Usefulness of Body Mass Index as a Sufficient Adiposity Measurement for Sex Hormone Concentration Associations in Postmenopausal Women

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Abstract

Background: **Both obesity and sex hormones are known risk factors for postmenopausal breast cancer. Although adiposity and sex hormones have been studied in the past, previous reports in postmenopausal women have not been conducted under carefully controlled dietary conditions. In this study, we investigated the usefulness of body mass index (BMI) as a sufficient adiposity measurement to assess associations with sex hormone levels.**

Methods: **This study was conducted as a cross-sectional analysis within the control segment (0 g alcohol group) of a randomized, crossover design, in which 51 postmenopausal women consumed 0 (control), 15 (one drink), and 30 (two drinks) g alcohol (ethanol)/d for 8 weeks each as part of a controlled diet. Dual-energy X-ray absorptiometry scans were administered to the women during the control (0 g alcohol) segment, and a blood sample was drawn at the end of that diet period for hormone analysis.**

Results: **In multivariate analysis (adjusted for age, race, family history of breast cancer, parity, and menarche <12 years), women who were overweight or obese had significantly higher serum concentrations of estradiol, bioavailable estradiol, estrone, and estrone sulfate and lower sex hormone-binding globulin than normal weight women (all $P < 0.05$). In models adjusted for BMI and the covariates above, none of the dual-energy X-ray absorptiometry adiposity measures added further information (all $P > 0.10$) for these five analytes beyond that of BMI alone.**

Conclusions: **In this population of postmenopausal women, under carefully controlled dietary conditions, we confirmed previous findings that higher levels of adiposity were associated with higher concentrations of estrogens and lower sex hormone-binding globulin, and we found that the use of the epidemiology-friendly BMI seems sufficient to assess associations with these hormone levels.** (Cancer Epidemiol Biomarkers Prev 2006;15(12):2502–7)

Introduction

Breast cancer risk increases after menopause because age is the single most important risk factor for this disease. Sex hormones, especially estrogens, have also been implicated in the development of breast cancer (1). After menopause, aromatization of androgens to estrogens in adipose tissue is the most important source of estrogen in the blood and peripheral tissues (2-4). There is considerable evidence that the risk of postmenopausal breast cancer is increased by obesity (5, 6) and that the distribution of body fat may be an additional risk factor. The increased breast cancer risk seen in postmenopausal women with adiposity might be related to elevated sex hormone levels (7-9). Earlier published studies reported the associations between high adiposity levels and high concentrations of estrogens and low concentrations of sex hormone-binding globulin (SHBG) after menopause (10-15). Most previous studies of adiposity-sex hormones in postmenopausal women assessed adiposity as body mass index (BMI) or waist-to-hip ratio (WHR), but none studied these associations under carefully controlled dietary conditions. The novel feature of the current report is that we assessed the associations between several sex hormones and adiposity measures under strict dietary conditions. This is important because diet composition influences sex hormone levels (16-18). In addition to the use of BMI, we also measured body fat distribution using dual-energy X-ray absorptiometry (DEXA). Understanding the relationship between hormonal risk factors for breast cancer, such as estrogens, and BMI, percentage body fat, and central and peripheral fat might be useful in promoting interventions based on adiposity phenotypes to prevent breast cancer or to stratify women into risk categories.

In assessing the adiposity-sex hormone breast cancer hypothesis, measures of adiposity, such as BMI and WHR, have limitations. Most notably, BMI does not discriminate between fat and muscle mass (19). In contrast, DEXA is a reference technique for adiposity measurements; it accounts for both s.c. and visceral fat and it is a more precise measure of adiposity than BMI. We hypothesized that the more precise DEXA measures of adiposity would improve on BMI alone in predicting sex hormone levels in postmenopausal women. Thus, we assessed and compared the associations between BMI, percentage body fat, and central and peripheral fat with sex hormone concentrations in postmenopausal women fed a controlled diet.

Subjects and Methods

Study Design. This study was conducted as a cross-sectional analysis within the control segment (0 g alcohol

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group) of the Women's Alcohol Study, a randomized, crossover design, in which 51 postmenopausal women consumed 0 (control), 15 (one drink), and 30 (two drinks) g alcohol (ethanol)/d for 8 weeks each as part of a controlled diet. Details of the Women's Alcohol Study design and procedures have been published previously (20, 21). Briefly, subjects were assigned to three separate 8-week diet periods during which they consumed a controlled diet and were provided a beverage (orange juice) each day that contained 0, 15, or 30 g alcohol (95% ethanol) in random order. Each subject completed all of the three diet periods. Subjects in one treatment arm were crossed over to another arm after a 2- to 5-week washout period. BMI and DEXA (model DPX-L, Lunar Corp., Madison, WI) whole-body scans were used for adiposity assessments and administered to the women during week 4 in the control segment (0 g alcohol treatment) of the Women's Alcohol Study.

Subjects. Postmenopausal women were recruited by advertisement from communities surrounding the Beltsville Human Nutrition Research Center (Beltsville, MD). Eligibility criteria were as follows: (*a*) women ≥50 years of age, (*b*) postmenopausal (last menses ≥12 months before the study started or follicle-stimulating hormone >40,000 mIU/L, natural menopause, or hysterectomy with at least one ovary intact), (*c*) not receiving hormone replacement therapy, (*d*) not taking prescription medications that might interfere with the study, (*e*) willing and able to consume the diet prepared or approved by the Center and no other foods or beverages, and (*f*) without personal or parental history of alcohol abuse.

Subjects were evaluated by a physician and determined to be in good health with no signs or symptoms of any disease or endocrine disorders.

This study was approved by the National Cancer Institute's Institutional Review Board and the Committee on Human Research of the Johns Hopkins University Bloomberg School of Hygiene and Public Health. All subjects were fully informed of the study requirements and required to read and sign a consent form detailing the objectives, risks, and benefits of the study. The subjects were compensated for their participation.

Diets and Feeding. All meals were prepared at the Beltsville Human Nutrition Research Center from typical U.S. foods on a 7-day menu cycle. The diet for each day provided 15% energy as protein, 50% energy as carbohydrate, and 35% energy as fat, with a polyunsaturated/monounsaturated/saturated fat ratio of 0.6:1:1. Daily fiber intake was 10 g/1,000 kcal, and daily cholesterol intake was 150 mg/1,000 kcal. Diets provided 100% of the U.S. recommended dietary allowances for vitamins and minerals (22). Calories were adjusted to maintain body weight throughout the study by varying portion sizes and total energy intake as needed.

DEXA Measurements. Body composition was determined by pencil-beam DEXA. Subjects were placed in a supine position with arms and legs close to their body for a whole-body scan following the manufacturer's recommended protocol. Whole-body and regional lean mass (mass of bone and nonfat soft tissue) and fat mass were determined using the manufacturer's algorithm (software version 1.33).

Biological Sample Collection and Analysis. Blood samples were collected between 6:30 a.m. and 9:00 a.m. for hormone analysis after an overnight fast on three separate days during the last week of the 0 g alcohol treatment group. Serum was separated and aliquots were frozen at −70°C. At the end of the 0 g alcohol treatment phase, an equal volume of serum from each day was pooled for analysis of hormone and SHBG. The samples were pooled to minimize the effect of day-to-day variability. The laboratory methods for the serum hormone measurements were described previously (21). Briefly, serum hormones were measured using specific RIAs and SHBG was measured by an immunoradiometric assay. Samples from each participant were grouped in random order and analyzed together in the same batch. With-in-batch coefficients of variation estimated from hormone measurements on two to four masked quality control samples included in each batch were as follows: estradiol, 12.1%; estrone, 16.8%; estrone sulfate, 7.8%; testosterone (one outlier excluded), 11.0%; androstenedione, 6.3%; dehydroepiandrosterone, 10.7%; dehydroepiandrosterone sulfate, 4.9%; progesterone, 20.7%; androstenediol, 9.4%; and SHBG, 3.1% (21).

Statistical Analysis. Hormone concentrations were log transformed using the natural log. All estimates of means and the difference between means were made using the log-transformed hormone concentration values. In the tables, we report means and regression coefficients returned to the original (arithmetic) scale.

Pearson and Spearman correlations between the different DEXA measurements and BMI (kg/m^2) calculated from measured weight and height were determined. Mean hormone concentrations for BMI categories were estimated separately using linear regression models that included a series of indicator variables for BMI categories (BMI, <25 or normal; >25 to ≤30 or overweight; and >30 or obese). BMI categories were also modeled as ordinal variables with values 0, 1, and 2. Additional models estimated percentage change in serum hormone concentrations per 1-unit change in BMI, 1% change in total body fat, and 1,000 g change in central or peripheral fat, all modeled as continuous variables. All models included age (continuous), parity (continuous), race (African American, yes/no), age of menarche (<12, yes/no), and family history of breast cancer (yes/no). Family history of breast cancer was defined as mothers or full sisters who had breast cancer. No woman stated that her daughters had breast cancer. One woman's breast cancer information was missing and she was excluded from models that included breast cancer history. Sensitivity models, including the woman as having or not having a family history of breast cancer, did not change analysis conclusions. A second model adding BMI to model 1 is also shown for DEXA measures. The addition of alcohol group assignment order, dietary period, hysterectomy, duration of menses, years since last menses, nulliparity, age at first birth (for those with children), and dietary kilocalorie level did not improve the precision estimates and these terms were not included in the final models. There was no evidence of effect modification as assessed by changes in likelihood ratio tests of model fit after the addition of cross-product terms to models that included main effects. Throughout the article, all *P* values are two-sided nominal (unadjusted) *P* values. *P* values for BMI and DEXA measurements were determined using likelihood ratio tests comparing models with the BMI or DEXA term of interest to models without that term. Partial correlation coefficients were also calculated from each of the regression coefficients. Statistical analyses were done using S-PLUS (S-PLUS version 6.2 for Windows, Insightful Corp. Seattle, WA; 2002).

Results

Fifty-one subjects successfully completed the entire study and are included in the present analysis. The physical characteristics and reproductive history of the subjects at baseline are provided in Table 1. All the participants were postmenopausal. Their ages ranged from 49.2 to 78.8 years with a median of 58.2 years. Most (74.5%) of the women were white, 21.6% were black, and 3.9% were Asian. The median body weight was 73.2 kg (range, 42.1-117.4 kg); BMI ranged from 17.7 to 42.5 kg/m^2; and total body fat ranged from 7,942 to 55,756 g (median, 26,808 g), whereas trunk, leg, and arm fat were of progressively

Table 1. Characteristics of the subjects (*N* = 51) at baseline

Characteristics	Mean	Median (range)
Age (y)	59.7	58.2 (49.2-78.8)
Height (cm)	163.9	163.1 (152.1-179.7)
Weight (kg)	74.8	73.2 (42.1-117.4)
BMI (kg/m^2)	27.8	26.9 (17.7-42.5)
Total body fat (g)	29,744	26,808 (7,942-55,756)
Central fat (g)	13,830	13,234 (3,056-26,396)
Peripheral fat (g)	14,299	12,476 (4,163-29,507)
Body fat (%)	41.3	42.5 (17.8-55.7)
Age at menarche (y)	12.7	13 (10-16)
Duration of menses (y)	33.4	35 (12-45)
Years since last menses	13.1	12 (1-38)
Parity (no. children)	2.6	2 (0-8)
Age at first birth (y)*	23.2	22 (16-36)
Estradiol (ng/dL)	0.93	0.80 (0.00-5.50)
Bioavailable estradiol (ng/dL)	0.53	0.30 (0.00-4.00)
Estrone (ng/dL)	3.14	2.60 (0.80-8.90)
Estrone sulfate (ng/dL)	58.69	43.80 (12.10-384.80)
Testosterone (ng/dL)	20.03	17.40 (4.40-65.00)
DHEA (ng/dL)	3.81	3.11 (0.86-9.52)
DHEAS (μg/dL)	69.73	62.00 (12.00-197.00)
Progesterone (ng/dL)	19.67	18.50 (4.10-47.30)
Androstenedione (ng/dL)	91.43	90.00 (51.00-161.00)
Androstenediol (ng/dL)	481.8	411.0 (134.00-1,232.00)
SHBG (nmol/L)	78.60	66.10 (22.00-181.80)

Characteristics	No. (%)
Race	
White	38 (74.5)
Black	11 (21.6)
Asian	2 (3.9)
Menopause type	
Natural	39 (76.5)
Hysterectomy	12 (23.5)
Family history of breast cancer	
Yes	11 (21.5)

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.
*Based on n = 43 subjects.

lesser magnitude. Descriptive statistics for the hormones are also presented in Table 1.

Table 2 shows the geometric means of serum sex hormone concentrations by categories of BMI. We found strong, significant positive associations between concentrations of all four estrogens examined and BMI. The magnitude of these differences across BMI categories was substantial: mean estrogen levels in obese subjects were 1.7- to 6.4-fold higher than in normal weight subjects. A similarly strong, significant inverse association was observed for SHBG with BMI where SHBG levels in obese women were only half of those in normal weight women.

Table 3 shows how much a unit change in BMI (1 kg/m^2), percentage body fat (1%), and central or peripheral fat (1 kg) affected sex hormone concentrations. For all four measures of adiposity evaluated, higher adiposity was associated with significantly higher concentrations of estradiol, bioavailable estradiol, estrone, and estrone sulfate and a lower concentration of SHBG. For example, higher levels of central fat were associated with higher bioavailable estradiol concentrations. After adjusting for age, parity, race, family history of breast cancer, and age of menarche, each additional 1 kg of central fat was associated with a 12.2% [95% confidence interval (95% CI), 5.0-20.0%] higher level of bioavailable estradiol. This association held true across the different measures of adiposity: a 1-kg increase in peripheral fat was associated with a 12.7% (95% CI, 6.1-19.6%) higher level of bioavailable estradiol; a 1% increase in total body fat was associated with a 7.9% (95% CI, 3.4-12.5%) higher level of bioavailable estradiol; and a 1-unit increase in BMI was associated with a 14.7% (95% CI, 8.0-21.8%) higher level of bioavailable estradiol. Therefore, a 1-unit difference in each of these adiposity measures was associated with a substantial difference in estrogens. In model 2, BMI was included as a covariate in the multivariate models for percentage body fat, central fat, and peripheral fat. There was no evidence that any of the DEXA measures provided additional information about the five hormones significantly associated with adiposity beyond BMI and the other covariates (all P values >0.1); partial correlation coefficients for DEXA adiposity variables ranged between −0.20 and 0.18; all P values were >0.19 (data not shown). BMI was strongly correlated with each DEXA adiposity measures; correlations ranged from 0.85 for percentage body fat to 0.93 for peripheral fat. The R^2 values from the linear regression models are provided in Table 3.

Discussion

Establishing BMI as sufficient to estimate changes in sex hormone levels associated with breast cancer risk in postmenopausal women is important because BMI is a simple and inexpensive technique and is widely used in epidemiologic studies. BMI is positively associated with increased breast cancer incidence and mortality in postmenopausal women (23). Previous studies of adiposity and sex hormones relied on

Table 2. Geometric mean serum hormone concentrations by categories of BMI

	Model*	BMI category			P_{trend} †	R^2
		Normal weight (BMI, <25), n = 20	Overweight (BMI, >25 to <30), n = 17	Obese (BMI, >30), n = 13		
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		
Estradiol (ng/dL)	1	0.36 (0.21-0.60)	0.50 (0.19-1.13)	1.57 (0.62-3.94)	0.004	0.28
Bioavailable estradiol (ng/dL)	1	0.15 (0.09-0.25)	0.25 (0.10-0.61)	0.96 (0.40-2.28)	0.0002	0.36
Estrone (ng/dL)	1	2.31 (1.71-3.11)	2.56 (1.87-3.50)	3.97 (2.94-5.36)	0.001	0.27
Estrone sulfate (ng/dL)	1	34.62 (25.29-47.40)	42.71 (30.16-60.48)	80.42 (57.68-112.11)	<0.0001	0.39
Testosterone (ng/dL)	1	16.29 (11.38-23.33)	15.10 (9.58-23.78)	19.80 (12.83-30.56)	0.42	0.09
Androstenedione (ng/dL)	1	89.14 (69.32-114.63)	78.26 (62.61-97.83)	95.51 (77.18-118.19)	0.63	0.18
DHEA (ng/dL)	1	3.94 (2.84-5.45)	2.48 (1.71-3.60)	3.48 (2.43-4.97)	0.39	0.35
DHEAS (μg/dL)	1	67.42 (48.07-94.56)	47.12 (31.47-70.55)	64.19 (43.66-94.38)	0.68	0.29
Progesterone (ng/dL)	1	19.28 (13.72-27.09)	13.84 (9.20-20.82)	18.62 (12.61-27.50)	0.75	0.19
Androstenediol (ng/dL)	1	483.89 (357.70-654.60)	354.62 (256.96-489.41)	455.21 (334.67-619.18)	0.58	0.30
SHBG (nmol/L)	1	88.83 (65.39-120.68)	76.90 (55.21-107.10)	44.40 (32.36-60.92)	0.0001	0.32

*Model 1 (N = 51): adjusted for age, race, family history of breast cancer, parity, and menarche <12 years.
†P_{trend} from linear regression models where trend is measured as a continuous value after assigning the normal weight category 0, overweight category 1, and obese category 2. P values for these models where BMI is measured as a noncategorized continuous variable are available in Table 3.

BMI and WHR, without adequate control for the influence of diet on sex hormones. Our study did not suffer from this limitation. The results of the controlled study described here, conducted in postmenopausal women within the normal BMI range for the United States (24), show that higher adiposity, however measured, is associated with higher concentrations of serum estrogens and lower concentration of SHBG. Further, our results show that measurement of adiposity just by using BMI seems sufficient to accurately characterize sex hormone levels in these postmenopausal women.

The R^2 values from the linear regression models presented in Table 3 reflect the percentage variance explained by each of the adiposity variable models (BMI, percentage body fat, central, and peripheral fat), all adjusted for the same covariates so that they can be compared with each other. These analyses indicate that the significant associations between hormone concentrations and the four adiposity measurements evaluated here were quite comparable, although there might be a slight preference for BMI, which explained the highest percentage of the variance for three of the five significantly associated hormones. We acknowledge, however, that unit by unit, each of the four adiposity measures is different, so a 1-unit change in BMI, for example, is not directly comparable with a 1% change in body fat. The consistency of our findings across these different measures of adiposity suggests that overall adiposity may be more important than regional body fat distribution in determining sex hormone concentrations in this population of healthy postmenopausal women. Our findings may not be true for other populations, such as premenopausal women, men, athletes, or people of other ethnicities.

Previous studies of adiposity and sex hormones in postmenopausal women have not adequately controlled for dietary intake. This is noteworthy because diet has been shown to influence hormone concentrations (16-18, 25), diet is highly variable in our Western society, and our methods of measuring dietary intake in free-living (and free eating) persons (typically by self-reports via questionnaires) are poor. To our knowledge, this is the first study to evaluate the associations between BMI, percentage body fat, and central and peripheral fat levels in relation to serum sex hormone concentrations in healthy postmenopausal women under controlled dietary conditions. In Table 4, we compared our findings with those of previously published studies of adiposity and sex hormone concentrations in postmenopausal women without strict dietary control. From these data, higher BMI was consistently associated with higher estrogens and lower SHBG. Although associations between adiposity and androgens in our study were essentially null, previous studies have reported this association, albeit mainly in

Table 3. Associations of BMI, central fat (trunk fat), and peripheral fat with serum sex hormones

	Model	BMI*	R^2	% Fat †	R^2	Central fat †	R^2	Peripheral fat †	R^2
		Δ (95% CI)		Δ (95% CI)		Δ (95% CI)		Δ (95% CI)	
Estradiol (ng/dL)	1	*10.9 ‡ (3.9-18.4)*	0.27	5.8§ (1.2-10.6)	0.22	8.6§ (1.2-16.6)	0.21	9.7§ (2.9-16.8)	0.25
	2dexa			−1.6 (−10.1 to 7.7)	0.27	−10.6 (−25.0 to 6.5)	0.30	−0.2 (−16.1 to 18.7)	0.27
	2bmi			*13.4 (−1.1 to 30.0)*		*22.7§ (3.5 to 45.4)*		*11.2 (−7.3 to 33.3)*	
Bioavailable estradiol (ng/dL)	1	*14.7‖ (8.0-21.8)*	0.38	7.9 ‡ (3.4-12.5)	0.29	12.2 ‡ (5.0-20.0)	0.28	12.7‖ (6.1-19.6)	0.33
	2dexa			−1.5 (−9.4 to 7.0)	0.38	−10.2 (−23.5 to 5.4)	0.40	−2.17 (−16.5 to 14.7)	0.38
	2bmi			*17.1§ (3.3-32.8)*		*26.3§ (8.1-47.5)*		*17.2 (−0.8 to 38.4)*	
Estrone(ng/dL)	1	*4.6‖ (2.5-6.7)*	0.33	2.9‖ (1.5-4.3)	0.30	4.0 ‡ (1.8-6.4)	0.25	4.5‖ (2.6-6.5)	0.35
	2dexa			0.9 (−1.9 to 3.8)	0.34	−2.3 (−7.5 to 3.2)	0.35	3.2 (−2.1 to 8.8)	0.36
	2bmi			*3.4 (−0.9 to 7.8)*		*6.8§ (1.3-12.6)*		*1.4 (−4.0 to 7.2)*	
Estrone sulfate (ng/dL)	1	*7.4‖ (5.2-9.6)*	0.53	4.2‖ (2.6-5.8)	0.40	6.8‖ (4.3-9.3)	0.42	6.1‖ (3.7-8.4)	0.40
	2dexa			−0.3 (−3.1 to 2.6)	0.53	−1.6 (−7.0 to 4.0)	0.53	−3.6 (−8.6 to 1.7)	0.55
	2bmi			*7.9 ‡ (3.3-12.6)*		*9.0 ‡ (3.3-15.1)*		*11.3‖ (5.2-17.7)*	
Testosterone (ng/dL)	1	*1.7 (−1.4 to 4.9)*	0.09	0.6 (−1.4 to 2.7)	0.07	0.2 (−2.9 to 3.5)	0.06	1.3 (−1.7 to 4.3)	0.08
	2dexa			−1.5 (−5.6 to 2.8)	0.10	−9.1§ (−16.0 to −1.7)	0.20	−2.0 (−9.6 to 6.3)	0.09
	2bmi			*3.8 (−2.7 to 10.6)*		*10.8§ (2.7-19.5)*		*3.7 (−4.7 to 12.9)*	
Androstenedione (ng/dL)	1	*0.8 (−0.7 to 2.4)*	0.15	0.4 (−0.6 to 1.5)	0.14	0.3 (−1.3 to 1.9)	0.13	0.6 (−0.9 to 2.1)	0.14
	2dexa			−0.1 (−2.2 to 2.0)	0.15	−3.3 (−7.2 to 0.7)	0.20	−0.9 (−4.9 to 3.1)	0.15
	2bmi			*1.0 (−2.2 to 4.3)*		*3.9 (−0.1 to 8.1)*		*1.8 (−2.5 to 6.2)*	
DHEA (ng/dL)	1	*−0.2 (−2.9 to 2.5)*	0.26	−0.1 (−1.9 to 1.7)	0.26	−0.6 (−3.4 to 2.1)	0.26	−0.6 (−3.1 to 2.0)	0.26
	2dexa			0.2 (−3.5 to 4.0)	0.26	−2.8 (−9.7 to 4.5)	0.27	−2.6 (−9.2 to 4.5)	0.27
	2bmi			*−0.5 (−5.9 to 5.3)*		*2.4 (−4.6 to 9.8)*		*2.4 (−4.9 to 10.2)*	
DHEAS (μg/dL)	1	*0.6 (−2.2 to 3.4)*	0.24	−0.2 (−2.0 to 1.7)	0.23	0.03 (−2.8 to 3.0)	0.23	−0.3 (−2.9 to 2.5)	0.23
	2dexa			−2.2 (−5.9 to 1.6)	0.26	−3.4 (−10.5 to 4.2)	0.25	−5.6 (−12.2 to 1.5)	0.28
	2bmi			*3.6 (−2.2 to 9.8)*		*3.8 (−3.6 to 11.7)*		*6.3 (−1.4 to 14.7)*	
Progesterone (ng/dL)	1	*0.2 (−2.6 to 3.1)*	0.14	−0.4 (−2.2 to 1.5)	0.14	−0.3 (−3.2 to 2.7)	0.14	0.4 (−2.3 to 3.2)	0.14
	2dexa			−2.0 (−5.7 to 1.9)	0.16	−3.1 (−10.2 to 4.7)	0.15	2.0 (−5.4 to 10.0)	0.14
	2bmi			*2.9 (−3.0 to 9.1)*		*3.0 (−4.4 to 10.9)*		*−1.7 (−9.1 to 6.3)*	
Androstenediol (ng/dL)	1	*−0.1 (−2.3 to 2.2)*	0.24	−0.2 (−1.7 to 1.3)	0.24	−0.6 (−2.9 to 1.8)	0.25	−0.4 (−2.6 to 1.7)	0.25
	2dexa			−0.6 (−3.7 to 2.5)	0.25	−3.2 (−8.9 to 2.9)	0.26	−2.6 (−8.3 to 3.3)	0.26
	2bmi			*0.8 (−3.9 to 5.7)*		*2.8 (−3.1 to 9.1)*		*2.6 (−3.6 to 9.1)*	
SHBG (nmol/L)	1	*−5.6‖ (−7.6 to −3.7)*	0.42	−3.4‖ (−4.8 to −2.0)	0.35	−5.8‖ (−7.8 to −3.8)	0.42	−4.9‖ (−6.8 to −2.8)	0.34
	2dexa			−0.5 (−3.3 to 2.4)	0.42	−2.8 (−8.1 to 2.7)	0.44	1.4 (−4.0 to 7.1)	0.43
	2bmi			*−5.1§ (−9.1 to −0.9)*		*−3.2 (−8.3 to 2.2)*		*−6.9§ (−12.1 to −1.5)*	

NOTE: Δ, percentage change for each hormone for a 1-unit change in each of the four adiposity measures (i.e., percentage change in hormone concentration per 1-unit change in BMI, per 1% increase in total body fat, and per 1-kg increase in central and peripheral fat).

*Model 1 (N = 50): adjusted for age, race, family history of breast cancer, parity, and menarche <12 years.

†Model 2 (N = 50): model 1 + BMI. ''2dexa'' rows provide covariate information about the DEXA measure in model 2; ''2bmi'' rows provide covariate information about BMI in model 2 (all coefficients for BMI variable are in italics).

‡$P < 0.005$.

§$P < 0.05$.

‖$P < 0.0005$.

Table 4. Adiposity and sex hormones in healthy postmenopausal women: a summary of findings

Study	Findings
Mahabir et al. (current study)	BMI: higher categories and levels significantly associated with increased concentrations of estradiol, bioavailable estradiol, estrone, estrone sulfate, and decreased concentrations of SHBG. DEXA adiposity: higher levels of percentage body fat, central fat, and peripheral fat significantly associated with increased concentrations of estradiol, bioavailable estradiol, estrone, estrone sulfate, and decreased concentrations of SHBG.
Bezemer et al. (28)	BMI: higher levels significantly associated with increased concentrations of estradiol, bioavailable estradiol, estrone, testosterone, and decreased concentrations of SHBG. Waist circumference: higher levels significantly associated with increased concentrations of estradiol, bioavailable estradiol, estrone, and decreased concentrations of SHBG.
Lukanova et al. (10)	BMI: higher categories significantly associated with increased concentrations of estradiol, bioavailable estradiol, estrone, testosterone, androstenedione, and decreased levels of SHBG.
Boyapati et al. (11)	BMI: higher categories significantly associated with increased concentrations of estradiol and decreased SHBG. WHR: higher categories associated with significant decreased concentrations of SHBG.
Verkasalo et al. (12)	BMI: higher categories significantly associated with increased concentrations of estradiol and decreased SHBG. WHR: higher categories associated with significant decreased concentrations of SHBG.
Goodman-Gruen and Barrett-Connor (15)	BMI: higher categories significantly associated with decreased SHBG. WHR: higher categories associated with significant decreased concentrations of SHBG and testosterone.
Kaye et al. (13)	BMI: higher levels significantly and positively correlated with estradiol and negatively correlated with SHBG, luteinizing hormone, and follicle stimulating hormone. WHR: higher levels significantly and negatively correlated with SHBG, luteinizing hormone, and follicle stimulating hormone.
Haffner et al. (14)	BMI: higher levels significantly and negatively correlated with SHBG. WHR: higher levels significantly and negatively correlated with SHBG.

women with polycytic ovary syndrome (26). Additionally, a pooled analysis (27) and three other studies (10, 28, 29) reported weak positive associations between BMI and androgens.

The main source of estrogen in postmenopausal women is from the conversion of androgens in the adipose tissue (2, 4, 30), and this leads to higher exposure of breast cells to estrogens (31). Mechanistically, estrogens may increase breast cancer risk in postmenopausal women via DNA damage (32), regulation of cell signaling pathways (33), and regulation of angiogenesis (34, 35), possibly by an estrogen-driven angiogenic switch (36). Because estrogen exposure is associated with increased risk of postmenopausal breast cancer (7-9), this could explain the greater incidence of breast cancer in overweight or obese postmenopausal women.

We used a cross-sectional design with only a modest number of subjects, but the strengths of this study include a homogeneous study population (e.g., women taking hormone replacement therapy were excluded) and measurement stability, which resulted from the use of a carefully controlled diet that was adjusted to maintain body weight. None of the women were smokers. The DEXA scans used are considered a reference method for body composition analysis (37). Although our study was conducted within the control (0 g) segment of the alcohol trial, like all crossover studies, there may be residual treatment effects and for these reasons the design included a 2- to 5-week washout period before the zero alcohol study period. We evaluated the potential influence of both alcohol group order and dietary period and neither changed the findings. We also assessed a wide range of sex hormones known to be related to breast cancer risk, including both estrogens and androgens. The RIAs used here were validated previously against mass spectrometry with very good results (24), as evidenced by correlations of BMI with estradiol and estrone of 0.68 and 0.61, respectively. Further, coefficients of variation on masked quality control samples were well within accepted limits (e.g., 12% for estradiol and 17% for estrone), and the range of values seen matched those reported in the literature for epidemiologic studies (25).

In conclusion, in this study, we found that DEXA adiposity measures were strongly associated with hormone levels and highly correlated with BMI; however, their inclusion did not improve estimation of hormone levels beyond the more epidemiology friendly BMI. It remains for other studies to determine if BMI and DEXA adiposity are similarly associated with breast cancer risk. This is important because of well-known limitations of BMI (19). For example, for a given BMI, Asians have higher body fat content and higher risk for conditions, such as diabetes, high blood pressure, and heart disease (38). In addition, prospective studies of adiposity, including both BMI and DEXA measures, will still be needed to fully assess the effects of adiposity on chronic disease in general, including not only breast cancer but also other major causes of morbidity and mortality, such as heart disease and osteoporosis.

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