Adiponectin and Breast Cancer Risk

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Adiponectin, an adipocyte-secreted hormone, is closely and inversely associated with insulin resistance and was recently found to be inversely and independently associated with endometrial cancer. Because insulin resistance in the setting of obesity has also been associated with the development of breast cancer, we have hypothesized that decreased adiponectin levels might underlie the association between breast cancer and obesity/insulin resistance. We evaluated the association of adiponectin with the occurrence of breast cancer in a case-control study comprising 174 women with newly diagnosed, histologically confirmed breast cancer and 167 controls. We found an inverse, fairly strong, and statistically significant association of serum adiponectin with breast cancer (odds ratio, 0.84; 95% confidence interval, 0.71–0.99). Importantly, despite a fairly robust inverse association of adiponectin with breast cancer risk among postmenopausal women (odds ratio, 0.82; 95% confidence interval, 0.67–1.00), no such significant association between adiponectin and breast cancer was found among premenopausal women. The observed associations were independent of possible effects of major components of the IGF system, leptin, body mass index, sociodemographic variables, and known risk factors for breast cancer. Future studies are needed to prove causality and provide further insights into both the mechanisms underlying the actions of this hormone and its potential role in breast cancer. (*J Clin Endocrinol Metab* 89: 1102–1107, 2004)

O BESITY AND ESTROGENS have long been implicated in the pathogenesis of breast cancer (1, 2). Adipose tissue serves as the site of peripheral aromatization of adrenal androgens to estrogens, which induce mitogenic activity in mammary tissue by binding to estrogen receptors. A strong association of obesity with insulin resistance, characterized by hyperinsulinemia, has also been well documented (3, 4), and there is evidence that insulin as well as IGFs may play an important mitogenic role in the development of breast cancer (5–10).

Adiponectin (acrp30, adipoQ, *apM1* gene product) is an adipocyte-secreted protein (11–14), decreased levels of which have been implicated in the pathogenesis of insulin-resistant states (14), such as obesity and type 2 diabetes mellitus (12, 15, 16). We have shown that adiponectin levels are decreased in premenopausal women with endometrial carcinoma, a malignancy closely associated with obesity and insulin resistance (17). Because insulin resistance in the setting of obesity has also been associated with the development of breast cancer (2, 18, 19), we have hypothesized that decreased adiponectin levels might underlie the association between breast cancer and obesity/insulin resistance.

To evaluate this hypothesis, we have conducted a case-control study of 174 pre- and postmenopausal women with newly diagnosed, histologically confirmed, breast cancer and 167 control women.

Subjects and Methods

Subjects

During an 8-month period from February to September 1998 inclusive, 83 consecutive incident cases of breast cancer were diagnosed and histologically confirmed in the mammographic screening centers of the University of Athens teaching hospitals E. Venizelou and Laiko. Five of these women refused to participate, whereas three others had a past history of cancer at another site. The remaining 75 cases were included in the study. Controls were selected among women with a mammogram indicating the absence of breast cancer and who had never been diagnosed with any type of cancer. Of 97 identified potential controls, 86 agreed to participate. During an additional 30-month period, from January 2000 to June 2002 inclusive, two of us (C.C. and D.M.) visited the mammographic screening centers of the above teaching hospitals once a week to identify potential cases. Cases included women who were histologically diagnosed with breast cancer during the present hospitalization. Among the 118 women who were identified, 99 agreed to participate and were included in the study. Controls were selected among women in the same hospitals who either had a mammogram indicating the absence of breast cancer or who were hospitalized in the orthopedic department for a minor trauma. Controls were included if they had never been diagnosed with any form of cancer. Among the 118

potential controls identified, 92 agreed to participate and were included in the study.

All cases and controls were interviewed by one of four trained interviewers. The interview lasted about 20 min and obtained information pertaining to demographic, anthropometric, and reproductive variables. Fasting blood samples were taken and stored at −70 C from all cases and controls (no later than 0900 h) in a blinded fashion as to case-control status for measurements of serum adiponectin, leptin, IGF-I, and IGF-binding protein-3 (IGFBP-3).

Ethics

The study protocol was approved by the University of Athens Medical School Ethics Committee and was in accordance with the Helsinki Declaration of 1975. All participants provided informed consent.

Hormone measurement

Serum adiponectin levels in all samples were measured in one run at the Beth Israel Deaconess Medical Center (Boston, MA) using an RIA with a sensitivity of 2 ng/ml and an intraassay coefficient of variation of 8.1%. Measurements of serum IGF-I, IGFBP-3, and leptin were performed in two runs (sets A and B, each including a similar number of cases and controls) using either the Nichols Advantage Automated Specialty System (Nichols Institute, San Juan Capistrano, CA) or commercially available RIA kits as previously described (20, 21). The assays for these analytes are similar with respect to sensitivity, specificity, precision, recovery, and linearity of dilution; thus, the methods are considered to generate comparable results.

Statistical analysis

Because leptin and components of the IGF system were analyzed in two different runs, a dummy variable specifying the contrast between set A and set B was introduced in all analyses even though the laboratory methods used were similar and cases and controls were distributed in a balanced way between the two runs. Additionally, even though all samples were immediately frozen after blood collection and processing, it is theoretically possible that the duration of storage might have affected measurements of the four indicated hormones. Thus, for each hormone, a regression of hormonal measurements on duration of storage was obtained, and residuals (differences) from the regression-predicted values were used in all subsequent analyses as storage duration-adjusted values.

For the statistical analysis, representative values (mean and SD) of the four measured hormones were calculated among the case and control subjects and were stratified according to menopausal status. Subsequently, cases and controls were distributed in marginal quintiles of the storage duration-adjusted values for each of the hormonal variables, and *P* values from simple test trends were determined. Lastly, the data were modeled through multiple logistic regression with case or control status as the outcome variable and one or more of the measured hormones as predictor variables (in increments equal to one marginal quintile of their storage duration-adjusted values). Models were controlled for age, education, height, body mass index (BMI), age at menarche, alcohol consumption, tobacco use, age at menopause (among postmenopausal women), and age at first birth (among parous women) as well as for inclusion in set A or set B.

Results

Table 1 shows the distribution of 174 women with incident breast cancer and 167 control women by demographic, anthropometric, and reproductive variables. These data are not directly interpretable because of mutual confounding. However, they reveal most of the established risk characteristics of women with breast cancer, including higher level of education (*P* = 0.05) and increased stature (*P* = 0.001), earlier age at menarche (*P* = 0.001), later age at menopause (*P* = 0.004), and their tendency to consume more alcoholic beverages (*P* = 0.001). BMI tended to be higher in cases com-

pared with controls; however, this difference did not achieve statistical significance (*P* = 0.25).

Table 2 shows mean values and SDs of the measured hormones among women with breast cancer and control women by menopausal status. No significant differences between cases and controls are noted with respect to any of the hormones, especially given the multiple comparisons performed herein. However, the values in Table 2 are not adjusted for either inclusion in set A or B or for storage duration. Therefore, Table 2 serves only crude descriptive purposes.

Table 3 shows the distribution of women with breast cancer and control women by marginal quintiles of storage duration-adjusted measurements of the four indicated hormones according to menopausal status. Adiponectin is inversely associated with breast cancer risk among postmenopausal women (*P* = 0.02), and this association is also reflected among all women (*P* = 0.02), probably because most women with breast cancer in our study were postmenopausal (71.8% of cases).

Table 4 shows multiple logistic regression-derived odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer according to a change in serum adiponectin, IGF-I, IGFBP-3, and leptin by one marginal quintile of the storage duration-adjusted measurements stratified by menopausal status. For IGF-I, there tends to be a positive association with breast cancer risk among premenopausal women (*P* = 0.45), which becomes more significant after controlling for the other measured hormones (*P* = 0.06). For IGFBP-3, there is an inverse association with breast cancer risk among premenopausal women (*P* = 0.13), which also becomes more significant after controlling for the other measured hormones (*P* = 0.01). An inverse association of serum leptin levels and risk of breast cancer (*P* = 0.32) does not achieve statistical significance among premenopausal women in unadjusted analysis or after controlling for the other measured hormones (*P* = 0.12). There is no evidence for an association of IGF-I, IGFBP-3, and leptin with breast cancer risk among postmenopausal women; however, there is evidence for a fairly robust inverse association of adiponectin with breast cancer risk among postmenopausal women (OR, 0.82; 95% CI, 0.67–1.00), which is also observed in the entire data set (OR, 0.84; 95% CI, 0.71–0.99). In contrast, there is no evidence for a significant inverse association between adiponectin and breast cancer risk among premenopausal women.

Discussion

The results of this case-control study demonstrate an inverse association of adiponectin with the risk of postmenopausal, but not premenopausal, breast cancer. As in previous studies (9), there is evidence in these data that IGF-I is positively and IGFBP-3 is inversely associated with the risk for the development of premenopausal, but not postmenopausal, breast cancer. The apparent differences in the associations between these hormonal factors and the risk for the development of breast cancer in pre- and postmenopausal periods need to be studied further.

Previous epidemiological studies have shown an association of central obesity and insulin resistance mainly with postmenopausal breast cancer (2, 18, 19). Similarly, overall

TABLE 1. Distribution of 174 women with breast cancer and 167 control women by demographic, somatometric, and reproductive variables

Variables	Cases		Controls		*P* value for trend or contrast
	n	%	n	%	
Age (yr)					0.62
<45	24	13.8	25	15.0	
45–54	38	21.8	33	19.7	
55–64	40	23.0	32	19.2	
65–74	52	29.9	54	32.3	
75+	20	11.5	23	13.8	
Education (yr)					0.05
<6	23	13.2	39	23.3	
6	51	29.3	58	34.7	
9	46	26.5	22	13.2	
12	32	18.4	26	15.6	
13+	22	12.6	22	13.2	
Alcohol consumption (glasses/wk)					0.001
<1	120	69.0	146	87.4	
≥1	54	31.0	21	12.6	
Smoking					0.54
No	124	71.3	124	74.3	
Yes/ex-smoker	50	28.7	43	25.7	
Height (cm)					0.001
<160	37	21.3	46	27.5	
160–164	54	31.0	82	49.1	
165+	83	47.7	39	23.4	
BMI (kg/m^2)					0.25
<25.0	69	39.7	77	46.1	
25.0–26.9	33	19.0	30	18.0	
27.0–28.9	31	17.8	26	15.6	
29.0+	41	23.5	34	20.3	
Age at menarche (yr)					0.001
<13	66	38.0	36	21.6	
13	56	32.2	49	29.3	
14	26	14.9	50	29.9	
15+	26	14.9	32	19.2	
Age at menopause (yr)					0.004
Premenopausal	49	28.2	44	26.4	
≤49	41	23.5	66	39.5	
50+	84	48.3	57	34.1	
Age at first birth (yr)					0.36
Nulliparous	26	14.9	27	16.2	
<30	107	61.5	111	66.5	
30+	41	23.6	29	17.3	

TABLE 2. Basic characteristics (mean, SD, and *P* value) from comparison of the means for adiponectin, IGF-I, IGFBP-3, and leptin among 174 women with breast cancer and 167 control women by menopausal status

Variable	All women (174 cases, 167 controls)			Premenopausal women (49 cases, 44 controls)			Postmenopausal women (125 cases, 123 controls)		
	Mean	SD	*P* value (*t* test)	Mean	SD	*P* value (*t* test)	Mean	SD	*P* value (*t* test)
Adiponectin (μg/ml)			0.54			0.35			0.31
Cases	16.7	10.0		14.5	7.8		17.6	10.6	
Controls	17.4	10.5		13.0	7.1		19.0	11.1	
IGF-I (ng/ml)			0.13			0.83			0.04
Cases	130.7	83.4		175.0	94.6		113.0	71.4	
Controls	145.2	91.1		179.6	113.5		133.2	78.8	
IGFBP-3 (μg/ml)			0.32			0.64			0.42
Cases	3.40	1.28		3.81	1.27		3.24	1.25	
Controls	3.27	1.19		3.70	1.17		3.11	1.16	
Leptin (ng/ml)			0.88			0.23			0.44
Cases	24.4	16.1		18.7	12.5		26.6	16.9	
Controls	24.1	18.4		22.0	14.5		24.9	19.6	

obesity, expressed as BMI, tends to be positively correlated with the risk of postmenopausal breast cancer, but is either weakly or inversely associated with premenopausal breast cancer (22–24). These observations suggest that central obe-

sity and insulin resistance, characterized by increased serum insulin levels, may play a more important role in the pathogenesis of postmenopausal breast cancer.

Adiponectin, a newly discovered protein, is secreted ex-

TABLE 3. Distribution of women with breast cancer and control women by marginal quintiles of storage duration adjusted measurement of the four indicated hormones by menopausal status

Variable	Storage duration adjusted quintiles										Trend (+/−), P value
	1st		2nd		3rd		4th		5th		
	n	%	n	%	n	%	n	%	n	%	
All women: 174 cases, 167 controls											
Adiponectin											(−) 0.02
Cases	35	20.1	43	24.7	35	20.1	31	17.8	30	17.3	
Controls	30	18.0	24	14.4	31	18.6	40	23.9	42	25.1	
IGF-I											(−) 0.56
Cases	31	18.1	47	27.5	25	14.6	35	20.5	33	19.3	
Controls	37	22.3	20	12.0	42	25.3	33	19.9	34	20.5	
IGFBP-3											(−) 0.34
Cases	38	21.8	33	19.0	39	22.4	32	18.4	32	18.4	
Controls	31	18.5	35	21.0	28	16.8	37	22.2	36	21.5	
Leptin											(+) 0.29
Cases	33	19.0	38	21.8	29	16.7	38	21.8	36	20.7	
Controls	32	19.2	40	23.9	39	23.3	29	17.4	27	16.2	
Premenopausal women: 49 cases, 44 controls											
Adiponectin											(−) 0.60
Cases	10	20.4	15	30.6	11	22.5	10	20.4	3	6.1	
Controls	12	27.3	6	13.6	11	25.0	11	25.0	4	9.1	
IGF-I											(+) 0.45
Cases	5	10.2	6	12.2	7	14.3	11	22.5	20	40.8	
Controls	7	16.3	5	11.6	7	16.3	8	18.6	16	37.2	
IGFBP-3											(−) 0.13
Cases	8	16.3	8	16.3	13	26.6	8	16.3	12	24.5	
Controls	4	9.1	5	11.4	10	22.7	11	25.0	14	31.8	
Leptin											(−) 0.32
Cases	14	28.6	15	30.6	5	10.2	10	20.4	5	10.2	
Controls	6	13.6	13	29.6	13	29.5	8	18.2	4	9.1	
Postmenopausal women: 125 cases, 123 controls											
Adiponectin											(−) 0.02
Cases	25	20.0	28	22.4	24	19.2	21	16.8	27	21.6	
Controls	18	14.6	18	14.6	20	16.3	29	23.6	38	30.9	
IGF-I											(−) 0.16
Cases	26	21.3	41	33.6	18	14.7	24	19.7	13	10.7	
Controls	30	24.4	15	12.2	35	28.5	25	20.3	18	14.6	
IGFBP-3											(−) 0.76
Cases	30	24.0	25	20.0	26	20.8	24	19.2	20	16.0	
Controls	27	22.0	30	24.4	18	14.6	26	21.1	22	17.9	
Leptin											(+) 0.07
Cases	19	15.2	23	18.4	24	19.2	28	22.4	31	24.8	
Controls	26	21.1	27	22.0	26	21.1	21	17.1	23	18.7	

clusively by adipocytes and acts as an insulin sensitizer (11, 12). Consistent with the role of this protein as an insulin sensitizer, adiponectin secretion is decreased in the setting of obesity (11, 15) and other insulin-resistant states, such as type 2 diabetes mellitus (16). Thus, decreased levels of adiponectin are associated with increased serum insulin levels, which accompany insulin resistance (25, 26).

The association of insulin resistance and hyperinsulinemia with breast cancer has been supported by most (5, 7, 27, 28), but not all, previous studies (29, 30). Insulin appears to stimulate the proliferation of breast cancer cells by binding to and signaling through the insulin (31) and IGF-I (32, 33) receptors. In addition, insulin may synergize with the mitogenic effects of estrogen (34) and may also up-regulate the expression of vascular endothelial growth factor (VEGF), a potent angiogenic agent that is secreted by breast cancer cells and endometrial carcinoma cells (35, 36). VEGF is suppressed by stimulation of peroxisome proliferator-activated receptor-γ, ligands of which increase levels of adiponectin (37, 38). Moreover, adiponectin inhibits the activation of nuclear factor-κB (39), a transcription factor that up-regulates VEGF in breast

cancer (40). Thus, it is reasonable to hypothesize that the central obesity-induced down-regulation of adiponectin expression increases breast cancer risk through a mitogenic effect of hyperinsulinemia and increased IGFs and estrogen levels as well as by up-regulating VEGF. Moreover, adiponectin has recently been inversely associated with estrogen levels (41). As postmenopausal breast cancer is also associated with increased risk of circulating estrogens, it remains possible that adiponectin may influence breast cancer risk by altering circulating estrogen levels. Whether adiponectin may also directly alter breast cancer risk remains to be studied further in the future.

We have recently reported a significant inverse association of adiponectin with risk of endometrial carcinoma among women less than 65 yr old (17). Finding a similar inverse association among postmenopausal women with breast cancer in this study provides further support for the importance of adiponectin in the pathogenesis of malignancies associated with obesity-induced insulin resistance and hyperinsulinemia. Although little is currently known about the site of action of adiponectin or its receptor, these studies suggest

TABLE 4. Multiple logistic regression-derived ORs and 95% CIs for breast cancer for a change in serum adiponectin, IGF-I, IGFBP-3, and leptin by one marginal quintile of the storage duration adjusted measurements by menopausal status

Variable	All women			Premenopausal			Postmenopausal		
	ORs	95% CI		ORs	95% CI		ORs	95% CI	
Model 1: adiponectin only	0.83	0.72	0.97	0.92	0.66	1.27	0.81	0.68	0.96
Model 2: adiponectin plus covariates in Table 1	0.85	0.72	1.00	0.87	0.60	1.26	0.83	0.68	1.00
Model 3: adiponectin plus covariates in Table 1 plus IGF-I, IGFBP-3, leptin plus set A *vs.* B	0.84	0.71	0.99	0.81	0.55	1.20	0.82	0.67	1.00
Model 1: IGF-I only	0.96	0.82	1.11	1.11	0.84	1.49	0.87	0.72	1.06
Model 2: IGF-I plus covariates in Table 1	1.00	0.84	1.19	1.17	0.84	1.62	0.95	0.76	1.19
Model 3: IGF-I plus covariates of Table 1 plus adiponectin, IGFBP-3, leptin plus set A *vs.* B	1.06	0.86	1.30	1.49	0.98	2.24	0.94	0.72	1.23
Model 1: IGFBP-3 only	0.93	0.80	1.08	0.79	0.58	1.07	0.97	0.82	1.16
Model 2: IGFBP-3 plus covariates of Table 1	0.92	0.78	1.09	0.78	0.55	1.09	0.98	0.80	1.22
Model 3: IGFBP-3 plus covariates in Table 1 plus adiponectin, IGF-I leptin plus set A *vs.* B	0.89	0.73	1.09	0.60	0.39	0.92	1.03	0.80	1.33
Model 1: leptin only	1.08	0.93	1.27	0.85	0.62	1.17	1.18	0.99	1.41
Model 2: leptin plus covariates of Table 1	1.00	0.83	1.21	0.77	0.52	1.14	1.05	0.84	1.31
Model 3: leptin plus covariates in Table 1 plus adiponectin, IGF-I, IGFBP-3 plus set A *vs.* B	0.97	0.80	1.18	0.72	0.47	1.10	1.00	0.80	1.27

that it is reasonable to speculate that low levels of adiponectin may play a permissive role in stimulating the neoplastic growth of breast cells.

In contrast to the role of adiponectin observed in postmenopausal women, we did not find an association of adiponectin with premenopausal breast cancer. We did, however, observe a positive association of IGF-I and an inverse association of IGFBP-3 with the risk for development of premenopausal breast cancer. These observations are in keeping with previous studies that have shown similar associations (6, 8–10).

Pathophysiologically, IGF-I appears to increase mitogenic stimulation of breast cells through both endocrine and paracrine mechanisms, and its effects may synergize with the mitogenic effects of estrogen. That IGF-I is positively correlated with the risk of premenopausal, but not postmenopausal, breast cancer may imply the importance of this hormone in the earlier stages of carcinogenesis and in subjects who have higher endogenous levels of both IGF-I and estrogens (9).

Among the strengths of our study is the inclusion of newly diagnosed pre- and postmenopausal women with a histological diagnosis of breast cancer. Laboratory specimens were obtained in a blinded fashion, and specimens were obtained in the fasting state to minimize diurnal variability in hormone levels. Random laboratory error or uncontrolled variability would have resulted in misclassification that would tend to dilute associations. Although subjects were recruited from two different sites, and laboratory analyses were performed in two different runs, we made proper adjustments for these conditions in the statistical analyses. Lastly, we controlled for the potential variability in hormonal levels due to storage duration time.

In conclusion, we found a significant inverse association of adiponectin with postmenopausal breast cancer and a positive association of IGF-I with premenopausal breast cancer. These observations support important underlying pathophysiological differences in these two disease states.

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