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Dietary Fat, Tamoxifen Use and Circulating Sex Hormones in Postmenopausal Breast Cancer Survivors

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Abstract

Evidence is inconsistent regarding whether dietary fat influences sex hormone concentrations. This issue is important for breast cancer survivors since clinical recommendations suggest maintaining low hormone levels primarily via pharmacologic agents. This study examines associations between dietary fat and circulating sex hormones among participants in the HEAL (Health, Eating, Activity and Lifestyle) Study, a cohort of breast cancer survivors (n=511). During a post-diagnosis interview, detailed data were collected on diet, physical activity, lifestyle habits, and medication use (including tamoxifen). Staff measured height and weight and collected fasting bloods. Multivariate linear regression modeled associations of dietary fat with serum sex hormones. Among women using tamoxifen, we observed modest inverse associations of dietary fat with estrone ($p < 0.01$), estradiol ($p < 0.05$), testosterone ($p < 0.01$), free testosterone ($p < 0.01$), and DHEA ($p < 0.01$) for higher vs. lower fat intake, but there was no evidence for a trend. Associations were consistent across measures (percent energy from fat, total, saturated and polyunsaturated fat) and modest effect modification was observed between fat intake and tamoxifen in relation to hormones. Among women not using tamoxifen, fat intake was not associated with hormone concentrations. Further work is needed to confirm the findings and to understand the clinical implications of these observations.

Keywords

Diet; dietary fat; sex steroid hormones; estrogen; testosterone; postmenopausal breast cancer; tamoxifen

INTRODUCTION

Lifestyle factors influence the synthesis, metabolism and catabolism of sex steroid hormones (1–4). Since breast cancer is a hormone-dependent disease, understanding the relationship between potentially modifiable factors, such as diet, obesity and physical activity with respect to hormone levels is important. These issues are particularly critical for breast cancer survivors, many of whom use pharmacologic therapies to reduce or control endogenous hormone levels as part of an overall treatment regimen to reduce the risk of disease recurrence or progression (5,6). For example, a standard treatment for breast cancer patients with estrogen-receptor positive tumors is adjuvant therapy with tamoxifen, which is a selective estrogen receptor modulator (SERM). Tamoxifen blocks the binding of estrogen to the estrogen receptor and is very effective for risk reduction of breast cancer recurrence (7,8).

Among the lifestyle factors that may influence hormone levels, diet has received considerable attention (9–13). Dietary fat is of particular interest since excess fat and energy intake promote adipose tissue deposition from which estrogen synthesis occurs via up-regulation of adipose-derived aromatase (13–16). However, results from both observational and intervention studies have not provided consistent data regarding the association of fat intake with sex steroid hormone levels (12,17). An observational study in Japanese men reported statistically significant positive associations of total, saturated, monounsaturated and polyunsaturated fat with both estrone and DHEAS (18). Other observational studies have reported no association of dietary fat with sex hormones (19). A Canadian intervention study testing a diet with 15% of energy from fat vs. usual diet in premenopausal women reported that estrogen concentrations intervention arm participants were 20% lower two years post-randomization compared to the control group (20). The Women's Health Initiative Dietary Modification Trial reported that participants in the low-fat dietary pattern intervention group (goal of < 20% of energy from fat) had 15% lower serum estradiol one year post-randomization (21). There were no changes in serum estradiol for women in the trial's comparison arm (21). A short-term, two month controlled feeding study in n=57 postmenopausal women compared three levels of fat intake (11% of energy, 25% of energy and 27% of energy from fat) but the intervention resulted in no differences in estradiol or sex hormone binding globulin (22).

Of particular importance is that these published studies were conducted primarily among healthy women at average risk for breast cancer. With the exception of two recently published randomized, controlled trials (23,24) few data are published with regard to dietary fat in breast cancer survivors. Only one small intervention study examined the effect of tamoxifen and a low-fat diet (20% of energy from fat), alone or in combination, in relation to sex hormone concentrations in postmenopausal breast cancer survivors. The low-fat diet plus tamoxifen increased SHBG and decreased estradiol while the low-fat diet alone did not result in any hormone changes (25). Because lifestyle factors and other predictors of breast cancer incidence may not be the same risk factors that predict survival, observational studies of diet and other factors are needed in breast cancer survivors.

The purpose of the present study was to assess associations between dietary fat and circulating sex hormones in a cohort of postmenopausal breast cancer survivors. We hypothesized that higher fat intake would be associated with higher sex hormone levels (1,21,26,27). Further, because tamoxifen influences sex hormones we assessed interactions of tamoxifen use with fat intake in relation to hormone levels.

METHODS

Study Design, Population and Recruitment

The Health, Eating, Activity and Lifestyle (HEAL) study is a population-based, multicenter, multiethnic prospective cohort study of 1,183 breast cancer patients designed to determine whether weight, physical activity, diet, sex hormones and other exposures affect breast cancer prognosis and survival. Details of the study design and procedures are published (3,28,29). Briefly, we utilized the National Cancer Institute's Surveillance, Epidemiology, End Results (SEER) registries in New Mexico, Los Angeles County (CA), and western Washington to ascertain and recruit women diagnosed with *in situ* to Stage IIIA breast cancer. In New Mexico, we recruited 615 women, aged 18 years or older, diagnosed between July 1996 and March 1999, and living in Bernalillo, Santa Fe, Sandoval, Valencia, or Taos Counties. In western Washington, we recruited 202 women, between the ages of 40 and 64 years, diagnosed between September 1997 and September 1998, and living in King, Pierce, or Snohomish Counties. In Los Angeles County, we recruited 366 African-American women who had previously participated in other breast cancer case-control studies. Thus, the Los Angeles participants were a subset of women diagnosed with breast cancer between May 1995 and May 1998, were aged 35 to 64 years at diagnosis, were English speaking and born in the U.S. Written informed consent was obtained from all participants at each study site. All HEAL procedures were approved by the Institutional Review Boards of the participating centers (Fred Hutchinson Cancer Research Center, University of Southern California and University of New Mexico), in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services (3).

HEAL participants completed extensive interviews within their first year after diagnosis (on average 7.5 months post-diagnosis) and 24 months later (within their third year after diagnosis; on average 31.5 months post-diagnosis) at each study center. Of the 1,223 women enrolled in the study at baseline, 39 (3.2%) women who were later found to have had a prior diagnosis of breast cancer and one woman (< 1.0%) who had metastatic disease at initial diagnosis were subsequently excluded. Of the remaining 1,183 women, 239 (20.2%) women did not return for the 24-month follow-up visit. Reasons for non-participation were death (n=44), too ill (n=2), refusal (n=104), spouse disallowed contact (n=1), moved (n=16) or unable to contact (n=72). A total of 944 women completed 24-month follow-up questionnaires, which included detailed questions on health, menopausal status, diet, dietary supplement use, physical activity, and alcohol and tobacco use. Study staff also measured height and weight and collected a fasting blood specimen from all participants. We used the data and specimens collected at the 24-month interview for the analyses presented in this report, restricting the study to 511 postmenopausal women who were not using hormone replacement therapy (n=44).

Data Collection and Measures

Breast Cancer Stage of Disease and Cancer Treatment—Data on breast cancer stage of disease at diagnosis were obtained from the local SEER registries. Participants were classified as having *in situ*, Stage I or Stage II–IIIA breast cancer based on AJCC stage of disease classification (30). Treatment and other clinical data were obtained during a medical records review that provided more detailed information on chemotherapy, radiation and hormonal therapy than that maintained by the registries. Breast cancer treatment was categorized into three mutually exclusive groups: (i) surgery only; (ii) surgery and radiation; (iii) any chemotherapy. Tamoxifen use was defined as current use at the 24-month interview. At the time of the interview aromatase inhibitors were not being used in general clinical practice.

Blood Collection and Sex Hormone Assays—A 30-ml fasting blood sample was collected at the 24-month follow-up interview. Blood was processed within 3 hours of collection; serum was stored in 1.8-ml aliquot tubes at -70° to -80° C until analysis. We measured estrone, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEAS) and sex hormone-binding globulin (SHBG). Free estradiol and free testosterone were calculated from SHBG and total estradiol and testosterone, respectively (31). We had insufficient blood to measure estradiol/free estradiol in nine participants.

For California participants, all assays except testosterone were performed at the Reproductive and Endocrine Research Laboratory at the University of Southern California. Testosterone assays were performed at the University of New Mexico. For Washington and New Mexico participants, estrone and estradiol were assayed at Quest Diagnostics (San Juan Capistrano, CA) and the remaining assays were conducted at the University of New Mexico. All samples were randomly assigned to assay batches and were randomly ordered within each batch. Biorad standards were also included to monitor assay performance within and between batches at both low and high concentrations. Laboratory personnel performing the assays were blinded to patient identity and personal characteristics.

Radio-immunoassay (RIA) was utilized to measure all serum analytes (32,33). Serum extraction and chromatographic purification were performed before RIA for estrone and estradiol. The sensitivity for the estrone assay was less than 5–10pg/mL and for estradiol was less than 2 pg/mL. Serum testosterone was determined using an RIA kit (Diagnostic Products Corp, Los Angeles, CA) with a sensitivity of 40pg/mL. SHBG levels were determined using the Wein Laboratories (Succasunna, NJ) RIA kit with a sensitivity of 6nmol/L.

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 estrone, estradiol, and SHBG were 26.2%, 15.4%, and 9.3%.

For New Mexico and western Washington, 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 participant samples were assayed per batch. The intra-assay and total CVs were 3.8% and 5.9% respectively, for SHBG, 12.0% and 14.4% for testosterone, 29.1% and 13.3% for estrone, 28.8% and 13.3% for estradiol. Data from the combined labs have comparability in previous analyses (3,34).

Dietary Assessment—Diet was assessed using a self-administered Food Frequency Questionnaire (FFQ) developed for the Women's Health Initiative (35). This FFQ was designed to capture dietary patterns in multi-ethnic and geographically diverse population groups and was adapted from the Block DHQ (36). The WHI-FFQ is divided into three sections: (a) adjustment questions; (b) food and food groups; (c) summary questions. Nineteen adjustment questions are used in the analysis software to estimate the nutrient content of specific foods. This approach permits more refined analyses of fat intake by asking about food preparation practices and fats added both in cooking and at the table. The main section of the questionnaire includes 122 line items of foods or food groups with questions on the usual frequency of intake (ranging from "never or less than once per month" to "2+ per day" for food and "6+ per day" for beverages) and portion size (small, medium or large compared with the stated medium portion size). The four summary

questions ask about usual intake of fruits and vegetables (excluding juices, salad, potatoes and mature beans) and of fat added to foods in cooking (37). These questions are used to reduce the measurement bias of over-reporting food consumption when there are long lists of foods (e.g., 22 vegetables and 10 fruits) within food groups. The nutrient database used to convert food information into nutrients is derived from the University of Minnesota Nutrition Coordinating Center's Nutrition Data Systems for Research (NDS-R, version 2005) (38).

Anthropometry—Staff measured height and weight using a standardized protocol. Participants wore light clothing without shoes and weight was measured to the nearest 0.1 kg using a balance-beam laboratory scale (New Mexico and Washington) or portable scale (Los Angeles). Height was measured without shoes to the nearest 0.1 cm using a stadiometer or measuring tape affixed to a wall. All measurements were performed and recorded twice in succession, then averaged for a final value. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared (kg/m^2). We used the WHO-National Institutes of Health categorizations of normal weight and obesity based on BMI: normal = $< 25.0 \text{ kg/m}^2$, overweight = $25.0\text{--}29.9 \text{ kg/m}^2$ and obese = $\geq 30.0 \text{ kg/m}^2$ (39).

Menopausal status—At the interview date, 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 55 years were also categorized as postmenopausal if they had not menstruated in the year prior to their interview. Women categorized as pre-menopausal or whose menopausal status was unknown were excluded from these analyses since we had no data on menstrual cycle phase (luteal or follicular) in relation to the blood draw date.

Other Data—Standardized data were collected on smoking, leisure/recreational physical activity and demographics (29).

Statistical Analysis

We used descriptive statistics to characterize the study sample and to examine the distributions of dietary fat intake and the sex steroid hormones. Hormone values were log-transformed to improve the normality of the distributions. The fat intake variables were divided into approximate quartiles and multivariate linear regression modeled the associations of dietary fat with the sex hormones. Results are expressed as geometric means and 95% confidence intervals for each sex hormone within the quartiles of the dietary variables. Tests for interaction were conducted to determine whether any observed associations of fat intake with hormone concentrations were modified by tamoxifen use. All analyses were adjusted for age (continuous), BMI (continuous), race/study site (non-Hispanic white from Washington, non-Hispanic White from New Mexico, African-American, Hispanic), total energy (kcal), fiber, alcohol, physical activity, breast cancer treatment and number of remaining ovaries. Dietary data for 28 women were excluded due to implausible FFQ data (average daily kcal >4000 or <600). Variables tested but not included in the final analysis included fruit and vegetable intake, dietary cholesterol and time since breast cancer diagnosis (40). These variables were neither statistically significant nor influential on parameter estimates and we chose to use the most parsimonious models. All statistical tests were based on *a priori* hypotheses and therefore adjustment for multiple testing was not done. Analyses based on the remaining 511 women were conducted with SAS (version 9.1, Cary, NC).

RESULTS

Demographic, lifestyle and health characteristics of HEAL participants are presented in Table 1. Of the 511 eligible postmenopausal women in HEAL, 255 (49.9%) reported tamoxifen use at the 24-month interview. Mean age and weight were similar between those who did and did not use tamoxifen. Tamoxifen users were more likely to have had chemotherapy and, as expected, have either estrogen receptor or progesterone receptor positive primary tumors. However, none of the differences in demographic or medical characteristics across tamoxifen vs. no tamoxifen use were statistically different.

Table 2 gives the distributions of HEAL participants' diet and hormone concentrations. Intake of total energy, total fat, percent energy from fat or any other measure of dietary fat did not differ between tamoxifen users and non-users. Unadjusted measures of free estradiol, testosterone, and free testosterone were all lower and SHBG was higher among the tamoxifen users, but these differences were not statistically significant.

Tables 3–5 present the results from multivariate-adjusted linear regression models testing associations of total fat, saturated fat, and polyunsaturated fat with circulating concentrations of seven sex hormones. Among women not taking tamoxifen, those with lower fat intake did not differ from those with higher total fat intake for any of the seven hormones. For tamoxifen users, however, higher vs. lower total fat intake was associated with modestly lower estrone, estradiol, testosterone, and DHEA. However, these relationships were relatively unremarkable until reaching the top quartile of fat intake where the hormone concentrations declined. For example DHEA was approximately 25% lower among women with a higher vs. lower fat intake, but the shape of the association was U-shaped instead of linear across the quartiles. The interaction tests for tamoxifen use with fat intake were statistically significant for estrone (p , interaction = 0.04) and suggestive (defined as p , interaction < 0.10) for free estradiol, testosterone and free testosterone.

Results for saturated fat were null for women not using tamoxifen with no statistically significant differences in hormone concentrations across the saturated fat intake quartiles (Table 4). Among tamoxifen users, however, estradiol and free estradiol were approximately 30%–40% lower for higher vs. lower intake. Free testosterone and DHEA were also significantly lower among those in the fourth vs. first quartile of saturated fat intake while SHBG was 20% higher among those with higher vs. lower saturated fat intake, with evidence of another U-shaped association with testosterone and DHEA. We observed a statistically significant interaction of fat intake with tamoxifen in relation to circulating testosterone (p , interaction = 0.04) and a suggestive (but not significant) interaction for free testosterone and DHEA (both p , interaction = 0.09 and p =0.08, respectively).

Table 5 presents results for associations of polyunsaturated fat (PUFA) with hormone concentrations where the patterns were similar to the total and saturated fat models. Estradiol was significantly lower in women with higher vs. lower PUFA intake. A marginal interaction between PUFA intake and tamoxifen slightly modified the association with serum estrone (p , interaction = 0.07).

We also conducted exploratory models with subsets of fat classes [trans fats, n-6 PUFA and eicosapentanoic + docosahexanoic acids (the long chain omega-3 fats derived from fatty fish)]. Estradiol and free estradiol were lower among women using tamoxifen with higher vs. lower trans fat intake (p , interaction = 0.07 and 0.05 for estradiol and free estradiol, respectively). Both n-6 PUFA and the omega-3 fish oils fats were not associated with any hormone concentrations (data not shown). Finally, we examined whether tumor hormone receptor status (ER/PR) influenced the study results. However, the direction of the association did not change and overall cell sizes were small since ER/PR status was not

available on many participants. These small cell sizes created unstable estimates, which we determined to be unreliable (data not shown).

DISCUSSION

Understanding diet-hormone relationships among breast cancer survivors is an important clinical issue since control of hormone availability is a key component of breast cancer treatment and prevention of disease recurrence (41,42). In this study of postmenopausal breast cancer survivors, most sex hormone values were lower and SHBG was higher in tamoxifen users vs. nonusers in nearly all comparisons. These associations were independent of weight, energy intake, physical activity and other variables associated with hormone concentrations. Among women using tamoxifen, there were significant associations of fat intake with sex hormones and sex hormone binding globulin. However, for women not using tamoxifen neither clear nor consistent associations of any fat measure with hormone values were observed.

A particularly interesting finding from our study was that hormone concentrations declined sharply among tamoxifen users in the highest fat intake quartile. To further explore whether participant characteristics may have confounded the observed associations of fat intake with hormone levels in tamoxifen users, we conducted additional analyses, including additional stratification by BMI, age, physical activity, years since menopause and number of remaining ovaries (data not shown). One potential explanation for the overall findings is that a slightly higher proportion of tamoxifen users vs. non-users in the top quartile of fat intake had no ovaries (28.8% vs. 21.3%). Women with no ovaries would be expected to have lower circulating sex hormones even though the ovarian postmenopausal hormone production is very low. Despite including the number of ovaries as a covariate, it may not have eliminated all confounding and this slight difference may partially explain the lower hormone values for tamoxifen users in the top quartiles of fat intake. Another possible explanation for our findings may involve a complex interplay between tamoxifen metabolism, fat intake and sex hormones. Metabolism of both tamoxifen and estrogens utilize the phase I enzyme systems (particularly CYP1B1, CYP1A1, CYP2D6). These enzyme systems are also sensitive to variation in macronutrient intake, including fat (43). Complex interactions may exist such that a higher fat intake together with tamoxifen might decrease, instead of increase circulating hormones. Finally, in some but not all women tamoxifen alters lipid metabolism, particularly triglycerides (44), but the extent to which dietary fat influences these relationships is unknown. To our knowledge, only one other study has reported on interactions of dietary fat with tamoxifen in relation to sex hormones (25). Clearly, sex hormone biochemistry is complex and much remains to be learned about predictors of sex hormone concentrations. Our findings on SHBG are consistent with those reported by with Rose et al (25).

We previously reported that measures of adiposity (BMI, body fat mass and percent body fat) were strong predictors of circulating sex hormones in the HEAL cohort (3). In the present study, slightly fewer tamoxifen users were obese, but careful examination of the hormone profiles between the two groups revealed that differences in BMI could not account for the observed results. This finding is consistent with our earlier report examining weight gain in breast cancer survivors where tamoxifen was not a predictor of weight gain (28). Similarly, while other studies have shown that breast cancer survivors are at risk for weight gain, tamoxifen use is not a strong predictor of post-treatment weight gain (45–47). BMI is an important predictor of sex hormone concentrations, particularly in postmenopausal women and postmenopausal breast cancer patients (3,45). However, the results presented in this report suggest that tamoxifen use may have the potential to modify associations of known predictors of hormones, such as diet, with hormone concentrations.

While little research has been published on interactions of dietary factors with tamoxifen in relation to sex hormone levels, findings from *in vitro* and preclinical animal models suggest that diet-tamoxifen interactions are biologically possible. For example, vitamin E (as alpha-tocopherol) applied to ER-positive, tamoxifen-treated breast cancer cells lines (MCF-7 and T47D) impaired the ability of tamoxifen to decrease proliferation and increase apoptosis(48). The soy isoflavones daidzein and genestein also interact with tamoxifen. Daidzein enhanced the effectiveness of tamoxifen to inhibit tumor growth in a mammary cancer model in rats (49). Similar results were observed in a study using the MMTV-wt-erbB-2 transgenic mouse in which all animals were treated with tamoxifen and fed with either soy, standard casein, low-dose isoflavone or high dose isoflavone-meal. The animals fed the low-dose isoflavone had the highest rate of tumor development and shortest tumor latency period, whereas tamoxifen treated animals fed high-dose isoflavones has fewer tumors and longer latency period (50). Similar interaction effects of tamoxifen with genestein were observed when treating MCF-7 human breast cancer cells; low-dose genestein plus tamoxifen promoted MCF-7 proliferation, while high-dose genestein plus tamoxifen inhibited MCF-7 growth (50). Adverse interactions of tamoxifen with diet, particularly isoflavones, were reported by Ju et al (51), but Mai et al showed that high-dose genestein and tamoxifen worked synergistically to reduce tumor growth in MCF-7 cells to a greater extent than tamoxifen did alone (52). Chen et al reported that flaxseed oil enhanced the ability of tamoxifen to inhibit tumor growth in a mammary mouse model (53), but sesame seeds may have an adverse interaction with tamoxifen (54). While none of the results from these animal and *in vitro* studies examined the same dietary factors as in the HEAL study, they imply that interactions between diet and tamoxifen are possible. It is also important to note that these *in vitro* and animal data are for different nutrient pathways than fat metabolism.

This study has several strengths. There are few large studies of breast cancer survivors and this multiethnic cohort provides an important opportunity to learn about hormone values in these women. Specifically, we are aware of only one other study supporting a potential interaction of fat with tamoxifen in relation to sex hormone concentrations (21). We used a dietary questionnaire that was designed for use by multi-ethnic postmenopausal women and its validity and reliability are very good (37). There are also limitations. Firstly, the coefficients of variation for some of the hormone assays were high (i.e., 10%), but within the range of many sex hormone assays (1,55,56). Secondly, while the measurement characteristics of the FFQ used in this study are quite good, there is a growing appreciation that measurement error and underreporting affect all methods of dietary self-report (10,57–59). There may be energy misreporting among HEAL participants given the relatively low reported average energy intake but high BMI. Although we would not expect bias in reporting to differ by tamoxifen use status, there may be selection bias due to exclusions in this observational study. Other limitations are the lack of serum lipid data and limitations with respect to capability of testing interactions with tumor hormone receptor status. We also note that these data were collected before aromatase inhibitors were used for breast cancer treatment. Associations of fat intake with these drugs may be different from those observed for tamoxifen.

In conclusion, in this multi-ethnic breast cancer survivor cohort, tamoxifen users had lower values for almost all hormones and higher values for SHBG and these values differed slightly by fat intake, albeit not in the direction originally hypothesized. However, among women not taking tamoxifen, fat intake was not associated with sex hormone concentrations. Further work is needed to understand these relationships and whether women using tamoxifen should follow particular dietary patterns to achieve maximal reduction in risk for breast cancer recurrence. Additional research should also evaluate

potential interactions of diet with aromatase inhibitors in relation to sex hormones and clinical endpoints.

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Table 1

Demographic and Medical Characteristics of HEAL participants by Tamoxifen Use Characteristic

	Tamoxifen Users N=255	Non-Tamoxifen Users N=256
	Mean (SD)	Mean (SD)
Age (years)	60.5 (9.4)	61.3 (9.8)
Study Site	N (%)	N (%)
FHCRC	65 (25.5)	41 (16.0)
UMN	139 (54.5)	146 (57.0)
USC	51 (20.0)	69 (27.0)
Weight (kg) mean (SD)	74.3 (18.9)	76.1 (18.5)
BMI (kg/m ²)	N (%)	N (%)
<25	102 (40.0)	85 (33.2)
25–29	75 (29.4)	85 (33.2)
30+	78 (30.6)	86 (33.6)
Race	N (%)	N (%)
Non-Hispanic White from Washington	57 (22.4)	34 (13.3)
Non-Hispanic White from New Mexico	110 (43.1)	121 (47.3)
African-American	51 (20.0)	70 (27.3)
Hispanic	30 (11.8)	24 (9.4)
Other	7 (2.8)	7 (2.7)
Income	N (%)	N (%)
<\$20,000 per year	48 (20.1)	59 (24.4)
\$20,000 – \$50,000 per year	93 (38.9)	112 (46.3)
>\$50,000 per year	98 (41.0)	71 (42.0)
Missing	16	14
Smoking Status	N (%)	N (%)
Never	122 (47.8)	119 (46.5)
Former	104 (40.8)	106 (41.4)
Current	29 (11.4)	31 (12.1)
Physical Activity	Mean (SD)	Mean (SD)
Moderate to Vigorous Activity (Met Hours/Week)	24.8 (23.4)	27.4 (29.0)
Estrogen Receptor Status of Primary Tumors	N (%)	N (%)
Positive	203 (79.6)	106 (41.4)
Negative	15 (5.9)	60 (23.4)
Unknown/Missing	37 (14.5)	90 (35.2)
Progesterone Receptor Status of Primary Tumors	N (%)	N (%)
Positive	163 (63.9)	81 (31.6)

	Tamoxifen Users N=255	Non-Tamoxifen Users N=256
	Mean (SD)	Mean (SD)
Negative	36 (14.1)	72 (28.1)
Unknown/Missing	56 (22.0)	103 (40.2)
Treatment	N (%)	N (%)
Any Chemotherapy	98 (38.4)	63 (24.6)
Surgery + Radiation	103 (40.4)	95 (48.0)
Surgery Only	54 (21.2)	98 (38.3)
Hysterectomy	N (%)	N (%)
No	164 (64.3)	161 (63.4)
Yes	91 (35.7)	93 (36.6)
Missing		2
Number of Ovaries Remaining	N (%)	N (%)
0	59 (23.1)	48 (18.8)
1	7 (2.8)	14 (5.5)
2	189 (74.1)	194 (75.8)

Table 2

Dietary Intake and Sex Steroid Hormone Concentrations of Postmenopausal HEAL Participants by Tamoxifen Use

Dietary Intake	Tamoxifen Users N=255 Mean (SD)	Non-Tamoxifen Users N=256 Mean (SD)
Total Energy (kcal)	1476 (593)	1422 (560)
Fiber (g/day)	15.1 (6.0)	14.6 (6.3)
Alcohol (g/day)	4.4 (9.9)	4.05 (8.6)
Total Fat (g/day)	59.3 (30.4)	57.9 (28.1)
Total Fat (% Energy)	35.6 (8.0)	36.2 (8.2)
Saturated Fat (g/day)	20.3 (11.6)	19.8 (10.6)
Saturated Fat (% Energy)	12.0 (3.3)	12.3 (3.5)
Monounsaturated Fat (g/day)	22.1 (11.4)	21.5 (10.6)
Monounsaturated Fat (% Energy)	13.3 (3.2)	13.4 (3.3)
Polyunsaturated Fat (g/day)	12.4 (6.5)	12.2 (6.2)
Polyunsaturated Fat (% Energy)	7.5 (2.3)	7.7 (2.5)
Trans Fat (g/day)	3.4 (2.2)	3.3 (2.1)
Trans Fat (% Energy)	2.0 (0.8)	2.1 (0.8)
N-6 Polyunsaturated Fat (g/day)	10.9 (5.8)	10.8 (5.6)
N-6/N-3 Polyunsaturated Fat (g/day)	8.4 (2.6)	8.4 (2.1)
EPA + DHA (g/day)	0.06 (0.06)	0.05 (0.06)
Sex Hormone Concentrations		
Estrone (pg/ml) ^{1,2}	25.3 (12.6)	26.2 (14.2)
Estradiol (pg/ml) ^{1,2}	17.1 (13.8)	18.7 (14.5)
Free Estradiol (pg/ml)	0.36 (0.29)	0.48 (0.39)
Testosterone (pg/ml)	212 (126)	228 (140)
Free Testosterone (pg/ml)	3.29 (2.06)	4.71 (3.00)
DHEAS (ug/dl)	68.3 (48.3)	68.0 (46.9)
SHBG (nmol/l)	71.7 (27.5)	42.6 (22.4)

¹ N=250 for Estradiol and Free Estradiol in tamoxifen users

² N=254 for Estradiol and Free Estradiol in non-tamoxifen users

Table 3

Adjusted[†] Geometric Means and 95% Confidence Intervals for Serum Sex Hormones by Quartile of Dietary Fat Intake, Stratified by Tamoxifen Use in Breast Cancer Survivors.

	Total Fat				<i>P</i> -Interaction
	<35 g/day	35–50 g/day	50–70 g/day	70+ g/day	
N[‡]	54, 48	76, 68	51, 73	75, 66	
Estrone (pg/ml)					<i>P</i> _{INT} =0.04
Non-Tamoxifen Users	22.2 (18.4, 26.7)	22.6 (19.5, 26.2)	21.2 (18.0, 24.9)	21.3 (17.9, 25.4)	
Current Tamoxifen Users	20.6 (17.1, 24.8) ^a	23.8 (20.3, 27.9) ^b	25.8 (22.2, 29.9) ^{a,c}	18.2 (15.1, 21.9) ^{b,c}	
Estradiol (pg/ml)					<i>P</i> _{INT} =0.11
Non-Tamoxifen Users	13.7 (10.8, 17.4)	13.2 (11.0, 16.0)	14.2 (11.5, 17.4)	14.3 (11.4, 17.9)	
Current Tamoxifen Users	16.7 (13.1, 21.1) ^a	13.1 (10.7, 16.1)	14.4 (11.9, 17.4)	11.5 (9.0, 14.5) ^a	
Free Estradiol (pg/ml)					<i>P</i> _{INT} =0.10
Non-Tamoxifen Users	0.37 (0.29, 0.47)	0.35 (0.29, 0.43)	0.38 (0.31, 0.47)	0.36 (0.29, 0.46)	
Current Tamoxifen Users	0.36 (0.28, 0.47) ^{a,b}	0.27 (0.22, 0.33) ^b	0.31 (0.25, 0.37) ^c	0.23 (0.18, 0.30) ^{a,c}	
Testosterone (pg/ml)					<i>P</i> _{INT} =0.08
Non-Tamoxifen Users	178 (138, 228)	180 (148, 219)	183 (147, 227)	173 (136, 219)	
Current Tamoxifen Users	166 (129, 213) ^a	161 (130, 200) ^b	221 (181, 269) ^{a,b,c}	135 (105, 172) ^c	
Free Testosterone (pg/ml)					<i>P</i> _{INT} =0.09
Non-Tamoxifen Users	3.81 (2.94, 4.94)	3.82 (3.11, 4.69)	3.90 (3.11, 4.89)	3.52 (2.76, 4.50)	
Current Tamoxifen Users	2.60 (2.00, 3.37)	2.46 (1.97, 3.07) ^A	3.44 (2.80, 4.22) ^{A,B}	2.00 (1.55, 2.59) ^B	
DHEA (ug/dl)					<i>P</i> _{INT} =0.09
Non-Tamoxifen Users	54.4 (42.2, 70.1)	55.5 (45.4, 67.7)	52.9 (42.5, 66.0)	48.9 (38.5, 62.1)	
Current Tamoxifen Users	48.1 (37.3, 62.0)	52.9 (42.6, 65.6) ^a	61.4 (50.3, 75.1) ^B	36.7 (28.5, 47.1) ^{a,B}	
SHBG (nmol/l)					<i>P</i> _{INT} =0.93
Non-Tamoxifen Users	33.9 (29.1, 39.5)	34.2 (30.3, 38.6)	34.3 (30.0, 39.1)	36.7 (31.8, 42.4)	
Current Tamoxifen Users	60.4 (51.9, 70.4)	63.9 (56.1, 72.8)	62.8 (55.7, 70.9)	70.1 (60.3, 81.6)	

[†] Adjusted for energy intake (kcal), fiber intake, alcohol intake, BMI, age, race/site, breast cancer treatment, tamoxifen use, moderate-to-vigorous physical activity, and number of ovaries remaining.

[‡] N=54, 75, 51, and 74 Non-Tamoxifen Users, N=47, 65, 73, and 65 for Tamoxifen Users for Estradiol and Free Estradiol Means with matching letters are significantly ($p<0.05$) different from each other, within Tamoxifen Use category. Capital letter indicates $p<0.01$.

Adjusted[†] Geometric Means and 95% Confidence Intervals for Serum Sex Hormones by Quartile of Dietary Saturated Fat Intake, Stratified by Tamoxifen Use in Breast Cancer Survivors.

Table 4

		Saturated Fat				<i>P</i> -Interaction
		<12 g/day	12–17 g/day	17–25 g/day	25+ g/day	
N [‡]		57, 62	69, 59	66, 64	64, 70	
Estrone (pg/ml)	Non-Tamoxifen Users	21.5 (17.8, 25.8)	23.0 (19.8, 26.8)	21.3 (18.3, 24.7)	21.1 (17.5, 25.5)	<i>P</i> _{INT} =0.33
	Current Tamoxifen Users	21.2 (17.8, 25.1)	23.5 (19.9, 27.7)	24.5 (21.0, 28.6) ^a	19.3 (16.1, 23.2) ^a	
Estradiol (pg/ml)	Non-Tamoxifen Users	15.5 (12.3, 19.6)	12.8 (10.5, 15.5)	13.8 (11.4, 16.6)	13.9 (11.0, 17.6)	<i>P</i> _{INT} =0.56
	Current Tamoxifen Users	17.2 (13.9, 21.4) ^{a, b, c}	12.6 (10.2, 15.6) ^a	13.3 (11.0, 16.2) ^b	12.2 (9.7, 15.3) ^c	
Free Estradiol (pg/ml)	Non-Tamoxifen Users	0.42 (0.33, 0.53)	0.34 (0.28, 0.41)	0.37 (0.31, 0.45)	0.35 (0.27, 0.45)	<i>P</i> _{INT} =0.44
	Current Tamoxifen Users	0.38 (0.31, 0.48) ^{A, b, c}	0.26 (0.21, 0.33) ^A	0.28 (0.23, 0.34) ^b	0.25 (0.19, 0.31) ^c	
Testosterone (pg/ml)	Non-Tamoxifen Users	187 (146, 239)	194 (158, 238)	169 (138, 206)	166 (129, 213)	<i>P</i> _{INT} =0.04
	Current Tamoxifen Users	174 (138, 219)	171 (137, 214)	213 (173, 262) ^A	132 (103, 168) ^A	
Free Testosterone (pg/ml)	Non-Tamoxifen Users	4.06 (3.14, 5.24)	4.09 (3.31, 5.05)	3.64 (2.96, 4.48)	3.31 (2.55, 4.29)	<i>P</i> _{INT} =0.09
	Current Tamoxifen Users	2.81 (2.21, 3.56) ^a	2.60 (2.07, 3.28)	3.26 (2.63, 4.03) ^b	1.94 (1.51, 2.49) ^{a, B}	
DHEA (ug/dl)	Non-Tamoxifen Users	59.6 (46.5, 76.3)	51.5 (41.9, 63.2)	56.0 (45.7, 68.5)	46.9 (36.4, 60.3)	<i>P</i> _{INT} =0.08
	Current Tamoxifen Users	50.6 (40.2, 63.8) ^a	56.7 (45.3, 70.9) ^B	60.7 (49.3, 74.8) ^C	35.6 (27.9, 45.4) ^{a, B, C}	
SHBG (nmol/l)	Non-Tamoxifen Users	33.3 (28.7, 38.7)	35.2 (31.1, 39.8)	32.8 (29.1, 37.0)	38.1 (32.8, 44.3)	<i>P</i> _{INT} =0.65
	Current Tamoxifen Users	57.8 (50.3, 66.4) ^a	63.7 (55.7, 72.9)	64.8 (57.2, 73.5)	71.4 (61.7, 82.7) ^a	

[†] Adjusted for energy intake (kcal), fiber intake, alcohol intake, BMI, age, race/site, breast cancer treatment, tamoxifen use, moderate-to-vigorous physical activity, and number of ovaries remaining.

[‡] N=57, 68, 66, and 63 Non-Tamoxifen Users, N=61, 57, 63, and 69 for Tamoxifen Users for Estradiol and Free Estradiol Means with matching letters are significantly ($p<0.05$) different from each other, within Tamoxifen Use category. Capital letter indicates $p<0.01$.

Adjusted[†] Geometric Means and 95% Confidence Intervals for Serum Sex Hormones by Quartile of Dietary Polyunsaturated Fat Intake, Stratified by Tamoxifen Use in Breast Cancer Survivors.

Table 5

	Polyunsaturated Fat				<i>P</i> -Interaction
	<7 g/day	7–11 g/day	11–15 g/day	15+ g/day	
N[‡]	57, 50	73, 79	53, 60	73, 66	
Estrone (pg/ml)					
Non-Tamoxifen Users	22.0 (18.5, 26.2)	22.9 (19.7, 26.7)	20.7 (17.7, 24.4)	22.6 (19.1, 26.6)	<i>P</i> _{INT} =0.07
Current Tamoxifen Users	21.3 (17.8, 25.5)	24.0 (20.7, 27.9) ^a	24.9 (21.1, 29.3) ^B	19.3 (16.3, 22.7) ^{a, B}	
Estradiol (pg/ml)					
Non-Tamoxifen Users	13.9 (11.2, 17.4)	12.8 (10.6, 15.6)	16.2 (13.2, 19.8)	13.1 (10.7, 16.2)	<i>P</i> _{INT} =0.31
Current Tamoxifen Users	16.1 (12.9, 20.2) ^a	13.3 (11.0, 16.1)	14.8 (12.0, 18.2) ^b	11.4 (9.2, 14.0) ^{a, b}	
Free Estradiol (pg/ml)					
Non-Tamoxifen Users	0.38 (0.30, 0.47)	0.34 (0.28, 0.41)	0.43 (0.35, 0.53)	0.34 (0.27, 0.42)	<i>P</i> _{INT} =0.53
Current Tamoxifen Users	0.34 (0.27, 0.43) ^a	0.27 (0.23, 0.33)	0.31 (0.25, 0.39) ^b	0.24 (0.19, 0.30) ^{a, b}	
Testosterone (pg/ml)					
Non-Tamoxifen Users	160 (127, 203)	179 (146, 220)	172 (138, 213)	201 (161, 251)	<i>P</i> _{INT} =0.38
Current Tamoxifen Users	160 (125, 203)	159 (130, 195)	196 (157, 244)	172 (138, 215)	
Free Testosterone (pg/ml)					
Non-Tamoxifen Users	3.58 (2.80, 4.57)	3.70 (2.99, 4.57)	3.61 (2.88, 4.52)	4.17 (3.31, 5.25)	<i>P</i> _{INT} =0.41
Current Tamoxifen Users	2.50 (1.95, 3.21)	2.41 (1.95, 2.97)	3.04 (2.42, 3.83)	2.63 (2.09, 3.31)	
DHEA (ug/dl)					
Non-Tamoxifen Users	57.5 (45.3, 72.9)	54.8 (44.6, 67.4)	50.6 (40.7, 62.9)	52.5 (42.0, 65.7)	<i>P</i> _{INT} =0.14
Current Tamoxifen Users	48.6 (38.1, 61.9)	54.9 (44.7, 67.3) ^a	57.8 (46.3, 72.2) ^b	40.9 (32.7, 51.2) ^{a, b}	
SHBG (nmol/l)					
Non-Tamoxifen Users	31.2 (27.1, 36.0) ^a	36.1 (31.9, 40.8) ^a	34.8 (30.5, 39.6)	36.3 (31.8, 41.5)	<i>P</i> _{INT} =0.82
Current Tamoxifen Users	61.3 (53.0, 70.8)	64.1 (56.7, 72.4)	63.8 (55.9, 72.9)	66.6 (58.3, 76.1)	

[†] Adjusted for energy intake (kcal), fiber intake, alcohol intake, BMI, age, race/site, breast cancer treatment, tamoxifen use, moderate-to-vigorous physical activity, and number of ovaries remaining.

[‡] N=57, 72, 53, and 72 Non-Tamoxifen Users, N=48, 78, 58, and 66 for Tamoxifen Users for Estradiol and Free Estradiol Means with matching letters are significantly ($p<0.05$) different from each other, within Tamoxifen Use category. Capital letter indicates $p<0.01$.