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Relationship of obesity and physical activity with c-peptide, leptin, and insulin-like growth factors in breast cancer survivors

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Abstract

Introduction—Obese *and physically inactive* breast cancer patients may have poorer survival compared with lighter-weight *and more active* women. Several obesity- *and physical activity*-related hormones and peptides may explain this association including insulin, leptin, insulin-like growth factor-I (IGF-I), and insulin-like growth factor binding protein-3 (IGFBP-3). Few studies have examined the associations between obesity, physical activity and these hormones/peptides among breast cancer survivors.

Purpose—To determine whether obesity and physical activity are associated with insulin, IGFs, and leptin levels in a population-based sample of 710 women diagnosed with *in situ* to Stage IIIA breast cancer and enrolled in the Health, Eating, Activity, and Lifestyle Study.

Methods—We collected a blood sample and information on physical activity among women diagnosed two to three years earlier using an interview-administered questionnaire. Trained staff measured weight. C-peptide, leptin, and IGFs were assayed by RIA. Mean hormone levels within BMI and physical activity categories were adjusted for confounders using analysis of covariance methods.

Results—We observed *higher* C-peptide (p trend = .0001) and leptin levels (p trend = .0001), and *lower* IGF-I levels (p trend = .0001) with *higher* levels of BMI. We observed *lower* C-peptide (p trend = .001) and leptin levels (p trend = .001), and *higher* IGF-I (p trend = .0037) and IGFBP-3 levels (p trend = .055) with *higher* levels of physical activity.

Conclusions—Increasing physical activity and decreasing body fat may be a reasonable intervention approach towards changing insulin and leptin, thereby *potentially* influencing breast cancer prognosis.

Keywords

exercise; weight; ethnicity; race; menopause

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INTRODUCTION

A handful of recent reviews and epidemiological studies have implicated insulin, insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3) in the progression of breast cancer (1–6). High fasting insulin levels have been associated with a two-fold increase in risk of distant recurrence and a three-fold increase in risk of death among postmenopausal breast cancer survivors (2). Plasma IGF-I levels have been associated with breast cancer recurrence and survival, with the survival probability greater in women with plasma IGF-I levels less than 120 ng/mL (7). High levels of IGFBP-3 have been associated with distant recurrence (5) and death (6). In one study, the effect of IGFBP-3 on distant recurrence was restricted to postmenopausal women and to those with estrogen receptor positive tumors (5). More recently, it has been suggested that leptin, a multi-functional hormone produced predominantly by adipocytes with circulating levels closely reflecting the percentage and amount of adipose tissue (8), acts as a mitogen on many cell types including normal and neoplastic breast cancer (9). While some studies (10,11) have observed associations between leptin and breast cancer risk, the association between leptin and breast cancer recurrence or survival is currently unknown. Thus, as evidence accumulates for an association between breast cancer prognosis and insulin, IGFs, and leptin, it becomes increasingly important to identify modifiable factors that determine these hormone and peptide levels.

At least two dozen studies have also identified obesity and weight gain as important negative prognostic factors for survival among women with this disease (12), although studies in clinical trial patients do not agree (13,14). A meta-analysis estimated that obesity is associated with a two times greater risk of breast cancer recurrence and a 60% increased risk of breast cancer death (12). Recently, higher levels of physical activity after a breast cancer diagnosis were associated with a reduced risk of death from this disease (15). After adjusting for factors predictive of survival after breast cancer, the relative risks of adverse outcomes including death, breast cancer death, and breast cancer recurrence were 26% to 40% lower comparing women with the highest to the lowest category of physical activity. The mechanisms by which lower levels of body fat and higher levels of physical activity may confer protection are poorly understood; however, one intriguing hypothesis links physical activity-induced changes in body fat with changes in insulin and the IGF axis (16). Among healthy women, exercise training, with or without weight loss, has been associated with reduced fasting insulin (17,18) and leptin levels (19,20). Exercise training has also been shown to alter IGF-I and IGFBP-3 in healthy women in some (21), but not all studies (22); and, to our knowledge, only one study has examined the effect of an aerobic physical activity intervention on insulin and IGFs among breast cancer survivors (23). In that study, conducted by Fairey et al.(23), increasing physical activity was associated with statistically significant decreases in IGF-I and increases in IGFBP-3 among breast cancer survivors randomized to a 15-week exercise program compared to controls. However, no significant differences between groups were observed for changes in fasting insulin levels.

Obesity is associated with high insulin and leptin levels among healthy women (8,24–26), but the relationship between obesity and IGFs has varied in previous investigations (27–30). Few studies have examined the associations between obesity and these hormones/peptides among breast cancer survivors (24). A relationship between obesity and IGFs is reasonable because obesity can affect growth hormone secretions, which is the primary determinant of IGF-I production in the liver (29,30).

If it were demonstrated that body fat and physical activity were associated with insulin, IGFs, and leptin levels among women with breast cancer, then additional pathways between obesity, physical activity, and breast cancer prognosis would be *suggested*. To determine

whether obesity and physical activity are associated with insulin, IGFs, and leptin levels, we analyzed data from a cohort of breast cancer survivors enrolled in the Health, Eating, Activity, and Lifestyle (HEAL) Study, a population-based prospective cohort study. This analysis examines *cross-sectional* associations between body fat and physical activity with fasting C-peptide (a marker of insulin production), leptin, IGF-I, and IGFBP-3 in 710 women diagnosed two to three years earlier with *in situ* to Stage IIIA breast cancer. We also examined the influence of ethnicity, menopausal status, and tamoxifen use on the body fat, physical activity, and hormone/peptide associations. To our knowledge, this paper is one of a few examining associations of physical activity and body fat with insulin, leptin, IGF-I and IGFBP-3 among cancer survivors.

METHODS

Study Setting, Subjects, and Recruitment

The HEAL Study is a population-based, multi-center, multi-ethnic prospective cohort study that has enrolled 1183 breast cancer survivors who are being followed to determine whether weight, physical activity, diet, sex hormones, and other exposures affect breast cancer prognosis. Women were recruited into the HEAL Study through Surveillance, Epidemiology, End Results (SEER) registries in New Mexico, Los Angeles County (CA), and Western Washington. Names and contact information were retrieved from the SEER registries. Participants were contacted to determine interest and eligibility (approximately 41% of women with breast cancer who were eligible by age, stage, and county of residence were enrolled into the study). Details of the aims, study design, and recruitment procedures have been published previously (31–33).

Briefly, in New Mexico, we recruited 615 women, aged 18 years or older, diagnosed with *in situ* to Stage IIIA breast cancer between July 1996 and March 1999, and living in Bernalillo, Sante Fe, Sandoval, Valencia, or Taos Counties. In Western Washington, we recruited 202 women, between the ages of 40 and 64 years, diagnosed with *in situ* to Stage IIIA breast cancer between September 1997 and September 1998, and living in King, Pierce, or Snohomish Counties. In Los Angeles County, we recruited 366 Black women with *in situ* to Stage IIIA breast cancer, who had participated in the Los Angeles portion of the Women's Contraceptive and Reproductive Experiences (CARE) Study, a case-control study of invasive breast cancer, or who had participated in a parallel case-control study of *in situ* breast cancer. HEAL Study eligible participants from these two studies were a subset of the women who were diagnosed with breast cancer between May, 1995 and May, 1998. Both studies restricted eligibility to women aged 35 to 64 years at diagnosis who were English speaking and born in the U.S.

Participants completed in-person interviews at baseline (within their first year after diagnosis, mean number of months from diagnosis to interview = 6 ± 5 months) and two-years after the baseline visit (within their third year after diagnosis, mean number of months from diagnosis to follow-up visit = 31 ± 6 months). Between the baseline and follow-up visit, 187 women were diagnosed with a new primary cancer, breast cancer recurrence, or died, and were removed from these analyses because of a potential influence of adjuvant treatment on hormone/peptide levels. A total of 150 women did not complete a follow-up visit, and an additional 54 women did not have body weight measured at the follow-up visit. Two women did not complete the follow-up physical activity interview and 80 women did not have a follow-up blood draw. Our analyses *are cross-sectional using only the follow-up visit information, and* are based on the remaining 710 women (60% of the original cohort). Baseline demographic, physiologic, *and prognostic (i.e., disease stage and adjuvant therapy) characteristics* of the 710 women included in the analysis and the 1185 women enrolled in the study did not differ. Written informed consent was obtained from each

subject. The study was performed after approval of the Institutional Review Boards of participating centers, in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Data Collection

Physical Activity Assessment—We collected information on physical activity using an interview-administered physical activity questionnaire at an in-person visit scheduled within the third year after diagnosis. Participants were asked to recall the type, duration, and frequency of physical activities performed in the past year. The questionnaire was based on the Modifiable Activity Questionnaire developed by Kriska and colleagues, which was designed to be easily modified for use with different populations, and which has been shown to be reliable and valid (34). The sports/recreation and household activity section of the questionnaire addressed 29 popular activities.

We then estimated hours per week for each activity by multiplying frequency and duration together. Two mutually exclusive groups were created based on type of activity (sports/recreation including walking or household/gardening). Three sports/recreational physical activity groups (tertiles) and three household/gardening physical activity groups (tertiles) were created in order to examine the mean hormone/peptide level by tertile of sports/recreational physical activity or tertile of household/gardening.

Each activity was also categorized into three mutually exclusive groups based on intensity (but including all types of physical activity, i.e., sports/recreational activity and household/gardening activity): light (< 3 METs)-, moderate (3–6 METs)-, or vigorous (> 6 METs)-intensity based on Ainsworth et al's Compendium of Physical Activities (35). Three moderate- to vigorous-intensity physical activity groups were then created in order to examine the mean hormone/peptide level by tertile of moderate- to –vigorous-intensity physical activity.

Anthropometrics—Trained staff measured weight in a standard manner at the clinic visit. Weight was measured to the nearest 0.1 kg using a balance-beam laboratory scale. The scale was calibrated and checked for accuracy before each weighing. Height was self-reported by participants at all three sites. Body mass index was computed as weight in kg divided by self-reported height in m^2. Three mutually exclusive BMI groups were created: lean weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30.0 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2) (36). In a subsample (n = 569), both self-reported height and measured height were collected. Measured height was collected without shoes to the nearest 0.1 cm using a stadiometer. All measurements were performed and recorded twice in succession. The two measurements were averaged for a final value for analyses. Among women who had data on both measured height and self-reported height, self-reported height was 1.3 ± 2.9 cm higher than measured height; and only three women (out of 569) had a change in BMI classification from overweight to normal weight when using the self-reported height rather than measured height.

Hormones and Peptides—A 30-ml fasting blood sample was collected at the clinic visit. Blood was processed within 3 hours of collection; serum was stored in 1.8-ml aliquot tubes at −70 to −80°C. The hormone assays were performed at the Reproductive and Endocrine Research Laboratory at the University of Southern California for California subjects. For the other two sites (Washington and New Mexico), IGF-I, and C-peptide assays were conducted in the University of New Mexico laboratory. All samples were randomly assigned to assay batches and were randomly ordered within each batch. Laboratory personnel performing the assays were blinded to subject identity and personal characteristics. The method of ^{125}I

radio-immunoassay (RIA) was utilized to measure serum hormone and protein levels including IGF-1 and C-peptide (31). The C-peptide of Insulin ^{125}I RIA kit from Incstar Corp. was used to measure C-peptide levels (sensitivity of 0.1ng/mL). IGF-I levels were determined by ^{125}I RIA kits supplied from Nichols Institute Diagnostics (sensitivity of 0.1ng/mL). Intra-assay variability was assessed in a reduced randomly selected sample for all hormones. The coefficients of variation (CV) were calculated to test the assay variability. In California, 24 blood samples were randomly selected for hormone assay repeats. The CV was estimated by the standard deviation of the difference of replicated measures divided by the mean of the two measures. The intra-assay CVs for IGF-1 and C-peptide were 6.2% and 10.5% respectively. In New Mexico, intra-assay CV's were calculated as the standard deviation of the difference between repeated measures divided by the mean of the two measures. Assays were done in batches, and duplicate aliquots of ten randomly selected subject samples were standardly assayed per batch. In addition, BioRad standard samples of known low and high concentrations were included in each batch of assays for both New Mexico and Washington. Between 12 and 24 duplicate aliquots of each standard were measured depending on the assay. The following table summarizes the intra-assay %CVs based on low and high BioRad standards by type of analyses:

Intra-assay CVs based on repeated assays of BioRad Standards with known concentrations at low and high levels

	Low		High		N of reps
	Standard Conc.	%CV	Standard Conc.	%CV	
IGF1 (ng/ml)	125.0	4.7	185.0	3.3	15
IGFBP3 (ug/ml)	1.0	5.8	3.5	4.6	14
C-Peptide (ng/ml)	1.0	9.4	10.0	5.6	12
Leptin (ng/ml)	3.0	3.6	40.0	7.9	11

We do not have estimates of intra-assay reliability at low and high concentrations based on BioRad standards for these analyses.

Stage of Disease and Cancer Treatment—We obtained data on stage of disease from the respective SEER registries (the New Mexico Tumor Registry, the Cancer Surveillance System of Western Washington, and the Cancer Surveillance Program of Los Angeles County) prior to recruitment of women into the HEAL Study. Participants were classified as having *in situ*, Stage I or Stage II-IIIA breast cancer using the SEER stage of disease classification (37). Adjuvant treatment was categorized into three mutually exclusive groups: surgery only (including those taking or not taking tamoxifen), surgery plus radiation (including those taking or not taking tamoxifen), or any chemotherapy (including surgery, those taking or not taking tamoxifen, as well as those having radiation or not). Two mutually exclusive groups were also created for tamoxifen use: not taking tamoxifen and taking tamoxifen.

Other Variables—Standardized questionnaire information was collected at the baseline and follow-up clinic visits on medical history, health habits, history of benign breast disease, family history of breast and other specific cancers, self-reported physician-diagnosed type 2 diabetes, smoking status, tamoxifen use, selected demographic data (e.g., age, education, and marital status), and self-reported race/ethnicity. Menopausal status was determined using an algorithm that assigned women into pre, post, or unclassifiable menopausal status based on the following questionnaire data: age, date of last menstruation, hysterectomy and oophorectomy status. Because of the inability to define menopausal status for women

without a uterus or those taking hormone replacement therapy, we first considered all women in these two groups who were over age 55 as postmenopausal. This decision was made based on the very low proportion of women over age 55 who are premenopausal. Women who were 55 years of age or older, and who had not menstruated in the last year or who did not know the date of their last menstruation but reported having had a hysterectomy, were categorized as postmenopausal. Women less than age 55 were also categorized as postmenopausal if they had not menstruated in the last year prior to their interview. The following groups of women were categorized as unknown menopausal status: women less than age 55, who had a hysterectomy, but had at least one ovary remaining; and women 55 years of age or older with an intact uterus, who were still menstruating but had used hormone replacement therapy within a year or more prior to interview. The remaining women were classified as premenopausal.

Statistical Analyses

We calculated means and standard deviations of demographic and physiological characteristics of the study sample overall and by ethnicity. Differences in means were compared using analysis of variance for continuous variables and chi-square analyses for categorical variables.

We used analysis of covariance methods to estimate least squares means and test for differences or trends in hormones across categories of BMI and tertiles of physical activity overall and stratified by ethnicity, menopausal status, and tamoxifen use. We adjusted for covariates associated with the hormones, BMI, or physical activity including study site, age (continuous), education (continuous), ethnicity, menopausal status, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, and smoking status. We included BMI in analyses examining physical activity and hormones, and physical activity in analyses of BMI and hormones. We used Tukey's Honestly Significant Difference test to identify statistically significant differences between groups with the overall level of statistical significance constrained to 5% (38). All analyses were conducted using SAS Version 8.2.

RESULTS

Among the 710 women included in this analysis, 65% were non-Hispanic white, 25% were Black, and 10% were Hispanic white (Table 1). Black women were younger, heavier, and less active than non-Hispanic and Hispanic white women ($p < .05$).

We observed a statistically significant trend of *higher* C-peptide (p for trend = .0001) and leptin levels (p for trend = .0001) with *higher* BMI in the analysis of covariance adjusted for study site, age, ethnicity, education, menopausal status, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, smoking status, and physical activity (Table 2). Conversely, we observed a statistically significant trend of *lower* IGF-I (p for trend = .0001) and the IGF-I:IGFBP-3 ratio (p for trend = .0001) with higher BMI. Nonsignificant associations were observed between BMI and IGFBP-3.

We also observed a statistically significant trend of *lower* C-peptide (p for trend = .001) and leptin levels (p for trend = .001) with *higher* levels of sports/recreational physical activity in the analysis of covariance adjusted for study site, age, ethnicity, education, menopausal status, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, and smoking status (Table 3). However, when we adjusted for BMI, the associations and trends were similar, but did not reach statistical significance. We observed trends of *higher* IGF-I (p for trend = .0037) and the IGF-I:IGFBP-3 ratio (p for trend = .024) with *higher* levels of sports/recreational physical activity. Nonsignificant associations were observed between sports/recreational physical activity and IGFBP-3 (p =.055). Associations between sports/

recreational physical activity and IGF-I remained significant when adjusting for BMI, but not for the ratio. When we examined associations between physical activity and hormones using participation reported in moderate- to vigorous-intensity physical activity or household activities rather than sports/recreational activity, similar, but not statistically significant, trends in the same direction were observed (data not shown).

We also examined BMI and hormone associations, and sports/recreational physical activity and hormone/peptide associations stratified by menopausal status (Table 4a and 4b), ethnicity (data not shown) and tamoxifen use (data not shown). Different BMI, physical activity and IGFBP-3 associations were observed for premenopausal women compared to postmenopausal women. Similar BMI, physical activity and hormone/peptide associations were observed in each ethnic group; however Black women were less active, more overweight and obese, had higher leptin levels and lower IGF-I levels compared to Non-Hispanic White and Hispanic White women ($p < .01$). Similar BMI, physical activity and hormone/peptide associations were observed for tamoxifen users and nonusers; however tamoxifen users had lower IGF-I levels compared to nonusers ($p < .01$).

DISCUSSION

C-peptide and leptin levels were positively and IGF-I negatively related to *higher* categories of BMI ($p < .0001$); whereas c-peptide and leptin were negatively and IGF-I positively related to *lower* levels of sports/recreational physical activity among breast cancer survivors ($p < .05$). While the BMI and C-peptide, leptin, and IGF-I associations remained statistically significant even after adjustment for potential confounders including physical activity, the physical activity and C-peptide, leptin, and IGF-I associations became less statistically significant, or nonsignificant in the case of C-peptide, after adjusting for BMI. Our findings imply that BMI explains more of the variation in these hormones and peptides than physical activity.

Our insulin and leptin associations with BMI and physical activity are consistent with studies conducted among healthy women (4,17–19,24), and the one study conducted among cancer survivors (23). Published studies in healthy, overweight/obese vs. normal-weight women have reported IGF-I concentrations to be high, normal, or reduced (28–30); inconsistent findings have also been observed between physical activity and IGF-I concentrations in studies among healthy women (21,22). The observation of higher IGF-I levels with lower BMI and higher physical activity levels implies that IGF-I is regulated by a complex system, most notably IGFBP-3 (1,39,40). Because IGFBP-3 can either suppress IGF-I by blocking its binding to the IGF-I receptor or enhance the action of IGF-I by protecting it from proteolysis and clearance (40), it is difficult to determine the actual association of IGF-I with obesity and physical activity. Although in vitro studies show both inhibition and potentiation of IGF-I activity (1,39), in vivo studies largely support the concept that IGFBP-3 provides a stable serum reservoir of bioactive IGF-I, thereby enhancing its growth-inducing effects (41). Further, in hyperinsulinemic states such as obesity, insulin inhibits the synthesis of IGFBP-3 and increases free IGF-I (27). The increase in free IGF-I, in turn, exerts a negative feedback on pituitary growth hormone secretion and causes a decrease in total IGF-I (27). This mechanism would explain our findings in relation to BMI, physical activity, and IGF-I levels.

In our study, higher levels of IGFBP-3 were associated with higher levels of physical activity, but no association was observed between IGFBP-3 levels and BMI. This physical activity and IGFBP-3 association is intriguing because it may indicate some functional changes in the IGF system and in insulin levels occurring with physical activity independent of body weight or body fat. It is known that exercise training may decrease insulin resistance

by a number of mechanisms independent of changes in body fat including increased post-receptor insulin signaling, increased glucose transporter protein and mRNA, decreased release and increased clearance of free fatty acids, increased muscle glucose delivery, and changes in muscle composition favoring increased glucose disposal (42). This exercise-induced reduction in insulin resistance may lower circulating levels of insulin, which, in turn, may decrease circulating IGF-I levels via increases in insulin-mediated changes in IGFBP-3 concentrations.

In healthy individuals, physical activity may not alter certain hormones that are already at "normal" levels. Thus, in post-hoc analyses we examined whether the associations between physical activity and C-peptide, leptin, and IGFs differed when only women at the upper half of the hormone and peptide distributions were included in the analyses. We also examined these associations in women in the upper half of the BMI distribution, and in women diagnosed with type 2 diabetes. The only difference between physical activity and the hormones/peptide associations when including only women at the upper half of the hormone/peptide distribution was for physical activity and IGF-I where no association was observed compared to a positive association observed in the whole sample of N = 710. Similar associations were observed between physical activity and the hormones/peptides in women at the upper half of the BMI distribution compared to the whole sample. In women diagnosed with type 2 diabetes (n = 69), higher levels of physical activity were associated with lower IGF-I levels. The mean IGF-I levels for < 2.6, 2.6–13.2, and ≥ 13.3 METhr/week of sports/recreational physical activity were 129.0 ± 10.9 ng/mL, 110.5 ± 15.4 ng/mL, and 109.9 ± 12.8 ng/mL), respectively. However, because of small sample sizes, the association was not statistically significant (p for trend = 0.29).

Because IGFs have been associated with estrogen levels (43), and both IGFs and estrogens are associated with breast cancer risk, we examined associations between BMI and physical activity with IGFs, c-peptide, and leptin levels stratified by menopausal status. In our study, a statistically significant positive association was observed between physical activity and IGFBP-3 levels among premenopausal women, but not postmenopausal women; and, while nonsignificant, a positive association between BMI and IGFBP-3 was observed in premenopausal women, yet a negative association in postmenopausal women. The associations between physical activity and BMI with IGF-I did not differ by menopausal status.

Very little is known about whether differences in BMI, physical activity, and/or the hormones/peptides examined in this analysis contribute to the disparities in breast cancer risk and prognosis between Black and White women (44). In our study, similar associations were observed between BMI and physical activity with c-peptide, leptin, IGF-I, and IGFBP-3 levels when stratifying by ethnic group. However, Black women were heavier, reported lower physical activity levels, had higher leptin levels, and lower C-peptide levels, IGF-I, and IGFBP-3 levels than non-Hispanic White women and Hispanic women. Other studies have also reported higher BMI and lower physical activity levels among healthy Black women compared to White women (45,46). Few studies have examined whether differences exist in insulin, leptin, and IGF levels by ethnic group in healthy women or in cancer patients.

The HEAL Study has several limitations and strengths. While the HEAL Study is a prospective cohort study, this analysis is cross-sectional in design. Another limitation of our study is that we cannot be sure that these findings pertain to all breast cancer survivors because our sample only included women with *in situ* to Stages IIIA breast cancer living in Los Angeles, Western Washington, and New Mexico. Major strengths of our study are that the HEAL Study is a well-characterized population-based cohort of breast cancer survivors;

the quality of the physical activity data was obtained from a reliable and valid 29-item interview-administered questionnaire; we measured body weight and followed standardized blood collection protocols; and we recruited non-Hispanic and Hispanic White and Black women.

In conclusion, there are few modifiable factors known to be associated with breast cancer recurrence and mortality that might provide opportunities for 20 improving prognosis in breast cancer patients. If insulin and BMI, and potentially leptin, are associated with an increased risk of breast cancer recurrence or mortality, then their responsiveness to lifestyle changes are key to novel strategies for improving prognosis. Physical activity is a modifiable behavior with a multitude of health benefits, including most recently a favorable association with breast cancer survival (16,47). Increasing physical activity and decreasing body fat may be a reasonable intervention approach towards decreasing breast cancer recurrence and increasing survival.

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Table I

Physiological and demographic characteristics of HEAL participants stratified by ethnicity (N = 710)

	All Mean ± SD (n = 710)	Non-Hispanic White Mean ± SD (n = 460)	Black Mean ± SD (n = 175)	Hispanic White Mean ± SD (n = 75)
Age (years)	55.1 ± 10.2	56.9 ± 10.2	50.4 ± 7.7[a]	55.0 ±11.9
Weight (kg)	75.0 ± 18.3	72.1 ± 15.9	85.5 ± 21.8[a]	68.5 ± 12.9
Height (cm)	164.5 ± 7.1	165.1 ± 6.7	165.2 ± 7.5[a]	159.7 ± 7.1[b, c]
Body Mass Index (wt in kg/ht in m^2)	27.7 ± 6.4	26.5 ± 5.6	31.3 ± 7.5	26.9 ± 4.8
Postmenopausal (%)	75%	77%	72%	69% [c]
Education (% High School graduate)	94%	97%	89% [a]	82% [b, c]
Study Site (%)				
New Mexico	53%	66%	0% [a]	96% [b, c]
Seattle	23%	34%	1% [a]	4% [b, c]
Los Angeles	25%	0%	99% [a]	0% [b, c]
Disease Stage (%)				
Stage 0	24%	26%	20%	23%
Stage I	55%	56%	46% [a]	64% [c]
Stage II-IIIA	21%	18%	34% [a]	13% [c]
Treatment (%)				
Surgery only	31%	29%	35%	37%
Surgery and Radiation	39%	45%	24% [a]	36%
Any Chemotherapy	30%	26%	41% [a]	27% [c]
Tamoxifen Users (%)	43%	46%	37% [a]	39%
Type 2 diabetes (%)	9.7%	8.5%	12.6%	10.7%
Current Smokers (%)	8.9%	8.0%	12.0% [a]	6.7% [c]
Sports/Recreational PA (hr/week) [1]	3.0 ± 3.9	3.2 ± 4.2	2.2 ± 3.1 [a]	3.8 ± 3.7
Sport/Recreational PA (METhr/week)	13.4 ± 19.0	14.1 ± 20.2	10.1 ± 15.8[a]	16.9 ± 17.2
Household PA (hr/week)[1]	19.3 ± 16.0	16.9 ±12.5	24.3 ± 20.9[a]	22.3 ±19.2[b]

	All	Non-Hispanic White	Black	Hispanic White
	Mean ± SD (n = 710)	**Mean ± SD (n = 460)**	**Mean ± SD (n = 175)**	**Mean ± SD (n = 75)**
Household PA (METhr/week)	51.2 ± 41.7	45.5 ± 33.1	62.9 ± 53.6[a]	59.4 ± 50.2[b]
C-peptide levels (ng/mL)	2.29 ± 1.08	2.29 ± 0.99	2.17 ± 1.31	2.53 ± 0.97[c]
Leptin levels (ng/mL)	24.6 ± 17.8	21.5 ± 15.2	34.0 ± 22.5[a]	22.1 ± 12.1[c]
IGF-I levels (ng/mL)	133.5 ± 58.3	143.1 ± 55.0	104.3 ± 51.5[a]	143.0 ± 70.0[c]
IGFBP-3 levels (ug/mL)	4.08 ± 1.0	4.17 ± 0.91	3.85 ± 1.02[a]	4.03 ± 0.99
IGF-I:IGFBP-3 (ng/mL)	32.7 ± 11.9	34.3 ± 11.1	27.7 ± 11.8[a]	34.9 ± 13.9[c]

[1] Past month physical activity assessed from interview-administered physical activity questionnaire conducted within their 3rd year after diagnosis.

[a] Black significantly different from Non-Hispanic White, $p < .05$.

[b] Hispanic white significantly different from Non-Hispanic White, $p < .05$.

[c] Hispanic white significantly different from Black, $p < .05$.

Table II

Association between body mass index (BMI) and hormones/peptides: Means ± SE among a sample of 710 women with breast cancer

	BMI < 25 Mean ± SE (n = 284)	BMI: 25 – 29.9 Mean ± SE (n = 216)	BMI ≥ 30 Mean ± SE (n = 210)	P for trend
C-Peptide (ng/mL)				
Unadjusted	1.83 ± 0.06	2.37 ± 0.07[a]	2.82 ± 0.07[b,c]	.0001
Adjusted[1]	1.79 ± 0.06	2.34 ± 0.06[a]	2.91 ± 0.07[b,c]	.0001
Adjusted[2]	1.81 ± 0.06	2.34 ± 0.06[a]	2.88 ± 0.07[b,c]	.0001
Leptin (ng/mL)				
Unadjusted	12.5 ± 0.8	23.5 ± 0.9[a]	42.2 ± 0.9[b,c]	.0001
Adjusted[1]	12.8 ± 0.8	23.6 ± 0.9[a]	41.6 ± 0.9[b,c]	.0001
Adjusted[2]	13.0 ± 0.8	23.7 ± 0.9[a]	41.3 ± 0.9[b,c]	.0001
IGF-I (ng/mL)				
Unadjusted	144.1 ± 3.4	137.8 ± 3.9[a]	114.9 ±3.9[b,c]	.0001
Adjusted[1]	142.5 ± 3.1	136.5 ± 3.5[a]	118.4 ±3.6[b,c]	.0001
Adjusted[2]	142.3 ± 3.4	136.5 ± 3.5[a]	118.7 ±3.6[b,c]	.0001
IGFBP-3 (ug/mL)				
Unadjusted	4.09 ± 0.06	4.10 + 0.07	4.04 ± 0.07	.57
Adjusted[1]	4.10 ± 0.06	4.08 ± 0.06	4.05 ± 0.07	.57
Adjusted[2]	4.10 ± 0.06	4.08 ± 0.06	4.05 ± 0.07	.60
IGF-I:IGFBP-3 (ng/mL)				
Unadjusted	35.1 ± 0.7	33.6 ± 0.8[a]	28.6 ± 0.8[b,c]	.0001
Adjusted[1]	34.7 ± 0.6	33.4 ± 0.7[a]	29.4 ± 0.8[b,c]	.0001
Adjusted[2]	34.7 ± 0.6	33.4 ± 0.8[a]	29.4 ± 0.7[b,c]	.0001

[1] Adjusted for study site, age, ethnicity, education, menopausal status, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, and smoking status.

[2] Adjusted for all the above covariates including sports/recreational MET-hr/week.

[a] BMI 25–29.9 significantly different from BMI < 25, p < .05.

[b] BMI ≥30 significantly different from BMI < 25, p < .05.

[c] BMI ≥30significantly different from BMI 25.0 – 29.9, $p < .05$.

Table III

Association between sports/recreational physical activity and hormones/peptides: Means ± SE among a sample of 710 women with breast cancer

	Tertile 1 (< 2.6 METhr/wk) Mean ± SE (n = 236)	Tertile 2 (2.6 – 13.2 METhr/wk) Mean ± SE (n = 238)	Tertile 3 (≥ 13.3 METhr/wk) Mean ± SE (n = 236)	P for trend
C-Peptide (ng/mL)				
Unadjusted	2.49 ± 0.07	2.34 ± 0.07	2.04 ± 0.07[b,c]	.001
Adjusted[1]	2.48 ± 0.07	2.35 ± 0.07	2.04 ± 0.07[b,c]	.001
Adjusted[2]	2.33 ± 0.06	2.35 ± 0.06	2.19 ± 0.06	.13
Leptin (ng/mL)				
Unadjusted	30.5 ± 1.1	24.5 ± 1.1[a]	18.9 ± 1.1[b,c]	.001
Adjusted[1]	30.0 ± 1.1	24.5 ± 1.1[a]	19.4 ± 1.1[b,c]	.001
Adjusted[2]	26.1 ± 0.8	24.3 ± 0.8	23.4 ± 0.8[b]	.020
IGF-I (ng/mL)				
Unadjusted	119.7 ± 3.7	136.1 ± 3.7[a]	144.7 ±3.7[b]	.0001
Adjusted[1]	125.8 ± 3.4	134.9 ± 3.3[a]	140.0 ±3.4[b]	.0037
Adjusted[2]	129.5 ± 3.4	135.0 ± 3.3	136.2 ±3.4[b]	.018
IGFBP-3 (ug/mL)				
Unadjusted	3.96 ± 0.06	4.09 ± 0.06	4.18 ± 0.06[b]	.011
Adjusted[1]	3.99 ± 0.06	4.08 ± 0.06	4.16 ± 0.06[b]	.055
Adjusted[2]	4.02 ± 0.06	4.08 ± 0.06	4.14 ± 0.06	.17
IGF-I: IGFBP-3 (ng/mL)				
Unadjusted	30.2 ± 0.8	33.5 ± 0.8[a]	34.5 ± 0.8[b]	.0001
Adjusted[1]	31.3 ± 0.7	33.3 ± 0.7[a]	33.6 ± 0.7[b]	.024
Adjusted[2]	32.1 ± 0.4	33.3 ± 0.7	32.8 ± 0.7	.47

[1] Adjusted for study site, age, ethnicity, education, menopausal status, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, and smoking status.

[2] Adjusted for all the above covariates including body mass index.

[a] Tertile 2 significantly different from Tertile 1, $p < .05$.

[b] Tertile 3 significantly different from Tertile 1, $p < .05$.

[c] Tertile 3 significantly different from Tertile 2, $p < .05$.

Table IV.I

Association between body mass index (BMI) and hormones stratified by menopausal status[1]: Means ± SE among a sample of 667 women with breast cancer.[2]

	BMI < 25 Mean ± SE (n = 284)	BMI: 25–30 Mean ± SE (n = 216)	BMI ≥ 30 Mean ± SE (n = 210)	P for trend
C-Peptide (ng/mL)				
Premenopausal	1.54 ± 0.09	1.92 ± 0.11[a]	2.69 ± 0.13[b c]	.0001
Postmenopausal	1.89 ± 0.07	2.45 ± 0.08[a]	2.95 ± 0.08[b c]	.0001
Leptin (ng/mL)				
Premenopausal	10.8 ± 1.4	18.7 ± 1.7[a]	36.9 ± 2.0[b c]	.0001
Postmenopausal	13.4 ± 0.9	24.8 ± 1.0[a]	43.0 ± 1.1[b c]	.0001
IGF-1 (ng/mL)				
Premenopausal	168.7 ± 6.6	166.0 ± 8.1	149.4 ± 9.7	.11
Postmenopausal	134.9 ± 3.6	128.9 ± 4.0	110.1 ± 4.2[b c]	.0001
IGFBP-3 (ug/mL)				
Premenopausal	4.09 ±0.10	4.10 ± 0.16	4.31 ± 0.15	.24
Postmenopausal	4.10 ±0.07	4.07 ± 0.07	4.00 ± 0.08	.33
IGF-I:IGFBP-3 (ng/mL)				
Premenopausal	41.5 ± 1.4	40.3 ± 1.7	35.1 ± 2.0[b c]	.013
Postmenopausal	32.8 ± 0.7	31.7 ± 0.8	27.7 ± 0.8[b c]	.0001

[1] Sample sizes for premenopausal women: BMI < 25: N = 63, BMI: 25–30: N = 41; BMI ≥30: N = 30; Postmenopausal women: BMI < 25: N = 210, BMI: 25–30: N = 165; BMI ≥30: N = 158.

[2] Adjusted for study site, age, ethnicity, education, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, smoking status, and sports/recreational MET-hr/week

[a] BMI 25–29.9 significantly different from BMI < 25, p < .05.

[b] BMI ≥30 significantly different from BMI < 25, p < .05.

[c] BMI ≥30significantly different from BMI 25.0 – 29.9, p < .05.

Table IV.II

Association between sports/recreational physical activity and hormones stratified by menopausal status[1]: Means ± SE among a sample of 667 women with breast cancer.[2]

	Tertile 1 (< 2.6 METhr/wk) Mean ± SE (n = 236)	Tertile 2 (2.6 – 13.2 METhr/wk) Mean ± SE (n = 238)	Tertile 3 (≥ 13.3 METhr/wk) Mean ± SE (n = 236)	P for trend
C-Peptide (ng/mL)				
Premenopausal	2.02 ± 0.13	1.91 ± 0.10	1.86 ± 0.09	.33
Postmenopausal	2.40 ± 0.07	2.46 ± 0.07	2.27 ± 0.08	.27
Leptin (ng/mL)				
Premenopausal	18.4 ± 1.8	21.6 ± 1.4	17.5 ± 1.3	.68
Postmenopausal	27.3 ± 0.9	24.8 ± 0.9	25.0 ± 1.0	.099
IGF-1 (ng/mL)				
Premenopausal	153.6 ± 9.3	160.7 ± 7.5	171.0 ± 6.8	.14
Postmenopausal	123.6 ± 3.8	126.9 ± 3.8	126.8 ± 4.0	.56
IGFBP-3 (ug/mL)				
Premenopausal	3.89 ±0.14	4.17 ± 0.12	4.26 ± 0.10[b]	.046
Postmenopausal	4.05 ±0.07	4.05 ± 0.07	4.08 ± 0.08	.77
IGF-I:IGFBP-3 (ng/mL)				
Premenopausal	39.4 ± 2.0	39.3 ±1.6	40.2 ± 1.4	.73
Postmenopausal	30.4 ± 0.8	31.5 ± 0.8	31.0 ± 0.8	.60

[1] Sample sizes for premenopausal women: Tertile 1: N = 31, Tertile 2: N = 45; Tertile 3: N = 58; postmenopausal women: Tertile 1: N = 189, Tertile 2: N = 176; Tertile 3: N = 168.

[2] Adjusted for study site, age, ethnicity, education, disease stage, adjuvant treatment, tamoxifen use, type 2 diabetes, smoking status, and body mass index.

[a] Tertile 2 significantly different from Tertile 1, $p < .05$.

[b] Tertile 3 significantly different from Tertile 1, $p < .05$.

[c] Tertile 3 significantly different from Tertile 2, $p < .05$.

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