Correlation between Adiponectin and Breast Cancer patients

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Abstract: Adipocytokines, such as resistin, and adiponectin, are associated with obesity and breast cancer. Several studies have indicated that adipocytokines may influence tumor growth or differentiation.We evaluated the relationship between serum adiponectin and resistin levels and breast cancer risk in 35 biopsy-proven breast cancer patients and 40 age and body mass index matched controls. Serum adiponectin level was significantly lower in the breast cancer group than the control group. There was a statistically significant difference in serum resistin levels between breast cancer vs control groups. The lymph node metastasis, tumor grade and tumor size were significantly increased in the patients with low serum adiponectin level (*P*= 0.024, 0.009 and 0.001). In the patients whose resistin level was high, the frequency of tumor with the higher histological grade and the larger tumor size were significantly increased (*P*= 0.01 and 0.03). Multivariate analysis showed that age at presentation > 30 years; nulliparity and increased BMI were significantly associated with increased breast cancer risk (P< 0.05). Regression analysis showed that reduced adiponectin (*P*□0.003), and elevated resistin (*P*□0.0008) increased the risk for breast cancer.We conclude that both the low serum adiponectin levels and high resistin levels are likely to be associated with increased breast cancer risk.
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1. Introduction

Breast cancer is a malignant tumor which severely harms the female health. Researchers have shown that obesity possibly correlates with risk for breast cancer, especially with onset and prognosis of postmenopausal breast cancer, but the concrete mechanism is in nubibus (1). A number of risk factors are associated with development of breast cancer including obesity (2). Body mass index (BMI) is a simple and widely used method for measuring body adiposity (3). As BMI increases, breast cancer risk increases in postmenopausal females. In premenopausal females; the association is less clearly established (4).

Obesity is related to many metabolic disorders like type 2 diabetes mellitus, coronary heart disease, and hypertension, and is notably associated with an increased risk for breast cancer in postmenopausal women (5). Numerous factors (obesity associated hyperinsulinemia and high adipose tissue induced estrogen levels) have been suggested to explain the relationship between obesity and breast cancer, but none have been totally conclusive (6). Fat tissue has been recognized as an important secretory organ that can produce various hormones, cytokines and growth factors, collectively called adipokines. Dys-regulated expression and functions of these adipokines play significant roles in the pathogenesis of obesity-related diseases (7).

These adipocytokines include leptin, adiponectin, complement components, plasminogen activator inhibitor-1, tumor necrosis factor- (TNF-alpha), interleukin-6 (IL-6), proteins of the rennin-angiotensin system, and resistin (8). Resistin, named for resistance to insulin, is a unique signaling molecule secreted from adipocytes. Circulating resistin levels are decreased by the anti-diabetic drugs, and increased in diet-induced and genetic forms of obesity. In addition, treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action. Insulin-stimulated glucose uptake by adipocytes is enhanced by neutralization of resistin and is reduced by resistin treatment. Thus, resistin may serve as a hormone that potentially links obesity to insulin resistance (9). However, the studies performed on humans lack coherence between the results, and further studies are needed to ascertain the role of resistin (10, 11).

Adiponectin is a large-molecular-weight adipocyte derived hormone involves in the regulation of glucose and fatty acid metabolism (12). It influences whole-body insulin sensitivity and protects arterial walls against the development of artherosclerosis (13). In the situation of obesity, insulin resistance has also been associated with the

development of breast cancer, and decreased adiponectin levels have been hypothesised to underline the association between breast cancer and obesity, as well as insulin resistance (14). Adiponectin can directly control cancer cell growth and reduction in plasma adiponectin levels could be a risk factor for breast cancer (15).

2. Material and Methods

From January 2012 to June 2012, Thirty five female patients who were newly diagnosed with breast cancer and surgically treated at a King Khalid Hospital were enrolled into the study as patients group. Forty women with normal mammographic findings and no previous history of any kind of cancer as age and body mass index matched controls.

Clinical information regarding age, the menopausal status, weight and height of the patients was recorded. Using the height and weight value of all participants, BMI was calculated as weight in kilograms divided by the square of height in meters. Using the height and weight value of all participants, body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

A BMI value of lower than 18.5 is considered underweight; 18.5-24.9 is normal; 25-29.9 is deemed overweight; and greater than 30 is considered obese. The blood samples were collected within the week before surgery. Serum estrogen, adiponectin, and resistin concentrations were measured. 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 and resistin levels were measured by ELISA (Invitrogen, USA) as described previously (16). Erogen receptor (ER) levels in breast cancer were measured by enzyme immunoassay using the kit provided by Invitrogen (USA).

4. Statistical analysis:

The correlation of plasma adiponectin or resistin concentration with clinicopathologic characteristics of tumors was analyzed by chi-square test. Pearson's correlation coefficients were used to determine the relationships between plasma adiponectin, resistin and body mass index. To determine the risk of breast cancer according to the levels of plasma adiponectin and resistin levels, a multiple logistic regression model was constructed. The level of significance was set at $P < 0.05$ (two-tailed). Statistical calculations were performed using SPSS for Windows V15.0.

3. Results

Table 1 shows the mean values and slandered deviations of the measured adiponectin and resistin levels among women with breast cancer and control women. Significant differences between cases and controls are noted with respect to both adiponectin and resistin serum levels (P=0.002, P=0.000).

Table 1. Serum adiponectin and resistin levels and breast cancer risk

	Mean	SD	P value (t test)
Adiponectin (µg/mL)			
Cases	8.92	1.60	0.002
Control	10.23	3.17	
Resistin (ng/ml)			
Cases	4.42	4.74	0.000
Control	1.84	2.35	

Table 2 shows the baseline characteristics of women, with and without breast cancer. Serum adiponectin, resistin, BMI, age at menarche and age at presentation of the study could have a confounding influence on the association of adiponectin with breast cancer. BMI tended to be higher in women with breast cancer (P=0.02), and these women also had significantly earlier menarche and older age at presentation compared with control (P=0.03, P=0.01 respectively).

Table 2. Risk factors among breast cancer patients

Risk factors		Breast cancer	Control	P
Serum adiponectin (µg/mL)	≤12	23	17	0.004
	>12	12	23	
Serum resistin (ng/ml)	≤3	14	27	0.002
	>3	21	13	
BMI (Kg/m2)	≤30	10	16	0.02
	>30	25	24	
Age at presentation (years)	≤30	6	22	0.01
	30-40	9	6	
	41-50	7	7	
	51-60	13	5	
Age at menarche (years)	≤ 14	30	22	0.03
	>14	5	18	
Multiparity	Yes	26	34	0.08
	No	9	6	
Lactation	Yes	22	26	0.75
	No	13	14	

Table 3 shows the **c**linicopathological characteristics of breast cancer women with the low serum adiponectin levels were compared with those in women with the high serum adiponectin levels. The frequency of large size tumors (>2 cm) and lymph node metastasis were significantly (P= 0.001, P= 0.024 respectively) higher in women in the low level than those in the high level, and the frequency of tumors with high histological grade (2 and 3) was significantly (P = 0.009) higher in women in the low adiponectin level than those in the high adiponectin level. ER statuses were not significantly different

between women in the low level of adiponectin and those in the high level (P= 0.097).

Table 3. Association between serum adiponectin levels and clinicopathological characteristics in breast cancer patients

	Adiponectin (µg/mL) ≤12	>12	P
Estrogen receptor			
Positive	13	10	0. 097
negative	7	5	
Tumor size			
≤ 2cm	6	12	0.001
> 2cm	11	6	
Lymph node etastasis			
Positive	11	8	0.024
negative	6	10	
Histological grade			
1	9	6	0.009
2&3	13	7	

Table 4 shows the **c**linicopathological characteristics of breast cancer women with the low serum resistin levels were compared with those in women with the high serum resistin levels. The frequency of large size tumors (>2 cm) was significantly (*P*= 0.03) higher in women in the high level than those in the low level, and the frequency of tumors with high histological grade (2&3) was significantly (*P* =0.01) higher in women in the high level than those in the low level of resistin. Other parameters such as lymph node status and ER status were not significantly different between women in the low level and those in the high level (P= 0.07).

Table 4. Association between serum resistin levels and clinicopathological characteristics in breast cancer patients

	Resistin (ng/ml) ≤3	>3	P
Estrogen receptor	6	6	
Positive	13	10	0. 07
negative			
Tumor size	14	10	
≤ 2cm	3	7	0.03
> 2cm			
Lymph node metastasis	12	11	
Positive	7	5	0.10
negative			
Histological grade	13	6	
1	6	10	0.01
2&3			

Table 5 and 6 showed that by multivariate Logistic regression analysis, the variables including adiponectin, and resistin were risk factors for breast cancer, and the OR for adiponectin and resistin was 0.632 (95%CI: 0.645–0.834 , P=0.003), 1.265 (95%CI: 1.210, P=1.934), respectively. In addition, the independent effects of different risk factors after controlling the effect of other potential factors are studied in a logestic regression model. BMI as the strongest risk factor, nulliparity and age at presentation are considered as independent significant risk factors for cancer breast (p<0.05).

Table 5. Analysis of multivariate regression with risk for breast cancer as a dependant variable

	B	OR	95%CI	P
Adiponectin	-0.379	0.632	0.645-0.834	0.003
Resistin	1.357	1.265	1.210-1.934	0.008

Table 6. Analysis of multivariate analysis of risk factors for breast cancer patients

Risk factors	OR	95%CI	P
Multiparty Multipara vs non Nullipara	4.3	0.68-18.79	0.02
Lactation Lactating vs non lactating	4.2	0.57-29.73	0.732
Age at presentation ≤30 vs > 3o	3.9	1.76-32.46	0.03
BMI(Kg/m2) ≤30 vs > 30	5.8	0.58-7.84	0.007

4. Discussions

Breast cancer is the most common cancer worldwide. Although breast cancer is more common in women older than 50 years worldwide, it is frequently diagnosed in younger women. In fact, breast cancer is the single leading cause of cancer death for women 20 to 59 years of age (17), thus posing a major public health concern. Obesity is a well-known risk factor for breast cancer, and obese women are likely to have metastatic breast cancer when they are first diagnosed, and to have a poor prognosis regardless of their menopausal status (18, 19).

The links between adiposity and breast cancer risk has not been clarified yet (20). This needs a study to lend support to the contention that the protective effect of adipose tissue on breast cancer risk women may be mediated by high resistin/low adiponectin. A previous health study had described a non-significantly elevated breast cancer risk with higher adiponectin levels in premenopausal women, while risk was lowered among postmenopausal women (21). Interestingly, several recent case-control studies have shown that decreased adiponectin levels are associated with the incidence of breast cancer, but the correlation between serum adiponectin and breast cancer risk is not clear yet, and the molecular basis for the link remains poorly understood (22-24). Adiponectin recently gained interest in correlation with cancer, and was inversely and independently

associated with breast, endometrial, gastric, prostate and colorectal cancer in case control studies (25-28).

Based on the relationship between obesity and breast cancer (29), it was hypothesized that adipokines, can influence breast cancer occurrence and recurrence. Of the adipokines, adiponectin has drawn keen interest because it is inversely associated with adiposity (30) and is a key regulator of insulin sensitivity and inflammation (31). The mechanism underlying the observed association between adiponectin and breast cancer is not well established. However, insulin-sensitizing, anti-inflammatory, anti-angiogenic, anti-proliferative, pro-apoptotic, and antioxidant mechanisms have been mentioned as possible explanations for the anti-tumor effect of adiponectin (32, 33). Our study showed that age at presentation was a significant risk factor for breast cancer which might be due to as age increases, body adiposity increases with the production of excessive amount of estradiol which increases the rate of proliferation of breast cells accompanied with activation of oncogenes and inactivation of tumor-supressor genes producing a sequence of genetic changes leading to breast carcinoma (34).

Although a metaanalysis of some studies reached the conclusion that in premenopausal women there is a significant trend for a decreased relative risk for breast cancer in association with increasing BMI (35), the present study showed that higher values of BMI (> 30 kg/m) were significantly associated with breast cancer risk. This result was concordant with the findings of Michels et al (36) who found a positive association between high BMI and breast cancer risk before the menopause. Multivariate Logestic regression analysis with multiple risk factors showed that age at presentation was a risk factor for breast cancer. This was concordant was Hewala et al, who found that age at presentation was a strong risk factor for cancer breast (37).

Many studies have shown the relation between adipocytokines and various types of cancer (22-24, 26). We also analyzed the serum levels of adiponectin and resistin levels in breast cancer patients. In our study, adiponectin levels were significantly lower in breast cancer patients than the control group. Earlier case control study among Japanese women by Miyoshi et al. has shown that breast cancer occurred in women with the low serum adiponectin levels (23). Tworoger and his colleguages first conducted a prospective study with 1477 breast cancer cases for this inverse correlation. In contradistinction to the other studies, they did not found an association overall between plasma adiponectin level and breast cancer (21). Moreover, Kang et al. found no statistically significant difference in serum adiponectin levels between cases and controls (38).

A study by Maskarinec et al, found no association between reduced adiponectin levels and premenopausal breast cancer risk (39). At the same time Miyoshi et al. had opposed these results as he reported that low serum adiponectin levels were significantly associated with increased risk of cancer breast (23). Another study proved that the decreased serum adiponectin levels and increased serum resistin and leptin levels are risk factors of breast cancer (1).

Adiponectin is a biologically active polypeptide which is exclusively produced by white adipose tissue that may improve insulin sensitivity. Takahata et al, showed that AdipoR1 and AdipoR2 were expressed in both normal breast epithelial cells and breast cancer cells (40). Dieudonne et al, reported that MCF-7 cells expressed adiponectin receptors and responded to adiponectin by reducing their growth, AMP kinase activation, and p42/p44 MAPkinase inactivation (41). Those findings indicated that adiponectin might inhibit the proliferation of breast cancer cells directly through binding to adiponectin receptors. Our study showed that hypoadiponectinemia might increase the risk of onset and lymph node metastasis of breast cancer, and be associated with high histological grade and increased tumor size which was also reported by a previous study (1). However, Miyoshi et al, found no significant difference of serum adiponcetin levels between patients with lymph node metastasis patients and patients without metastasis in their study (23). The disparity might be relevant to failing to control the confounding factors such as age.

Adiponectin has a direct inhibitory effect on proliferation of vascular smooth muscle cells and myelomonocytic progenitors (42), 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 (23).

In breast cancer it is likely that obesity is often related to estrogen reseptor status (38; 43). Miyoshi et al, Chen DC et al, and Tworoger et al, did not find an association between adiponectin levels and estrogen receptor status in their trials (21, 23, 24). On the other hand, Tian et al, showed a statistically significant inverse association between adiponectin levels and breast cancer risks in ER-positive but not ER-negative breast cancer patients (44). Kang

revealed that ER negativity was significantly increased in patients with a decreased adiponectin level (38). The association between receptor status and adiponectin is controversial. Our study showed that the relation between serum adiponectin levels and hormone reseptor status was not statistically significant.

We determined serum resistin levels in patients with breast cancer and the healthy controls, and found that serum resistin levels were significantly increased in patients as compared to controls, and were correlated with the tumor size but not associated with lymph node metastasis. This was in concordance with findings of Wei-Kei et al, who found significant correlation with the size of the tumor (1). However, he reported significant association with lymph node metastasis which was in contrast to our study which showed that serum resistin concentration might not increase the risk of lymph node metastasis. High resistin expression was correlated significantly with tumor grade in our study which was also reported by a previous study (45).

Our study showed that plasma resistin level had significant relation to the histological grade of cancer breast patients. A study by Kang et al, had found that patients whose plasma resistin level was higher than the median, the frequency of tumor with the highest histological grade was significantly increased (46). These results suggest the possibility that high serum resistin levels might be another adiponcytokine that contribute to increase breast cancer risk. Because the previous studies revealed that resistin is expressed not only from adipose tissue but also from monocytes and macrophages, and correlated with C-reactive protein, TNF- , and IL-6 directly, the role of resistin as another marker of inflammation has received growing interest (47). Chronic inflammation is known to be one of the causes of cancer development, and inflammation may be represented by biomarkers of early pathologic changes in breast cells and be associated with risk for the development of breast cancer (48, 49). Thus, the correlation between plasma resistin levels and breast cancer risk might be partly explained by inflammation.

Multivariate analysis showed that there might be a close correlation between resistin and breast cancer. However, the underlying mechanisms of this association are not clear. Steppan et al, searched for genes that were downregulated by TZDs and discovered a new mRNA coding a novel protein (9). The protein which can induce glucose intolerance and insulin resistance was called resistin. The biological activity of resistin is not very clear now. In recent years, studies show that resistin is strongly associated with tumors of gastrointestinal system and hematological system. Pamuk et al, researched resistin levels in patients with various hematological malignancies, and found that serum resistin level was significantly increased in lymphoma group when compared to the control group and leukemia group, although the underlying mechanisms of this association are not clear (50). In our study, we found that resistin can increase the risk of breast cancer, and its concentration is increased with advanced stages of the disease as its concentration was higher among grade 2 and 3 cancer breast patients than grade 1 group, suggesting that resistin might increase the risk cancer breast.

In conclusion, the low serum adiponectin and high resistin levels might be associated with increased breast cancer risk. The clinicopathologic characteristics of the tumor suggested that these adipokines might influence the progression of breast cancer.This association was not found to demonstrate statistically significant variation with the estrogen receptor in the breast cancer group. However, adiponectin levels decreased with increases in the stage of breast cancer. So in addition to making adiponectin a potentially important tool for predicting a woman's risk for breast cancer, this also might make adiponectin an interesting target for the development of new breast cancer therapy strategies in Tabuk. A large-scaled prospective study should be supported in the future.

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