Adiposity and Sex Hormones in Postmenopausal Breast Cancer Survivors

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Purpose: **Overweight and obese women with breast cancer have poorer survival compared with thinner women. One possible reason is that breast cancer survivors with higher degrees of adiposity have higher concentrations of tumor-promoting hormones. This study examined the association between adiposity and concentrations of estrogens, androgens, and sex hormone–binding globulin (SHBG) in a population-based sample of postmenopausal women with breast cancer.**

Methods: **We studied the associations between body mass index (BMI), body fat mass, and percent body fat, measured by dual-energy x-ray absorptiometry scan, waist circumference, and waist-to-hip circumference ratio, with concentrations of estrone, estradiol, testosterone, SHBG, dehydroepiandrosterone sulfate, free estradiol, and free testosterone in 505 postmenopausal women in western Washington and New Mexico with incident stage 0 to IIIA breast cancer. Blood and adiposity measurements were performed between 4 and 12 months after diagnosis.**

Results: **Obese women (BMI ≥ 30) had 35% higher concentrations of estrone and 130% higher concentrations of estradiol compared with lighter-weight women (BMI < 22.0; *P* = .005 and .002, respectively). Similar associations were observed for body fat mass, percent body fat, and waist circumference. Testosterone concentrations also increased with increasing levels of adiposity (*P* = .0001). Concentrations of free estradiol and free testosterone were two to three times greater in overweight and obese women compared with lighter-weight women (*P* = .0001).**

Conclusion: **These data provide information about potential hormonal explanations for the association between adiposity and breast cancer prognosis. These sex hormones may be useful biomarkers for weight loss intervention studies in women with breast cancer.**

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OVERWEIGHT AND obese women with breast cancer have poorer survival compared with thinner women, but the reasons for this are unknown. Women with a high body mass index (BMI) have twice the risk of recurrence over 5 years and a 60% increased risk of death over 10 years, compared with normal-weight or thinner women.[1] In postmenopausal women without breast cancer, increased BMI is associated with high concentrations of blood estrogens and low concentrations of sex hormone–binding globulin (SHBG).[2-4] The high estrogen concentrations likely represent conversion of androgens to estrogens by the enzyme aromatase in adipose tissue.[5,6] Both estrogen and testosterone promote breast cancer cell growth.[7] In this Health, Eating, Activity, and Lifestyle (HEAL) study, we assessed the associations of BMI, percent body fat, waist circumference, and waist-to-hip ratio with serum sex hormone concentrations in a population-based cohort of postmenopausal breast cancer survivors.

METHODS

Eligibility and Recruitment

HEAL is a population-based, multicenter, multiethnic prospective cohort study of 1,185 women with breast cancer to determine whether weight, physical activity, diet, sex hormones, and other exposures affect breast cancer prognosis. The current analyses were limited to two of the three centers (western Washington and New Mexico), because the third center (southern California) did not collect blood at study enrollment. We identified patients with newly diagnosed stage 0 to IIIA breast cancer between 1996 and 1999 who were living in the King, Pierce, or Snohomish counties in Washington or in the Bernalillo, Sante Fe, Sandoval, Valencia, or Taos counties in New Mexico. The patients needed to be interviewed, have anthropometric and body composition measures, and have blood drawn within 4 to 12 months of diagnosis. Of the 2,073 women with breast cancer in western Washington and New Mexico who were eligible by age, stage, and county of residence, 856 (41%) were enrolled onto the study. A group of patients (n = 278) in western Washington were interviewed for another study and could not be approached for the HEAL study. Of 202 western Washington and 654 New Mexico women interviewed, 198 (98%) and 542 (83%) provided a blood sample, respectively.

Written informed consent was obtained from each patient. The study was performed after approval by the institutional review boards of participating centers, in accord with an assurance filed with and approved by the United States Department of Health and Human Services.

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Data Collection

We used a standardized questionnaire (self-administered in western Washington, in-person interviews in New Mexico). Anthropometric, body composition, and physical activity data were collected at a clinic visit or at home. The data for the present analyses were limited to those collected at study entry.

Anthropometric Measures

Trained staff measured height and weight in a standard manner at a clinic or home visit. Waist circumference was measured in centimeters at the smallest circumference (western Washington) or just above the superior margin of the iliac crests (New Mexico). Hip circumference was measured in centimeters at the largest circumference (western Washington) or at the maximal posterior projection of the buttocks (New Mexico). Percent body fat was primarily measured from whole-body scans using a dual-energy x-ray absorptiometry (DXA) scanner (Lunar model DPX [GE Medical Systems, Milwaukee, WI] in New Mexico; Hologic model QDR 1500 [Hologic Inc, Walthan, MA] in western Washington). BMI data were missing for two women, and DXA data were missing for 90 women.

Other Variables

Questionnaire information was collected on dietary intake (120-item food frequency questionnaire); health habits; history of benign breast disease; reproductive and menstrual history (age at menarche, regularity of periods when menstruating, age at menopause, type of menopause, hysterectomy status, pregnancy history including age at first and last full-term pregnancy, and lactation history); history of oral contraceptive and hormone replacement therapy use; history of endocrine and other medical problems; history of benign breast disease; family history of breast cancer, other cancers, and diabetes mellitus; history of tobacco, caffeine, and alcohol use; lifetime weight patterns; detailed current and prediagnostic leisure, household, and work physical activity habits; mammographic screening; and education, income, and race or ethnicity.

Blood Collection and Sex Hormone Assays

A 30-mL sample of blood was collected at interview when the patient was either fasting (western Washington) or not fasting (New Mexico). Blood was processed within 1 hour of collection and serum, plasma, and buffy coat were aliquoted into 1.8-mL tubes and stored at −70° to −80° C. Dates of sample collection and processing, time of day of blood collection, current use of tamoxifen, and time since last meal were recorded. There were a small number of patients for whom we had insufficient blood to perform all assays (number of patients with missing data is detailed in Tables 2 and 3).

Estrone and estradiol assays were performed at Quest Diagnostics (San Juan Capistrano, CA) between February 1999 and June 1999 (for western Washington) and between September 1997 and December 1999 (for New Mexico). Estradiol was not measured in postmenopausal women from New Mexico; therefore, data are available only for the 118 postmenopausal patients from western Washington. SHBG and dehydroepiandrosterone sulfate (DHEAS) assays were conducted (in the laboratory of R.B.) at the University of New Mexico between April 1999 and October 1999 (for western Washington samples) and between September 1997 and December 1999 (for New Mexico samples). Testosterone assays were conducted (in the laboratory of R.B.) at the University of New Mexico between October 2002 and December 2002 (for western Washington samples) and between September 1997 and December 1999 (for New Mexico samples). Samples were randomly assigned to assay batches and were randomly ordered within each batch. Laboratory personnel performing the assays were blinded to patient identity and personal characteristics.

Estrone and estradiol assay methods consisted of organic solvent extraction, followed by celite column partition chromatography before quantification by radioimmunoassay (sensitivities of 10 and 2 pg/mL, respectively). Testosterone was measured using a radioimmunoassay kit (sensitivity of 40 pg/mL; Diagnostic Products Corp, Los Angeles, CA). SHBG was measured with the Radim radioimmunoassay quantitation SHBG Kit (sensitivity of 6 nmol/L; Wien Laboratories, Succasunna, NJ). DHEAS concentrations were determined using a DHEAS radioimmunoassay kit (sensitivity of 1.1 μg/dL; Diagnostic Products Corp).

To estimate intra-assay variability, the western Washington assays for SHBG and DHEAS included a total of 10 blinded replicates in the same assay batch for 10 patients. In addition, samples from two different patients were included in every assay batch for SHBG and DHEAS to estimate inter-assay variability. For testosterone, 24 pooled quality-control samples were included (two samples per batch). Replicated samples were not included in the estrogen assays at the baseline analysis; however, 20 replicated samples and eight pooled quality-control samples (two samples per batch) were included in an analysis of follow-up blood assays completed between July 2001 and August 2001 in the same laboratory. The intra- and interassay variabilities were derived from these data.

To estimate the intra-assay and total coefficients of variation (CV), we used a random effects model to assess the respective variance components. Hormone values were natural-log transformed, and identification and batch number were included as random effects in the model. We used the square root of the mean squared error as a measure of the intra-assay CV on the original scale.[8] We estimated the total CV by taking the square root of the sum of the mean squared error and the mean squared variability due to the batches. The intra-assay and total CVs were 3.8% and 5.9% for SHBG, respectively, and 4.6% and 9.5% for DHEAS, respectively. For testosterone, the intra-assay CV was 12.0%, and the total CV was 14.4%. For estradiol and estrone, the intra-assay CV results were 28.8% and 13.3%, respectively, and the total CV results were 29.1% and 13.3%, respectively. Other than the CVs for estradiol, these CVs are similar to those observed in other studies using similar assay methods to test samples with low concentrations of sex hormones.

Data Analysis

We categorized BMI (kg/m^2) as light (< 22.0), normal weight (22.0 to 24.9), moderately overweight (25.0 to 27.5), severely overweight (27.6 to 29.9), or obese (≥ 30.0). We also categorized BMI using the World Health Organization public health cut points for obese (BMI ≥ 30.0), overweight (BMI ≥ 25.0), and normal or underweight (BMI < 25.0).[9] We categorized percent body fat, waist circumference, and waist-to-hip ratio into quartiles. We calculated total fat mass by multiplying DXA-derived percent body fat by weight, and we divided participants into quartiles of this variable.

We calculated free estradiol and free testosterone concentrations (unbound to either SHBG or albumin) using values for estradiol, testosterone, and SHBG with the equations of Sodergard et al.[10] We applied a natural-log transformation to all hormone values to reduce the positive skewness of the distributions. We deleted data from two women who had out-of-range testosterone concentrations ($> 4{,}000$ pg/mL) and from two women who had out-of-range estradiol concentrations (319 and 639 pg/mL, respectively).

For women who had hormone concentrations below the detectable levels, we assigned a value halfway between zero and the lower limit of detection. Thus, 34 women were assigned an estrone value of 5 pg/mL and 49 women were assigned a testosterone value of 20 pg/mL.

We calculated geometric mean values and 95% confidence intervals (CIs) for hormone concentrations within categories of four measures of adiposity (BMI, percent body fat, waist circumference, and waist-to-hip ratio). We performed tests for linear trends across increasing categories of adiposity using a generalized linear modeling approach[8,11] to investigate associations between adiposity and hormone values adjusted for the following variables: age, ethnicity, current tamoxifen use (yes or no), breast cancer treatment (surgery alone, surgery plus radiation, surgery plus chemotherapy, and surgery plus radiation plus chemotherapy), time between diagnosis and blood draw, oophorectomy and hysterectomy status, physical activity, alcohol use, smoking, and cancer stage at diagnosis. We also performed analyses with and without adjustment for daily caloric intake, and because the results were similar, we present data unadjusted for this variable. We assessed the associations between adiposity and hormones separately for the western Washington and New Mexico subjects. The associations between adiposity and hormones did not differ by clinical site, and therefore, we combined the data. We adjusted all combined analyses for clinical site. We also analyzed

Table 1. Characteristics of the HEAL Patients Compared With All Eligible SEER Patients (western Washington and New Mexico only)*

	Western Washington						New Mexico					
	SEER Patients		All HEAL (n = 202)		Postmenopausal HEAL Patients (n = 120)		SEER Patients		ALL HEAL Patients (n = 654)		Postmenopausal HEAL Patients (n = 485)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years, mean ± SD†	52.4 ± 6.7		52.5 ± 6.4		56.2 ± 4.8		60.4 ± 13.9		59.5 ± 12.7		64.1 ± 10.0	
Race or ethnicity‡												
White, non-Hispanic	1,259	89.0	174	86.1	109	90.9	1,227	74.1	497	76.0	304	79.0
African-American	51	3.6	1	0.5	1	0.8						
Hispanic	0	0	6	3.0	2	1.7	429	25.9	153	23.4	78	20.2
Asian-American	75	5.4	14	7.0	6	5.0						
American Indian	2	0.1	2	1.0	1	0.8			4	0.6	3	0.8
Unknown	27	1.9	5	2.5	1	0.8						
Stage of disease												
0, in situ	327	23.1	66	32.4	34	28.3	285	17.2	121	18.5	69	17.9
I	605	42.8	100	49.5	63	52.5	674	40.7	409	62.5	256	66.5
II	424	30.0	33	16.3	20	16.7	482	29.1	122	18.7	60	15.6
III	58	4.1	3	1.4	3	2.5	13	2.0				
Unable to determine							182	11.0	2	0.3		
Lymph nodes												
None	1,036	73.2	160	79.2	95	79.2	1,176	71.0	494	75.5	307	79.7
Regional	336	23.8	34	16.8	23	19.2	398	24.0	137	20.1	68	17.7
Distant	0	0	0	0	0	0	1	0.1	0	0	0	0
Unknown	42	3.0	8	4.0	2	1.6	81	4.9	23	3.5	10	2.6
Estrogen receptor status												
Positive	872	61.7	115	56.9	75	62.5	721	43.5	374	57.1	237	61.6
Negative	168	11.9	21	10.4	11	9.2	351	21.2	91	13.9	40	10.4
Borderline	0	0	0	0	0	0	11	0.7	2	0.3	0	0
Unknown or not performed	379	26.4	64	31.7	34	28.3	575	34.6	187	28.6	108	28.0

Abbreviations: HEAL, Health, Eating, Activity, and Lifestyle; SEER, Surveillance, Epidemiology, and End Results.

*SEER data for patients with breast cancer stage 0 to IIIA, who are residents of King, Pierce, or Snohornish countries of western Washington or of Bernalillo, Santa Fe, Sandoval, Valencia, or Taos countries of New Mexico.

†Western Washington, ages 40 to 64 years only; New Mexico, ages 18+ years.

‡Western Washington, all races eligible except African-Americans who could not be approached because they were being interviewed for another Fred Hutchinson Cancer Research Center study; New Mexico, Hispanic and non-Hispanic whites only eligible.

the data separately for Hispanic and non-Hispanic white women but found no differences by ethnicity in the associations between adiposity and hormones, and thus, we combined all of the women and adjusted for ethnicity in the analysis.

We tested the differences between tamoxifen users and nonusers with respect to adiposity and hormone associations using linear regression. A model was first fitted with an adiposity measure and tamoxifen use, and then with the adiposity measure, tamoxifen use, and the interaction of these two measures, to determine whether there was a significant influence of tamoxifen use for various categories of adiposity. Because the slope of the dose-response curves did not differ between tamoxifen users and nonusers, we present all data for tamoxifen users and nonusers combined.

RESULTS

Table 1 lists select characteristics of the HEAL study participants, compared with characteristics of all breast cancer patients from the respective Surveillance, Epidemiology, and End-Results (SEER) registries from which HEAL participants were recruited, who met eligibility criteria for age, stage at diagnosis, and county of residence. Overall, the HEAL cohort of patients was similar to the SEER patient cohort with respect to age and ethnicity (Table 1). In western Washington, there was a higher proportion of patients with in situ disease and a lower proportion with stage II disease in the HEAL cohort compared with the SEER registry cohort. In New Mexico, the HEAL cohort and SEER cohort had similar proportions of patients with in situ breast cancer, but the HEAL cohort had a smaller proportion of patients with stage II disease. In both western Washington and New Mexico, a larger proportion of HEAL patients were lymph-node negative compared with SEER patients. In western Washington, a greater proportion of SEER patients had estrogen receptor–positive tumors compared with HEAL patients, whereas in New Mexico, the opposite trend was observed.

A total of 505 women (mean age, 62.2 years) were postmenopausal at the time of interview and had both BMI and hormone data available. The sample included 80 Hispanic white, 413 non-Hispanic white, one African-American, and six Asian-American patients and five patients of unknown race. At diagnosis, 21% of the women were stage 0 (in situ), 63% were stage I, and 16% were stage II to IIIA. On average, the women were overweight (mean BMI, 26.9) and had a high percent of body weight comprised of fat (mean, 38.3%). Forty percent of women had a hysterectomy, 20% had a history of bilateral oophorectomy, and 43% were using tamoxifen at the time of blood collection.

BMI

Obese women (BMI $>$ 30.0) had a 35% higher concentration of estrone compared with women with a BMI of less than 22.0 (P = .005; Table 2). Estradiol concentration was increased by

Table 2. Association Between Body Mass Index and Serum Hormones: Geometric Means and 95% Confidence Interval Among a Sample of 503 Postmenopausal Women With Breast Cancer

		Body Mass Index										
	No. of Patients	< 22 (n = 107)		22-25 (n = 112)		25-27.5 (n = 99)		27.5-30 (n = 60)		> 30 (n = 125)		
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	P*
Estrone, pg/mL	491	19.7	17.1 to 22.7	22.3	19.1 to 26.1	21.2	18.8 to 24.0	22.7	19.6 to 26.3	26.5	23.9 to 29.3	.005
Estradiol, pg/mL, †	118	4.7	3.4 to 6.4	8.3	6.2 to 11.0	8.0	5.6 to 11.3	10.6	6.6 to 17.0	10.7	8.6 to 13.4	.002
DHEAS, ng/dL	502	50.5	43.3 to 58.8	53.2	46.4 to 61.1	55.6	48.5 to 63.7	60.0	51.6 to 69.8	59.3	52.2 to 67.4	.21
SHBG, nmol/L	495	73.9	67.2 to 81.3	66.2	60.8 to 72.0	52.1	47.7 to 56.9	43.4	37.9 to 49.6	38.1	34.2 to 42.4	.0001
Testosterone, pg/mL	498	94.5	77.1 to 115.7	118.1	100.7 to 138.5	127.4	105.7 to 153.6	126.0	96.7 to 164.1	176.5	151.4 to 205.7	.0001
Free estradiol, pg/mL†	118	0.10	0.9 to 0.14	0.18	0.14 to 0.24	0.20	0.14 to 0.27	0.28	0.17 to 0.46	0.28	0.23 to 0.36	.0001
Free testosterone, pg/mL	495	2.1	1.6 to 2.6	2.9	2.4 to 3.5	4.0	3.2 to 5.0	4.6	3.3 to 6.6	7.6	6.2 to 9.3	.0001

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone–binding globulin.

*Test for linear trend.

†Number of subjects for estradiol and free estradiol for the five categories of BMI are 17, 25, 24, 14, and 38, respectively.

130% in obese women compared with the lightest women ($P = .002$). Increasing adiposity was associated with increasing testosterone concentrations; obese women had testosterone concentrations that were almost twice as high as those of the lightest women ($P = .0001$). Concentrations of free estradiol and free testosterone were two to three times greater in overweight and obese women compared with the lightest women ($P = .0001$). Concentrations of SHBG decreased with increasing BMI; obese women had an average SHBG concentration that was half that of the women with a BMI of less than 22 ($P = .0001$). Concentrations of DHEAS increased with increasing adiposity, but the test for trend was not statistically significant. When we categorized women by the common cut points for normal (BMI < 25.0), overweight (BMI, 25.0 to 29.9), and obese (BMI ≥ 30.0), a similar gradient of increasing estrogen and decreasing SHBG concentrations was seen, and the results for individual hormones had a similar statistical significance as the results for the data categorized by the more refined categories (data not shown).

Body Fat

Concentrations of several estrogens and androgens increased and SHBG decreased with increasing body fat mass, as measured by DXA scans (Table 3). Women who were in the top quartile for body fat mass had almost twice the serum concentration of estradiol as women in the lowest quartile, and the result was statistically significant ($P = .048$). Free estradiol was significantly increased with increasing quartile of body fat mass ($P = .003$). Concentrations of testosterone and free testosterone increased with increasing quartiles of body fat mass ($P = .0001$). DHEAS also increased with increasing fat mass, but the result was not statistically significant. The concentration of SHBG decreased significantly with increasing quartile of body fat mass ($P = .0001$). The associations between percent body fat and serum hormone concentrations were very similar to those observed for body fat mass, although the results were only statistically significant for testosterone, free testosterone, and SHBG (data not shown).

Waist Circumference and Waist-to-Hip Ratio

Clinical site-specific and combined analyses showed that increased waist circumference was positively associated with estrogens and negatively associated with SHBG, similar to the results for BMI and percent body fat (data not shown). There were no associations observed between waist-to-hip circumference and hormone concentrations (data not shown).

DISCUSSION

A statistically significant association between obesity and recurrence or survival was reported in 23 studies (total women, N = 27,077), whereas no association was reported in seven

Table 3. Association Between Body Fat Mass and Serum Hormones: Geometric Mass and 95% Confidence Intervals Among a Sample of 414 Postmenopausal Women With Breast Cancer (western Washington)

		Quartiles of Body Fat Mass (kg)								
	No. of Patients	< 20 (n = 106)		20-27 (n = 121)		27-34 (n = 94)		> 34 (n = 93)		
		Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	P*
Estrone, pg/mL	404	19.9	17.3 to 22.9	21.2	18.4 to 24.3	20.7	18.5 to 23.2	26.1	23.1 to 29.5	.009
Estradiol, pg/mL†	59	6.6	4.2 to 10.5	6.4	4.8 to 8.4	5.8	3.6 to 9.4	12.2	8.4 to 17.7	.048
DHEAS, μg/dL	413	48.4	41.8 to 56.0	55.1	48.1 to 63.2	55.0	47.6 to 63.6	57.3	50.0 to 65.6	.121
SHBG, nmol/L	407	73.6	67.0 to 81.0	62.5	56.8 to 68.7	49.7	44.1 to 56.1	38.4	33.4 to 44.1	.0001
Testosterone, pg/mL	409	99.9	82.8 to 120.6	112.5	95.5 to 132.6	132.1	109.1 to 160.0	168.6	139.8 to 203.4	.0001
Free estradiol, pg/mL†	59	0.14	0.09 to 0.22	0.13	0.10 to 0.18	0.14	0.09 to 0.22	0.35	0.24 to 0.50	.003
Free testosterone, pg/mL	407	2.2	1.7 to 2.7	2.8	2.2 to 3.4	4.1	3.2 to 5.3	7.2	5.5 to 9.4	.0001

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone–binding globulin.

*Test for linear trend.

†Number of subjects for estradiol and free estradiol for the four categories of body fat mass are 14, 15, 12, and 18, respecively.

studies (total women, N = 4,155).[7] The negative effect of high body weight and BMI on breast cancer recurrence and survival has been observed in both premenopausal and postmenopausal women.[7,13-16] However, potential interactions among adjuvant therapy, obesity, and clinical outcome have not been systematically addressed.

In a meta-analysis, the hazard ratio for recurrence at 5 years by body weight (highest *v* lowest category) was 1.91 (range, 1.52 to 2.40), and for death at 10 years, it was 1.6 (range, 1.38 to 1.76), indicating that women with excess weight at diagnosis are significantly more likely to develop recurrence and less likely to survive.[1] Goodwin et al[15] found that after 3 to 9 years of follow-up, women with newly diagnosed breast cancer (N = 535; median age, 50 years) with a BMI of 27.8 or greater had a 70% increased risk of recurrence (hazard ratio 1.7; 95% CI, 1.3 to 2.3) and an 80% increased risk of death (hazard ratio 1.8; 95% CI, 1.3 to 2.5) compared with lighter-weight women.

In several studies, overweight and obese postmenopausal women without breast cancer have been observed to have higher estrogen and androgen concentrations and lower SHBG concentrations compared with lighter-weight women.[2-4,17-22] High concentrations of estrogens and androgens have been associated with increased risk for incident breast cancer in several cohort studies,[23] indicating that these hormones may be breast-tumor promoters.[7]

One study examined the association between BMI and sex hormone concentrations in 36 women with breast cancer and 36 controls and found that testosterone increased with increasing BMI ($P = .08$).[24] Furthermore, SHBG level was positively associated with increased upper body fat distribution as measured by skin folds. No association between BMI and estrone was observed. However, the sample included both premenopausal and postmenopausal women, and data for patients and controls were combined in the analysis. Therefore, our study is the first to report on the association between adiposity and sex hormones in a relatively large cohort of breast cancer survivors limited to postmenopausal women.

We found statistically significant trends toward increasing estrone, estradiol, testosterone, free estradiol, and free testosterone with increasing BMI, body fat mass, percent body fat, and waist circumference. SHBG significantly decreased with increasing levels of all measures of adiposity.

Our consistent findings among several measures of adiposity (BMI, body fat mass, percent body fat, and waist circumference) and the finding that waist-to-hip ratio was not associated with hormone concentrations at either clinical site, indicate that overall amount of body fat may be more important than distribution of body fat in determining sex hormone concentrations in postmenopausal women with breast cancer. Conversely, numerous studies have reported that hyperandrogenism is more strongly associated with centralized or visceral obesity than generalized obesity in postmenopausal women and is associated with increased cortisol and insulin levels in this obesity phenotype.[25] Some investigators have indicated that waist-to-hip circumference ratio may be an inadequate index of body fat distribution, particularly in postmenopausal women, for a variety of reasons, including the influence of age-related variation in muscle mass and tone.[26]

There are several limitations to these data. Although the study was population-based, only 41% of age- and stage-eligible incident patients were enrolled onto the cohort. Although our analyses were limited to within-cohort comparisons, we cannot be sure that these associations pertain to all breast cancer survivors. Certain races were underrepresented in theses analyses, namely African-American and Asian-American women. Because an additional HEAL site in Los Angeles County has enrolled 273 African-American women with breast cancer (blood not available at baseline), we will be able to assess associations of body mass and hormones in blood collected during the follow-up stage of the study for that racial group.

The methods of data collection were not identical between the two sites for several measures, namely the type of DXA scanner, method of waist circumference measurement, and fasting status at blood draw. We assessed all associations first within each clinical site and only combined data when associations were the same between the two sites, and we adjusted for clinical site in all analyses to compensate for these differences.

The CVs for some hormones, particularly estradiol, were large, although consistent with published CVs for these hormones, and reflect the difficulty with measuring estrogens at the low levels present in postmenopausal women. We did not collect information on whether women were currently undergoing chemotherapy or radiation treatment at the time of their blood draw, and thus, the results could be confounded by current treatment status. However, we did not see a difference in association between serum hormones and adiposity by stage, which indicates that current treatment is unlikely to have been a major confounder because few women with in situ disease underwent radiation or chemotherapy.

These data were cross-sectional only and do not imply cause and effect. Specifically, we did not measure the effect of gain or loss of body mass or body fat on sex hormones. Similarly, although we adjusted our analyses for variables that might be associated with both body mass and hormone levels, there could be other confounding factors that we did not take into account.

Differential variation in sex hormones by body mass and body fat may be one explanation for the poorer survival experienced by overweight women with breast cancer and the poorer response to tamoxifen therapy in overweight or obese women compared with lighter-weight women.[7] In the HEAL population-based cohort of breast cancer survivors, 30% were overweight (BMI, 25.0 to 29.9), and 23% were obese (BMI $\geq$ 30.0). Thus, if reduction of body fat can improve prognosis and survival, a large number of breast cancer survivors might be expected to benefit from weight-loss interventions.

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