Association of Serum Adiponectin Levels with Breast Cancer Risk

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ABSTRACT

Purpose: Adiponectin is a peptide hormone secreted from the adipose tissue, affecting the proliferation and insulin sensitivity of various types of cells. Because association of obesity with breast cancer risk is well established, it is possible that adiponectin plays some role in the development of breast cancer. Thus, in the present study, the association of the serum adiponectin levels with breast cancer risk was investigated.

Experimental Design: A case-control study was conducted on 102 breast cancer patients (cases) and 100 healthy women (controls). The serum adiponectin levels of cases and controls were examined in their association with breast cancer risk after adjustment for the various classical risk factors (family history, age at menarche, parity, body mass index, and so forth). In addition, the relationship between the serum adiponectin levels and the various clinicopathological characteristics of breast cancers was studied.

Results: Women in the low tertile of serum adiponectin levels were associated with a significantly (P < 0.005) increased risk for breast cancer compared with women in the high tertile [odds ratio (OR), 3.63; 95% confidence interval (CI), 1.61–8.19]. Such an association was observed both in the premenopausal women (OR, 3.46; 95% CI, 0.89–13.50) and in the postmenopausal women (OR, 3.90; 95% CI, 1.61–8.19]. The frequency of large (>2 cm) tumors and that of high histological grade (2+3) tumors were significantly (P < 0.005 and P < 0.05, respectively) higher in breast cancer patients in the low tertile of the serum adiponectin levels than those in the high and intermediate tertiles.

Conclusions: These results suggest that the low serum adiponectin levels are significantly associated with an increased risk for breast cancer and that tumors arising in women with the low serum adiponectin levels are more likely to show a biologically aggressive phenotype. The association between obesity and breast cancer risk might be partly explained by adiponectin.

INTRODUCTION

The association of BMI1 with breast cancer risk has been well established (1–3). Because estrogens are mostly synthesized in the peripheral adipose tissue through aromatization of androgens derived from the adrenal glands in postmenopausal women (4), it is speculated that women with high BMI are likely to have an increased level of estrogens and then an increased risk for breast cancer. This speculation is supported by several studies that demonstrate the association of BMI with serum estrogen levels as well as the association of serum estrogen levels with breast cancer risk in postmenopausal women (5–11). However, the fact that BMI serves as a risk factor for breast cancer being independent of the serum estrogen levels (5, 11) indicates that enhancement of estrogen biosynthesis in the peripheral adipose tissue is not a sole mechanism through which BMI affects breast cancer risk in postmenopausal women. Furthermore, enhancement of estrogen biosynthesis in the peripheral adipose tissue is unlikely to explain the association between BMI and breast cancer risk in premenopausal women, because estrogens are mostly produced in the ovaries and there is, in fact, no significant association between BMI and the serum estrogen levels in premenopausal women (5). These results strongly indicate the presence of other mechanisms through which BMI affects breast cancer risk than enhancement of estrogen biosynthesis in the peripheral adipose tissue.

Recent studies have disclosed that the adipose tissue is not merely a fat-storing tissue but also an endocrine organ producing various cytokines, including adiponectin. Adiponectin is a peptide hormone secreted from only the adipose tissue, and it belongs to the collectin family (12, 13). This peptide has been shown to play a preventive role in the pathogenesis of atherosclerosis through the inhibition of vascular smooth muscle and endothelial cell proliferation (14, 15) and in the pathogenesis of diabetes through the modulation of glucose and fatty acid metabolism and insulin sensitivity in various stromal and epithelial cells (16–19).

Although the effects of adiponectin on the breast epithelial cells and breast cancer cells have not been studied yet, it is possible that adiponectin affects their growth and differentiation. Interestingly, it is reported that serum adiponectin levels are inversely related to BMI (20–22). This relationship seems to suggest a possible association of the serum adiponectin levels with breast cancer risk. To our knowledge, no report has been

1The abbreviations used are: BMI, body mass index; ER, estrogen receptor; OR, odds ratio; CI, confidence interval.
Serum Adiponectin Levels and Breast Cancer Risk

Informed consents as to the study were obtained from all participants in this study as controls from June 2001 to December 2001. All controls were confirmed as free from breast cancer by physical examination and mammography. Written informed consents as to the study were obtained from all participants.

Materials and Methods

Cases and Controls. Eligible cases were 102 primary breast cancer patients who were treated consecutively with mastectomy or breast-conserving surgery in Osaka University Hospital from March 2000 to March 2001. Blood samples for adiponectin assay were obtained immediately before surgery. Histological diagnosis of breast cancer was confirmed in each case (93 infiltrating ductal carcinomas, 2 noninfiltrating ductal carcinomas, and 7 other types of carcinoma). One hundred healthy women who participated in the breast cancer screening program at the affiliated institutes in Osaka were recruited consecutively in this study as controls from June 2001 to December 2001. All controls were confirmed as free from breast cancer by physical examination and mammography. Written informed consents as to the study were obtained from all participants.

Serum Adiponectin and Estrone Analysis. All blood samples were obtained at fasting early in the morning, and the serum was immediately separated by centrifugation and stored at −20°C until use. Serum adiponectin levels were measured by ELISA as described previously (20), and serum estrone levels were measured by RIA using the kits provided by Diagnostic Systems Laboratories (DSL-8700; Webster, Texas).

ER Assay. ER levels in breast cancers were measured by enzyme immunoassay using the kit provided by Abbott Research Laboratories (Chicago, IL). The cutoff value for ER was defined as 13 fmol/mg protein, according to the manufacturer’s instructions.

Statistical Analysis. Serum adiponectin levels in cases and controls were assessed by Student’s t test. The relationship between the serum adiponectin levels and breast cancer risk was determined using a logistic regression model to obtain the OR and 95% CI, being adjusted for the classical epidemiological risk factors such as age, family history, age at menarche, age at first live birth or nulliparity, and BMI. When the analysis was performed among postmenopausal women, age at menopause was also adjusted in addition to the other risk factors mentioned above. These risk factors were categorized according to those reported previously (23): family history of first-degree relatives (yes or no), age at menarche (≤12, 13, and ≥14), parity (first live birth at ≤23, 24–25, 26–29, ≥30, or nulliparity), BMI (<21.0 kg/m², 21.0 to <23.0 kg/m², and ≥23.0 kg/m²), and age at menopause (≤48, 49–51, and ≥52). The relationship between the serum adiponectin levels and clinicopathological parameters of tumors was assessed using the χ² test. Comparison of the serum adiponectin levels and estrone levels among the various groups was performed using Student’s t test. Pearson correlation statistics were used to determine the correlation between the serum adiponectin and estrone levels in controls. P < 0.05 was considered significant.

RESULTS

Serum Adiponectin Levels and Breast Cancer Risk. The frequencies of epidemiological risk factors in cases and controls are listed in Table 1. There was no significant difference in age, family history, age at menarche, parity, BMI, and age at menopause between cases and controls. Serum adiponectin levels in cases [7.57 ± 0.31 μg/ml (mean ± SE)] were significantly (P < 0.01) lower than those in controls (8.83 ± 0.38 μg/ml; Fig. 1). Controls were divided into the three groups...
The association between the serum adiponectin levels and breast cancer risk is shown in Table 3. Women in the low tertile showed nonsignificant ($P < 0.05$) risk compared with those in the high tertile in the ER-positive cases (OR, 5.92; 95% CI, 1.85–18.90), respectively. **Serum Adiponectin Levels and Clinicopathological Characteristics of Tumors.** Clinicopathological characteristics of tumors arising in women with the low serum adiponectin levels were compared with those in women with the high and intermediate serum adiponectin levels (Table 4). The frequency of large tumors ($>2$ cm) was significantly ($P < 0.005$) higher in women in the low tertile (70%) than those in the high and intermediate tertiles (41%), and the frequency of tumors with high histological grade (2+3) was significantly ($P < 0.05$) higher in women in the low tertile (84%) than those in the high and intermediate tertiles (63%). Other parameters such as lymph
node status and ER status were not significantly different between women in the low tertile and those in the high and intermediate tertiles.

**Correlation between BMI and Serum Adiponectin and Estrone Levels.** The correlation between BMI, serum adiponectin levels, and the serum estrone levels was studied in postmenopausal controls. The serum adiponectin levels in women in the high BMI tertile (≥23.0 kg/m²) were significantly (P < 0.001) lower than those in the low BMI tertile (<21.0 kg/m²; Table 5). In contrast, the serum estrone levels in women in the high BMI tertile (≥23 kg/m²) were significantly (P < 0.005) higher than those in the low BMI tertile (<21.0 kg/m²).

No significant correlation was observed between the serum adiponectin and estrone levels (r = 0.13; P = 0.40; Fig. 2).

**DISCUSSION**

Recent success in a chemoprevention trial (National Surgical Adjuvant Breast and Bowel Project P-1) with tamoxifen seems to have opened the door for a new era when prevention of breast cancer is much more emphasized than treatment of established breast cancer (24). In considering tamoxifen use for prevention, risk assessment of breast cancer is the most important step. The Gail model is usually used for risk assessment of breast cancer (25). However, to predict the breast cancer risk more accurately and to perform chemoprevention more efficiently, it seems to be important to develop new predictive factors for breast cancer risk. In the present study, we have been able to show that the serum adiponectin levels are associated with breast cancer risk both in premenopausal and postmenopausal women and that the low serum adiponectin levels can serve as a significant risk factor, being independent of the classical epidemiological risk factors. These results seem to suggest a possibility that the risk assessment of breast cancer can be performed accurately by incorporating the serum adiponectin levels with the classical epidemiological risk factors. Because the National Surgical Adjuvant Breast and Bowel Project P-1 trial has shown that tamoxifen is effective in reducing the incidence of ER-positive, but not ER-negative, breast cancer (24), it is also important to predict the risk for ER-positive breast cancer to perform chemoprevention with tamoxifen more efficiently. In the present study, the serum adiponectin levels have been shown to be associated with both ER-positive and ER-negative breast cancer risk.

The mechanism through which adiponectin modulates breast cancer risk is currently unknown. However, a lack of correlation between the serum adiponectin levels and the estrone levels seems to indicate that adiponectin is unlikely to modulate breast cancer risk through affecting the serum estrone levels in postmenopausal women. Ideally, serum adiponectin and estrone levels should be compared in premenopausal women, too. However, because blood collection on the synchronous menstrual cycle in premenopausal women is very difficult, we have assayed serum estrone levels only in postmenopausal women in the present study. Adiponectin plays an important role in glucose metabolism (16–19), and a decrease in the serum adiponectin levels is shown to be associated with an increase in the glucose levels (21). Because high glucose levels stimulate the proliferation of cultured breast cancer cells (26), these observations taken together, it is speculated that adiponectin modulates the breast cancer risk through affecting the glucose metabolism. In addition, adiponectin has a direct inhibitory effect on proliferation of vascular smooth muscle cells (14) and myelomonocytic progenitors (27), and, thus, it is also speculated that adiponectin might inhibit the proliferation of breast epithelial cells, so that the low serum adiponectin levels are associated with an increased proliferation of breast epithelial cells, resulting in an increased risk for breast cancer. Interestingly, the low serum adiponectin levels were significantly associated with large tumor size (>2 cm) and high histological grade (2+3), indicating that tumors with high proliferation activity are more likely to develop under the low adiponectin condition. It is well established that obesity is associated with poor prognosis (28, 29). This association might be partly explained by the low serum adiponectin levels seen in obese breast cancer patients.

**Table 4** Association between serum adiponectin levels and clinicopathological characteristics in breast cancer patients

<table>
<thead>
<tr>
<th>Adiponectin level (μg/ml)</th>
<th>≤6.9</th>
<th>&gt;6.9</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>14 (30)</td>
<td>30 (59)</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>33 (70)</td>
<td>21 (41)</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>36 (75)</td>
<td>40 (77)</td>
<td>0.82</td>
</tr>
<tr>
<td>Positive</td>
<td>12 (25)</td>
<td>12 (23)</td>
<td></td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (16)</td>
<td>19 (37)</td>
<td></td>
</tr>
<tr>
<td>2+3</td>
<td>38 (84)</td>
<td>33 (63)</td>
<td>0.02</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20 (44)</td>
<td>30 (61)</td>
<td>0.10</td>
</tr>
<tr>
<td>Negative</td>
<td>25 (56)</td>
<td>19 (39)</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 5** Relationship between BMI and serum adiponectin levels or estrone levels in controls

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Adiponectin (μg/ml)</th>
<th>Estrone (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21.0</td>
<td>4.66 ± 0.70</td>
<td>6.81 ± 1.10</td>
</tr>
<tr>
<td>21.0–23.0</td>
<td>9.48 ± 0.69</td>
<td>9.49 ± 1.38b</td>
</tr>
<tr>
<td>≥23.0</td>
<td>6.97 ± 0.52a</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001 when compared with the BMI <21.0 kg/m² group.  
bp < 0.005 when compared with the BMI <21.0 kg/m² group.

![Fig. 2](https://example.com/fig2.jpg)  
**Fig. 2** Correlation of the serum adiponectin levels and estrone levels in controls (r = 0.13; P = 0.40).
Leptin is a peptide hormone mainly secreted from the adipose tissues, but unlike adiponectin, the serum leptin levels increase in proportion to BMI (30–32). Recently, leptin has been demonstrated to stimulate the proliferation of normal breast epithelial cells and breast cancer cells in vitro (33, 34). Tessitore et al. (35) reported that the serum leptin levels in breast cancer patients were significantly higher than those in healthy controls, indicating that the serum leptin levels can serve as a risk factor for breast cancer. However, Mantzoros et al. (36) were unable to show such an association. Furthermore, Petridou et al. (37) reported that the serum leptin levels were inversely related to breast cancer risk. Thus, the relationship between the serum leptin levels and breast cancer risk is still controversial and remains to be established.

In conclusion, we have shown a significant association between the low serum adiponectin levels and an increased risk for breast cancer. In addition, breast cancers arising in women with the low serum adiponectin levels are more likely to show an aggressive phenotype being exemplified by large tumor size and high histological grade. These results seem to suggest a possibility that the serum adiponectin levels could be a new risk factor for breast cancer and to provide a new insight into understanding of the association between obesity and breast cancer risk. The limitation of the present study lies in that this is a retrospective case-control study and serum samples were obtained from cases with breast cancer. Our preliminary results need to be confirmed by a prospective study including a large number of subjects as well as by the functional analysis of adiponectin through in vitro studies in the future.

REFERENCES


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