and colleagues [34, 35].

Heterogeneity among studies was examined with the chi-square-based Q -test and the I^2 -test. In dose-response analysis, heterogeneity was assessed by goodness of fit test [35]. When significant heterogeneity (P -value < 0.05 and $I > 50\%$) was detected, the pooled OR and 95% CI were estimated with a random-effect model; otherwise, a fixed-effect model was used. Subgroup analyses were further carried out by study location, menopausal status (pre- or postmenopausal women), and postmenopausal hormone replace treatment. For the purpose of concision, only dose-response analysis was performed in subgroup analyses.

Sensitivity analysis was conducted to evaluate the influence of each individual study on the pooled results. Any potential publication biases were determined using Begg's and Egger's tests. All statistical analyses were conducted with Stata software, version 12.0 (Stata Corp, College Station, Texas, USA). A P -value less than 0.05 was considered to be statistically significant.

Results

Literature research

A diagram of the literature search was shown in Figure 1. Initially, 310 potentially relevant articles were identified; 289 of these were excluded based on the titles and abstracts. The full texts of the remaining 21 articles were reviewed. Nine studies were excluded for the following reasons: six studies did not calculate their data on effects-estimates (i.e. HR, RR or OR); two were review studies; one study did not provide data about the effect on endometrial cancer. Finally, 12 articles were included in this study [21-32].

Study characteristics

This study included four nested case-control studies involving 659 endometrial cancer patients and 1398 controls [25-28]. In addition, there were eight case-control studies involving 1257 endometrial cancer patients and 2008 controls [21-24, 29-32]. These studies were published between 2003 and 2013. Four studies were from Europe, five from America, and three from Asia. One of the case-control studies [31] showed sharply different levels of adiponectin which were dozens of times lower than those of other studies. Another one [21] only analyzed the association between per one standard deviation or per one quintile increase of adiponectin and endometrial cancer risk. We contacted the author of this paper but failed

Fig. 1. A flow diagram of the literature search.

Table 1. General character of studies included in this study. Note: NR = not reported. * Factors were described as percent in different categories not as Mean $\pm$ SD or Median (Inter-Quartile Range)

Study ID	Design	Country /Region	Race(%)	Sample size Case/controls	Age (years)* Case/controls	BMI (kg/m ²)* Case/controls
Ma Y(2013)[22]	Case-control	China	Asian	206/310	53.2 (26-81)/ 53.3(27-82)	NR
Ohbuchi Y (2013)[23]	Case-control	Japan	Asian	43/62	61.2 $\pm$ 9.8/ 58.1 $\pm$ 8.3	26.1 $\pm$ 4.5/ 23.3 $\pm$ 3.8
Erdogan S (2013)[24]	Case-control	Turkey	NR	60/70	56.6 $\pm$ 9.1/ 49.7 $\pm$ 7.6	31.1 $\pm$ 4.2/ 27.5 $\pm$ 3.2
Friedenreich CM(2012)[29]	Case-control	Canada	NR	514/962	59(53, 65)/59(52, 66)	31.0 (26.4, 36.8) /27.2 (24.1, 30.9)
Ashizawa N.(2010)[30]	Case-control	Japan	Asian	146/150	59.9 /57.5	23.7 $\pm$ 4.6/ 22.0 $\pm$ 3.3
Soliman PT (2006)[31]	Case-control	US	Caucasian (83.4%)	117/238	66.6 (25-88)/61.2 (50-80)	33.2/28.0
Dal Maso L(2004)[32]	Case-control	Italy	NR	87/132	62/61	< 25: 23/ 45; 25-30: 39/ 42; $\geq$ 30: 38/12*
Petridou E (2003)[21]	Case-control	Greece	NR	84/84	< 55: 20.2/20.2; 55-64: 32.1/26.2 65-74: 36.9/42.9; 74 + : 10.7/10.7*	< 25: 20.2/29.8; 25-26: 15.5/36.9 26-28: 21.4/10.7; 29-30: 15.5/11.9 $\geq$ 31: 27.4/10.7*
Luhn P (2013)[25]	Nested case-control	US	White non-Hispanic (94.3) Black non-Hispanic(2.6) Asian(3.1)	167/327	< 60: 25.8/26.3; 60-64: 35.3/35.6 65-69: 28.7/28.1; 70 + : 10.2/10.4*	< 25: 27.5/ 43.4; 25-30: 33.5/ 31.8 30-35: 17.4/18.0; 35 + : 21.6/6.7*
Dallal CM (2013)[26]	Nested case-control	US	Caucasian	62/124	67.4 $\pm$ 5.5/67.5 $\pm$ 5.1	29.5 $\pm$ 6.9/26.8 $\pm$ 4.7
Soliman PT(2011)[27]	Nested case-control	US	Caucasian (99%)	146/399	57 (47-67) /57 (47-67)	27.2/25.5
Cust AE(2007)[28]	Nested case-control	Europe	NR	284/548	56.9 (45.4-67.9) /56.9 (45.0-68.0)	28.1(20.9-37.6)/26.5 (20.2-34.8)

Table 2. Data obtained from included studies. * T3 the third tertile, T1 the first tertile, Q4 the fourth quartile, Q1 the first quartile; Δ measured both total and multimers of adiponectin. Abbreviations: BMI Body mass index; HRT hormone replacement therapy; IGF insulin-like growth factor; IGFBP IGF binding protein; OR odds ratio; QUICKI quantitative insulin sensitivity check index; SHBG sex hormone binding globulin

Study ID	Adiponectin (μ g/ml) Case/control	Adiponectin Assays	Risk definition*	Estimate Effects	Values(95% CI)	Adjusted confounding factors
Case-control studies						
Ma Y(2013)[22]	2.3 $\pm$ 0.2/ 2.6 $\pm$ 0.1	ELISA	T3 vs. T1	OR	0.52 (0.32, 0.83)	Age, BMI, glucose, TC, TG, HDL-c, insulin and leptin-to-adiponectin
Ohbuchi Y (2013)[23]	4.9(1.6,13.5)/7.0(2.9,26.1)	ELISA ^a	Quantile 2 vs quantile 1	OR	0.503(0.073, 3.448)	Age, BMI, hypertension, and diabetes mellitus
Erdogan S (2013)[24]	4.1 (0.7 - 43.6)/17.1(2.6, 108.7)	ELISA	T1 vs. T3	OR	10.80 (2.76, 42.24)	Age, BMI, HOMA-IR and QUICKI
Friedenreich CM(2012)[29]	11.6 (7.7, 17.3)/ 14.6(10.0, 21.5)	ELISA	Q4 vs. Q1	OR	0.55(0.37, 0.80)	Age, parity, HRT, hypertension, weight, WHR, glucose, leptin, insulin.
Ashizawa N.(2010)[30]	6.2 $\pm$ 0.4/ 9.0 $\pm$ 0.4	ELISA	T3 vs. T1	OR	0.6(0.3, 1.2)	Age, BMI, hypertension, and diabetes mellitus.
Soliman PT (2006)[31]	0.089 $\pm$ 0.006/0.148 $\pm$ 0.068	ELISA	T1 vs. T3	OR	10.5(4.18, 26.35)	Age, BMI, hypertension, diabetes.
Dal Maso L(2004)[32]	11.4(6.5-17.1)/16.0(8.4-22.5)	RIA	T3 vs. T1	OR	0.42 (0.19, 0.94)	Age, education, parity, smoking status, BMI, and HRT.
Petridou E (2003)[21]	13.5 $\pm$ 5.3	RIA	1 quintile increase	OR	0.74 (0.56, 0.97)	Age, education, BMI, parity, IGF-I, IGF-II, IGFBP-3, and leptin.
Nested case-control studies						
Luhn P (2013)[25]	12.2(6.8, 22.9)/14.8(7.5, 25.9)	RIA	T3vsT1	OR	0.73 (0.43, 1.27)	Age, BMI, current smoking status, family history of breast or endometrial cancer, education level, parity, diabetes, oral contraceptive use, estradiol.
Dallal CM (2013)[26]	14.3(6.7, 26.0)/14.6(11.0, 30.6)	ELISA ^a	T3 vs. T1	OR	1.31(0.55, 3.12)	Age, BMI or estradiol and C-peptide
Soliman PT(2011)[27]	12.9/12.9	ELISA	T3 vs. T1	OR	0.98(0.57, 1.68)	Age, BMI, parity, diabetes.
Cust AE(2007)[28]	8.4 (8.0-8.9) 9.9 (9.5-10.3)	ELISA	Q4 vs. Q1	RR	0.63 (0.36, 1.10)	Age, BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone.

to gain more information. These two studies were omitted from meta-analysis. Both of them suggested an inverse association between blood adiponectin level and endometrial cancer risk (Tables 1 and 2).

Meta-analysis Results of case-control studies

We initially performed a meta-analysis of case-control studies. Six studies [21, 23, 24, 29, 30, 32] (Tables 1 and 2) were included in the pooled analysis. As shown in Figure 2, the pooled OR was 0.50 (95% CI: 0.39-0.64; $P < 0.001$) for the highest versus the lowest category of adiponectin levels. No statistical heterogeneity was found. Sensitivity analyses showed that the result from one study had significantly affected the pooled OR (data not show). In this study [24], the lowest tertile of serum adiponectin had been linked to a much elevated risk of endometrial cancer (OR=10.80, 95%CI: 2.76-42.24). Even after eliminating this study, the pooled results still showed an inverse relationship between serum adiponectin level and endometrial cancer risk (pooled OR=0.53, 95% CI: 0.41-0.69; $P < 0.001$).

Fig. 2. Meta-analysis results of Case-control studies and Nested case-control studies.

Fig. 3. Dose-response analysis of four case-control studies.

Fig. 4. Dose-response analysis of four nested case-control studies.

Four studies had data available for dose-response analysis. The combined OR for an increment of 10 $\mu\text{g}/\text{ml}$ of adiponectin was 0.74 (95% CI: 0.66-0.83; $P < 0.001$) (Fig. 3). The results of subgroup analyses consistently showed inverse correlations between adiponectin levels and the risks of endometrial cancer development in most subgroups (Table 3).

Meta-analysis of nested case-control studies

We then performed a meta-analysis of four nested case-control studies [25-28] (Tables 1 and 2). The pooled OR from the nested case-control studies was not statistically significant (OR=0.82, 95%CI: 0.61-1.10; $P = 0.188$, Fig. 2) for the highest versus the lowest category of adiponectin levels. No statistical heterogeneity was found. No single study significantly affected the pooled OR in sensitivity analyses. Dose-response analysis showed that the combined OR of endometrial cancer for an increment of 10 $\mu\text{g}/\text{ml}$ of adiponectin was 0.82 (95% CI: 0.67, 1.00; $P = 0.055$) (Fig. 4).

Further subgroup analysis in postmenopausal women revealed an increment of 10 $\mu\text{g}/\text{ml}$ of adiponectin was potentially associated with a reduced risk of endometrial cancer with marginal statistical significance (pooled OR=0.81, 95%CI: 0.65-1.00, $P = 0.06$). Interestingly,

Table 3. Subgroup analysis of an increment of 10 µg/ml of serum adiponectin and endometrial cancer. * Others indicate all subjects or a part of subjects in a study were current HRT users. No study analyzed separately in former HRT users

Subgroups	Number of study	Pooled OR(95%CI)	P value for assessment	P value for heterogeneity	I ²
Case control Studies					
Study location					
Asian	2	0.56(0.34,0.94)	0.027	0.192	4.73
Europe or North America	2	0.75(0.66,0.84)	<0.001	0.460	3.62
Menopause status					
Pre- or perimenopause	1	0.59(0.31,1.10)	0.097	---	---
Postmenopause	3	0.64(0.49,0.84)	0.001	0.947	0.36
Current HRT use					
Others*	3	0.74(0.66,0.83)	<0.001	0.160	9.24
Non current user	1	0.67(0.39,1.16)	0.152	---	---
Nested case control studies					
Study location					
Asian	0	--	---	---	---
Europe or North America	4	0.82(0.67,1.00)	0.055	0.938	4.85
Menopause status					
Pre-Peri menopause	2	1.01(0.73,1.40)	0.942	0.785	2.44
Post menopause	4	0.81(0.65,1.00)	0.060	0.891	2.94
Current HRT use					
Others*	2	1.10(0.77,1.57)	0.602	0.522	2.25
Non current user	3	0.62(0.44,0.86)	0.004	0.935	1.3

Table 4. Quality analysis of included studies

Study ID	Selection				Comparability		Exposure Same methods of ascertainment for case and controls	Non-response rate
	Is the case definition adequated	Representative of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure		
Case control studies								
Ma Y(2013)[22]	*	*	*	*	*	*	*	*
Ohbuchi Y (2013)[23]	*	*	---	*	*	*	*	---
Erdogan S (2013)[24]	*	*	---	---	*	*	*	---
Friedenreich CM(2012)[29]	*	*	*	*	*	*	*	*
Ashizawa N.(2010)[30]	*	*	---	---	*	*	*	---
Soliman PT (2006)[31]	*	*	---	*	---	*	*	---
Dal Maso L(2004) [32]	*	*	---	*	*	*	*	*
Petridou E (2003)[21]	*	*	---	*	*	*	*	---
Nested case-control studies								
Luhn P (2013)[25]	*	*	*	*	**	**	*	*
Dallal CM (2013)[26]	*	*	*	*	**	**	*	*
Soliman PT(2011)[27]	*	*	*	*	*	*	*	*
Cust AE(2007)[28]	*	*	*	*	**	**	*	*

in postmenopausal women who were not currently treated with hormone replacement therapy, the pooled OR reached statistical significance (OR=0.62, 95%CI: 0.44-0.86, P=0.004). No such association was observed in premenopausal women (Table 3).

Publication Bias

No publication biases were found in meta-analyses of both case-control studies and nested case-control studies.

Discussion

This is the first systematic meta-analysis of currently available clinical studies with respect to adiponectin and endometrial cancer. The reduction of blood concentrations of adiponectin, the most abundant circulating adipokine, has been postulated in a series of studies as a potential mechanism in linking obesity and elevated risk of endometrial cancer

[36]. Adiponectin can suppress cellular growth through AMPK-mediated or non-AMPK-mediated modulation of mTOR-S6K1, PI3K-AKT, JUN-STAT3, MAPK signaling pathways in a variety of cancer cells [7-15] including endometrial cancer cells [37]. Our meta-analysis of currently available case-control studies showed that high serum adiponectin concentration was inversely related to low risk of endometrial cancer. In nested case-control studies, however, this association existed only in postmenopausal women who were not under current hormone replacement therapy. There were only six case-control studies and four nested case-control studies presented available data for pooled analysis, the numbers were fewer when it comes to subgroup analyses, so such results should be explained with caution.

Recent studies have suggested that high molecular-weight (HMW) adiponectin is the bioactive form of the protein [6]. To date, there has only been two studies that analyzed the association between higher level of HMW adiponectin and endometrial cancer, both of which had null results (0.87, 95% CI 0.37–2.09 and 3.45, 95%CI 0.52–22.73) [23, 26]. One study [23] also analyzed this association between middle molecular weight (MMW) and endometrial cancer, and suggested low MMW was the only independent risk factor for endometrial cancer (OR=4.892, 95%CI 1.252–19.114). The apparent contradicting effects of different isoforms of adiponectin on the risk of endometrial cancer need to be further investigated.

Leptin is another hormone that is elevated in obese women and secreted from adipocytes. The leptin/adiponectin ratio could, therefore, theoretically be more powerful in the prediction of endometrial cancer. Two nested case-controls and two case-control studies analyzed the involvement of leptin/adiponectin ratio and endometrial cancer risk [25, 26, 29, 30]. However, the pooled analysis of these studies produced a null result (data not shown), which might be due to the small number of studies and the small sample size available for analysis. Additional prospective studies are needed to further investigate these issues.

The major limitation of this meta-analysis was that the number of currently available studies, particularly the prospective studies, was still limited. Such limitation was even more obvious in subgroup analysis, e.g. only one case-control study provided data about postmenopausal women without current HRT, and no sufficient studies for graphical description of results of dose responsive analysis. This limitation certainly weakened the results of this analysis. The second one was that few studies presented data about former use of HRT. One of the important results of the present study was that the association between adiponectin and endometrial cancer was obvious in postmenopausal women who were currently not under HRT therapy. This results suggested estrogen activity in HRT still play the dominant role over the effect of adiponectin-deficiency on endometrial cancer development. Future studies should lay emphasis on former users of HRT, which could shed more light on the effects of exogenous estrogen on the link of adiponectin to endometrial cancer. The third limitation is the potential limitation of publication bias. Although no evidence of publication bias was found in the meta-analysis, studies with null results might have existed. To minimize this risk, we searched the ISI web of knowledge database and qualified reviews for potential unpublished studies with null results, with no such studies were found.

Conclusion

The existing evidence suggests an inverse relationship between blood adiponectin levels and endometrial cancer risk, particularly in postmenopausal women without current hormone replacement therapy. Additional prospective studies with large sample sizes are needed to fully support such potential linkage.

Disclosure Statement

The authors have no conflicts of interest to declare.

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