

# Obesity and Breast Cancer: Association of Serum Adiponectin, Leptin, and Adiponectin–Leptin Ratio as Risk Biomarkers

## Abstract

**Introduction:** Obesity has been associated with the development of breast cancer. The objectives were to study the association of serum adiponectin, serum leptin, and adiponectin–leptin ratio (ALR) in patients with breast cancer and matched controls, and to study their relationship with the various clinicopathological characteristics of breast cancer. **Materials and Methods:** A prospective, hospital-based case–control study was conducted on 40 patients with a first-confirmed histopathology diagnosis of breast cancer and 40 controls comprising individuals without a history of cancer simultaneously recruited from the health examination clinics during the same study period. Serum adiponectin and leptin concentrations were measured in a single run using commercially available kits (Human ADP/Acrp30 [adiponectin] enzyme-linked immune-sorbent assay [ELISA] kit and Human Leptin ELISA kit, Elabscience Biotechnology Co., Ltd) according to the manufacturer's instructions. **Results:** Serum adiponectin levels were reduced significantly in breast cancer patients, in comparison to controls ( $P = 0.04$ ), while serum leptin levels were increased significantly in breast cancer patients, in comparison to controls ( $P = 0.03$ ). ALR was significantly lower in breast cancer cases, in comparison to controls ( $P = 0.05$ ). There was no correlation between receptor status (estrogen receptor, progesterone receptor, Her2/neu), aggressiveness of disease in terms of tumor size, nodal metastases, stage, tumor grade, and serum adiponectin levels, leptin levels, or ALR. Body mass index was negatively correlated with serum adiponectin levels and ALR ( $r = 0.33$ ,  $P = 0.03$ ;  $r = 0.39$ ,  $P = 0.01$ , respectively) and positively correlated with serum leptin levels ( $r = 0.34$ ,  $P = 0.02$ ). **Conclusion:** In summary, our results suggest that low serum adiponectin levels, ALR, and high serum leptin levels are associated with breast cancer.

**Keywords:** Adiponectin, adiponectin–leptin ratio, breast cancer, leptin

## Introduction

Obesity has been associated with the development of breast cancer.<sup>[1]</sup> The main underlying mechanisms that link obesity to cancer development and progression include abnormalities of insulin resistance and the insulin-like growth factor system, impact of adiposity on the biosynthesis and bioavailability of endogenous sex hormones, obesity-induced low-grade chronic systemic inflammation, and alterations in the levels of adipocyte-derived growth factors.<sup>[2]</sup>

Adiponectin, a 244-amino acid protein hormone, also known as AdipoQ, Acrp30 (adipocyte complement-related protein of 30 kDa), apM1 (gene product of the adipose most abundant gene transcript-1), and GBP28 (gelatin-binding protein-28), is the most abundant adipocyte-derived factor, with insulin-sensitizing, anti-inflammatory, and

antiatherogenic properties.<sup>[3]</sup> Leptin, a peptide hormone produced by the ob gene of adipocytes, increases in concert with adiposity and has been shown to have mitogenic effects on epithelial cells and to promote cellular proliferation, migration, and invasion in breast cancer cell lines, properties potentially increasing breast cancer risk and progression.<sup>[4]</sup> Studies have examined and considered the ratio of these adipokines to be more important in breast cancer than their absolute concentrations.<sup>[5]</sup>

The objectives of the study were to determine the association of serum adiponectin, serum leptin, and adiponectin–leptin ratio (ALR) in patients with breast cancer and matched controls, and to study their relationship with the various clinicopathological characteristics of breast cancer.

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## Materials and Methods

### Patients

A prospective, hospital-based case–control study was conducted on 40 patients with a first-confirmed histopathology diagnosis of breast cancer before treatment commencement and 40 controls comprising individuals without a history of cancer simultaneously recruited from the health examination clinics during the same study period. Data on the status of estrogen receptor (ER), progesterone receptor (PR), and Her-2/Neu were obtained. One control case was matched to each case by age, menopausal status, date of enrollment ( $\pm 3$  months), and duration of fasting ( $\pm 4$  h). Cases not histologically proven, male breast cancer patients, patients with previous history of breast or other cancers, history of diabetes mellitus on treatment, and subjects who reported a recent (within the previous 1–6 months) weight gain or loss of 5% or more of their current weight were excluded from the study.

### Collection of questionnaire data

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed by the Institutional Ethics Committee. All patients gave written informed consent and underwent a personal interview. Data were collected on sociodemographic characteristics, menstrual and reproductive history, menopausal status, lifestyle behavior, and medical history as well as family history of breast and other cancers. Menopausal status was defined as last menstruation after 1 year free of menstrual cycle and no attempt was made to distinguish between women with artificial and those with natural menopause.

### Assay principle

A 10 ml blood sample for measurement of serum adiponectin and leptin was collected in vacutainer tubes (EDTA-treated), and all tubes were centrifuged at 4°C for collection of serum. These were stored at –20°C until analysis. Serum adiponectin and leptin concentrations were measured in a single run using commercially available kits (Human ADP/Acrp30 [adiponectin] enzyme-linked immune-sorbent assay [ELISA] kit and Human Leptin ELISA kit, Elabscience Biotechnology Co., Ltd) according to the manufacturer's instructions. The kit is a direct ELISA for quantitative determination of adiponectin and leptin in human serum, plasma, or other biological fluids. The detection range of serum adiponectin kit was 0.78–50 ng/ml, and the minimum detectable dose of adiponectin was 0.47 ng/ml. The detection range of serum leptin kit was 0.156–10 ng/ml, and the minimum detectable dose of leptin was 0.094 ng/ml. All matched case–control blood samples were handled identically and assayed in the same analytical run.

### Statistical analysis

Mean and frequencies were used to assess the distribution of sample characteristics. Student's *t*-tests and analysis of

variance were used to evaluate the differences in adipokine concentrations by categorical variables. Multiple linear regression models were used to investigate the associations between adipokine concentrations and demographic, reproductive, and pathological variables. For all analyses, *P* values were 2-sided and *P* < 0.05 was considered statistically significant. All statistical tests were done using Data Analysis ToolPak (Microsoft Excel Version 2013).

## Results

The baseline demographic characteristics and reproductive variables of cases and controls are summarized in Table 1. The sociocultural factors unique to the study population are an early age at marriage and first full-term birth, the absence of cases of habitual smoking and alcohol consumption and almost nonexistent oral contraceptive use and hormone replacement therapy. The clinicopathologic characteristics of cases included in the study are summarized in Table 2. The low cancer literacy among Indian women and reluctance to seek immediate medical attention is reflected in the prolonged duration of symptoms (mean  $\pm$  standard deviation: 8.27  $\pm$  13.17 months).

There was large interindividual variation for serum adipokines, with levels ranging from 3.2 to 15  $\mu$ g/ml for adiponectin and 0.215–12.15 ng/ml for leptin. Serum adiponectin levels were reduced significantly in breast cancer patients, in comparison to controls (*P* = 0.04), while serum leptin levels were increased significantly in breast cancer patients, in comparison to controls (*P* = 0.03). ALR was significantly lower in breast cancer cases, in comparison to controls (*P* = 0.05) [Table 3].

Multiple linear regression analysis indicated body mass index (BMI) as the only statistically significant independent correlate of serum adiponectin, serum leptin, and ALR. BMI was negatively correlated to serum adiponectin levels and ALR (*r* = 0.33, *P* = 0.03; *r* = 0.39, *P* = 0.01, respectively) and positively correlated to serum leptin levels (*r* = 0.34, *P* = 0.02). There was no correlation between receptor status (ER, PR, Her2/neu), aggressiveness of disease in terms of tumor size, nodal metastases, stage, tumor grade, and serum adiponectin levels, leptin levels, or ALR [Table 4].

## Discussion

Obese women have on average a 33% higher risk of total (95% confidence interval [CI]: 21%–47%) and breast cancer-specific mortality (95% CI: 19%–50%) compared to nonobese women.<sup>[6]</sup> Adipose tissue is now recognized as metabolically active and a source of adipose tissue-derived hormones and cytokines (adipokines) such as leptin, adiponectin, and inflammatory cytokines.

Elevated leptin levels stimulate breast tumor cell proliferation through several signal transduction pathways and by altering cell-cycle checkpoints via upregulation

**Table 1: Demographic characteristics and reproductive variables of cases and controls**

Characteristic	Cases	Controls
Number of patients	40	40
Age, mean (range)	52 (25-75)	50 (30-70)
Education, <i>n</i> (%)		
No formal education	21 (52.5)	15 (37.5)
Primary school	4 (10)	6 (15)
Secondary school	13 (32.5)	16 (40)
Graduate	1 (2.5)	1 (2.5)
Postgraduate	1 (2.5)	2 (5)
Family history of breast cancer/first degree relative with breast cancer, <i>n</i> (%)	5 (12.5)	2 (5)
Supplementation of vitamins/minerals, <i>n</i> (%)	5 (12.5)	8 (20)
Alcohol consumption, <i>n</i> (%)	0	0
Tobacco, <i>n</i> (%)		
Smoker	0	0
Gutka chewer	1 (2.5)	0
Physical activity, <i>n</i> (%)		
Mild	32 (80)	29 (72.5)
Moderate	3 (7.5)	5 (12.5)
Vigorous	5 (12.5)	6 (15)
Oral contraceptive pill use, <i>n</i> (%)	1 (2.5)	0
Hormone replacement therapy, <i>n</i> (%)	4 (10)	0
Age at menarche (years), <i>n</i> (%)		
≤12	11 (27.5)	9 (22.5)
13-14	24 (60)	28 (70)
≥15	5 (12.5)	3 (7.5)
Parity, <i>n</i> (%)		
Nulliparous status	3 (7.5)	1 (2.5)
1	1 (2.5)	4 (10)
2-3	23 (57.5)	25 (62.5)
≥4	13 (32.5)	10 (25)
Age at first full term birth (years), <i>n</i> (%)		
15-17	15 (40.5)	13 (33.3)
18-20	12 (32.4)	10 (25.6)
21-25	9 (24.3)	11 (28.2)
>25	1 (2.7)	5 (12.8)
Breast feeding, <i>n</i> (%)	31 (77.5)	35 (87.5)
Age at menopause (years), <i>n</i> (%)		
<45	12 (38.7)	12 (37.5)
45-49	11 (35.4)	10 (31.2)
50-54	8 (25.8)	10 (31.2)
≥55	0	0

of cyclin D1 and cyclin-dependent kinase 2.<sup>[7,8]</sup> In contrast to leptin, adiponectin levels are diminished in obesity. Adiponectin via its antagonism of leptin reduces aromatase activity and local estrogen production, signaling through the phosphatidylinositol-3-kinase pathway, and proliferation.<sup>[9,10]</sup> Adiponectin blocks activation of nuclear factor-kappa B by cytokines such as transforming growth factor- $\alpha$  and thus reduces subsequent production of proinflammatory adipocytokines and insulin resistance.<sup>[11]</sup> By upregulating peroxisome

**Table 2: Clinicopathological characteristics of breast cancer cases**

Characteristic	Cases ( <i>n</i> =40)
Duration of symptoms (in months), mean (SD) and range	8.27 (13.17) and 1-72
History of benign breast disease, <i>n</i> (%)	4 (10)
Radiation to chest between age 10 and 30 years, <i>n</i> (%)	0
Side, <i>n</i> (%)	
Left	15 (37.5)
Right	25 (62.5)
Location if present, <i>n</i> (%)	
Upper outer quadrant	18 (45)
Upper inner quadrant	6 (15)
Lower outer quadrant	5 (12.5)
Lower inner quadrant	2 (5)
Central	9 (22.5)
Description of lump, <i>n</i> (%)	
Skin changes	14 (35)
Pain	8 (20)
Nipple discharge	4 (10)
Axillary lymphadenopathy	23 (57.5)
Stage grouping, <i>n</i> (%)	
Stage 0-1B	0
Stage IIA	10 (25)
Stage IIB	9 (22.5)
Stage IIIA	6 (15)
Stage IIIB	4 (10)
Stage IIIC	5 (12.5)
Stage IV	6 (15)
Hormonal receptor status	
ER positive	21 (52.5)
PR positive	15 (37.5)
Her2/neu positive (IHC)	9 (22.5)
Her2/neu positive (FISH)	2 (5)
Grade	
1	0
2	13 (32.5)
3	15 (37.5)

Her2 – Human epidermal growth factor receptor 2; ER – Estrogen receptor; PR – Progesterone receptor; IHC – Immunohistochemistry; FISH – Fluorescence *in situ* hybridization; SD – Standard deviation

proliferator-activated receptor- $\gamma$ , which forms heterodimers with the retinoid X-receptor, adiponectin promotes differentiation and apoptosis through p53-dependent mechanisms.<sup>[12]</sup> Finally, adiponectin upregulates the tumor suppressor liver kinase B1 and increases 5' adenosine monophosphate-activated protein kinase, which in turn blocks activation of the mammalian target of rapamycin pathway and reduces motility and angiogenesis.<sup>[13]</sup>

Serum adiponectin levels and ALR were significantly reduced whereas serum leptin levels were increased in breast cancer cases in comparison to controls which were in agreement with previous studies.<sup>[3,5]</sup> The mean adiponectin

levels of cases ( $8.69 \mu\text{g/ml} \pm 2.95$ ) in the present study were comparable to other studies ( $2\text{--}20 \mu\text{g/mL}$ ).<sup>[14,15]</sup> However, the optimal level of adipokines for breast health and levels that should be considered unhealthy have not been established and vary by race and assay methodology.<sup>[16]</sup>

Neither receptor status (ER, PR, and HER-2/neu receptor) nor aggressiveness of disease (tumor size, nodal metastases, stage, and grade) had an effect on the serum adiponectin levels, leptin levels, or ALR in cases. Some but not all studies have suggested that breast tumors arising in women with hypoadiponectinemia may present a more aggressive phenotype (large size of tumor, higher histological grade, and ER negativity).<sup>[17-19]</sup> Studies have found a significant association of serum adiponectin with either receptor-negative breast cancer<sup>[18,20]</sup> or receptor-positive breast cancer.<sup>[21]</sup> However, there are several studies which have found no significant associations in regard to hormonal receptor status.<sup>[22,23]</sup>

BMI was negatively correlated with serum adiponectin levels and ALR and positively correlated with serum leptin levels and was the only statistically significant independent correlate. In other words, the association of serum adiponectin and serum leptin levels with breast cancer was not independent of measures of adiposity in the present study.

### Limitations

The cross-sectional design of this study meant that there was a potential for selection bias, particularly in the selection

of controls. However, controls came from the same study base as our cases and criteria for inclusion and exclusion were strictly adhered to minimize any influence on results of the study. It has been hypothesized that adiponectin may exert carcinogenic effects through modulation of insulin sensitivity.<sup>[3]</sup> Therefore, another limitation of this study is the lack of information on insulin levels in cases and controls. The results of the study are based on a one-time measurement of serum adipokine levels. However, previous studies have confirmed the stability and reliability of a one-time measure to be high.<sup>[24]</sup> Another limitation of this study is its small sample size.

### Recommendations for future work

The foremost reason why investigators have been attempting to accurately define the link between obesity and breast cancer is understanding that it offers an opportunity at chemoprevention. The interventions that have been tested to raise adiponectin, particularly for overweight or insulin-resistant individuals, include, encouraging weight loss,<sup>[25]</sup> bariatric surgery,<sup>[26]</sup> antidiabetic drugs of the thiazolidinedione class,<sup>[27]</sup> lipid-lowering drugs including statins,<sup>[28]</sup> omega-3 fatty acids,<sup>[29]</sup> and fibrates,<sup>[30]</sup> antihypertensives such as angiotensin-converting enzyme inhibitors<sup>[31]</sup> and beta blockers.<sup>[32]</sup>

### Conclusion

In summary, our results suggest that low serum adiponectin levels, low ALR and high serum leptin levels are associated with breast cancer. BMI was the only statistically significant independent correlate of serum adiponectin, serum leptin and ALR. The inconsistencies in data attempting to define the relationship between obesity and breast cancer reinforce the complexity and multifactorial nature of the relationship.

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Nil.

**Table 3: Adipokine levels in cases and controls**

Characteristic	Cases	Controls	P
Serum adiponectin ( $\mu\text{g/ml}$ ), mean (SD)	8.69 (2.95)	10.15 (3.56)	0.04
Serum leptin (ng/ml), mean (SD)	7.93 (2.90)	6.26 (3.86)	0.03
Adiponectin leptin ratio, mean (SD)	1.91 (3.17)	5.76 (11.92)	0.05

SD – Standard deviation

**Table 4: Multiple linear regression analysis with serum adiponectin, leptin, and adiponectin–leptin ratio as the independent variables**

Variable	Adiponectin ( $\mu\text{g/ml}$ )			Leptin (ng/ml)			Adiponectin leptin ratio		
	Correlation coefficient (r)	SE	P	Correlation coefficient (r)	SE	P	Correlation coefficient (r)	SE	P
ER status	0.21	2.91	0.17	0.200	2.885	0.211	0.22	3.12	0.15
PR status	0.15	2.95	0.33	0.160	2.907	0.321	0.25	3.1	0.11
Her2/neu receptor status	0.03	2.98	0.83	0.030	2.944	0.851	0.09	3.19	0.54
Grade	0.17	2.94	0.27	0.195	2.889	0.226	0.12	3.18	0.42
Stage	0.12	2.96	0.43	0.130	2.920	0.422	0.02	3.21	0.87
Tumour size	0.13	2.96	0.41	0.167	2.904	0.301	0.29	3.07	0.06
Nodal status	0.1	2.97	0.53	0.055	11.860	0.735	0.1	3.19	0.53
BMI	0.33	2.82	0.03*	0.346	2.763	0.028*	0.39	2.94	0.01*
Physical activity	0.12	2.96	0.42	0.133	2.919	0.411	0.12	3.18	0.44
Parity	0.09	2.97	0.57	0.087	2.934	0.589	0.2	3.14	0.2

SE – Standard error; Her2 – Human epidermal growth factor receptor 2; ER – Estrogen receptor; PR – Progesterone receptor; BMI – Body mass index; \*P value for BMI

## Conflicts of interest

There are no conflicts of interest.

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