Anthropometric measures, plasma adiponectin, and breast cancer risk

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Abstract

Adiponectin is a peptide hormone secreted exclusively by adipocytes, and obesity is an established risk factor for breast cancer. We have, thus, evaluated the associations of anthropometric measures of adiposity and adiponectin with the development of breast cancer in a case–control study. Questionnaire information, anthropometric measures, and blood samples were taken before treatment from 244 incident cases with breast cancer, including 141 premenopausal and 103 postmenopausal cases, and 244 controls admitted for health examination at the Tri-Service General Hospital, Taipei between 2004 and 2005. Plasma levels of adiponectin were measured by RIA. The relationship between anthropometric measures of adiposity and breast cancer risk was modified by menopausal status, with a significant increase in risk observed in postmenopausal but not premenopausal women. Moreover, a fairly robust inverse association of adiponectin with the risk was observed only in postmenopausal women (adjusted odds ratio (OR), 0.55; 95% confidence interval (CI), 0.23–0.97), but not in premenopausal women. Additionally, the plasma adiponectin levels tended to be inversely associated with estrogen receptor (ER)-positive (adjusted OR, 0.53; 95% CI, 0.27–0.98) but not ER-negative breast tumors. Furthermore, the associations of adiponectin with breast cancer risk overall and by menopausal and ER status remained after adjustment for obesity indices. These results suggest that adiponectin may have an independent role in breast carcinogenesis, particularly in the postmenopausal and ER-positive breast cancer risk.

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Introduction

Evidence is accumulating that obesity and insulin resistance are implicated in the etiology of breast cancer (Rose et al. 2004). Adipose tissue is the site of peripheral aromatization of adrenal androgens to estrogens (Bulun et al. 1994), and obesity-related elevations in estrogens have been associated with increased breast cancer risk (Yager & Davidson 2006). A strong association of obesity with insulin resistance has also been well-documented (Haslam & James 2005). There is evidence that insulin and insulin-like growth factors may play an important mitogenic role in the pathogenesis of breast cancer (Rose et al. 2004, Fletcher et al. 2005).

It has been indicated that the adipose tissue is not only a fat-storing tissue but also an endocrine organ secreting various cytokines, including adiponectin. Adiponectin is a recently identified adipocyte-secreted hormone (Chandran et al. 2003). Adiponectin stimulates the sensitivity of peripheral tissues to insulin, and its circulating levels are low in conditions characterized by insulin-resistant states, such as obesity and...
Materials and methods

Case and control selection

This case–control study was conducted at the Tri-Service General Hospital, Taipei, Taiwan, from January 2004 to December 2005. Based on the hospital chart number, the cases involved 244 women consecutively selected from subjects with a first confirmed histopathologic diagnosis of breast carcinoma in the age range of 22–87 years. The histopathological profile included 173 cases of infiltrating ductal carcinoma and 71 cases of intraductal or intralobular carcinoma. Overall, 44 of the cases were in situ and 195 of the cases were invasive. In addition, there were 141 premenopausal and 103 postmenopausal cases with breast cancer. The data on the status of estrogen receptor (ER) of breast tumors were obtained from the Department of Pathology of the Tri-Service General Hospital that routinely conduct biochemical assays to determine the ER status of tumor tissues from breast cancer patients. Accordingly, ER status was known for 205 (84%) out of the 244 cases. For women with known receptor status, 150 (73%) were ER-positive and 55 (27%) were ER-negative. Additionally, the proportion of ER-positive in pre- and postmenopausal cases with breast cancer was 74% and 72%, respectively. Control subjects comprising individuals without a history of cancer were simultaneously recruited from the health examination clinics of the same hospital during the same study period. One control subject was matched to each case by menopausal status, date of enrollment (study period. One control subject was matched to each examination clinics of the same hospital during the same of cancer were simultaneously recruited from the health Control subjects comprising individuals without a history cases with breast cancer was 74% and 72%, respectively. proportion of ER-positive in pre- and postmenopausal cases were in situ and 195 of the cases were invasive. In addition, there were 141 premenopausal and 103 postmenopausal cases with breast cancer. The data on the status of estrogen receptor (ER) of breast tumors were obtained from the Department of Pathology of the Tri-Service General Hospital that routinely conduct biochemical assays to determine the ER status of tumor tissues from breast cancer patients. Accordingly, ER status was known for 205 (84%) out of the 244 cases. For women with known receptor status, 150 (73%) were ER-positive and 55 (27%) were ER-negative. Additionally, the proportion of ER-positive in pre- and postmenopausal cases with breast cancer was 74% and 72%, respectively. Control subjects comprising individuals without a history of cancer were simultaneously recruited from the health examination clinics of the same hospital during the same study period. One control subject was matched to each case by menopausal status, date of enrollment (±3 months), and duration of fasting (±4 h). There were 244 case–control sets included in this study.

Collection of questionnaire data and blood specimens

Once case patients and control subjects agree to participate, written informed consent was obtained from all subjects. The research protocol was approved by the Institutional Review Board at the Tri-Service General Hospital, Taipei. All participants underwent personal interview administered by well-trained interviewers in conformance with institutional guidelines for studies including human subjects. Data were collected on sociodemographic characteristics, men- strual and reproductive history, menopausal status, lifestyle behaviors and medical history as well as family history of breast, and other cancers. More specifically, in this study, 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. Immediately after the interview, a 10 ml blood sample was drawn into coded EDTA-treated tubes and centrifuged at 1467 g for 10 min at room temperature within 10 h of collection. Plasma, buffy coat, and red blood cells were separated and stored at −70 °C until subsequent analysis. Because questionnaire data and biospecimens were obtained prior to cases’ acceptance with surgery and radio- or chemotherapy, any influence of treatment is unlikely.

Anthropometric measurements and laboratory analysis of plasma adiponectin levels

Participants reported information regarding height and weight. Body mass index (BMI), as an indicator of generalized obesity, was calculated as weight in kilograms divided by the square of height in meters. In addition, measurements of waist and hip circumferences were performed by trained clinical staff using standardized techniques. Waist girth was determined with a measuring tape placed horizontally around the midpoint between the iliac crest and lower margin of the ribs. Hip girth was the maximum circumference around the buttocks posteriorly and the symphysis pubis anteriorly. As a result, waist-to-hip ratio (WHR) represents a measure of central adiposity. Plasma adiponectin concentrations were measured in a single run using a commercially available RIA kit (R&D systems Inc., Minneapolis, MN, USA) according to manufacturer’s instructions. Adiponectin standards were prepared using recombinant human adiponectin, with a sensitivity of 0.25 ng/ml and intra- and inter-assay coefficients of variation of 3.53% and 6.50%, respectively. All matched case–control blood samples were handled identically and assayed in the same analytical run. The blood samples were labeled by number only and ordered randomly within each case–control pair. Accordingly, laboratory personnel were unaware of the case–control status.

Statistical analysis

Differences between cases and controls in age at menarche, age at first full-term pregnancy, age at
menopause, and parity numbers were tested using the Student’s $t$-test. Because the average quantity of cigarettes and alcohol consumed by Chinese women is not large in Taiwan, habitual cigarette smoking was defined as smoking cigarettes at least once a week for more than 1 year. Similarly, habitual alcohol drinking was defined as consuming any alcoholic beverage at least once a week for more than 1 year. Distributions in cigarette smoking and alcohol intake status, menopausal status, as well as use of oral contraceptives between cases and controls were evaluated using the chi squared test. Conditional logistic regression, which preserves the matching of cases and controls, was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the plasma adiponectin levels and breast cancer risk.

## Results

The baseline characteristics of cases and controls are summarized in Table 1. The mean age ($\pm$ s.d.) of the cases and controls was 51.5($\pm$ 11.4) and 48.4($\pm$ 7.9) years, respectively. There were no significant differences between cases and controls in terms of age at menarche (13.9±1.6 vs 13.6±1.5 years), age at first full-term pregnancy (25.9±4.2 vs 26.7±3.7 years), age at menopause (49.5±5.3 vs 48.9±4.8 years), and parity number (2.6±1.4 vs 2.2±0.8). No significant differences were also found between cases and controls in terms of the proportions of women with cigarette smoking (7.8% vs 4.9%), alcohol drinking (11.1% vs 13.5%), and use of oral contraceptives in premenopausal period or hormone replacement therapy in postmenopausal period (15.9% vs 15.9%). When subjects were subdivided by menopausal status, cases and controls were similar in their distribution of most of the aforementioned variables. However, postmenopausal cases with breast cancer were significantly older than their matched controls ($P=0.0012$).

The distribution of anthropometric characteristics and ORs for breast cancer by logistic regression is shown in Table 2. Overall, a measure of central adiposity as reflected by WHR was significantly related to breast cancer risk (adjusted OR, 2.17; 95% CI, 1.42–3.32; between subjects in the top tertile and those below the highest tertile). Additionally, in the subgroup analysis stratified by menopausal status, we found that the risk for breast cancer increases with larger anthropometric measures including BMI (adjusted OR, 2.94; 95% CI, 1.53–5.68), waist circumference (adjusted OR, 2.02; 95% CI, 1.05–3.91), and WHR (adjusted OR, 3.64; 95% CI, 1.88–7.05) in postmenopausal women. However, no any anthropometric characteristic was significantly associated with risk in premenopausal women.

To evaluate the relationships of plasma adiponectin levels with anthropometric measures of adiposity, we performed a correlation analysis among control subjects. Plasma adiponectin was significantly inversely correlated with BMI (Spearman $r=-0.32$, $P=0.0001$), waist circumference ($r=-0.35$, $P=0.01$), and WHR ($r=-0.32$, $P=0.0001$). We further categorized plasma adiponectin as high or low levels based on the 75 percentile in the control group for subsequent analyses. Table 3 shows the association of breast cancer with plasma adiponectin levels. In a conditional logistic regression model that were adjusted for age at enrollment, date at enrollment, fasting, and menopausal status as well as BMI, and WHR, women in the high adiponectin level had a

### Table 1 Characteristics of breast cancer cases and their matched controls at enrollment

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>All</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cases Controls</td>
<td>Cases Controls</td>
<td>Cases Controls</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>141</td>
<td>141</td>
<td>103</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at enrollment (years)</td>
<td>44.4 (6.3)</td>
<td>43.7 (5.5)</td>
<td>61.2 (9.4)</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>13.5 (1.4)</td>
<td>13.3 (1.4)</td>
<td>14.5 (1.7)</td>
</tr>
<tr>
<td>Age at first birth (years)</td>
<td>27.5 (3.7)</td>
<td>27.4 (3.7)</td>
<td>24.0 (4.0)</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td></td>
<td></td>
<td>49.5 (5.3)</td>
</tr>
<tr>
<td>Number of parity</td>
<td>1.9 (0.9)</td>
<td>2.0 (0.7)</td>
<td>3.3 (1.5)</td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>9.9</td>
<td>5.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>14.9</td>
<td>12.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Premenopausal oral contraceptives use or postmenopausal HRT</td>
<td>14.2</td>
<td>15.6</td>
<td>18.4</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy.
non-significant 25% lower risk of breast cancer than those in the low level (adjusted OR, 0.75; 95% CI, 0.42–1.34). In the subset analysis according to the menopausal status, premenopausal women in the high adiponectin level showed non-significant decrease in breast cancer risk when compared with those in the low level (adjusted OR, 0.84; 95% CI, 0.46–1.52), while postmenopausal women in the high level showed a significantly decreased risk for breast cancer compared with those in the low level (adjusted OR, 0.55; 95% CI, 0.23–0.97).

The association between the plasma adiponectin levels and breast cancer risk according to clinicopathological characteristics in breast cancer patients is shown in Table 4. A statistically significantly inverse association between adiponectin levels and breast cancer risk was observed in ER-positive (adjusted OR, 0.53; 95% CI, 0.27–0.98) but not ER-negative breast cancer patients. Furthermore, no significant relationship between plasma levels of adiponectin and breast cancer risk was observed in the subset analysis according to the histology of breast tumors.
Discussion

Data from the present study confirm previous findings that the relationship between anthropometric measures of adiposity and breast cancer risk was modified by menopausal status, with higher BMI, waist circumference, and WHR associated with increased risk for postmenopausal women (Ng et al. 1997, Huang et al. 1999, Shu et al. 2001, Morimoto et al. 2002, Harvie et al. 2003, Lahmann et al. 2004, Modugno et al. 2006, Rinaldi et al. 2006). The possible biological mechanism underlying excess adiposity and postmenopausal breast cancer risk is that increased adiposity tends to be associated with higher circulating levels of estrogens through greater peripheral conversion of androgens to estrogens by aromatase in adipose tissue among postmenopausal obese women (Silteri 1987, Potischman et al. 1996). In addition, excess adiposity, especially increased abdominal fat, causes insulin resistance and chronically elevated blood insulin levels, which in turn lower the hepatic synthesis and blood levels of sex hormone-binding globulin (SHBG; Kirschner et al. 1990, Kaaks 1996, Calle & Kaaks 2004). The corresponding hyperestrogenic state resulting from increase in non-SHBG-bound bioactive estriadiol may contribute to increased risk for breast cancer.

As obesity has been associated with the development of breast cancer, adipocytokines, a group of polypeptide growth factors and cytokines which are produced exclusively by adipose tissue, may underlie the association between obesity and breast cancer risk. Adiponectin is a protein hormone secreted exclusively by adipocytes (Chandran et al. 2003), and circulating adiponectin levels are inversely associated with the risk of obesity-related malignancies, including endometrial cancer (Petridou et al. 2003, Dal Maso et al. 2004, Soliman et al. 2006), breast cancer (Miyoshi et al. 2003, Mantzoros et al. 2004, Tworoger et al. 2007), colon

<table>
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<tr>
<th>Table 3</th>
<th>Relationship between plasma adiponectin levels and breast cancer risk</th>
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<tbody>
<tr>
<td>Adiponectin level (μg/ml)</td>
<td>Cases no. (%)</td>
</tr>
<tr>
<td>All women</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 14.05)</td>
<td>190 (77.9)</td>
</tr>
<tr>
<td>High (&gt; 14.05)</td>
<td>54 (22.1)</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 13.37)</td>
<td>111 (78.7)</td>
</tr>
<tr>
<td>High (&gt; 13.37)</td>
<td>30 (21.3)</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 15.69)</td>
<td>90 (87.4)</td>
</tr>
<tr>
<td>High (&gt; 15.69)</td>
<td>13 (12.6)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
*Categorized by the third quartile value in the control group.
*Adjusted for age at enrollment, date at enrollment, fasting status, menopausal status, body mass index, and waist-to-hip ratio.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Association of plasma adiponectin levels with breast cancer risk according to clinicopathological characteristics in breast cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin level (μg/ml)*</td>
<td>Cases no. (%)</td>
</tr>
<tr>
<td>ER-positive</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 15.02)</td>
<td>129 (86.00)</td>
</tr>
<tr>
<td>High (&gt; 15.02)</td>
<td>21 (14.00)</td>
</tr>
<tr>
<td>ER-negative</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 13.23)</td>
<td>37 (67.27)</td>
</tr>
<tr>
<td>High (&gt; 13.23)</td>
<td>18 (32.73)</td>
</tr>
<tr>
<td>In situ cancers</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 15.37)</td>
<td>33 (75.00)</td>
</tr>
<tr>
<td>High (&gt; 15.37)</td>
<td>11 (25.00)</td>
</tr>
<tr>
<td>Invasive cancers</td>
<td></td>
</tr>
<tr>
<td>Low (≤ 13.95)</td>
<td>154 (78.97)</td>
</tr>
<tr>
<td>High (&gt; 13.95)</td>
<td>41 (21.03)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
*Categorized by the third quartile value in the control group.
*Adjusted for age at enrollment, date at enrollment, fasting status, menopausal status, body mass index, and waist-to-hip ratio.
cancer (Wei et al. 2005), and leukemia (Petridou et al. 2006). Similar to previous studies (Miyoshi et al. 2003, Mantzoros et al. 2004, Tworoger et al. 2007), the current study showed that plasma adiponectin levels are inversely associated with breast cancer risk.

Interestingly, the results of this study demonstrate an inverse association of adiponectin with the risk of postmenopausal but not premenopausal breast cancer, which were in agreement with previous studies (Mantzoros et al. 2004, Tworoger et al. 2007). However, Miyoshi et al. (2003) conducted a case–control study on 102 breast cancer patients and 100 healthy women and observed a similar association by menopausal status. The authors are unable to explain fully the discrepant findings between studies. It has recently emerged that the bioactivity of adiponectin is dependent on its isoform (Trujillo & Scherer 2005) and ethnic variation in adiponectin isoform distribution has been documented (Retnakaran et al. 2006). Thus, it is reasonable to hypothesize that the inconsistent results may be due to differences in ethnicity between studies. Alternatively, one could hypothesize that discrepancies between studies may relate to differences in lifestyle factors between populations. The apparent differences in the association between adiponectin levels and breast cancer risk in pre- and postmenopausal periods need to be studied further. Indeed, previous epidemiological studies have shown an association of obesity and insulin resistance mainly with postmenopausal breast cancer (Stoll 2002, Michels et al. 2003). Finding a significant inverse relationship between adiponectin and breast cancer risk among postmenopausal women in this and previous studies (Mantzoros et al. 2004, Tworoger et al. 2007) provides further support for the importance of adiponectin in the pathogenesis of malignancies associated with obesity-induced insulin resistance and hyperinsulinemia.

Moreover, the plasma adiponectin levels were found to be inversely associated with ER-positive but not ER-negative breast cancer risk in the present investigation. Although most epidemiological research has viewed breast cancer as a single disease that is associated with a common set of risk factors, a recent systematic review of the literature has provided evidence that breast cancer are heterogenous (Althuis et al. 2004), which is in agreement with clinical, pathologic, and molecular evidence (Tavassoli 2003). That is, hormonal factors including reproduction-related exposure and postmenopausal obesity tended to be associated with increased risk of ER-positive but not ER-negative breast cancer (Althuis et al. 2004). Moreover, adiponectin has been shown to be inversely associated with estrogen levels (Gavrila et al. 2003). Thus, it is reasonable to speculate that adiponectin modulates the hormone-related breast cancer risk.

The mechanism through which adiponectin modulate breast cancer risk is currently unknown. It has been noted that adiponectin stimulates the sensitivity of peripheral tissue to insulin, and decreased levels of adiponectin are associated with increased serum insulin levels, which accompany insulin resistance (Cnop et al. 2003). Insulin has been shown to stimulate the proliferation of breast cancer cells by binding and signaling through the insulin and insulin-like growth factor I (IGF-I) receptors (Milazzo et al. 1992, Lai et al. 2001). In addition, insulin may synergize with the mitogenic effects of estrogen (van der Burg et al. 1988) and may also upregulate the expression of vascular endothelial growth factor (VEGF), a potent angiogenic agent that is secreted by breast cancer cells (Bachelder et al. 2002). Moreover, adiponectin has been inversely associated with estrogen levels (Gavrila et al. 2003). It remains possible that adiponectin may influence breast cancer risk by altering circulating estrogen levels. It is thus reasonable to hypothesize that the reduced adiponectin levels increase the risk of postmenopausal breast cancer and ER-positive breast tumors through a mitogenic effect of hyperinsulinemia and increased IGFs and estrogen levels as well as by upregulating VEGF. Furthermore, it has been shown that adiponectin potently inhibits endothelial cell proliferation and migration, and induces a cascade of activation of caspases-8, -9, and -3, which leads to cell death (Brakenhielm et al. 2004). Additionally, it has been found that treatment with adiponectin is able to modulate apoptosis of human breast cancer cells in vitro (Korner et al. 2006, Pfeiler et al. 2006) and may be involved in cell signaling pathways associated with carcinogenesis (Kelesidis et al. 2006). These findings suggest other possible mechanisms underlying reduced adiponectin and breast cancer risk.

Of particular note, the associations between plasma adiponectin concentrations and breast cancer risk overall and by menopausal and ER status remained after adjustment for obesity indices in the current study. In other words, the inverse associations with adiponectin level were independent of measures of adiposity. Likewise, the associations between measures of adiposity and breast cancer risk remained after adjustment for plasma adiponectin levels. These results seem to suggest a possibility that obesity and adiponectin have independent roles in breast cancer risk and the two mechanisms, possibly reflecting excess estrogen levels and insulin resistance, have multiplicative effects in breast carcinogenesis.
Although our study was hospital based, it is unlikely that bias and confounding substantially influenced the main findings. The catchment areas of cases and controls were similar, and interview and blood collection were made in the majority of study subjects on the first day of hospital admission and for cancer cases always before surgical or radiation treatment. In addition, the distributions of plasma adiponectin among cases and controls in this study were similar to findings from a previous Taiwanese study (Chen et al. 2005). The limitation of the present study lies in that this is a case–control study, and blood samples were obtained from cases with breast cancer. In addition, it has been hypothesized that adiponectin may exert carcinogenic effects through modulation of insulin sensitivity (Kelesidis et al. 2006). A limitation of this study is that information on insulin levels is not available. More studies to confirm and expand on these findings should be undertaken. Another limitation of this study was the availability of only a one-time blood measurement. However, previous studies showed that the stability and reliability of a one-time measure (as in this study) to be high (Pischon et al. 2003), and circulating levels do not appear to be affected significantly by either fasting or oral intake (Gavrila et al. 2003). Thus, any random error in the assays would tend to lead to underestimation of the true association.

In conclusion, the findings of this study indicate an important role of adiponectin in the postmenopausal and ER-positive breast cancer risk. These associations were independent of measures of adiposity. More studies to confirm and expand on these findings should be undertaken, and mechanistic studies to fully elucidate the mechanisms underlying adiponectin’s effects should be pursued in future studies.

Acknowledgements
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