Association between Alcohol Intake and Serum Sex Hormones and Peptides Differs by Tamoxifen Use in Breast Cancer Survivors

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Abstract

Objective: **To measure the association between alcohol intake and 11 hormones and peptides in postmenopausal breast cancer survivors and to evaluate whether this association differs by tamoxifen use.**
Methods: **Self-reported alcohol intake was assessed via food frequency questionnaire on average 30 months post-breast cancer diagnosis in 490 postmenopausal women from three western states. Concurrently, a fasting blood sample was obtained for assay of estrone, estradiol, free estradiol, testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), leptin, C-peptide, insulin-like growth factor-I (IGF-I), and IGF-binding protein-3. Adjusted means of these hormones and peptides were calculated for categories of alcohol intake, overall and stratified by tamoxifen use.**
Results: **The association between alcohol intake and serum hormone and peptide levels differed by tamoxifen use. We found statistically significant inverse associations between alcohol intake and both leptin and SHBG values but only among tamoxifen users. In women not using tamoxifen, we found a positive association between alcohol intake and DHEAS but no association in tamoxifen users.**
Conclusion: **Tamoxifen may modify the association between alcohol intake and serum hormones and peptides. The significant associations found for DHEAS and SHBG are in a direction considered unfavorable for breast cancer prognosis. Postmenopausal breast cancer survivors may benefit from decreasing their alcohol intake.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):3224–32)

Introduction

Most epidemiologic studies have found a positive association between alcohol intake and breast cancer incidence (1-4). This relationship appears to be modest in magnitude yet consistent across a variety of populations and study designs. One possible explanation for the association between alcohol and breast cancer is that alcohol consumption increases circulating estrogen and androgen levels, which in turn promote breast cancer development (3). Alcohol intake may also be associated with other important biomarkers, such as leptin and insulin-like growth factors (5-8), which have proliferative effects independent of the steroid hormone mechanisms (9-11). In addition to being implicated in breast cancer incidence, these hormone and peptide measures may also promote recurrence and poor prognosis among women diagnosed with breast cancer (12-17); however, we are not aware of published research examining the relationship between alcohol and these serum measures in women with a previous diagnosis of breast cancer.

The positive association between alcohol intake and serum hormone levels appears to be enhanced by the use of exogenous estrogens. Women taking estrogen replacement therapy are reported to have a much greater relative increase in estradiol with increased alcohol consumption compared with those not taking estrogen (18). Although women with a prior breast cancer diagnosis are unlikely to be taking exogenous estrogens, the use of the antiestrogen drug tamoxifen is common (19). Therefore, an important clinical question is whether an exogenous hormone such as tamoxifen alters associations between alcohol and these hormones and peptides implicated in breast cancer risk and recurrence.

The purpose of this study was 2-fold. First, we examined the relationship between alcohol intake and serum hormone and peptide levels in postmenopausal breast cancer survivors. We hypothesized that alcohol would have the same direct association with serum

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hormones and peptides in these women as it does in women without breast cancer. Second, we investigated potential interactions of tamoxifen use with any observed associations. Because the presence of exogenous estrogens appears to increase the direct association between alcohol and serum estrogens, we hypothesized that any associations found between alcohol and serum hormones or peptides would be weaker in tamoxifen users than in nonusers.

Materials and Methods

Study Population. The Health, Eating, Activity and Lifestyle Study is a multicenter, multiethnic prospective cohort study of 1,183 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 Health, Eating, Activity and Lifestyle Study through Surveillance, Epidemiology, and End Results registries in New Mexico, Los Angeles county (California), and western Washington. Details of the study aims, design, and recruitment procedures have been published previously (20-22). All three study sites included women diagnosed with *in situ* to stage IIIA breast cancer, but the age ranges and dates of diagnosis differed by site: New Mexico included 615 women, ages ≥18 years, who were diagnosed between July 1996 and March 1999, and lived in Bernalillo, Santa Fe, Sandoval, Valencia, or Taos counties; western Washington included 202 women, ages 40 to 64 years, diagnosed between September 1997 and September 1998, and living in King, Pierce, or Snohomish counties; and the Los Angeles county cohort consisted of 366 Black women who were diagnosed between May 1995 and May 1998.

Baseline data were collected via in-person interviews (for New Mexico and Los Angeles) and self-administered questionnaires (Washington) conducted within 1 year of diagnosis (on average 7.5 months postdiagnosis). Follow-up data were collected 24 months after the baseline visit (within the third year after diagnosis; on average, 31.5 months postdiagnosis). Data on age, education, self-reported race/ethnicity, and measured height were collected at the baseline interview. All other data presented here were obtained at the 24-month follow-up interview.

Written informed consent was obtained from each study participant. The study was done with the approval of the institutional review boards of participating centers (University of New Mexico, Fred Hutchinson Cancer Research Center, and University of Southern California) in accord with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Hormone/Peptide Assays. A 30-mL fasting blood sample was collected at the 24-month follow-up interview. Blood was processed within 3 h of collection; serum was stored in 1.8-mL aliquot tubes at -70°C to -80°C until analysis. We measured estrone, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), leptin, C-peptide, insulin-like growth factor-I (IGF-I), and IGF-binding protein-3 (IGFBP3). Free estradiol and free testosterone were calculated from SHBG and total estradiol and testosterone, respectively (23). We had insufficient blood to measure IGF-I in one subject, C-peptide in two participants, and estradiol/free estradiol in nine participants.

For California participants, all assays, except testosterone, were done at the Reproductive and Endocrine Research Laboratory at the University of Southern California. Testosterone assays were done at the University of New Mexico. For Washington and New Mexico participants, estrone and estradiol were assayed at Quest Diagnostics 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. Bio-Rad 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.

RIA was used to measure all serum analytes (24). Serum extraction and chromatographic purification were done before RIA for estrone and estradiol. The sensitivity for the estrone assay was <5 to 10 pg/mL and for estradiol was <2 pg/mL. Serum testosterone was determined using a RIA kit (Diagnostic Products) with a sensitivity of 40 pg/mL. SHBG levels were determined using the Wein Laboratories RIA kit with a sensitivity of 6 nmol/L. The C-peptide of insulin ^{125}I RIA kit (Incstar) was used to measure C-peptide levels (sensitivity of 0.1 ng/mL). IGF-I and IGFBP3 levels were determined by ^{125}I RIA kits supplied from Nichols Institute Diagnostics (sensitivity of 0.1 and 62.5 ng/mL, respectively). Leptin was assayed using Linco RIA kits (sensitivity of 0.5 ng/mL).

Intra-assay variability was assessed in a reduced randomly selected sample for all hormones. The coefficients of variation were calculated to test the assay variability. In California, 24 blood samples were randomly selected for hormone assay repeats. The coefficient of variation was estimated by the SD of the difference of replicated measures divided by the mean of the two measures. The intra-assay coefficients of variation for estrone, estradiol, SHBG, IGF-I, and C-peptide were 26.2%, 15.4%, 9.3%, 6.2%, and 10.5%, respectively.

For New Mexico and western Washington, intra-assay coefficients of variation were calculated as the SD of the difference between repeated measures divided by the mean of the two measures. Assays were done in batches, and duplicate aliquots of 10 randomly selected participant samples were assayed per batch. The intra-assay and total coefficients of variation were 3.8% and 5.9%, respectively, for SHBG, 12.0% and 14.4% for testosterone, 29.1% and 13.3% for estrone, and 28.8% and 13.3% for estradiol.

Alcohol Intake. Dietary intake data were collected using a self-administered food frequency questionnaire designed for the Women's Health Initiative (25). Participants were asked frequency and portion size (small, medium, or large) of beer, wine, and liquor (1 medium serving was defined as 12 oz. beer, 4 oz. wine, or 1.5 oz. liquor). Responses were used to calculate grams per day of alcohol intake. Because our earlier work showed independent associations between fiber and fat intake and hormone levels, we also included data for these

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dietary variables in the analysis (26). The nutrient database used to convert food information into nutrients is derived from the University of Minnesota's Nutrition Coordinating Center's Nutrition Data Systems for Research (version 2005). New Mexico participants reported their usual dietary intake for the preceding year, and participants at the other two sites reported intake for the preceding month. We cannot determine if these different referent periods affected the amount or type of alcohol reported by the three sites because we cannot separate referent period from study site; however, we did control for study site in our analyses.

Menstrual Status. At the time of the 24-month follow-up interview, women who were ages ≥55 years 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 ages <55 years were also categorized as postmenopausal if they had not menstruated in the year before their interview. Ninety-five percent of women reporting natural menopause were menopausal by age 56 years. Women categorized as premenopausal or whose menopausal status was unknown were excluded from these analyses.

Body Mass Index/Physical Activity. Trained staff measured weight and height using a standardized protocol at the clinic or home visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A total of 143 participants were missing values for measured height; for these women, we used self-reported height to calculate BMI. We have previously compared results of BMI calculated from a subset of women who have both measured and self-reported height and have found high concordance: only 3 of 569 women had a change in BMI classification from overweight to healthy weight when using self-reported height rather than measured height (27). We classified BMI according to the WHO categories: normal weight, overweight, and obese (<25, 25-29.9, and ≥30 kg/m^2, respectively; ref. 28).

We collected information on physical activity using a questionnaire administered in-person at the 24-month follow-up visit. The questionnaire was based on the Modifiable Activity Questionnaire developed by Kriska (29). The type, duration, and frequency of activities done in the past year were assessed, and for each activity, frequency was multiplied by duration to quantify activity level. For the present analysis, physical activity was defined as the number of metabolic equivalent (MET) hours per week in sports and recreational activities. A MET is defined as the ratio of the associated metabolic rate for a specific activity divided by the resting metabolic rate (e.g., a 2-MET activity requires two times the resting metabolic energy expenditure of sitting quietly; ref. 30).

Data Analysis. The sample size for this analysis began with 607 postmenopausal women who had serum and dietary data available from the 24-month interview. We excluded 44 women due to implausible values for dietary data (energy intake <600 or >4,000 kcal/d) and 47 women who reported taking hormone therapy (other than tamoxifen). At the time of the study, no participants were taking aromatase inhibitors. We also excluded 14 participants whose race/ethnicity was classified as "Other" and 12 with missing values for BMI leaving a final sample of 490. We excluded 15 individual hormone/peptide values, which were extremely high and deemed to be implausible outliers: estrone >200 pg/mL, estradiol >160 pg/mL, testosterone >1,330 pg/mL, DHEAS >350 μg/dL, IGF-I >600 ng/mL, C-peptide >7 ng/mL, and leptin >100 ng/mL. For women with hormone values below the detectable limits, we assigned a value halfway between zero and the lower limit of detection such that 17 women were assigned a testosterone value of 13 pg/mL, 33 were assigned an estrone value of 5 pg/mL, and 1 woman was assigned an estradiol value of 1 pg/mL.

IGFBP3 and C-peptide concentrations were normally distributed. The remaining hormone and peptide concentrations were log-normally distributed and were log-transformed; geometric means are presented for these variables. Alcohol intake was divided into the following categories to make them comparable with other similar studies (31): <1, 1 to 4.9, 5 to 14.9, and ≥15 g/d. There

Table 1. Demographic and lifestyle characteristics and serum hormone and peptide measures of Health, Eating, Activity and Lifestyle Study participants at the 24-month follow-up, *n* = 490

	Mean (SD)
Age	60.7 (9.4)
Race/ethnicity/study site	*n* (%)
Non-Hispanic White, New Mexico	221 (45.1)
Non-Hispanic White, western Washington	92 (18.8)
Hispanic	53 (10.8)
Black	124 (25.3)
Education	
High school or less	140 (28.6)
Some college/technical school	177 (36.1)
College graduate	173 (35.3)
BMI categories (kg/m^2)	
Healthy weight (<25)	180 (36.7)
Overweight (25-29.9)	155 (31.6)
Obese (≥30)	155 (31.6)
Activity	Median
Sports/recreation activities (MET-h/wk)	5.6
Tamoxifen use	*n* (%)
No	248 (50.6)
Yes	242 (49.4)
Drink alcohol?	
No	262 (53.5)
Yes	228 (46.5)
Alcohol intake (g/d)	
<1	297 (60.6)
1-4.9	77 (15.7)
5-14.9	70 (14.3)
≥15	46 (9.4)
Hormones/peptides	Mean (95% CI)
Estrone, pg/mL*	22.7 (21.5-23.9)
Estradiol, pg/mL (*n* = 483)*	14.4 (13.5-15.4)
Free estradiol, pg/mL (*n* = 483)*	0.33 (0.31-0.35)
Testosterone, pg/mL*	179.9 (168.4-192.2)
Free testosterone, pg/mL*	3.1 (2.9-3.4)
DHEAS, μg/dL*	53.8 (50.4-57.4)
Leptin, ng/mL*	20.2 (18.9-21.5)
SHBG, nmol/L*	50.1 (47.7-52.6)
IGF-I, ng/mL (*n* = 489)*	112.4 (107.8-117.2)
IGFBP3, μg/mL	4.1 (4.0-4.1)
C-peptide, ng/mL (*n* = 488)	2.4 (2.3-2.5)

*Geometric mean.

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Table 2. Univariate associations between categories of demographic and lifestyle characteristics and mean (95% CI) serum hormone and peptide measurements and percent alcohol drinkers

	Estrogens			Androgens		
	Estrone (pg/mL)	Estradiol (pg/mL)	Free estradiol (pg/mL)	Testosterone (pg/mL)	Free testosterone (pg/mL)	DHEAS (μg/dL)
Race/ethnicity						
Non-Hispanic, White, New Mexico	20.2 (18.7-21.8)	16.7 (15.2-18.4)	0.38 (0.34-0.42)	152.0 (136.6-169.2)	2.6 (2.3-2.9)	45.0 (41.0-49.4)
Non-Hispanic, White, Washington	22.5 (19.8-25.5)	10.8 (9.2-12.8)	0.27 (0.23-0.32)	216.7 (195.7-239.8)	4.0 (3.6-4.5)	71.0 (62.8-80.2)
Hispanic	17.4 (14.5-20.9)	14.4 (11.5-18.2)	0.33 (0.26-0.42)	145.9 (116.7-182.4)	2.5 (1.9-3.2)	50.2 (40.1-62.8)
Black	31.4 (29.2-33.8)	13.7 (12.7-14.8)	0.31 (0.28-0.34)	231.4 (207.3-258.3)	3.9 (3.4-4.4)	62.0 (54.3-70.8)
P for any difference	<0.001	<0.001	0.002	<0.001	<0.001	<0.001
Age group						
<60	23.5 (21.7-25.5)	14.0 (12.7-15.3)	0.32 (0.29-0.36)	184.8 (168.6-202.5)	3.3 (3.0-3.6)	65.3 (60.0-71.1)
60-69	22.0 (20.2-23.8)	13.8 (12.5-15.3)	0.32 (0.29-0.36)	184.4 (165.3-205.7)	3.3 (2.9-3.7)	48.0 (42.7-53.8)
70-79	21.8 (19.0-25.0)	17.0 (14.3-20.4)	0.37 (0.31-0.45)	156.4 (125.8-194.3)	2.6 (2.1-3.3)	40.8 (34.1-48.7)
≥80	21.7 (15.3-30.8)	17.6 (12.9-24.2)	0.37 (0.27-0.52)	163.7 (118.6-226.1)	2.5 (1.8-3.6)	33.7 (24.8-45.8)
P_{trend}	0.23	0.05	0.20	0.17	0.05	<0.001
Education						
High school or less	23.9 (21.4-26.7)	14.9 (13.1-17.0)	0.34 (0.30-0.39)	185.5 (163.8-210.0)	3.2 (2.8-3.7)	52.0 (46.6-58.0)
Some college/ technical school	23.4 (21.5-25.4)	14.5 (13.1-16.1)	0.33 (0.30-0.37)	179.6 (161.7-199.4)	3.1 (2.8-3.5)	53.3 (47.6-59.6)
College graduate	21.1 (19.4-22.9)	13.8 (12.4-15.4)	0.32 (0.29-0.36)	175.9 (156.7-197.4)	3.1 (2.7-3.5)	55.8 (49.7-62.6)
P_{trend}	0.06	0.35	0.57	0.53	0.68	0.39
BMI category (kg/m^2)						
<25	20.1 (18.4-22.0)	14.2 (12.6-15.9)	0.30 (0.27-0.34)	158.4 (140.7-178.3)	2.5 (2.2-2.8)	47.4 (42.1-53.3)
25-29.9	21.2 (19.4-23.1)	12.9 (11.5-14.4)	0.30 (0.27-0.34)	166.5 (148.1-187.2)	3.0 (2.6-3.4)	55.3 (49.7-61.6)
≥30	27.9 (25.5-30.6)	16.5 (14.9-18.2)	0.40 (0.36-0.44)	225.4 (204.9-247.9)	4.3 (3.9-4.8)	60.6 (54.3-67.5)
P_{trend}	<0.001	0.07	0.001	<0.001	<0.001	0.002
Sports and recreational activities (MET-h/wk)						
<2	23.7 (21.6-26.0)	14.7 (13.3-16.3)	0.34 (0.31-0.38)	173.0 (154.1-194.2)	3.1 (2.7-3.5)	51.4 (45.4-58.1)
2-11.5	24.2 (22.1-26.5)	14.6 (13.0-16.4)	0.34 (0.30-0.38)	193.1 (173.6-214.8)	3.4 (3.0-3.8)	57.4 (51.9-63.5)
>11.5	20.4 (18.6-22.3)	13.9 (12.4-15.5)	0.31 (0.27-0.35)	174.2 (154.5-196.4)	2.9 (2.6-3.3)	52.7 (47.0-59.2)
P_{trend}	0.02	0.46	0.21	0.94	0.63	0.75
Tamoxifen use						
No	23.0 (21.4-24.8)	15.1 (13.8-16.5)	0.38 (0.35-0.42)	189.6 (172.6-208.3)	3.8 (3.5-4.2)	54.7 (49.9-59.9)
Yes	22.3 (20.7-24.1)	13.7 (12.5-15.0)	0.28 (0.26-0.31)	170.5 (155.4-187.0)	2.5 (2.3-2.8)	52.9 (48.1-58.1)
P for any difference	0.59	0.13	<0.001	0.11	<0.001	0.61

	Leptin/SHBG		Peptides			Alcohol use
	Leptin (ng/mL)	SHBG (nmol/L)	IGF-I (ng/mL)	IGFBP3 (μg/mL)	C-peptide (ng/mL)	% Alcohol drinkers
Race/ethnicity						
Non-Hispanic, White, New Mexico	17.7 (16.1-19.5)	50.6 (47.0-54.5)	122.8 (115.8-130.3)	4.1 (4.0-4.2)	2.4 (2.3-2.6)	52.5
Non-Hispanic, White, Washington	18.8 (16.3-21.8)	44.2 (39.5-49.4)	125.8 (117.3-135.0)	4.2 (4.0-4.3)	2.2 (2.0-2.4)	51.1
Hispanic	18.1 (15.6-21.0)	51.0 (43.8-59.3)	109.3 (94.6-126.4)	4.0 (3.8-4.3)	2.6 (2.3-2.8)	45.3
Black	28.1 (25.0-31.7)	53.6 (48.8-58.8)	89.3 (81.9-97.3)	3.9 (3.7-4.1)	2.4 (2.1-2.6)	33.1
P for any difference	<0.001	0.08	<0.001	0.12	0.26	0.01
Age group						
<60	21.3 (19.4-23.4)	49.3 (46.1-52.8)	119.7 (112.6-127.2)	4.2 (4.1-4.4)	2.4 (2.2-2.5)	51.9
60-69	19.4 (17.5-21.5)	48.5 (44.6-52.9)	109.6 (102.8-116.9)	4.0 (3.9-4.2)	2.4 (2.2-2.5)	42.1
70-79	19.3 (16.1-23.1)	54.2 (47.0-62.6)	104.9 (92.3-119.1)	3.7 (3.5-4.0)	2.6 (2.3-2.9)	40.3
≥80	17.2 (12.2-24.1)	62.0 (49.1-78.2)	83.2 (69.6-99.4)	3.3 (2.9-3.7)	2.5 (2.1-2.9)	40.0
P_{trend}	0.09	0.09	<0.001	<0.001	0.18	0.04
Education						
High school or less	22.9 (20.4-25.7)	50.0 (45.3-55.2)	102.0 (94.2-110.5)	3.9 (3.8-4.1)	2.3 (2.2-2.5)	35.7
Some college/ technical school	20.0 (17.9-22.4)	50.3 (46.4-54.5)	107.6 (100.6-115.2)	3.9 (3.8-4.0)	2.5 (2.3-2.6)	44.1
College graduate	18.4 (16.6-20.4)	50.0 (46.4-54.0)	127.2 (119.0-135.9)	4.3 (4.1-4.4)	2.4 (2.2-2.5)	57.8
P_{trend}	0.01	0.99	<0.001	0.002	0.60	<0.001
BMI category (kg/m^2)						
<25	10.8 (10.0-11.7)	62.3 (58.5-66.4)	125.2 (117.6-133.3)	4.1 (4.0-4.2)	2.0 (1.8-2.1)	60.0
25-29.9	21.4 (20.0-22.9)	47.7 (43.9-51.9)	115.2 (107.1-123.9)	4.0 (3.8-4.2)	2.4 (2.3-2.6)	41.9
≥30	39.4 (36.8-42.2)	40.8 (37.1-44.9)	96.9 (89.7-104.6)	4.0 (3.9-4.2)	2.9 (2.7-3.1)	35.5
P_{trend}	<0.001	<0.001	<0.001	0.49	<0.001	<0.001

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Table 2. Univariate associations between categories of demographic and lifestyle characteristics and mean (95% CI) serum hormone and peptide measurements and percent alcohol drinkers (Cont'd)

	Leptin/SHBG		Peptides			Alcohol use
	Leptin (ng/mL)	SHBG (nmol/L)	IGF-I (ng/mL)	IGFBP3 (μg/mL)	C-peptide (ng/mL)	% Alcohol drinkers
Sports and recreational activities (MET-h/wk)						
<2	23.2 (20.6-26.2)	47.8 (43.7-52.3)	100.7 (93.1-108.8)	4.0 (3.9-4.2)	2.6 (2.4-2.8)	32.9
2-11.5	21.7 (19.6-24.0)	49.4 (45.5-53.5)	118.0 (110.4-126.1)	4.1 (3.9-4.2)	2.4 (2.2-2.6)	48.8
>11.5	16.4 (14.8-18.2)	53.3 (49.1-57.8)	119.5 (111.5-128.0)	4.1 (3.9-4.2)	2.2 (2.0-2.3)	57.6
P_{trend}	<0.001	0.08	0.001	0.63	<0.001	<0.001
Tamoxifen use						
No	21.0 (19.1-23.1)	37.6 (35.2-40.2)	129.2 (122.0-136.7)	4.0 (3.8-4.1)	2.4 (2.2-2.5)	45.2
Yes	19.4 (17.8-21.1)	67.2 (64.0-70.6)	97.5 (92.2-103.1)	4.1 (4.0-4.2)	2.4 (2.3-2.6)	47.9
P for any difference	0.21	<0.001	<0.001	0.11	0.72	0.54

NOTE: Geometric means for all serum measures except IGFBP3 and C-peptide.

were three race/ethnicity categories in the Health, Eating, Activity and Lifestyle Study: Hispanic, Black, and non-Hispanic White. All but 3 of 53 Hispanics were from New Mexico; all but 1 Black was from Los Angeles; non-Hispanic Whites came from both western Washington and New Mexico. We found important differences in hormone levels between non-Hispanic Whites depending on which study site the participant was from. For this reason, we present data for non-Hispanic White women by study site. We used least squares regression analysis to estimate the association of alcohol intake with hormone and peptide concentrations. We included in the model any of the demographic or health-related characteristics that were significantly associated with at least some of the hormone/peptide measures and with alcohol use. Because our analysis evaluates the associations between hormones and alcohol stratified by tamoxifen use, we decided to keep tamoxifen use in the final model regardless of whether it was significantly associated with serum hormone values or alcohol intake. The final model included age (continuous), BMI (continuous), education (high school or less, some college, college graduate, or higher), activity level (tertiles), tamoxifen use (yes/no), a combined variable for race/ethnicity and study site (Hispanic, Black, and non-Hispanic White from New Mexico and non-Hispanic White from western Washington), and number of ovaries (0, 1, and 2). We then ran the models separately by tamoxifen use to investigate possible differential effects. We first examined the distributions of the stratified results to determine whether outlying values may have contributed to the occasional spike or dip in adjusted means and found no evidence of obvious outlying values. The data were analyzed using SAS software (version 9.1.3, SAS Institute).

Results

Table 1 describes the study participants at the 24-month follow-up interview. Their average age was 60.7 years. Almost half (45.1%) of study participants were non-Hispanic Whites from New Mexico, 18.8% were non-Hispanic Whites from western Washington, 10.8% were Hispanic, and 25.3% Black. Participants were about equally distributed among the three BMI categories of normal weight, overweight, and obese, and almost half of the participants reported use of tamoxifen at the 24-month follow-up interview. Over half (53.5%) reported no use of alcohol; another 7% reported intakes <1 g/d so that >60% of the study group fell into the lowest category of alcohol intake: <1 g/d. Sixteen percent reported daily intakes of between 1.0 and 5.0 g, 14% consumed 5.0 to 14.9 g/d, and <10% reported drinking ≥15.0 g/d.

The associations between various demographic and health-related characteristics and the hormone and peptide concentrations are shown in Table 2. We also present alcohol intake (% drinkers) by each of these variables. There were statistically significant differences between most variables by race/ethnicity. The observed differences between hormone levels for non-Hispanic White women from western Washington and from New Mexico were mainly due to age differences in the two groups: women from western Washington were all ages <65 years on entry to the study compared with the women from New Mexico who had a maximum age of 91 years.

Increasing age was significantly associated with decreasing DHEAS, IGF-I, IGFBP3, and alcohol use. More years of education were significantly associated with increasing IGF-I, IGFBP3, and alcohol use and decreasing circulating leptin concentrations. BMI was significantly associated with 9 of the 11 hormone/peptide measures and with alcohol use ($P_{trend} \leq 0.05$); this association was positive for the estrogens, androgens, leptin, and C-peptide and negative for SHBG, IGF-I, and alcohol. Conversely, physical activity was inversely associated with estrone, leptin, and C-peptide but positively associated with IGF-I and alcohol use. Women taking tamoxifen had significantly lower levels of free estradiol, free testosterone, and IGF-I but higher levels of SHBG than did women not taking the drug. Intake of dietary fat was directly associated with leptin and C-peptide and negatively associated with IGF-I, whereas the associations were reversed for dietary fiber intake with leptin and IGF-I.

We investigated the association between prior chemotherapy and hormone levels and alcohol intake (data not shown). We found that estradiol, free estradiol, DHEAS, and leptin differed significantly by prior chemotherapy, but there was no association between alcohol intake and chemotherapy ($P = 0.53$). We also found dietary fat and fiber intake to correlate with some of the serum measures but not with alcohol intake ($P = 0.18$ and 0.51,

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respectively). Because of our decision to use in the final model only those variables that were significantly associated with both hormone levels and alcohol intake, we did not include chemotherapy, dietary fat, or dietary fiber in our final analytic model.

Adjusted means of each of the 11 hormone/peptide measures by alcohol intake are shown in Table 3 for all subjects combined and separately by tamoxifen use. We observed statistically significant ($P < 0.05$), positive associations between alcohol intake and testosterone, free testosterone, and DHEAS for the combined study sample ($n = 490$); we also observed a negative association between alcohol and leptin ($P = 0.06$) in this group.

The association between alcohol intake and serum measures differed by tamoxifen use in that significant negative associations between alcohol intake and leptin and SHBG values were seen in tamoxifen users but not in nonusers. There was also a significant positive association between alcohol intake and DHEAS only among those women who did not report tamoxifen use. The association between alcohol intake and SHBG in tamoxifen users is notable because the range of SHBG differs considerably from that in nonusers (57.5-71.0 versus 36.9-41.0 nmol/L, respectively). We tested for interaction by creating a cross-product term for alcohol category by tamoxifen use; this interaction term was statistically significant in the model with SHBG as the dependent variable ($P = 0.01$; data not shown). A similar interaction variable was not significant in models predicting DHEAS and leptin ($P = 0.44$ and 0.51, respectively). We did 33 tests of significance in Table 3; the six statistically significant associations found in Table 3 are more than the 1 or 2 that would be expected by chance.

We next evaluated whether the association between alcohol use and SHBG in tamoxifen users was influenced by either estrogen receptor status or BMI and stratified the analyses by these two factors (data not shown). For estrogen receptor status, we were missing data for 25% of

Table 3. Least squares mean (95% CI) hormone and peptide levels by category of alcohol intake

Alcohol intake (g/d)	*n**	Estrogens			Androgens		
		Estrone (pg/mL)	Estradiol (pg/mL)	Free estradiol (pg/mL)	Testosterone (pg/mL)	Free testosterone (pg/mL)	DHEAS (μg/dL)
<1.0	297	22.2 (20.8-23.7)	14.0 (12.9-15.2)	0.32 (0.29-0.34)	171.4 (158.1-185.8)	2.9 (2.7-3.2)	49.1 (45.3-53.1)
1.0-4.9	77	23.9 (21.1-27.0)	15.3 (13.0-17.8)	0.35 (0.29-0.41)	175.9 (150.0-206.1)	3.1 (2.6-3.6)	61.6 (52.7-71.9)
5.0-14.9	70	23.6 (20.6-26.9)	14.6 (12.3-17.2)	0.34 (0.28-0.40)	210.6 (178.1-248.8)	3.7 (3.1-4.4)	65.0 (55.2-76.5)
>15	46	22.2 (18.7-26.1)	15.1 (12.2-18.5)	0.35 (0.28-0.43)	200.8 (162.9-247.5)	3.6 (2.8-4.4)	57.5 (46.8-70.4)
P_{trend}		0.63	0.45	0.14	0.03	0.01	0.01
By tamoxifen use							
Tamoxifen users							
<1.0	140	21.5 (19.6-23.5)	13.2 (11.7-14.8)	0.26 (0.23-0.30)	164.1 (146.4-183.8)	2.4 (2.1-2.6)	48.0 (42.6-54.1)
1.0-4.9	45	25.4 (21.6-29.8)	16.0 (13.0-19.6)	0.33 (0.26-0.40)	161.4 (132.2-196.9)	2.4 (1.9-3.0)	63.7 (51.6-78.5)
5.0-14.9	33	26.8 (22.1-32.4)	15.0 (11.6-19.3)	0.33 (0.25-0.43)	227.7 (179.8-288.1)	3.6 (2.7-4.5)	66.3 (51.7-84.9)
>15	24	17.1 (13.6-21.5)	11.2 (8.3-14.9)	0.24 (0.17-0.33)	158.5 (119.5-210.1)	2.6 (1.9-3.5)	47.8 (35.5-64.3)
P_{trend}		0.91	0.88	0.39	0.31	0.08	0.18
Not using tamoxifen							
<1.0	157	22.9 (20.9-24.9)	14.7 (13.1-16.4)	0.38 (0.33-0.41)	179.0 (159.4-201.0)	3.6 (3.2-4.0)	50.3 (45.2-55.9)
1.0-4.9	32	22.0 (18.1-26.7)	14.3 (11.2-18.3)	0.37 (0.28-0.46)	195.2 (150.8-252.5)	3.9 (3.0-5.1)	59.1 (46.7-74.6)
5.0-14.9	37	21.4 (17.8-25.5)	14.7 (11.7-18.4)	0.37 (0.29-0.46)	198.4 (156.3-251.8)	4.0 (3.1-5.0)	64.4 (51.8-79.9)
>15	22	28.8 (22.7-36.6)	20.5 (15.1-27.7)	0.50 (0.37-0.68)	253.9 (185.1-348.2)	5.0 (3.6-6.8)	67.4 (50.6-89.8)
P_{trend}		0.40	0.16	0.18	0.06	0.09	0.01

Alcohol intake (g/d)	Leptin/SHBG		Peptides		
	Leptin (ng/mL)	SHBG (nmol/L)	IGF-I (ng/mL)	IGFBP3 (μg/mL)	C-peptide (ng/mL)
<1.0	20.7 (19.6-21.9)	51.1 (48.6-53.7)	109.6 (104.8-114.5)	4.0 (3.8-4.1)	2.4 (2.2-2.5)
1.0-4.9	19.9 (17.8-22.1)	49.5 (44.9-54.5)	115.7 (106.0-126.1)	4.1 (3.8-4.3)	2.5 (2.2-2.6)
5.0-14.9	20.3 (18.1-22.7)	47.8 (43.2-52.9)	119.8 (109.3-131.2)	4.3 (4.0-4.4)	2.4 (2.1-2.6)
>15	17.3 (14.9-19.8)	48.2 (42.4-54.7)	115.0 (102.5-128.8)	4.1 (3.7-4.3)	2.2 (1.9-2.4)
P_{trend}	0.06	0.20	0.12	0.14	0.40
By tamoxifen use					
Tamoxifen users					
<1.0	20.5 (19.0-22.1)	71.0 (66.8-75.4)	95.2 (89.5-101.0)	4.1 (3.9-4.2)	2.4 (2.2-2.6)
1.0-4.9	19.1 (16.7-21.6)	65.3 (58.7-72.5)	102.9 (92.6-114.2)	4.4 (4.1-4.6)	2.5 (2.1-2.7)
5.0-14.9	17.1 (14.6-19.8)	62.0 (54.6-70.2)	97.8 (86.3-110.7)	4.1 (3.8-4.4)	2.2 (1.9-2.5)
>15	16.9 (14.1-20.2)	57.5 (49.5-66.8)	101.1 (87.1-117.3)	4.1 (3.6-4.4)	2.4 (1.9-2.7)
P_{trend}	0.01	0.004	0.39	0.65	0.42
Not using tamoxifen					
<1.0	21.1 (19.4-22.9)	37.4 (34.6-40.3)	125.8 (117.7-134.2)	3.9 (3.7-4.0)	2.3 (2.1-2.5)
1.0-4.9	20.9 (17.4-25.0)	37.7 (31.8-44.6)	128.0 (110.6-148.0)	3.8 (3.4-4.1)	2.5 (2.1-2.8)
5.0-14.9	23.4 (19.7-27.6)	36.9 (31.5-43.1)	145.4 (127.0-166.2)	4.4 (4.0-4.7)	2.6 (2.2-2.8)
>15	17.3 (13.8-21.6)	41.0 (33.3-50.4)	129.7 (108.5-155.0)	4.0 (3.5-4.4)	2.1 (1.6-2.4)
P_{trend}	0.57	0.60	0.20	0.15	0.88

NOTE: Variables are adjusted for age, education, BMI, race/ethnicity/study site group, activity level, tamoxifen use, and number of ovaries. Geometric means for all serum measures except IGFBP3 and C-peptide.

*N for hormones with sample size = 490.

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the participants and number of women with estrogen receptor-negative tumors (59 taking tamoxifen and 15 not taking tamoxifen) was too small to draw meaningful conclusions. For participants with estrogen receptor-positive tumors, we found no statistically significant association between alcohol intake and SHBG in either category of tamoxifen use. For BMI, we found no association between alcohol intake and SHBG in nonusers of tamoxifen regardless of whether subjects had a normal BMI or a BMI > 25 kg/m^2; for tamoxifen users, there was a significant decrease in SHBG by alcohol intake that was greater for women whose BMI > 25 kg/m^2 (SHBG = 65.4, 58.6, and 42.7 nmol/L for alcohol categories <1, 1-14.9, and ≥15 g, respectively; $P = 0.02$) compared with those with BMI ≤ 25 kg/m^2 (SHBG = 78.7, 74.2, and 68.0 nmol/L; $P = 0.09$).

Discussion

In this cross-sectional study of postmenopausal breast cancer survivors, we found significant associations between alcohol intake and serum hormone and peptide values that differed by tamoxifen use. These associations were strong and significant despite the relatively low range of alcohol intake in study participants. In tamoxifen users, we found statistically significant inverse associations between alcohol intake and both leptin and SHBG values, which, to our knowledge, have not been reported previously. The positive association we found between alcohol intake and DHEAS has been reported by other researchers; however, in the Health, Eating, Activity and Lifestyle Study, this association exists only in women not using tamoxifen.

We had hypothesized a positive association between alcohol intake and serum DHEAS in our study of breast cancer survivors because this positive association has been found fairly consistently in postmenopausal women without breast cancer. This association has been shown in controlled feeding studies (32-34) as well as cross-sectional analysis (31, 35). The mechanism by which alcohol influences DHEAS is not completely understood; however, DHEAS is produced by the adrenal glands (36), and at least in animals, alcohol is known to stimulate the hypothalamic-pituitary-adrenal axis (37). Most studies have found high DHEAS levels to be associated with an increased risk of breast cancer (38-40) and with a poorer outcome after diagnosis (41, 42).

Our second hypothesis that tamoxifen use would dampen any associations between alcohol intake and the serum measures was supported by the DHEAS results. However, we found unexpected negative associations between alcohol intake and both SHBG and leptin in tamoxifen users. Both SHBG and leptin have been implicated in breast cancer incidence and prognosis, but the evidence is stronger for SHBG. SHBG binds estradiol reducing the bioavailability of this hormone (43), and postmenopausal women with low serum SHBG appear to have increased risk of breast cancer (44-46). The higher levels of bioavailable estrogen associated with low serum SHBG may also affect breast cancer prognosis because high serum estrogen concentrations have been associated with increased recurrence of breast cancer (17) and also because antiestrogen therapy is an established treatment for the prevention of breast cancer recurrence (15, 16). The implications of low leptin levels are less clear than those of SHBG. A recent review summarizes 10 case-control studies of the association between leptin and breast cancer: 3 found high leptin levels associated with increased risk of breast cancer and 7 found no association (9). Similarly, studies investigating the association of leptin with breast cancer prognosis are inconsistent (47, 48).

Although we found no published studies on the relationship between alcohol and serum hormones and peptides in breast cancer survivors, one article examined risk factors for change in estrogen metabolites in breast cancer patients (49). Specifically, the study measured change in the ratio of 2-hydroxyestrogen to 16-hydroxyestrone in breast cancer patients before and after surgery. A high ratio is believed to be associated with reduced risk for breast cancer and better prognosis because 2-hydroxyestrogen acts as a weak estrogen or as an antiestrogen, whereas 16-hydroxyestrone is procarcinogenic. The authors did not look at the effect of alcohol separately by tamoxifen use; however, they reported results from a multivariable model showing the strongest factors associated with a favorable shift in this estrogen ratio were tamoxifen combined with radiation therapy, increasing alcohol intake, and high coffee consumption. The effect of alcohol was significant only for women in the highest category of alcohol intake (at least 4 drinks per week). Estrogen metabolites are different from serum hormone levels and we would not necessarily expect these two measures to be related to alcohol intake in a similar manner. The fact that findings differ depending on which outcome measures are evaluated suggests that more studies of alcohol and hormone levels in breast cancer survivors are needed.

Tamoxifen use has been shown to increase SHBG levels (50, 51), but it is unclear why this drug, an exogenous hormone, would influence the association between alcohol and endogenous hormones. There is, however, evidence that exogenous estrogen use influences the association between alcohol intake and endogenous estradiol levels. A randomized, placebo-controlled study found a significant increase (300% above baseline) in estradiol levels in women using estrogen replacement therapy following alcohol ingestion, whereas a placebo resulted in minimal increases in estradiol, and alcohol did not change plasma estradiol levels in women not using estrogen replacement therapy (18). The authors indicate that the mechanism behind this is unclear, but other studies have found an increased risk of breast cancer for women on estrogen replacement therapy who also drink alcohol (52, 53), above that of either variable alone.

A limitation to this study is the small range of alcohol reportedly consumed. A majority of participants reported drinking <1 g/d alcohol. Less than 10% drank >15 g or the equivalent of 1.5 drinks/d. It is not clear if breast cancer survivors underreport amount of alcohol use as is common in other populations (54). The small number of women reporting high alcohol intake also prevented us from investigating associations by type of alcoholic beverage (wine, beer, and liquor). This is an observational study that uses self-report of alcohol intake as opposed to a controlled drinking study where alcohol intake is known. Self-reports generally lead to underestimates of total alcohol consumed (55); however, there

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is no reason to suspect this underestimate would differ by any of the outcome measures.

Our findings suggest that, in postmenopausal women with a previous diagnosis of breast cancer, the use of tamoxifen modifies the association between alcohol and hormones and peptides implicated in breast cancer prognosis. The associations we report, a negative association between alcohol intake and SHBG and leptin in tamoxifen users and a positive association with DHEAS in nonusers, occurred in women whose alcohol intake could be considered light to moderate. The significant associations found for DHEAS and SHBG are in a direction considered unfavorable for breast cancer prognosis. These preliminary findings suggest that breast cancer survivors may benefit from moderating their alcohol intake.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–45.
2. McDonald JA, Mandel MG, Marchbanks PA, et al. Alcohol exposure and breast cancer: results of the Women's Contraceptive and Reproductive Experiences study. Cancer Epidemiol Biomarkers Prev 2004;13:2106–16.
3. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA 2001;286:2143–51.
4. Petri AL, Tjonneland A, Gamborg M, et al. Alcohol intake, type of beverage, and risk of breast cancer in pre- and postmenopausal women. Alcohol Clin Exp Res 2004;28:1084–90.
5. Lavigne JA, Baer DJ, Wimbrow HH, et al. Effects of alcohol on insulin-like growth factor I and insulin-like growth factor binding protein 3 in postmenopausal women. Am J Clin Nutr 2005;81:503–7.
6. Rojdmark S, Calissendorff J, Brismar K. Alcohol ingestion decreases both diurnal and nocturnal secretion of leptin in healthy individuals. Clin Endocrinol (Oxf) 2001;55:639–47.
7. Rojdmark S, Brismar K. Decreased IGF-I bioavailability after ethanol abuse in alcoholics: partial restitution after short-term abstinence. J Endocrinol Invest 2001;24:476–82.
8. Roth MJ, Baer DJ, Albert PS, et al. Relationship between serum leptin levels and alcohol consumption in a controlled feeding and alcohol ingestion study. J Natl Cancer Inst 2003;95:1722–5.
9. Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. Endocr Relat Cancer 2007;14:189–206.
10. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, de Jong-Bakker M, Nooijen WJ. Insulin resistance and breast-cancer risk. Int J Cancer 1992;52:511–6.
11. Han C, Zhang HT, Du L, et al. Serum levels of leptin, insulin, and lipids in relation to breast cancer in China. Endocrine 2005;26:19–24.
12. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. Oncology 1999;57:330–40.
13. Borugian MJ, Sheps SB, Kim-Sing C, et al. Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? Cancer Epidemiol Biomarkers Prev 2004;13:1163–72.
14. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42–51.
15. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189–97.
16. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
17. Rock CL, Flatt SW, Laughlin GA, et al. Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:614–20.
18. Ginsburg ES, Mello NK, Mendelson JH, et al. Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA 1996;276:1747–51.
19. Ellmen J, Hakulinen P, Partanen A, Hayes DF. Estrogenic effects of toremifene and tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res Treat 2003;82:103–11.
20. McTiernan A, Rajan KB, Tworoger SS, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol 2003;21:1961–6.
21. Irwin ML, Crumley D, McTiernan A, et al. Physical activity levels before and after a diagnosis of breast carcinoma. Cancer 2003;97:1746–57.
22. Irwin ML, McTiernan A, Bernstein L, et al. Physical activity levels among breast cancer survivors. Med Sci Sports Exerc 2004;36:1484–91.
23. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. J Steroid Biochem 1982;16:801–10.
24. Sparks R, Ulrich CM, Bigler J, et al. UDP-glucoronosyltransferase and sulfotransferase polymorphisms, sex hormone concentrations, and tumor receptor status in breast cancer patients. Breast Cancer Res 2004;6:R488–98.
25. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178–87.
26. Wayne SJ, Neuhouser ML, Ulrich CM, et al. Dietary fiber is associated with serum sex hormones and insulin-related peptides in postmenopausal breast cancer survivors. Breast Cancer Res Treat. Epub 2007.
27. Irwin ML, McTiernan A, Bernstein L, et al. Relationship between obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors. Cancer Epidemiol Biomarkers Prev 2005;15:2881–8.
28. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults: clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr 1998;68:899–917.
29. Kriska A. Modifiable activity questionnaire. Med Sci Sports Exer 1997;29:S73–8.
30. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 1990;13:555–65.
31. Onland-Moret NC, Peeters PH, van der Schouw YT, Grobbee DE, van Gils CH. Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study. J Clin Endocrinol Metab 2005;90:1414–9.
32. Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst 2001;93:710–5.
33. Mahabir S, Baer DJ, Johnson LL, et al. The effects of moderate alcohol supplementation on estrone sulfate and DHEAS in postmenopausal women in a controlled feeding study. Nutr J 2004;3:11.
34. Sierksma A, Sarkola T, Eriksson CJ, van der Gaag MS, Grobbee DE, Hendriks HF. Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: a diet-controlled intervention study. Alcohol Clin Exp Res 2004;28:780–5.
35. Rinaldi S, Peeters PH, Bezemer ID, et al. Relationship of alcohol intake and sex steroid concentrations in blood in pre- and postmenopausal women: the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control 2006;17:1033–43.
36. Longcope C. Adrenal and gonadal androgen secretion in normal females. Clin Endocrinol Metab 1986;15:213–28.
37. Rivier C. Alcohol stimulates ACTH secretion in the rat: mechanisms of action and interactions with other stimuli. Alcohol Clin Exp Res 1996;20:240–54.

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38. Tworoger SS, Missmer SA, Eliassen AH, et al. The association of plasma DHEA and DHEA sulfate with breast cancer risk in predominantly premenopausal women. Cancer Epidemiol Biomarkers Prev 2006;15:967–71.
39. Dorgan JF, Stanczyk FZ, Longcope C, et al. Relationship of serum dehydroepiandrosterone (DHEA), DHEA sulfate, and 5-androstene-3β,17β-diol to risk of breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 1997;6:177–81.
40. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
41. Morris KT, Toth-Fejel S, Schmidt J, Fletcher WS, Pommier RF. High dehydroepiandrosterone-sulfate predicts breast cancer progression during new aromatase inhibitor therapy and stimulates breast cancer cell growth in tissue culture: a renewed role for adrenalectomy. Surgery 2001;130:947–53.
42. Calhoun K, Pommier R, Cheek J, Fletcher W, Toth-Fejel S. The effect of high dehydroepiandrosterone sulfate levels on tamoxifen blockade and breast cancer progression. Am J Surg 2003;185:411–5.
43. Catalano MG, Frairia R, Boccuzzi G, Fortunati N. Sex hormone-binding globulin antagonizes the anti-apoptotic effect of estradiol in breast cancer cells. Mol Cell Endocrinol 2005;230:31–7.
44. Zeleniuch-Jacquotte A, Shore RE, Koenig KL, et al. Postmenopausal levels of oestrogen, androgen, and SHBG and breast cancer: long-term results of a prospective study. Br J Cancer 2004;90:153–9.
45. Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer 2005; 12:1071–82.
46. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995;87:190–7.
47. Miyoshi Y, Funahashi T, Tanaka S, et al. High expression of leptin receptor mRNA in breast cancer tissue predicts poor prognosis for patients with high, but not low, serum leptin levels. Int J Cancer 2006; 118:1414–9.
48. Revillion F, Charlier M, Lhotellier V, et al. Messenger RNA expression of leptin and leptin receptors and their prognostic value in 322 human primary breast cancers. Clin Cancer Res 2006;12: 2088–94.
49. Klug TL, Bageman E, Ingvar C, Rose C, Jernstrom H. Moderate coffee and alcohol consumption improves the estrogen metabolite profile in adjuvant treated breast cancer patients: a pilot study comparing pre- and post-operative levels. Mol Genet Metab 2006;89: 381–9.
50. Lofgren L, Wallberg B, Wilking N, et al. Tamoxifen and megestrol acetate for postmenopausal breast cancer: diverging effects on liver proteins, androgens, and glucocorticoids. Med Oncol 2004;21: 309–18.
51. Browne-Martin K, Longcope C. Regulation of sex hormone-binding globulin secretion in human hepatoma G2 cells. Steroids 2001;66: 605–7.
52. Chen WY, Colditz GA, Rosner B, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Ann Intern Med 2002;137:798–804.
53. Gapstur SM, Potter JD, Sellers TA, Folsom AR. Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am J Epidemiol 1992;136:1221–31.
54. Stockwell T, Donath S, Cooper-Stanbury M, Chikritzhs T, Catalano P, Mateo C. Under-reporting of alcohol consumption in household surveys: a comparison of quantity-frequency, graduated-frequency and recent recall. Addiction 2004;99:1024–33.
55. Gruenewald PJ, Johnson FW. The stability and reliability of self-reported drinking measures. J Stud Alcohol 2006;67:738–45.

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