

*Short Communication*Serum Sex Hormones and Breast Cancer Risk Factors in Postmenopausal Women¹

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Abstract

Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. We evaluated associations of serum estrogen and androgen levels with age, anthropometry, and reproductive history to assess whether these characteristics could potentially modify breast cancer risk through hormonal mechanisms. A cross-sectional study was conducted among 133 postmenopausal women who donated blood to the serum bank (Columbia, MO) and served as controls in a previous prospective nested case control study of serum hormones and breast cancer risk. Standard regression methods were used to calculate adjusted means and test for trends in relationships of serum hormone concentrations with breast cancer risk factors. All analyses were performed on the log_e scale, and all models included assay batch, date, and time of blood collection. Serum levels of estradiol, non-sex hormone binding globulin bound estradiol, estrone, estrone sulfate, and testosterone increased significantly with increasing body mass index (BMI), whereas sex hormone binding globulin levels decreased. After adjusting for BMI, nulliparous women tended to have higher testosterone levels compared with parous women ($P = 0.05$), but there was no evidence of a trend of decreasing testosterone with increasing parity. Dehydroepiandrosterone, its sulfate, and androstenediol decreased significantly with increasing age. Although BMI and parity could potentially modify breast cancer risk through hormonal mechanisms, age-related increases in breast cancer incidence do not appear to be mediated through changes in serum levels of the hormones evaluated.

Introduction

Most prospective studies show positive associations between sex hormones and postmenopausal breast cancer risk (1–6) and an inverse relationship between SHBG³ and risk (1, 2). In a pooled analysis of these studies, postmenopausal women whose serum estrogens and androgens were in the highest quintile were approximately twice as likely to develop breast cancer compared with those in the lowest quintile (7). Reproductive history and body size have been associated with breast cancer in numerous epidemiological studies and could potentially influence risk through sex hormones (8). Parous women are at a decreased risk of breast cancer relative to nulliparous women, and pregnancy could alter hormone metabolism long term. Breast cancer risk associated with earlier menarche and later menopause could reflect underlying differences in sex hormone metabolism or duration of exposure to high levels of circulating estrogens and progesterone. The increased risk of breast cancer in heavier postmenopausal women may result from an increased capacity to convert androgens to estrogens because of their larger stores of adipose tissue.

We reported previously positive associations of serum estrogens and androgens to breast cancer risk in postmenopausal serum bank (Columbia, MO) participants (1, 5). Here, we evaluate relationships of reproductive and anthropometric characteristics to serum sex hormones to elucidate mechanisms by which these risk factors could influence breast cancer development.

Materials and Methods

Participants in this cross-sectional analysis were the 133 controls for a prospective nested case control study based on the serum bank that evaluated relationships of serum estrogens, androgens, and SHBG to breast cancer development in postmenopausal women. Results of that study, details about participants, data collection, serum collection, and storage were reported previously (1, 5). All participants were postmenopausal, not taking replacement estrogens at blood collection, had no previous cancer (except nonmelanoma skin cancer), and were not diagnosed with benign breast disease within the 2 years before blood collection. Women were initially classified as postmenopausal if they reported natural menopause, bilateral oophorectomy, or were ≥ 51 years old with a history of hysterectomy without oophorectomy. Any woman with a follicle-stimulating hormone level < 35 IU/ml was considered potentially premenopausal, and her date of last menses, age, and hormonal profile were reviewed to make a final determination of eligibility. All participants gave informed consent.

Clinical data were obtained by self-report or medical re-

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³ The abbreviations used are: SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone; BMI, body mass index.

Table 1 Geometric mean (SE) serum estrogen and SHBG levels by age, anthropometry, and reproductive history

Characteristic	No.	Total estradiol (pmol/liter)	Non-SHBG-estradiol (pmol/liter)	Estrone (pmol/liter)	Estrone sulfate (pmol/liter)	SHBG (nmol/liter)
Age (y) ^a						
50.6–57.6	33	46.7 (8.2)	22.0 (4.2)	120 (11)	545 (56)	54 (6)
57.7–62.2	33	42.5 (7.3)	20.0 (3.8)	109 (10)	474 (48)	48 (6)
62.3–66.9	34	46.8 (8.3)	19.5 (3.8)	115 (10)	551 (57)	54 (6)
67.0–76.5	33	40.5 (7.3)	16.5 (3.2)	101 (9)	453 (48)	51 (6)
<i>P</i> _{trend}		0.48	0.18	0.15	0.37	0.84
Height (cm) ^b						
147–156	27	44.1 (8.7)	19.4 (4.1)	112 (11)	480 (54)	53 (7)
157–166	44	42.1 (6.5)	18.7 (3.1)	107 (8)	546 (48)	50 (5)
161–164	22	40.1 (8.7)	16.6 (3.9)	102 (11)	393 (49)	59 (8)
165–173	40	47.5 (7.4)	21.6 (3.6)	118 (9)	528 (47)	50 (5)
<i>P</i> _{trend}		0.63	0.49	0.39	0.83	0.56
BMI ^b						
18.8–22.9	33	29.9 (5.2)	12.4 (2.3)	89 (8)	432 (44)	71 (7)
23.0–25.1	33	46.0 (8.2)	19.4 (3.7)	112 (10)	486 (51)	58 (6)
25.2–28.9	34	51.4 (8.7)	22.8 (4.1)	121 (10)	519 (52)	51 (5)
29.0–46.2	33	57.9 (10.0)	29.3 (5.4)	133 (12)	615 (63)	31 (3)
<i>P</i> _{trend}		0.03	0.001	0.02	0.02	0.0001
Age at menarche (y) ^c						
9–11	26	44.1 (8.2)	20.5 (4.0)	119 (11)	549 (60)	51 (6)
12	28	35.8 (6.7)	14.9 (2.9)	93 (9)	446 (48)	54 (6)
13	41	49.2 (7.7)	21.8 (3.6)	111 (9)	495 (45)	53 (5)
14–17	38	47.9 (7.9)	21.8 (3.8)	124 (10)	546 (53)	46 (4)
<i>P</i> _{trend}		0.76	0.67	0.50	0.80	0.08
Number of pregnancies ^c						
0	19	48.5 (11.0)	20.7 (5.0)	119 (14)	514 (68)	64 (8)
1–2	46	40.6 (6.0)	18.2 (2.8)	101 (8)	498 (43)	51 (4)
3–4	48	48.8 (7.1)	21.4 (3.3)	120 (9)	498 (43)	48 (4)
5–8	20	39.9 (9.1)	18.7 (4.5)	110 (13)	544 (73)	45 (6)
<i>P</i> _{trend}		0.94	0.92	0.95	0.72	0.12
Age 1 st pregnancy (y) ^c						
17–20	31	39.2 (7.3)	17.1 (3.4)	106 (10)	450 (49)	56 (6)
21–23	27	35.8 (7.7)	16.2 (3.7)	104 (11)	523 (65)	47 (6)
24–26	29	49.7 (9.5)	21.3 (4.3)	108 (11)	550 (61)	53 (6)
27–39	27	47.1 (9.0)	22.3 (4.5)	119 (12)	501 (55)	41 (4)
<i>P</i> _{trend}		0.66	0.50	0.74	0.42	0.12
Age at menopause (y) ^c						
35–47	35	49.0 (8.5)	22.4 (4.1)	116 (10)	503 (51)	49 (5)
48–49	20	44.8 (9.3)	18.6 (4.1)	112 (12)	517 (63)	53 (6)
50–51	41	46.7 (7.6)	21.7 (3.7)	111 (9)	543 (52)	53 (5)
52–62	37	38.8 (6.4)	16.8 (2.9)	108 (9)	467 (45)	49 (5)
<i>P</i> _{trend}		0.29	0.27	0.34	0.71	0.82

^a Adjusted for assay batch and date and time of blood collection.

^b Adjusted for assay batch, age at collection, and date and time of blood collection.

^c Adjusted for assay batch, age at blood collection, date and time of blood collection, and BMI.

cord review. Blood was collected using standard procedures, and serum was stored at -70°C for a median of 16 years until sex hormones and SHBG were assayed as described previously (1, 5). Assay coefficients of variation were 20.2% for estradiol, 9.2% for estrone, 9.7% for estrone sulfate, 8.9% for testosterone, 4.1% for androstendione, 1.2% for DHEAS, 15.8% for DHEA, 2.7% for androstenediol, and 4.3% for SHBG (9).

Hormone concentrations were \log_e transformed before analyses. Analysis of covariance was used to estimate adjusted mean hormone concentrations for different levels of risk factors and test for statistical significance. All models were adjusted for hormone analysis batch and date and time of day of blood collection. Models to evaluate associations of hormones with height, weight, and BMI [weight (kg)/height (m^2)] also included age, and models to evaluate associations with reproductive risk factors included age and BMI. Analyses were performed using SAS Statistical Software (10).

Results

Participants' median age at blood collection was 62 years, and except for one, all were Caucasian. Median time from menopause to blood collection was 12 years (5–95% = 2–25 years).

Tables 1 and 2 summarize relationships of age, body size, and reproductive history with serum hormones and SHBG. Age was not associated with estrogen levels, but it was significantly inversely associated with DHEA, DHEAS, and androstenediol. Although patterns across quartiles were erratic, the oldest women had levels of these hormones that were 34–38% lower compared with the youngest women.

Significant gradients of increasing serum hormone levels with increasing BMI were observed for all estrogens and testosterone. The mean estradiol concentration for women in the highest BMI quartile was almost double that of women in the lowest quartile, and the difference was even greater for non-

Table 2 Geometric mean (SE) serum androgen levels by age, anthropometry, and reproductive history

Characteristic	No.	Testosterone (nmol/liter)	Androstenedione (nmol/liter)	DHEA (nmol/liter)	DHEAS (μ mol/liter)	Androstenediol (nmol/liter)
Age (y)^a						
50.6–57.6	33	0.52 (0.10)	3.06 (0.31)	7.01 (0.77)	2.62 (0.31)	1.29 (0.12)
57.7–62.2	33	0.69 (0.12)	2.73 (0.26)	4.43 (0.52)	1.71 (0.20)	0.80 (0.08)
62.3–66.9	34	0.51 (0.09)	2.96 (0.29)	5.90 (0.67)	2.04 (0.24)	1.01 (0.10)
67.0–76.5	33	0.52 (0.10)	2.64 (0.26)	4.55 (0.54)	1.62 (0.20)	0.85 (0.09)
<i>P</i> _{trend}		0.68	0.29	0.03	0.02	0.02
Height (cm)^b						
147–156	27	0.68 (0.14)	2.97 (0.31)	5.95 (0.76)	1.87 (0.25)	1.01 (0.11)
157–160	44	0.54 (0.09)	2.59 (0.22)	5.18 (0.54)	1.90 (0.20)	1.00 (0.09)
161–164	22	0.55 (0.12)	2.71 (0.32)	5.20 (0.73)	1.87 (0.28)	0.91 (0.11)
165–173	40	0.53 (0.09)	3.09 (0.27)	5.25 (0.56)	2.08 (0.22)	0.96 (0.09)
<i>P</i> _{trend}		0.30	0.58	0.62	0.44	0.93
BMI^b						
18.8–22.9	33	0.49 (0.09)	2.59 (0.26)	5.54 (0.66)	1.77 (0.22)	0.96 (0.10)
23.0–25.1	33	0.45 (0.08)	2.64 (0.26)	4.98 (0.59)	2.00 (0.25)	0.86 (0.09)
25.2–28.9	34	0.58 (0.10)	2.79 (0.26)	5.68 (0.65)	2.06 (0.25)	1.07 (0.11)
29.0–46.2	33	0.81 (0.15)	3.45 (0.33)	5.19 (0.62)	2.02 (0.25)	0.97 (0.10)
<i>P</i> _{trend}		0.008	0.11	0.34	0.76	0.72
Age at menarche (y)^c						
9–11	26	0.46 (0.08)	2.84 (0.30)	5.10 (0.69)	2.00 (0.26)	0.94 (0.11)
12	28	0.60 (0.12)	2.62 (0.27)	5.00 (0.65)	1.83 (0.24)	0.91 (0.10)
13	41	0.61 (0.10)	2.99 (0.27)	5.48 (0.56)	1.72 (0.19)	1.02 (0.09)
14–17	38	0.60 (0.10)	2.89 (0.27)	5.64 (0.63)	2.35 (0.27)	0.98 (0.10)
<i>P</i> _{trend}		0.36	0.62	0.57	0.26	0.81
Number of pregnancies^c						
0	19	0.86 (0.20)	3.00 (0.38)	5.38 (0.86)	1.96 (0.31)	1.02 (0.15)
1–2	46	0.51 (0.08)	2.75 (0.23)	5.15 (0.51)	1.82 (0.19)	0.94 (0.08)
3–4	48	0.54 (0.08)	2.88 (0.24)	5.34 (0.51)	1.96 (0.20)	0.93 (0.08)
5–8	20	0.52 (0.12)	2.82 (0.37)	5.90 (0.96)	2.30 (0.37)	1.11 (0.16)
<i>P</i> _{trend}		0.19	0.52	0.81	0.70	0.74
Age 1st pregnancy (y)^c						
17–20	31	0.49 (0.08)	2.76 (0.26)	5.10 (0.53)	1.71 (0.20)	0.95 (0.09)
21–23	27	0.52 (0.11)	2.45 (0.26)	5.01 (0.60)	1.87 (0.25)	0.94 (0.11)
24–26	29	0.67 (0.12)	3.00 (0.29)	5.10 (0.57)	1.83 (0.22)	0.91 (0.10)
27–39	27	0.54 (0.10)	3.01 (0.30)	5.69 (0.67)	2.26 (0.27)	1.00 (0.11)
<i>P</i> _{trend}		0.63	0.19	0.43	0.095	0.66
Age at menopause (y)^c						
35–47	35	0.59 (0.11)	2.76 (0.27)	5.08 (0.57)	1.89 (0.23)	0.94 (0.09)
48–49	20	0.66 (0.14)	3.35 (0.39)	6.51 (0.94)	2.26 (0.33)	1.04 (0.13)
50–51	41	0.51 (0.09)	2.71 (0.25)	5.31 (0.58)	1.85 (0.21)	0.98 (0.09)
52–62	37	0.55 (0.09)	2.69 (0.24)	5.03 (0.57)	1.88 (0.22)	0.94 (0.10)
<i>P</i> _{trend}		0.55	0.58	0.68	0.38	0.80

^a Adjusted for assay batch and date and time of blood collection.

^b Adjusted for assay batch, age at blood collection and date and time of blood collection.

^c Adjusted for assay batch, age at blood collection, date and time of blood collection, and BMI.

SHBG-bound estradiol. SHBG was significantly inversely associated with BMI. Similar results were observed for weight (data not shown). Height, however, was not associated with serum levels of any of the hormones.

After adjusting for age and BMI, parous women had lower testosterone levels ($P = 0.046$) than nulliparous women; their mean levels were 0.52 and 0.86 nmol/liter, respectively. However, testosterone levels did not decrease as the number of full-term births increased. Serum hormones and SHBG did not vary by ages at menarche, menopause, or first full-term pregnancy or with duration since menopause when blood was collected (data not shown).

Discussion

We evaluated the relationships of established breast cancer risk factors with serum sex hormone concentrations in postmenopausal women to determine whether these risk factors could

potentially modify breast cancer risk via serum estrogens and androgens. BMI and weight were positively associated with estrogens and testosterone and inversely associated with SHBG. Therefore, heavier postmenopausal women's increased risk of breast cancer may be related to their having higher estrogen and possibly testosterone levels and lower SHBG levels compared with leaner women. Nulliparous women had higher testosterone levels compared with parous women, which could potentially contribute to the increased risk of breast cancer in nulliparous women. Other anthropometric, menstrual, and reproductive characteristics that are associated with breast cancer development were not significantly associated with any estrogens, androgens, or SHBG in our analysis.

Heavier postmenopausal women are at an increased risk of breast cancer (8). In postmenopausal women, BMI is positively associated with serum estradiol, estrone, and estrone sulfate in most studies (8, 11–16), although there are some exceptions (17).

BMI is inversely associated with SHBG in most studies (13, 14, 17), and as we observed, the association of BMI with non-SHBG-bound estradiol tends to be stronger than with total estradiol (6). Relationships of BMI with serum androgens are less well established, but Cauley *et al.* (15) reported a weak positive association between testosterone and BMI in postmenopausal women.

Taller postmenopausal women are at an increased risk of breast cancer (8), but height was not associated with estrogens, androgens, or SHBG in our analysis. Hankinson *et al.* (11) also did not observe an association of height with estrogens or SHBG in postmenopausal women, but associations between height and serum estrogens have been reported (13).

Nulliparous women are at an increased risk of developing breast cancer (8). In our analysis, nulliparous women had significantly higher testosterone levels compared with parous women. However, testosterone did not decrease with increasing numbers of full-term pregnancies. Similar to us, most investigators have not observed associations of parity or age at first birth with other androgens, estrogens, or SHBG (12, 13). Hankinson *et al.* (18), however, reported inverse associations of estrone sulfate with parity and percentage of bioavailable estradiol with age at first birth. Although ages at menarche and menopause are established breast cancer risk factors, we did not observe associations of these characteristics with any of the estrogens or androgens measured or with SHBG in postmenopausal women. Verkasalo *et al.* (12) also did not observe associations of ages at menarche and menopause with serum estradiol and SHBG in postmenopausal women. However, Madigan *et al.* (13) reported significant inverse associations between age at menarche and estradiol, non-SHBG-bound estradiol, estrone, and androstenedione and a significant positive association between age at menopause and androstenedione.

Risk of breast cancer increases with increasing age (8). In our analysis, DHEA, DHEAS, and androstenediol decreased with increasing age, but serum concentrations of the other hormones and SHBG were not related to age. The inverse associations of DHEA and DHEAS with age reflect the well-established decline in adrenal androgen production with advancing age during adulthood. Our finding of no age-related changes in estrogens, androstenedione, and testosterone is consistent with most other studies (13, 19, 20), although age-related decreases in serum estrogens have been reported (16).

Limitations of our study include its cross-sectional design and the fact that results are based on hormone measurements in a blood sample collected at a single time point. However, serial measurements of serum hormones in postmenopausal women suggest that a single measurement can reliably categorize women, at least over the short term. Intraclass correlation coefficients of hormone measurements in serum collected over a 3-year period were reported to be between 0.68 and 0.78 for the estrogens, 0.66 and 0.88 for the androgens, and 0.92 for SHBG (21).

We provided previously evidence from the cohort that postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. Results of the current analysis suggest that higher estrogens and possibly testosterone could potentially mediate the increased risk of breast cancer associated with obesity in postmenopausal women. Furthermore, higher testosterone levels could potentially contribute to the increased risk of breast cancer among nulliparous postmenopausal women. Our results do not support a role for changes in serum estrogen, androgen, or SHBG levels in explaining the age-related increase in breast cancer incidence.

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