Prognostic Effect of Circulating Adiponectin in a Randomized 2 × 2 Trial of Low-Dose Tamoxifen and Fenretinide in Premenopausal Women at Risk for Breast Cancer

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See accompanying editorial on page 124

A B S T R A C T

Purpose

Adipokines are linked to obesity and insulin sensitivity and have recently been related to breast cancer risk and prognosis. We investigated the associations of plasma leptin and adiponectin with mammographic density and disease status and assessed their prognostic effect on recurrence-free survival in premenopausal women at risk for breast cancer.

Patients and Methods

We measured circulating lipids, insulin-like growth factor 1, glucose, insulin and insulin sensitivity (calculated by homeostasis model assessment [HOMA] index), leptin, adiponectin, and leptin-to-adiponectin ratio in 235 premenopausal women with pT1mic/pT1a breast cancer ($n = 21$), intraepithelial neoplasia ($n = 160$), or 5-year Gail risk of 1.3% or greater ($n = 54$) who participated in a 2 × 2 trial of low-dose tamoxifen, fenretinide, both agents, or placebo over a 2-year period.

Results

At baseline, adiponectin levels were directly associated with mammographic density and HDL cholesterol and negatively associated with leptin, leptin-to-adiponectin ratio, body mass index (BMI), and HOMA index. Median adiponectin levels were lower in affected than in unaffected women ($P = .006$). After a median of 7.2 years and total of 57 breast neoplastic events, there was a 12% reduction in the risk of breast neoplastic events per unit increase of adiponectin (adjusted hazard ratio, 0.88; 95% CI, 0.81 to 0.96; $P = .03$). There was no interaction between treatment and adiponectin levels.

Conclusion

Low adiponectin levels are associated with a history of prior intraepithelial neoplasia or pT1mic/pT1a breast cancer and higher risk of second breast neoplastic events in premenopausal women. The associations are independent of BMI, mammographic density, and treatment. Our findings support the role of adiponectin as a potential target for premenopausal breast cancer prevention and treatment.

J Clin Oncol 30:151-157. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Obesity and disordered energy balance have been shown to play an important role in breast cancer risk and progression, although the association is modified by menopausal status. Several studies have shown a positive association between obesity and breast cancer among postmenopausal women,¹⁻³ whereas an inverse association has been found among premenopausal women as regards general obesity, although central obesity has been reported to be possibly associated with an increased breast

cancer risk before menopause.^{4,5} The higher breast cancer risk observed in obese women can partially be explained by the role of adipose tissue in controlling the levels and bioactivity of sex steroids. Moreover, the emerging role of adipocytes in the regulation of energy homeostasis through the secretion of adipokines⁶ is currently under investigation for its putative relationship with cancer.

Leptin and adiponectin are the two major adipokines secreted by adipocytes. Leptin levels increase in obesity and decrease during fasting,^{7,8} whereas adiponectin is reduced in obesity and

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Submitted February 11, 2011; accepted August 24, 2011; published online ahead of print at www.jco.org on December 12, 2011.

Supported by National Cancer Institute Grant No. CA-77188; a contract from the Italian Foundation for Cancer Research; Associazione Italiana per la Ricerca sul Cancro Regional Grant No. 1068/2005 on second tumors; and Progetto Integrato Oncologia, Italian Health Ministry, Contracts No. RFPS-2006-1-339898 and RFPS-2006-1-339856.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3002-151/\$20.00

DOI: 10.1200/JCO.2011.35.2237

insulin-resistant states and increases in response to severe weight loss.⁹⁻¹¹ Recent evidence demonstrates that the leptin-to-adiponectin (L-A) ratio could be a useful index for insulin resistance in diabetic patients in clinical practice.¹² Insulin levels have been found to be positively associated with breast cancer risk¹³ and with distant recurrence and specific mortality.¹⁴ The observation that insulin resistance in obese patients is also associated with breast cancer development^{15,16} has prompted studies designed to investigate whether decreased adiponectin levels might explain the association between breast cancer and obesity or insulin resistance.¹⁷ However, the association of adiponectin with premenopausal breast cancer is unclear, with a few studies finding no association¹⁸⁻²¹ and others finding only a trend for weak association.^{22,23}

In the present study, we assessed plasma adiponectin and leptin levels in premenopausal women to determine their association with disease status and mammographic density, one of the strongest predictors of breast cancer risk, and also to evaluate their role as predictors of second breast neoplastic events. Ours was a 2 × 2 phase II trial of low-dose tamoxifen and fenretinide for breast cancer prevention.

PATIENTS AND METHODS

Participants

A total of 235 premenopausal women were enrolled onto a randomized, double-blind, placebo-controlled 2 × 2 trial of tamoxifen and fenretinide—a vitamin A derivative—for breast cancer prevention (Fig 1). Description of study design, participant characteristics, and main findings have been published previously.^{24,25} Briefly, 160 premenopausal women with an intraepithelial neoplasia (IEN; ductal intraepithelial neoplasia [DIN], 130; lobular intraepithelial neoplasia [LIN], 30) or microinvasive breast cancer (pT1mic or

pT1a, N0; n = 21) and 54 healthy women at increased risk ($\geq 1.3\%$ according to Gail model) were randomly assigned to receive either tamoxifen 5 mg/d or fenretinide 200 mg/d, both agents, or placebo for 2 years. Women were stratified according to center and disease status (Gail v IEN/T1). All participants signed a consent form approved by the local institutional review board.

Assay Methods

Fasting blood samples were collected at baseline and yearly for 2 years of treatment duration and 1 year of follow-up. Blood samples were centrifuged at 1,800 g, and serum and plasma were stored at -80°C . Serum glucose concentration and lipid profile were measured on fresh samples, whereas insulin-like growth factor I (IGF-I), insulin, and leptin were determined on frozen samples using methods previously described.²⁶ We used the homeostasis model assessment (HOMA) as a surrogate index of insulin sensitivity, which was calculated as $[\text{fasting insulinemia (mU/L)} \times \text{glycemia (mmol/L)}]/22.5$, in accordance with methods previously described.^{26,27}

Plasma adiponectin was measured using a commercial enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN). In this assay, the minimum detectable dose was 0.25 ng/mL; intra-assay coefficients of variability were 2.5% (19.8 ng/mL), 3.4% (69.9 ng/mL), and 4.7% (143 ng/mL); interassay precisions from 40 different assays of three samples of known concentrations of 20.5, 74.4, and 157 ng/mL were 6.8%, 5.8%, and 6.9%, respectively. Plasma samples underwent at most one freeze-thaw cycle before leptin determination and at most two freeze-thaw cycles before adiponectin measurement during an average of 4.5 and 7 years of storage for leptin and adiponectin, respectively. Notably, leptin and adiponectin concentrations were reported not to be influenced by freeze-thaw cycles^{28,29} or prolonged storage.³⁰⁻³² Mammographic percent density was measured at baseline and 12, 24, and 36 months using the computer-assisted method described by Boyd et al³³ and validated by our group.^{25,34}

Follow-Up and Survival Update

After study completion, participants underwent follow-up, with at least one annual visit. Women who were not seen in the clinic were contacted annually by telephone to ascertain disease and vital status. Disease-free survival

Fig 1. CONSORT diagram.

was defined as time from random assignment to next breast event (ie, disease recurrence at local, regional, or distant site; new contralateral breast cancer; or death). All medical records of breast events were examined centrally to assess clinical confirmation of disease.

Statistical Analysis

Median values, range interquartiles, and results from nonparametric Wilcoxon tests were presented to investigate differences in adiponectin and leptin levels and L-A ratio according to risk strata and breast events. χ^2 or Fisher's exact tests were used to analyze the association between categorical variables. We calculated Spearman correlation coefficients between adiponectin, leptin, L-A ratio, IGF-I, HDL cholesterol (HDL-C), body mass index (BMI), and HOMA index with mammographic percent density, a recognized prognostic factor of breast cancer.

Adiponectin and leptin levels and L-A ratio were investigated as continuous and categorical variables, considering median and quartile values. Analysis of covariance was used to evaluate the association between these biomarkers and mammographic percent density. Residual plots assessed the validity of model assumptions. Risk analyses were conducted using logistic regression, and odds ratios were calculated to assess the probability of having IEN/T1, as compared with unaffected high-risk women, or of having a breast event by biomarkers.

Time to death and time to recurrence were defined as time from surgery to event of interest. All patients alive or free of disease at last follow-up date were considered right censored. Disease-free survival was estimated by the Kaplan-Meier method. Log-rank and linear-rank tests were used to compare survival time between groups and evaluate linear trends. A Cox proportional hazards model was used to identify independent predictors of survival, with adjustment for relevant covariates. We evaluated the influence of mammographic percent density, HOMA index, BMI, waist-hip ratio (WHR), age, treatment group, risk stratum, family history, reproductive factors, and several biomarkers on the association of adiponectin and leptin levels with breast events. We further evaluated the influence of positive margins and radiotherapy on the association of adiponectin with breast events in the subgroup of affected women. Given the different breast cancer risks by disease status and the prognostic relevance of mammographic percent density, Cox models evaluating the influence of adiponectin were adjusted for these two potential confounding factors. All statistical tests were two sided, and *P* values less than .05 were considered statistically significant. Statistical analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC).

RESULTS

After a median follow-up of 7.2 years, a total of 57 breast neoplastic events (IEN/T1 stratum, 53; Gail stratum, four) were observed. All events but four (*n* = 53) were second breast neoplasms in women with prior IEN (*n* = 50) or pT1mic/T1a disease (*n* = 3): DIN, 19; LIN, two; sarcoma, one; stage I breast cancers, 31; ipsilateral neoplasms, 40; and contralateral neoplasms, 13. In the Gail stratum, one woman developed LIN, and three women developed invasive breast cancers.

Baseline patient and tumor characteristics by treatment allocation arm are reported in Table 1. Margin involvement was present in 12% of affected women, and 35% of women with DIN or microT1 received radiotherapy following institutional guidelines. Adiponectin, leptin, and L-A ratio at baseline and 24 months (end of treatment) were not different by treatment group, and changes in biomarker levels during treatment were not significant (data not shown).

Table 2 lists baseline median values and interquartile ranges of plasma adiponectin, leptin, and L-A ratio according to disease status at baseline and new breast events occurring during follow-up. We found a significantly lower median level of adiponectin (*P* = .006) and a higher L-A ratio (*P* = .035) in women in the IEN/T1 stratum compared with women in the Gail stratum, whereas

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	Tamoxifen Plus Placebo (n = 58)	Fenretinide Plus Placebo (n = 59)	Tamoxifen Plus Fenretinide (n = 60)	Placebo Plus Placebo (n = 58)
Disease status, No.				
Gail	14	13	14	13
LIN	7	9	9	5
DIN	32	32	30	36
T1a	5	5	7	4
Age at entry, years				
Median	47	46	46	46
IQ range	42-49	43-50	41-49	43-49
Body mass index, kg/m²				
Median	23	23	23	23
IQ range	22-25	21-25	21-25	21-25
ER status, No.				
Positive	24	24	26	29
Negative	5	5	5	7
Unknown	15	17	15	9
PgR status, No.				
Positive	24	21	19	30
Negative	5	8	12	6
Unknown	15	17	15	9
Mammographic percent density				
Median	48	47	47	45
IQ range	40-61	36-57	35-60	32-58
IGF-I, ng/mL				
Median	130	143	140	146
IQ range	111-165	116-182	118-182	114-181
HDL-C, mg/dL				
Median	65	71	69	68
IQ range	57-78	57-81	60-79	60-78

NOTE. No significant differences by treatment group.
Abbreviations: DIN, ductal intraepithelial neoplasia; ER, estrogen receptor; HDL-C, high-density lipoprotein cholesterol; IGF-I, insulin-like growth factor I; IQ, interquartile; LIN, lobular intraepithelial neoplasia; PgR, progesterone receptor.

no significant difference in leptin levels was observed. Similarly, adiponectin levels were significantly lower (*P* = .002) and L-A ratio significantly higher (*P* = .02) in women with a subsequent breast neoplastic event compared with women who had no new breast event during follow-up. The relationships of adiponectin, leptin, and L-A ratio with IGF-I, HDL-C, BMI, HOMA index, and mammographic percent density are summarized in Table 3. Adiponectin was negatively correlated with leptin, BMI, HOMA index, and L-A ratio, whereas a significant positive association with mammographic percent density and HDL-C was observed. Leptin and L-A ratio showed similar statistically significant correlations, although they occurred in the opposite direction. As expected, there was a strong negative correlation between baseline BMI and mammographic percent density (*P* < .001). BMI was similar in women with baseline adiponectin levels below and above the median value of 10 μ g/mL (22.7 v 22.9 kg/m²). Furthermore, BMI was similar by risk group (22.5 and 23.0 kg/m² for Gail and IEN/T1, respectively).

When we evaluated the association between mammographic percent density and adiponectin levels in an analysis of covariance model adjusting for BMI, we found a significant positive association

Table 2. Baseline Adiponectin, Leptin, and L-A Ratio by Disease Stratum and New Breast Cancer Events During Follow-Up

Biomarker	No. of Patients	Median	IQ Range
Risk stratum			
Adiponectin, $\mu\text{g/mL}^*$			
Gail	54	12	8.6-16.1
IEN/T1	181	9.8	6.9-13.5
Leptin, ng/mL			
Gail	54	10	6.2-16
IEN/T1	181	10.8	7.3-15.6
L-A ratio†			
Gail	54	0.87	0.54-1.35
IEN/T1	181	1.13	0.63-1.85
New breast cancer events			
Adiponectin, $\mu\text{g/mL}^\ddagger$			
No	178	10.9	7.8-14.4
Yes	57	8.1	6.5-12.2
Leptin, ng/mL			
No	178	10.6	6.8-15.4
Yes	57	11.7	7.3-16.2
L-A ratio§			
No	178	0.98	0.55-1.6
Yes	57	1.32	0.8-2.26

Abbreviations: IEN, intraepithelial neoplasia; IQ, interquartile; L-A, leptin-to-adiponectin.

*Wilcoxon test $P = .006$.

†Wilcoxon test $P = .035$.

‡Wilcoxon test $P = .002$.

§Wilcoxon test $P = .02$.

($P = .03$), indicating that adiponectin may be independently associated with mammographic density. We then compared women with prior IEN/T1 with unaffected high-risk women and found that adiponectin was associated with disease status; risk of having baseline IEN/T1 decreased by 8% per each unit increase of adiponectin (odds ratio [OR], 0.92; 95% CI, 0.86 to 0.98; $P = .007$, adjusted for BMI and mammographic percent density). The observed association remained statistically significant after adjustment for other variables shown in Table 3.

Known breast cancer risk factors and new breast events, mostly second breast neoplasms, according to median adiponectin level are summarized in Table 4. We observed that participants with lower adiponectin values presented greater WHR and HOMA index but lower mammographic percent density and a higher frequency of new diagnosed breast events. Adjusting for BMI, mammographic percent density, and disease status, we found a significantly lower risk of breast events for women with adiponectin higher than the median value of 10 $\mu\text{g/mL}$ (OR, 0.87; 95% CI, 0.79 to 0.95; $P = .003$). The association did not change when we adjusted for treatment arm allocation (OR, 0.86; 95% CI, 0.78 to 0.95; $P = .002$). A similar trend was observed when adiponectin was categorized into quartiles (7, 10, and 14 $\mu\text{g/mL}$). Women with baseline adiponectin levels in the higher quartile were at decreased risk for breast neoplastic events compared with women with adiponectin levels in the lowest quartile (OR, 0.20; 95% CI, 0.07 to 0.62; $P = .002$).

Disease-free survival curves according to median adiponectin levels are shown in Figure 2. There was a reduced breast cancer risk with increasing baseline adiponectin level. Log-rank test for median and quartile values of adiponectin indicated a significant association with disease-free survival ($P = .02$; P for trend among quartile values = .005). None of the potential confounding factors considered in Table 4 achieved statistical significance when included in the multivariate Cox model. The hazard ratio (HR) from the Cox model, adjusting for disease status and mammographic percent density, was 0.88 (95% CI, 0.81 to 0.96; $P = .002$) for one unit increase of adiponectin level and 0.40 (95% CI, 0.24 to 0.85) for adiponectin higher than 10 $\mu\text{g/mL}$ versus lower values. When we further adjusted for BMI and treatment arm allocation, the risk remained significant (HR, 0.88; 95% CI, 0.81 to 0.96; $P = .003$ for one unit of increase). When we included WHR instead of BMI, among the confounders, the HR did not change (HR, 0.86; 95% CI, 0.77 to 0.94). Adiponectin was associated with new breast events independently from all other confounding factors, including BMI, WHR, and HOMA index. The change in adiponectin at different times (2 and 3 years) was not significantly associated with disease-free survival. However, there was a tendency for more women without an event to show an increase in adiponectin level compared with women with an event (60% v 50%). Further

Table 3. Baseline Spearman Correlations (ρ) and No. of Observations

Variable	Adiponectin		Leptin		L-A Ratio		BMI		MX % Density		HOMA Index		IGF-I		HDL-C	
	ρ	No.	ρ	No.	ρ	No.	ρ	No.	ρ	No.	ρ	No.	ρ	No.	ρ	No.
Adiponectin	1	235	-0.16*	235	-0.65†	235	-0.18‡	235	0.23‡	195	-0.20‡	235	0.003	234	0.29†	235
Leptin			1	235	0.83†	235	0.66†	235	-0.30†	195	0.34†	235	-0.06	234	-0.14*	235
L-A ratio					1	235	0.58†	235	-0.35†	195	0.36†	235	-0.06	234	-0.27†	235
BMI							1	235	-0.39†	195	0.27†	235	-0.09	234	-0.26†	235
MX % density									1	195	-0.20‡	195	-0.11	194	0.11	195
HOMA index											1	235	0.19‡	234	-0.16*	235
IGF-I													1	234	0.03	234
HDL-C															1	235

NOTE. Pairwise comparisons were not significant unless otherwise indicated.

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; IGF-I, insulin-like growth factor I; L-A, leptin-to-adiponectin; MX, mammographic.

* $P < .05$.

† $P < .001$.

‡ $P < .01$.

Table 4. Known Breast Cancer Risk Factors and New Breast Events by Adiponectin Level

Risk Factor	Patients		Adiponectin (μg/mL)				P*
			> 10		≤ 10		
	No.	%	No.	%	No.	%	
Total	235		117		118		
Age, years							.75
Median			46		46		
Q1-Q3			42-49		42-49		
BMI							.05
Median			23		23		
Q1-Q3			21-24		22-26		
WHR							.02
Median			0.81		0.83		
Q1-Q3			0.76-0.87		0.79-0.90		
HOMA index							.02
Median			2.74		3.10		
Q1-Q3			2.05-3.65		2.37-4.01		
MX % density							.01
Median			51.1		43.8		
Q1-Q3			38.6-61.2		33.9-54.1		
Breast cancer family history	85		43	37	42	36	.9
Any pregnancy	197		98	84	99	84	.9
IEN/T1 stratum	181		85	73	96	81	.11
Gail stratum	54		32	27	22	19	
New breast events	57		20	17	37	31	.01
IEN/T1 stratum	53 of 181	29	19 of 85	22	34 of 96	35	.05
New breast event in Gail stratum	4 of 54	7	1 of 32	3	3 of 22	14	.15

Abbreviations: BMI, body mass index; HOMA, homeostasis model assessment; IEN, intraepithelial neoplasia; MX, mammographic; Q1-Q3, first to third quartile; WHR, waist–hip ratio.

*χ² or Wilcoxon test.

Abbreviations: BMI, body mass index; HOMA, homeostasis model assessment; IEN, intraepithelial neoplasia; MX, mammographic; Q1-Q3, first to third quartile; WHR, waist-hip ratio.

* χ^2 or Wilcoxon test.

analysis was carried out excluding LIN as a breast neoplastic event. Results for disease-free survival excluding LIN as outcome measure did not change (HR, 0.87; 95% CI, 0.80 to 0.95; $P = .0011$ for one unit increase of adiponectin). When radiotherapy was included in the subgroup analysis of affected women, the HR for adiponectin level remained significant (HR, 0.93; 95% CI, 0.87 to 0.99; $P = .02$). HOMA

Fig 2. Disease-free survival according to median baseline adiponectin level of 10 $\mu\text{g/mL}$.

index and mammographic percent density were not associated with breast neoplastic events.

DISCUSSION

In this prospective analysis within our randomized chemoprevention trial in premenopausal women, we found that participants with low plasma adiponectin levels had a significantly higher risk of a breast neoplastic event. The association seemed to be independent of known risk factors such as BMI and mammographic percent density. We observed that at the baseline time point, adiponectin levels were lower in women with a history of breast neoplastic events compared with unaffected women at risk according to the Gail model. More importantly, baseline adiponectin levels predicted new breast events during follow-up; women with adiponectin less than 10 $\mu\text{g/mL}$ were at 2.47-fold increased risk of developing a new breast neoplastic event.

Our results are consistent with some,^{18-20,22,35} but not all,^{21,23,32,36} case-control studies showing an inverse association between adiponectin level and breast cancer risk. Moreover, significantly lower adiponectin levels were found only in postmenopausal women with breast cancer compared with healthy controls,^{18-21,23} whereas other reports have shown a stronger association in premenopausal and obese women.^{22,36} It has also been suggested that the L-A ratio could be a suitable marker to determine breast cancer risk rather than adiponectin alone.³⁶

We found that adiponectin levels were directly associated with mammographic percent density, whereas leptin and L-A ratio were inversely correlated. This is in line with a recent report by Maskarinec et al,³⁷ although they conversely found no more association after adjustment for BMI. We also found that adiponectin was inversely correlated with BMI, whereas leptin and L-A ratio showed direct correlations, in line with previous reports.^{18,20,23,32,35,36} A positive correlation between adiponectin level and percent breast density, a strong predictor of subsequent breast cancer risk, may mean that the potential protective effect of adiponectin on breast cancer is not mediated by mammographic density.

In the NHS (Nurses Health Study) and NHS II cohorts,²¹ the relationship between adiponectin level and breast cancer risk significantly differed by ductal versus lobular breast cancer type among postmenopausal women, with an inverse association noted only in ductal cancers. No differences were observed by in situ versus invasive status.^{20,21} Our results cannot support any definitive conclusion because of the limited power of this subgroup analysis.

Studies evaluating concentrations and expression of adiponectin and its receptors in breast cancer tissue further support the inverse association between adiponectin and breast cancer risk. Adiponectin expression has been found to be higher in the adjacent adipose tissue compared with breast cancer tissues, in which it is weak or not expressed.^{22,38} Conversely, adiponectin receptors AdipoR1 and AdipoR2 have been found to be expressed more highly in in vitro malignant cells and in breast cancer tissue compared with normal breast tissue.^{22,39} The higher AdipoR1 expression in epithelial and stromal cells of invasive breast cancer tissue compared with preinvasive lesion tissues⁴⁰ suggests that lower adiponectin levels in patients with invasive breast cancer may trigger upregulation of AdipoR1 expression in breast cancer tissue as a feedback loop.

The mechanisms linking adiponectin with insulin resistance, obesity, and human diseases have been studied extensively.^{6,41-46} Accumulating evidence indicates that adiponectin plays a remarkable role in glucose and lipid metabolism. In the liver, adiponectin enhances insulin sensitivity, reduces hepatic glucose output, increases fatty acid oxidation,^{43,47} and exerts anti-inflammatory and antiatherogenic properties.^{42,44} In our study, adiponectin levels were inversely correlated with the HOMA index, supporting the close connection between adiponectin and insulin resistance. A recent report from the HEAL (Health, Eating, Activity, and Life-style) study, a prospective cohort study to evaluate whether diet, weight, physical activity, lifestyle, hormones, or other factors affect breast cancer prognosis,⁴⁸ showed that elevated HOMA score and low adiponectin levels were associated with increased breast cancer mortality. Interestingly, a causal role of adiponectin reduction in the development of insulin resistance, type 2 diabetes, metabolic syndrome, and atherosclerosis has been proposed. Adiponectin levels were reduced in obesity, which is also associated with decreased expression levels of adiponectin receptors, thereby reducing adiponectin signaling and finally leading to insulin resistance through a “vicious cycle.”^{42(p446)}

To date, the mechanisms underlying the protective role of adiponectin in carcinogenesis are not fully understood. Adiponectin may act either directly on cancer cells or indirectly by regulating whole-body insulin sensitivity.⁴⁴ Another potential mechanism could involve regulating the bioavailability of growth factors and steroid hormones.⁴⁹ Overall, available data suggest a possible protective role of adiponectin in breast cancer development, and our results are consistent with previous such findings.

In our study, we found that both tamoxifen and fenretinide did not affect adiponectin level. Different compounds have been shown to modulate adiponectin levels in humans. We previously showed that fenretinide decreased the HOMA index, thus reducing insulin resistance, in women with BMI greater than 25 kg/m² in the same study, whereas tamoxifen had an opposite effect.²⁶ Conversely, metformin alone in young women with polycystic ovary syndrome or in diabetic patients^{50,51} and metformin plus pioglitazone or pioglitazone alone in diabetic patients have been associated with adiponectin increase.^{52,53} Also, rosiglitazone and imatinib have been shown to increase adiponectin concentrations in nondiabetic patients with metabolic syn-

drome⁵⁴ and in patients with chronic myeloid leukemia,⁵⁵ respectively, whereas atorvastatin has decreased adiponectin in hypercholesterolemic patients.⁵⁶ Moreover, diet, weight loss, and physical exercise have been shown to increase adiponectin levels in obese patients,^{11,57,58} and adiponectin increase has been observed with safflower oil,⁵⁹ stabilized rice bran,⁶⁰ and dairy-supplemented diet⁶¹ in obese or diabetic patients. Further investigation is necessary to assess the role of adiponectin as a breast cancer risk biomarker and its potential direct effect on breast carcinogenesis pathways.

In conclusion, we found that participants with low plasma adiponectin levels had a significantly higher risk of breast neoplastic events in our randomized chemoprevention trial in premenopausal women. Our findings suggest that adiponectin is a risk biomarker for breast cancer, but additional prospective studies should be conducted before the conclusion can be made that low adiponectin has a causal or promotional role in premenopausal breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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