LETTER TO THE EDITOR

Premenopausal Breast Cancer: Estrogen Receptor Status and Insulin-Like Growth Factor-I (IGF-I), Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3), and Leptin

To the Editor:

The serum endocrine factors such as insulin-like growth factor I (IGF-I), IGF binding protein-3 (IGFBP-3), and leptin have been linked with premenopausal breast cancer (1–3). Several reports have evaluated these endocrine factors in relation to breast cancer estrogen receptor (ER) status. In postmenopausal Danish women, higher levels of IGFBP-3 are associated with ER positive breast cancer while no link was found with IGF-I (4). Conversely, Goodwin et al. report higher levels of IGFBP-3 and leptin in association with ER negative disease in a cohort comprised of both pre and postmenopausal women (5,6). While Chen, in a smaller sample, found no association between leptin levels and tumor ER status. The associations of the IGF pathway and leptin in premenopausal breast cancer only are not known. Menopausal status may be of particular importance in respect to these body size-related factors as the IGF factors and obesity have contrary effects on breast cancer risk in pre versus postmenopausal women.

To better determine the relationship of these factors we examined a group of premenopausal women with newly diagnosed breast cancer to further define the relationships between tumor ER status, the IGF pathway, and leptin. We hypothesized that high IGF-I, high leptin, and low IGFBP-3 levels would be associated with ER-positive disease status compared with ER-negative tumors and that BMI may modify this association, such that the associations would be stronger among larger premenopausal women.

Cases were enrolled in two trials that shared a protocol for eligibility, blood draws, and a demographic and body composition questionnaire at The University of Texas M. D. Anderson Cancer Center from March 1998 to March 2001. Participants were premenopausal women of age 18–52 years who were diagnosed with non-invasive or early stage invasive breast cancer within 6 months of study enrollment and had received no chemo or hormonal therapy prior to blood draw. One hundred eight premenopausal cases (82 ER-positive, 26 ER-negative) with stored serum, questionnaire data, and breast cancer pathology reports were available for analysis.

Serum samples were drawn at the time of study entry and stored frozen at −70°F. Samples were analyzed for total IGF-I, IGFBP-3, and leptin by sandwich-type ELISAs (Diagnostic Systems Laboratories, Inc. Webster, TX). For IGF-I, duplicate aliquots of each serum sample were pretreated according to the manufacturer's instructions and assayed; IGFBP-3 and leptin were also assayed in duplicate. Individual samples with %CV >15% were reassayed as above to obtain values with %CV <15% and only results for tests with %CV <15% are reported. The mean values of the duplicate results from each individual were used in the data analysis.

After evaluating distributions for normality, baseline characteristics were compared by *t*-test or Chi-square as appropriate. Tertile cut points for IGF-I, IGFBP-3, and leptin were determined by using the data from the ER-positive cases as the referent group. To capture the amount of unbound IGF-I, we analyzed the ratio of IGF-I to IGFBP-3. For analysis of IGF-I, IGF-I/IGFBP-3 ratio, and leptin, the lowest two tertiles were combined and compared with the highest tertile. For IGFBP-3, the top two tertiles were combined and compared with the lowest tertile. We also compared differences in mean hormone levels in normal weight women to those of their overweight and obese counterparts combined. The significance of differences between mean hormone levels by ER status was tested by using the Students *t*-test. Univariate and multivariable logistic regression was used to calculate odds ratios as estimates of relative risks predicting risk of ER-negative disease versus ER-positive disease for high

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Table 1. Mean hormone levels by normal versus overweight and hormone receptor status

	BMI < 25			BMI ≥ 25		
	N = 62			*N* = 46		
	ER+ (*N* = 47)	ER− (*N* = 15)	p-value	ER+ (*N* = 35)	ER− (*N* = 11)	p-value
IGF-I(ng/mL)	164.8	171.1	0.73	170	171.6	0.94
IGFBP-3(ng/mL)	4356.2	4617.2	0.43	4437.3	4814	0.25
IGF-I/IGFBP-3	0.038	0.038	0.97	0.038	0.036	0.50
Leptin(ng/mL)	17.6	28	0.03	50.3	48.3	0.83

IGF-I, high leptin, and low IGFBP-3 levels, and a high ratio of IGF-I to IGFBP-3. As results were not different when other variables were entered into the model as potential confounders, the results for the univariate analyses are reported here. All statistical analysis was done using SAS v. 8.0 (SAS Institute Inc., Cary, NC).

Except for ethnicity and disease stage, we found no difference in the selected characteristics by ER status. Additionally, there was no significant difference in mean levels of cytokine hormones by parity. However, we found patients with ER-negative tumors to have higher IGFBP-3 levels than their counterparts with ER-positive disease (61.5% versus 34.2%), albeit not significantly so. Overall, higher levels of IGF-I, IGFBP-3, and leptin, and a larger ratio of IGF-I to IGFBP-3 were not associated with increased risk of having a specific ER type of cancer.

No differences in mean IGF-I, IGFBP-3, IGF-I/IGFBP-3 ratio, and leptin were seen within normal weight women by ER status or within overweight and obese individuals. As we expected, overweight and obese women had higher leptin regardless of tumor type. Unexpectedly, among nonoverweight women, patients with ER-negative cancers had significantly higher average leptin levels than those with ER-positive disease. (Table 1) Regardless of BMI, those with ER-negative tumors tended to have higher levels of IGFBP-3.

In summary our analysis of premenopausal breast cancer cases found no significant associations between serum IGF-I, IGFBP-3, and leptin levels and the ER status of tumors. Yet, we made two intriguing observations: first, women with ER negative tumors had higher IGFBP-3 levels than their counterparts with ER positive disease. The findings support our a priori hypothesis that greater levels of IGFBP-3 would be inversely associated with ER positivity. Second, we also observed that nonoverweight premenopausal patients with ER-negative tumors had higher leptin levels than their counterparts with ER-positive disease. This observation supports findings for higher leptin levels among pre and postmenopausal breast cancer patients with ER-negative tumors reported by Goodwin et al. (6). One could imagine that leptin has a different role in carcinogenesis and determining ER status below a certain BMI threshold, just as obesity is associated with both increased and decreased risk of breast cancer depending upon menopausal status (7).

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