RESEARCH ARTICLE

Relation of Serum Adiponectin Levels and Obesity with Breast Cancer: A Japanese Case-Control Study

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Abstract

Background: It is known that obesity is one of the risk factors for breast cancer although the association may differ between ethnic groups and with the menopausal status. Recently obesity-related risk factors including serum adiponectin and insulin levels have been analyzed together with BMI in association with breast cancer risk. Materials and Methods: We measured serum high molecular weight (HMW) adiponectin and insulin levels in a hospital based case-control study, including 66 sets of Japanese female breast cancer cases and age and menopausal status matched controls. Serum levels of HMW adiponectin, insulin levels and body mass index (BMI) were examined in association with breast cancer risk with adjustment for the various known risk factors by menopausal status. Results: Women in the highest HMW adiponectin levels showed significant reduced risk of breast cancer in both pre and postmenopausal women (odds ratio (OR), 0.01; 95% confidence interval (CI), 0.00-0.26 and 0.13; 0.03-0.57, respectively). Lower BMI showed decreased breast cancer risk in both pre and postmenopausal women (OR, 0.04; 95% CI, 0.00-0.69, OR, 0.28; 95% CI, 0.07-1.11, respectively). Conclusions: These results indicated that higher serum HMW adiponectin levels and lower BMI are associated with a decreased breast cancer risk in both pre and postmenopausal women in Japan, adding evidence for the obesity link.

Keywords: Breast cancer - adiponectin - obesity - ethnicity - menopausal status - Japanese women

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Introduction

Obesity has been known as one of the risk factors for breast cancer (Lukanova et al., 2006), especially in postmenopausal women (Cheraghi et al., 2012; Dalamaga, 2013). However, the association of increased BMI with breast cancer risk is strong in Asia-Pacific populations in both pre and postmenopausal women, while this association is observed mainly in postmenopausal women in western populations (Renehan et al., 2008).

Obesity-related protein, adiponectin, seems to be involved in the relationship with breast cancer. Adiponectin is an adipocyte-secreted protein (Hu et al., 1996; Nakano et al., 1996), known to have anti-atherogenic, anti-diabetic, and anti-inflammatory actions (Trujillo et al., 2005). Adiponectin circulates in plasma in three forms, trimer, hexamer and high molecular weight (HMW) forms (Pajvani et al., 2003). Among different forms HMW adiponectin is considered the active form of the hormone (Barb et al., 2007). Some evidences are revealing that HMW adiponectin is significant as it correlates well with various metabolic disorders (Pajvani et al., 2004). It is known that serum adiponectin levels are inversely related to BMI (Arita et al., 1999; Yang et al., 2002). Additionally, adiponectin has been inversely related to estrogen levels (Gavrila et al., 2003), therefore it is possible that adiponectin may influence breast cancer risk by altering circulating estrogen levels. In epidemiological studies, it has shown that decreased adiponectin levels were observed in breast cancer patients (Miyoshi et al., 2003; Mantzoros et al., 2004; Rose et al., 2004; Chen et al., 2006). However, the mechanism how adiponectin modulates breast cancer risk remains unknown.

The association of obesity with insulin resistance has been also well documented (Mantzoros et al., 1995). Overweight and adiposity are directly correlated with insulin resistance. The stimulation of pancreatic insulin secretion by adiponectin causes hyperinsulinemia, which leads to lower insulin sensitivity (Arita et al., 1999). Chronic hyperlipidemia is associated with increased ovarian estrogen production and increased free estradiol levels (Calle and Kaaks, 2004), which modifies circulating

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estrogen levels. However, the associations between insulin levels and breast cancer risk from epidemiological studies are still not clear (Jernstrom and Barrett-Connor, 1999; Muti et al., 2002: Mink et al., 2002).

In vitro studies, biomarkers for breast cancer have an impact on the response of human breast cancer cell lines to adiponectin (Kang et al., 2005; Grossmann et al., 2008; Grossmann et al., 2010), these studies may indicate the complex interaction of the breast cancer cell line with respect to response to adiponectin.

Previously we have reported that serum HMW adiponectin levels were inversely associated with breast cancer risk (Minatoya et al., 2013). In this study, we present analyses of serum HMW adiponectin, insulin levels and BMI on breast cancer risk based on 66 sets of age and menopausal status matched case-control study.

Materials and Methods

Cases and controls

We recruited patients with newly diagnosed and histologically confirmed breast cancer from Sapporo Medical University hospital from September 2012 to July 2013. Patients with present neoplastic disease at any other site, previous breast cancer, other major chronic disease, or diabetic were excluded from the study. Potential controls were recruited among hospitalized women in Sapporo Medical university hospital from December 2012 to April 2012 for cardiovascular disease, hypertension, arrhythmia, nephritis, nephrosis, or similar conditions and showed no evidence of breast cancer and diabetic. One control subject was matched to each case on the basis of age (within 3 years) and menopausal status. There were 66 case-control sets included in this study.

Ethics

The study protocol and procedures were approved by the Institutional Review Boards at Sapporo Medial University Hospital. All participants provided informed consent.

Data collection

Information on breast cancer risk factors was obtained by a self-administrated questionnaire of comparable format including information such as demographic, anthropometric, and reproductive variables. Clinical information including the primary tumor characteristics, surgical procedure, and adjuvant treatment was obtained from medical record of each object. Medical history including previous history of breast cancer and diabetics was used from medical record as well.

Laboratory methods

All blood samples were obtained after fasting early in the morning. Blood samples of breast cancer patients were obtained after operation and under treatment of adjuvant therapies, radiation therapies and/or hormone therapies. All available serum samples were analyzed blinded as to case-control status for insulin and HMW adiponectin. Insulin and HMW adiponectin levels were measured using chemiluminescent enzyme immunoassay (CLEIA) with sensitivities of 0.31 μIU/ml and 0.20 μg/ml, respectively. All analyses were performed at the SRL (Tokyo, Japan).

Statistical analysis

Descriptive characteristics of the group variables are expressed as mean (standard deviation; SD) in the tables. The p-values of continuous variables were determined by unpaired t-tests and of categorical variables were determined by chi-square tests. For analyses of breast cancer risk, cases and controls were stratified by menopausal status and were distributed into tertile groups based on the distribution of serum HMW adiponectin and insulin levels within the control population and the ORs and 95% CIs were obtained by using conditional logistic regression models. The models were modified for age at menarche, parity, oral contraceptive (OC) /hormone replacement therapy (HRT) use, alcohol intake, tobacco use and BMI. Similarly cases and controls were divided into tertile groups based on BMI of the control population for analysis of breast cancer risk. The p-values for test trend were determined by modeling log-transformed continuous variables. All the statistical analyses were performed by SPSS version 19.0 (SPSS Inc., Chicago, IL). All p-values were two-sided and $p<0.05$ was considered significant.

Results

Table 1 shows demographic, anthropometric, reproductive and biochemical characteristics of cases and controls stratified by menopausal status. BMI is higher in cases compared with controls in both pre and postmenopausal women. Age at menarche is younger in cases compared with controls in both pre and postmenopausal women but the difference is not statistically significant. Serum HMW adiponectin levels are significantly higher in controls in both pre and postmenopausal women ($p=0.015$ and $p=0.001$, respectively).

Table 2 shows the relationships between BMI, serum HMW adiponectin and insulin levels and breast cancer risk stratified by menopausal status. For BMI, there is an inverse association with breast cancer risk in both pre and postmenopausal women (Ptrend=0.018 and Ptrend=0.043, respectively). Especially in premenopausal women, breast cancer risk is significantly decreased in the lowest tertile of BMI ($p=0.027$). For serum HMW adiponectin levels, an inverse association with breast cancer risk is observed in both pre and postmenopausal women (Ptrend=0.001 and Ptrend=0.014, respectively). The highest tertile of serum HMW adiponectin levels show significant decrease in breast cancer risk in both pre and postmenopausal women ($p=0.008$ and $p=0.007$, respectively). For serum insulin levels, the highest tertile showed decreased breast cancer risk on both pre and postmenopausal women, but difference is not statistically significant. Overall there is no clear association with breast cancer risk in either pre or postmenopausal women.

It was found that serum HMW adiponectin levels were inversely related to BMI ($r=-0.471$ for premenopausal women, $r=-0.323$ for postmenopausal women) with

Table 1. Characteristics of Breast Cancer Cases and their Matched Controls

	Premenopausal			Postmenopausal		
	Case (N=22)	Control (N=22)	p value[d]	Case (N=44)	Control (N=44)	p value[d]
Age at menarche (yrs)	12.0 (1.2)	12.6 (2.3)	0.255	13.6 (2.0)	13.9 (1.6)	0.334
Age at menopause[c] (yrs)				49.9 (5.2)	48.7 (4.1)	0.234
Parity[a]	1.9 (0.6)	2.0 (0.7)	0.523	2.1 (0.8)	2.1 (0.7)	0.741
Age at first birth[a] (yrs)	26.6 (3.6)	27.5 (3.7)	0.534	25.3 (6.0)	24.9 (3.6)	0.733
Alcohol intake			0.764			0.654
Never	10 (45.5%)	11 (50.0%)		27 (61.4%)	27 (61.4%)	
Former	1 (4.5%)	1 (4.5%)		0 (0.0%)	4 (9.1%)	
Current	11 (50.0%)	10 (45.5%)		17 (38.6%)	13 (29.5%)	
Smoking			0.467			0.639
Never	10 (45.5%)	12 (54.5%)		30 (68.2%)	28 (63.6%)	
Former	6 (27.3%)	6 (27.3%)		10 (22.7%)	11 (25.0%)	
Current	6 (27.3%)	4 (18.2%)		4 (9.1%)	5 (11.4%)	
OC[b]/HRT[c] use	1 (4.5%)	4 (18.2%)	0.161	1 (2.3%)	4 (9.1%)	0.179
BMI (kg/m^2)	22.1 (2.7)	21.2 (3.9)	0.369	22.9 (3.5)	21.8 (4.2)	0.18
HMW Adiponectin (μg/ml)	4.2 (1.8)	7.6 (5.9)	0.015*	5.2 (3.6)	9.2 (6.7)	0.001*
Insulin (μIU/ml)	5.4 (3.0)	5.4 (3.5)	0.942	8.8 (8.8)	8.5 (7.0)	0.878

*p<0.05 is considered significant; Mean (SD) or number (%); [a]Not including nulliparous women; [b]Premenopausal women only; [c]Postmenopausal women only; [d]Chi-square test for categorical variables or unpaired t-test for continuous variables

Table 2. Relationship between BMI, HMW Adiponectin and Insulin Levels and Breast Cancer Risk Stratified by Sex-Menopausal Status

Premenopausal	Case (%)	Control (%)	OR (95% CI)[a]
BMI (kg/m^2)			
<19.6	2 (9.1%)	7 (31.8%)	0.04* (0.00-0.69)
≥19.6, <22.5	9 (40.9%)	8 (36.4%)	1.00
≥22.5	11 (50.0%)	7 (31.8%)	1.17 (0.23-6.10)
P for trend[c]			0.018*
HMW Adiponectin level (μg/ml)			OR (95% CI)[b]
<3.67	9 (41.0%)	7 (31.8%)	1.00
≥3.67, <8.99	12 (54.5%)	7 (31.8%)	0.75 (0.11-5.11)
≥8.99	1 (4.5%)	8 (36.4%)	0.01* (0.00-0.26)
P for trend[c]			0.001*
Insulin level (μIU/ml)			OR (95% CI)[b]
<3.52	6 (27.3%)	7 (31.8%)	1.00
≥3.52, <6.88	10 (45.5%)	8 (36.4%)	0.88 (0.05-3.73)
≥6.88	6 (27.3%)	7 (31.8%)	0.44 (0.13-5.80)
P for trend[c]			0.695
Postmenopausal			
BMI (kg/m^2)			OR (95% CI)[a]
<19.1	4 (11.6%)	14 (31.8%)	0.28 (0.07-1.11)
≥19.1, <22.3	15 (37.2%)	14 (31.8%)	1.00
≥22.3	25 (51.2%)	16 (36.4%)	1.39 (0.50-.3.86)
P for trend[c]			0.043*
HMW Adiponectin level (μg/ml)			OR (95% CI)[b]
<4.82	26 (59.1%)	14 (31.8%)	1.00
≥4.82, >9.92	14 (31.8%)	15 (34.1%)	0.46 (0.15-1.47)
≥9.92	4 (9.1%)	15 (34.1%)	0.13* (0.03-0.57)
P for trend[c]			0.014*
Insulin level (μIU/ml)			OR (95% CI)[b]
<4.42	14 (31.8%)	14 (31.8%)	1.00
≥4.42, >10.50	21 (47.7%)	16 (36.4%)	0.96 (0.32-2.88)
≥10.50	9 (20.5%)	14 (31.8%)	0.43 (0.12-1.51)
P for trend[c]			0.996

* p<0.05 is considered significant; [a]Adjusted for age at menarche, smoking, alcohol intake, parity, and OC/HRT use; [b]Adjusted for age at menarche, smoking, alcohol intake, parity, OC/HRT use, and BMI; [c]Basedon the wald X^2 test of log-transformed continuous variables

statistical significance (p=0.001, p=0.002, respectively).

Discussion

Obesity is a well-known risk factor for breast cancer and our result supported it. Most studies focused on BMI as a marker of general obesity and demonstrated an overall increased risk of postmenopausal breast cancer in overweight/obese population among all ethnic groups (Wenten et al., 2002; Kuriyama et al., 2005; Tehard and Clavel-Chapelon, 2006; Iwasaki et al., 2007; Berstad et al., 2010; Kawai et al., 2010; Sarkissyan et al., 2011). Obesity has been associated with increasing estrogen due to increased peripheral aromatization of adrenal androgens in adipose tissue among postmenopausal women (Travis and Key, 2003; Renehan et al., 2008) However, BMI serves as a breast cancer risk factor independent of serum estrogen levels (Verkasalo et al., 2001), suggesting that mechanisms other than estrogen stimulation of the breast may influence breast cancer risk.

In premenopausal women, studies among Asian population showed inconsistent results and several studies suggested that higher BMI may be associated with an increased risk for premenopausal breast cancer (Kuriyama et al., 2005; Wu et al., 2006; Mathew et al., 2008; Kawai et al., 2010). Recent meta-analysis found that an increase in BMI was inversely associated with the risk of premenopausal breast cancer. The inverse association was significant among Caucasian and African women, while a significant positive association was observed among Asian women (Amadou et al., 2013). Additionally a recent large-scale analysis conducted in Japanese population observed that a borderline-significant positive association between BMI and premenopausal breast cancer, which suggesting that body mass in Asian women might have opposite effects on breast cancer compared with Western women (Wada et al., 2014). Generally it is well mentioned that differences in body build and body composition result in a different relationship between BMI and body fat distribution in different ethnic groups (Rush et al., 2009). It has been proposed that general obesity have distinct influence on hormone secretion (Harvie et al., 2003; Harris et al., 2011). Before the menopause, estrogen is mainly produced in ovary and the circulating levels are controlled by homeostatic regulation and plasma estrogen concentrations are not directly influenced by body fat mass (Rose and Vona-Davis, 2010). However, obese

premenopausal women were found to show decreased levels in their plasma estrogens. Increased BMI is associated with decrease in progesterone levels, ovulatory subfertility and anovulatory infertility in women with BMI over 32 at age 18 (Pandey et al., 2010). Obese women had greater prevalence of menstrual disorders than non-obese women (Kiddy et al., 1990). These changes in hormone environment could give reasonable explanations for the association between BMI and risk of premenopausal breast cancer observed in Caucasian whose obese prevalence are higher than Asians.

There has been suggested that the role of oxidative stress in breast cancer development may depend on adiposity (Dai et al., 2009). Karimi and Roshan (2013) demonstrated decreases in oxidative stress and increases in adiponectin after lifestyle intervention in breast cancer patients. Hence design an epidemiological study including these oxidative stress markers may help better understanding and deeper investigation of obesity and breast cancer pathology.

Previously, we demonstrated that serum levels of HMW adiponectin were significantly lower in breast cancer patients than in controls in postmenopausal women, but there was no association in premenopausal women (Minatoya et al., 2013). The results from present study demonstrated an inverse association of serum HMW adiponectin level with the risk of both pre and postmenopausal. Our result of this study was supported by several Asian population-based studies (Miyoshi et al., 2003; Kang et al., 2007; Shahar et al., 2010; Gulcelik et al., 2012) while recent reviews found that high adiponectin level linked to a decreased risk only for postmenopausal breast cancer (Dalamaga et al., 2012; Liu et al., 2013). Several biological mechanisms are suggested to explain these epidemiological results. Increased adiposity may have an impact on sterol synthesis and on the metabolism of estrogens. Additionally obesity induces chronic low-grade inflammation resulting in an increase of local and systemic levels of cytokines and adipokines, therefore it may influence on mitosis, apoptosis, angiogenesis, and cell migration (Calle and Kaaks, 2004). Recent studies revealed that the AMP-activated protein kinase (AMPK) may play an important role in the limits of cancer cells proliferation by adiponectin (Kim et al., 2010). Additionally there suggested that several molecules including AdipoRs, APPL1, AMPK, JNK, AKT, MAPK-glucose transporter 4 (MAPK-GLUT4), GSK-3β, IκB kinase/NF-κB, caspase, and so on may be involved in signaling pathways linking adiponectin with tumorigenesis (Chen and Wang, 2011).

We found no association between serum insulin levels and breast cancer risk in both pre and postmenopausal women. Our previous study showed no association between serum insulin levels and an increased risk for breast cancer (Minatoya et al., 2013). Our findings from this study did not support the hypothesis that serum insulin level is associated positively with breast cancer risk (Bruning et al., 1992; Del Goudice et al., 1998; Lahmann et al., 2005; Prentice et al., 2006). On the other hand, in a recent meta-analysis, non-significant results of breast cancer risk for the exposure insulin versus no insulin were observed (Karistad et al., 2013). It has been found that high blood levels of insulin and insulin-like growth factor (IGF-I) stimulate the growth of cancer cells in both pre and postmenopausal women and their production can be increased by estrogen (Toniolo et al., 2000; Schairer et al., 2004; Key et al., 2010), suggesting that estrogen may play an important role in breast cancer development. However, as we have reviewed previously (Minatoya et al., 2013), the association between insulin levels and breast cancer remains unclear.

It should be noted that this study has several important limitations such as the measurement of only baseline serum levels of insulin, and HMW adiponectin, the only Asian population based study, the small number of cases and controls, the hospital-based case-control study, where measurements were obtained after diagnosis and possibly affected by the effects of breast cancer or other diseases. Our findings from the present study showed that in Asian population, BMI as a marker of obesity and serum HMW adiponectin levels can be a good predictor of breast cancer risk for both pre and postmenopausal women, but serum insulin level may not be. In conclusion this present study indicated an important role of serum HMW adiponectin levels in both pre and postmenopausal breast cancer risk. The findings from the present study suggested positive association between BMI and premenopausal breast cancer in Japanese population and the association may vary depending on the ethnicity. Therefore more epidemiological studies in different ethnic groups are necessary to support our findings meanwhile mechanisms underlying adiponectin's effect on breast cancer should be studied to fully explain epidemiological observations.

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