

Racial/Ethnic Differences in Postmenopausal Endogenous Hormones: The Multiethnic Cohort Study

Veronica Wendy Setiawan,¹ Christopher A. Haiman,¹ Frank Z. Stanczyk,² Loïc Le Marchand,³ and Brian E. Henderson¹

Departments of ¹Preventive Medicine and ²Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles and ³Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii

Abstract

Postmenopausal women with increased estrogens and lowered sex hormone-binding globulin (SHBG) concentrations are at increased risk of breast cancer. In the Multiethnic Cohort Study, the highest incidence rates of postmenopausal breast cancer were observed among Native Hawaiians followed by Japanese Americans, Whites, African Americans, and Latinas. Ethnic differences in endogenous sex hormone profiles may contribute to some of the variation in breast cancer incidence. Plasma concentrations of androstenedione, testosterone, estrone (E₁), estradiol (E₂), and SHBG were measured in 739 postmenopausal women from the Multiethnic Cohort Study (240 African Americans, 81 Native Hawaiians, 96 Japanese Americans, 231 Latinas, and 91 Whites). After adjusting for age, known breast cancer risk factors and lifestyle factors, the mean levels of testosterone, estrogen, and SHBG varied across populations (P s ≤ 0.004). Across racial/ethnic groups, Native Hawaiians had the highest mean levels of andros-

tenedione, testosterone, and estrogens and the lowest mean levels of SHBG. Compared with Whites, Native Hawaiians had higher androstenedione (+22%, $P = 0.017$), total testosterone (+26%, $P = 0.013$), bioavailable testosterone (+33%, $P = 0.002$), E₁ ($\geq 21\%$; $P = 0.009$), total E₂ (+26%, $P = 0.001$), bioavailable E₂ (+31%, $P < 0.001$), and lower SHBG (-12% $P = 0.07$) levels. Compared with Whites, Japanese Americans had higher E₂ (+15%, $P = 0.036$) and bioavailable E₂ (+18%, $P = 0.024$) levels. African Americans also had higher E₁ (+21%, $P = 0.004$), E₂ (+20%, $P = 0.007$), and bioavailable E₂ (+20%, $P = 0.015$) levels compared with Whites, whereas mean levels in Latinas were similar to those of Whites. Many of the differences in endogenous postmenopausal hormonal milieu across these five racial/ethnic groups are consistent with the known differences in breast cancer incidence across these populations. (Cancer Epidemiol Biomarkers Prev 2006; 15(10):1849–55)

Introduction

Breast cancer incidence rates vary considerably across racial/ethnic groups (1). The incidence in Japanese women in Japan and in the United States has increased steadily over the years (2–6). In the Multiethnic Cohort Study (MEC), Japanese-American women have slightly higher postmenopausal breast cancer rates than White women, whereas rates among African-American and Latino women are lower (7). Native Hawaiians have the highest rate of breast cancer of any racial/ethnic group in our cohort.

A large and compelling body of epidemiologic and experimental data implicates endogenous estrogens in the etiology of breast cancer (8). Results of a pooled analysis of nine prospective studies provide evidence for an important role of estrogens and their androgen precursors in the development of breast cancer in postmenopausal women (9). The relative risks of breast cancer for women whose estrogen and androgen levels were in the top quintile compared with those whose levels were in the bottom quintile were ~ 2 . The results also showed that women with high circulating sex hormone-binding globulin (SHBG) levels, a protein that binds to and restricts the biological activity of estradiol and testosterone, had lower breast cancer risk (9).

Racial/ethnic differences in endogenous sex hormone levels might explain some of the variation in breast cancer incidence across racial/ethnic groups. There are only a small number of studies on differences in endogenous hormone levels between racial/ethnic groups in the United States (10–15), and comparisons with Native Hawaiians have not been reported. In the present study, we examined racial/ethnic differences in postmenopausal sex steroid hormone concentrations in a cross-sectional study of 739 postmenopausal women from the MEC (240 African Americans, 81 Native Hawaiians, 96 Japanese Americans, 231 Latinas, and 91 Whites).

Materials and Methods

MEC Background. Women in this study are participants in the MEC, a large prospective cohort in Hawaii and California (mainly Los Angeles). The details of the study design and baseline characteristics have been described previously (16). Briefly, the recruitment of the cohort began in 1993 and was completed in 1996. Potential participants were identified through driver's license files from the Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration data files. The cohort consists of $>215,000$ men and women (ages 45–75 years at baseline) and comprises mainly five self-reported racial and ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites living in Hawaii and California. Persons of mixed ethnicity were assigned to one of the above racial/ethnic groups according the following priority ranking: African American, Native Hawaiian, Latino, Japanese American, and White; this follows the Surveillance, Epidemiology and End Results guidelines of giving preference to non-White races for individuals of mixed ethnicity.

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Requests for reprints: Veronica Wendy Setiawan, University of Southern California/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Room 4425, Los Angeles, CA 90033.

Phone: 323-865-0411; Fax: 323-865-0127. E-mail: vsetiawa@usc.edu

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In our cohort, >95% of every ethnic group except Hawaiians reported one race only. Each participant completed a self-administered mail questionnaire that included diet, demographic factors, anthropometric measures, other lifestyle factors, history of prior medical conditions, family history of cancer, and for women, menstrual, reproductive history, and exogenous hormone use (oral contraceptives and postmenopausal hormones).

Incident breast cancer cases were identified by record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry. All tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology and End Results program of cancer registration. Deaths within the cohort were determined by annual linkage to state death certificate files in California and Hawaii and periodically to the National Death Index. Case ascertainment and death information were complete through December 31, 2002.

Beginning in 1994, blood samples were collected from a random sample of MEC participants to serve as a control pool for genetic association studies. Blood samples were collected at the participants' homes after an overnight fast, processed within 8 hours, and stored at -80°C .

Study Population. Subjects of this study were drawn from the control group of the MEC nested case-control study of breast cancer. Details of this case-control study have been previously published (17). Women were selected for hormone measurements if they met all of the following criteria: ≥ 56 years old at the time of blood draw, reported no history of breast, endometrial or ovarian cancer on the baseline questionnaire, body weight and body mass index (BMI) information available, and not using postmenopausal hormones at baseline and at the time of blood draw. Seven hundred thirty-nine women were included in this study; of these, 240 were African Americans, 81 were Native Hawaiians, 96 were Japanese Americans, 231 were Latinas, and 91 were Whites. The mean age at blood draw was 66.9 years, ranging from 56 to 82 years. All study participants have provided informed consent, and the Institutional Review Boards at the University of Hawaii and at the University of Southern California approved the protocol.

Hormone Assays. Plasma hormone assays were done at the Reproductive Endocrine Research Laboratory at the University of Southern California, directed by one of the authors (F.Z.S.). All samples across ethnic groups were assayed together and samples from each ethnic group were included within each batch. Samples were also blinded so that laboratory personnel could not identify which ethnic group the samples were from. Plasma concentrations of androstenedione, testosterone, estrone (E_1), and estradiol (E_2) were measured by sensitive and specific immunoassays after organic solvent extraction and Celite column partition chromatography. SHBG were quantified by a solid-phase, two-site chemiluminescent immunoassay, using the Immulite analyzer (Diagnostic Products Corp., Inglewood, CA). Bioavailable (non-SHBG bound) testosterone and E_2 concentrations were calculated using a validated algorithm on the basis of total testosterone, total E_2 , and SHBG measurements (18-20). Replicate-blinded quality control samples (5%) were included to check reproducibility of the hormone assays; the intraclass correlation coefficients between duplicates for androstenedione, testosterone, E_1 , E_2 , and SHBG were 0.89, 0.98, 0.87, 0.82, and 0.98, respectively. In addition, quality control samples with low, medium, and high concentrations (one pair per level) were included in each batch. The interassay coefficients of variation for sex steroid hormones were $\leq 14\%$, $\leq 12\%$, and $\leq 13\%$ at low, medium, and high levels, respectively. The interassay coefficients of variation for SHBG were all $\leq 5\%$.

Statistical Methods. Twenty-two postmenopausal women with either E_1 values >125 pg/mL, E_2 values >75 pg/mL, or testosterone values >125 ng/dL (indicating postmenopausal hormone use) were excluded from the study. Three women (<60 years old at blood draw) who either had unknown menopausal status or were premenopausal at baseline had E_2 values >75 pg/mL and were also excluded from the study, leaving 714 women available for the analyses. Information on breast cancer risk factors and other lifestyle factors that might influence hormone levels (21-36) was obtained from the MEC baseline questionnaire. These factors were body weight, height, age at menarche, age at first birth, parity, age and type of menopause, alcohol drinking, smoking status, vigorous physical activity, calorie intake, percent calories from fat, dietary fiber intake, and soy intake. BMI was calculated as weight (kg)/height (m^2). The median interval between baseline questionnaire date and blood draw was 4 years (range, 1-8 years). All hormone values were natural log-transformed to produce approximately normal distributions. Geometric mean hormone levels according to race/ethnicity were calculated using multivariate regression analysis while adjusting for age at blood draw and assay batch. Further adjustment was also done for risk/lifestyle factors that were significantly associated with a particular hormone fraction. These risk factors included BMI and soy intake that were modeled as continuous variables, and age at menarche (≤ 12 , 13-14, and ≥ 15 years), age and type of menopause [natural (<44 , 45-49, ≥ 50 years), bilateral oophorectomy (<44 , ≥ 45 years), hysterectomy (<44 , ≥ 45 years), and unknown], and smoking status (never, past, and current), which were modeled as categorical variables. Analysis of covariance was used to test for differences in mean hormone levels across race/ethnicity, and P s for heterogeneity of effects across groups were also reported. For racial/ethnic differences, the main comparison group was White women, as this group had been used as the comparison group in a previous study (11). Breast cancer incidence rates in the MEC were calculated among women ages ≥ 55 years at baseline and included all incident cases of breast cancer through December 31, 2002. Rates were truncated to age 55 to 79 years and age-adjusted to the U.S. 1970 standard population. All P s are two sided. The SAS statistical package version 9.0 (SAS Institute, Cary, NC) was used for all analyses.

Results

Descriptive characteristics by racial/ethnic groups are presented in Table 1. Japanese-American women were older at blood draw (mean age = 68.8 years), whereas Latinas and Native Hawaiians were slightly younger (65.5 and 65.8 years, respectively). Body size characteristics (weight, height, and BMI) differed significantly across ethnic groups ($P < 0.001$). African Americans were the heaviest as a group, and despite their greater average height, they had the highest mean BMI (28.8 kg/m^2). The mean BMI of Native Hawaiians and Latinas were lower at 28.2 and 28.0 kg/m^2 , respectively, but greater than Whites (26.5 kg/m^2). Japanese Americans weighed much less than any other group, and despite the fact that they were shorter on average than any other group, their mean BMI was only 23.2 kg/m^2 . Among parous women, Latinas and Native Hawaiians had the most children, whereas Japanese had the fewest. Latinas and Native Hawaiians reported the highest average calorie intake. Overall, Japanese Americans had the lowest proportion of calories from fat, whereas African Americans had the highest. Whites (14%) were more likely to have late age at first birth than other groups (4-8%). Compared with other ethnic groups, Japanese Americans were more likely to have later age at menopause. African Americans were more likely to have undergone simple hysterectomy

Table 1. Characteristics of study population by racial/ethnic group

	African American	Native Hawaiian	Japanese American	Latina	White
No. women (%)	234 (33.8)	77 (10.8)	93 (13.0)	222 (31.1)	88 (12.3)
Mean age (SD), y	67.8 (6.7)	65.8 (6.4)	68.8 (6.2)	65.5 (6.2)	67.7 (6.8)
Mean height (SD), m	1.63 (0.07)	1.62 (0.06)	1.54 (0.06)	1.60 (0.06)	1.63 (0.07)
Mean weight (SD), kg	76.4 (16.1)	74.2 (17.9)	54.9 (8.3)	71.9 (14.4)	70.1 (16.4)
Mean BMI (SD), kg/m ²	28.8 (5.8)	28.0 (6.0)	23.2 (3.3)	28.2 (5.5)	26.5 (5.6)
Mean no. children* (SD)	3.5 (1.9)	4.1 (1.7)	3.0 (1.2)	4.2 (1.8)	3.2 (1.5)
Mean calorie intake (SD), kcal/d	1,900 (1,061)	2,114 (850)	1,751 (625)	2,197 (1,077)	2,007 (787)
Mean % calories from fat (SD)	31.8 (8.0)	29.1 (6.0)	27.1 (6.3)	29.4 (6.8)	29.9 (7.6)
Age at menarche ≤ 12 y (%)	42.9	52.0	45.7	49.1	56.8
Age at first birth ≥ 31 y* (%)	5.8	5.9	8.1	3.5	13.9
Nulliparous (%)	9.3	9.1	6.5	9.1	8.0
Age at menopause ≥ 50 y [†] (%)	35.0	39.1	55.1	41.2	45.8
Hysterectomy (%)	21.2	12.7	7.1	18.3	15.3
Bilateral oophorectomy (%)	15.6	12.7	7.1	8.7	7.1
Alcohol drinkers [‡] (%)	7.1	6.6	2.2	5.1	17.1
Current smokers (%)	21.4	19.7	10.9	9.4	15.9

*Among parous women only.

[†]Natural or surgical.[‡]At least one drink per day.

(21%) and bilateral oophorectomy (16%) compared with other groups. White women consumed alcohol to a greater extent than the other groups, with 17% consuming at least one drink per day. The corresponding figure for African Americans and Latinas was around 7%; this decreased to 5% for Latinas and to 2% for Japanese Americans. The highest proportion of current smokers was among African Americans (21%), and the lowest was among Japanese Americans (9%). The distribution of descriptive factors in this sample were consistent with that observed in the entire female cohort (7, 16).

Table 2 shows the associations between plasma hormone concentrations and breast cancer risk factors or lifestyle factors that have been found to be associated with hormone levels in previous studies. As expected, we observed a large increase in E_1 and E_2 levels and a large decrease in SHBG levels with increasing BMI (P s < 0.001). We observed an increase in bioavailable testosterone with increasing BMI, but this increase in bioavailable testosterone is likely to be explained by the substantial decrease in SHBG concentrations because no association was observed with total testosterone. Although the number of children and age at first birth was not associated with significant differences in hormone levels, late age at menarche was modestly associated with lower estrogen concentrations (P s ≤ 0.05). Age and type of menopause was associated with difference in testosterone levels (P s < 0.001). We observed that smoking was associated with differences in androgen levels but not with estrogen or SHBG levels. Increasing soy intake was modestly related with lower testosterone levels ($P = 0.04$). No statistically significant relationships were observed between hormone levels and vigorous physical activity, alcohol drinking, calorie intake, and proportion calories from fat or fiber intake. Ethnic-specific associations between selected risk/lifestyle factors and hormone levels are provided in Supplementary Table S1.

In Table 3, we provide the updated incidence rates of breast cancer and geometric means hormone levels by racial/ethnic group. As we have shown previously (7), Native Hawaiians had the highest incidence rates of breast cancer followed Japanese Americans, Whites, African Americans, and Latinas. These lower breast cancer rates observed in African Americans and Latinas than in White women in our cohort reflect the pattern previously reported for women in the Surveillance, Epidemiology and End Results program (37). In age-adjusted analyses, hormone levels varied significantly across racial/ethnic groups for all hormones (P s < 0.001) except for androstenedione ($P = 0.10$) and SHBG ($P = 0.07$). Further adjustment for risk/lifestyle factors yielded significant racial/ethnic variation in SHBG levels ($P = 0.004$).

Across racial/ethnic groups, Native Hawaiian women had the highest age-adjusted mean levels of androstenedione, total and bioavailable testosterone, and total and bioavailable E_2 and the lowest age-adjusted mean levels SHBG. Although further adjustment for risk factors somewhat influenced mean hormone levels in Native Hawaiians, it did not explain the observed differences between Native Hawaiian and White women. In the multivariate analyses, compared with White women, Native Hawaiians had 22% higher androstenedione ($P = 0.017$), 26% higher testosterone ($P = 0.013$), 33% higher bioavailable testosterone ($P = 0.002$), 21% higher E_1 ($P = 0.009$), 26% higher E_2 ($P = 0.001$), 31% higher bioavailable E_2 ($P < 0.001$), and 12% lower SHBG ($P = 0.07$) levels.

African Americans in our study had higher age-adjusted mean levels of E_1 (+24% $P = 0.002$), E_2 (+25% $P = 0.002$), and bioavailable E_2 (+26% $P = 0.005$) compared with Whites; further adjustment for risk factors (BMI and age at menarche) reduced these differences, but they remained statistically significant. In the multivariate models, African-American women had 21% higher E_1 ($P = 0.004$), 20% higher E_2 ($P = 0.007$), and 20% higher bioavailable E_2 ($P = 0.015$) levels compared with White women. Across ethnic groups, African Americans had the highest levels of SHBG despite being the heaviest group. Compared with Native Hawaiians, they had 22% higher SHBG levels ($P = 0.001$), but compared with Whites, the difference in SHBG levels was not significant (+7%, $P = 0.224$).

In age-adjusted analyses, Japanese-American women had similar mean hormone levels to that of Whites. However, after adjustment for BMI and age at menarche, Japanese Americans were found to have 15% higher E_2 ($P = 0.036$) and 18% higher bioavailable E_2 ($P = 0.024$) levels than Whites.

There were no significant differences in plasma hormone concentrations between Latina and White women.

In our cohort, the prevalence of bilateral oophorectomy varied across ethnic groups, and this might influence ethnic differences in testosterone levels; we, thus, repeated our analyses while excluding women who had reported bilateral oophorectomy on the questionnaire ($n = 72$). We observed similar results before and after the exclusion of women with a bilateral oophorectomy. We also repeated our analyses while restricting the analyses to women with covariate data collected within 4 or 5 years of blood draw, and our results did not change.

In our study, 13% of the Japanese-American and 46% of Latina women were born outside the United States. Compared with U.S. born Japanese, Japanese women born outside the United States had lower levels of androgens and estrogens and

Table 2. Geometric mean plasma hormone levels by breast cancer risk factors and other lifestyle factors

	No. women* (%)	Androstenedione (pg/mL)	Testosterone (ng/dL)	Bio testosterone (ng/dL)	E ₁ (pg/mL)	E ₂ (pg/mL)	Bio E ₂ (pg/mL)	SHBG (nmol/L)
BMI (kg/m ²)								
<25	261 (36.6)	494	21.3	9.7	30.7	9.9	6.1	46.6
25.0-29.9	259 (36.3)	501	21.5	11.0	35.2	12.2	8.1	36.7
≥30.0	194 (27.2)	473	22.2	11.7	41.5	15.3	10.4	34.2
P _{trend}		0.42	0.44	<0.001	<0.001	<0.001	<0.001	<0.001
Age at menarche (y)								
≤12	341 (47.9)	497	22.1	10.9	36.1	12.3	8.0	39.1
13-14	278 (39.0)	485	21.1	10.5	34.2	11.9	7.8	39.0
≥15	93 (13.1)	484	20.9	10.0	32.9	11.1	7.1	42.7
P _{trend}		0.54	0.25	0.16	0.036	0.07	0.05	0.23
Age at first birth [†] (y)								
≤20	252 (39.4)	511	22.7	10.9	36.3	12.2	7.8	41.4
21-30	346 (54.2)	496	20.9	10.5	34.0	11.7	7.7	37.9
≥31	41 (6.4)	493	22.3	11.3	38.5	12.9	8.6	38.3
P _{trend}		0.49	0.21	0.85	0.55	0.79	0.57	0.06
Parity [†]								
1 child	71 (11.0)	494	21.8	11.0	34.4	12.4	8.2	38.1
2-3 children	272 (42.3)	500	21.8	10.7	35.9	12.1	7.8	39.9
≥4 children	300 (46.7)	491	20.8	10.3	34.1	11.6	7.6	39.0
P _{trend}		0.81	0.37	0.32	0.45	0.15	0.20	0.95
Age (y) and type of menopause								
Natural								
<44	69 (10.4)	487	2.0	10.9	34.0	11.9	7.8	39.3
45-49	142 (21.5)	482	1.2	10.5	33.4	11.2	7.3	40.1
≥50	241 (36.5)	522	3.9	11.9	36.4	12.6	8.2	39.5
Bilateral oophorectomy								
<44	46 (7.0)	475	18.6	8.8	33.2	11.8	7.6	42.7
≥45	26 (3.9)	484	16.1	7.9	38.3	12.5	8.1	38.7
Hysterectomy								
<44	76 (11.5)	445	19.7	9.8	31.5	11.5	7.5	39.2
≥45	35 (5.3)	439	17.7	9.0	31.4	10.7	7.1	36.8
Unknown [‡]	26 (3.9)	487	19.5	9.2	36.1	11.7	7.3	41.8
P _{heterogeneity}		0.30	<0.001	<0.001	0.11	0.24	0.35	0.92
Alcohol drinking								
Nondrinkers	455 (65.2)	483	21.4	10.5	34.6	11.8	7.7	39.7
<1 drink/d	194 (27.8)	502	21.2	10.6	35.2	12.1	7.9	38.8
≥1 drink/d	49 (7.0)	541	25.3	12.5	36.0	12.7	8.2	40.2
P _{trend}		0.12	0.21	0.14	0.49	0.32	0.31	0.85
Smoking								
Never	399 (57.2)	474	20.4	10.1	34.5	11.8	7.7	38.7
Past	191 (27.4)	494	22.5	11.2	35.3	12.1	7.9	38.9
Current	108 (15.5)	546	24.3	11.6	36.2	12.5	7.9	43.3
P _{heterogeneity}		0.034	0.010	0.030	0.56	0.38	0.72	0.08
Vigorous physical activity (h/wk)								
<3	612 (89.3)	495	21.6	10.7	35.3	12.0	7.9	39.2
≥3 (90th)	73 (10.7)	458	21.5	10.4	32.3	11.9	7.6	41.5
P _{heterogeneity}		0.22	0.95	0.66	0.11	0.92	0.57	0.32
Calorie intake (kcal/d)								
<1,348	174 (24.9)	475	20.6	10.2	36.2	12.2	8.0	38.8
1,348-1,837	175 (25.1)	508	23.5	11.5	35.6	12.4	8.0	40.2
1,838-2,455	174 (24.9)	504	23.0	11.2	34.8	12.1	7.8	41.2
≥2,456	175 (25.1)	482	19.7	10.0	33.0	11.2	7.4	37.7
P _{trend} [§]		0.79	0.31	0.36	0.07	0.06	0.10	0.67
% Calories from fat								
<24.7	174 (24.9)	473	21.2	10.4	34.7	12.0	7.8	40.4
24.7-30.2	175 (25.1)	487	22.5	11.4	36.0	12.2	8.1	37.4
30.3-35.1	174 (24.9)	501	20.9	10.6	34.5	11.9	7.9	37.2
≥35.2	175 (25.1)	513	21.9	10.2	34.3	11.6	7.3	43.9
P _{trend} [§]		0.11	0.88	0.60	0.53	0.39	0.27	0.26
Total fiber intake, density (g/kcal/d)								
<9.9	175 (25.1)	527	22.6	10.9	35.6	12.5	8.0	41.6
9.9-12.6	174 (24.9)	501	22.4	11.1	33.9	11.5	7.5	38.6
12.7-16.2	175 (25.1)	459	20.4	10.2	35.2	12.0	7.8	38.9
≥16.3	174 (24.9)	478	20.9	10.5	34.8	11.7	7.7	38.6
P _{trend} [§]		0.07	0.12	0.40	0.35	0.51	0.90	0.21
Total soy intake, density (g/kcal/d)								
<2.7	523 (74.9)	496	22.7	11.3	35.1	12.2	8.0	39.3
≥2.7 (75th)	175 (25.1)	485	19.8	9.7	34.5	11.5	7.5	39.8
P _{trend} [§]		0.67	0.043	0.042	0.69	0.22	0.25	0.92

NOTE: Adjusted for age at blood draw (continuous), race/ethnicity (categorical), and assay batch (categorical); further adjusted for BMI (continuous) for bio testosterone, estrogens, and SHBG.

*Numbers may not add up to total due to missing values.

[†]Among parous women only.

[‡]Women were premenopausal at baseline but were postmenopausal at blood draw (age ≥56 y) with unknown age and type of menopause.

[§]Continuous variables.

Table 3. Incidence rates of breast cancer and geometric mean plasma hormones by racial/ethnic group

	African American	P*	Native Hawaiian	P*	Japanese American	P*	Latina	P*	White	P [†]
Incidence rate [‡] (per 100,000)	359		615		432		283		467	
Androstenedione (pg/mL)										
Age adjusted	474	0.84	577	0.011	489	0.54	460	0.88	466	0.10
Multivariate [§]	480	0.97	585	0.017	512	0.39	471	0.84	479	0.17
Testosterone (ng/dL)										
Age adjusted	22.7	0.17	25.9	0.006	21.0	0.66	18.8	0.44	20.2	<0.001
Multivariate [§]	21.9	0.11	23.9	0.013	21.2	0.23	17.8	0.45	19.0	<0.001
Bio testosterone (ng/dL)										
Age adjusted	11.0	0.16	13.3	<0.001	10.1	0.66	9.4	0.68	9.7	<0.001
Multivariate [§]	10.2	0.14	12.0	0.002	10.7	0.06	8.5	0.55	9.0	<0.001
E ₁ (pg/mL)										
Age adjusted	39.4	0.002	39.4	0.004	31.8	0.97	32.3	0.80	31.7	<0.001
Multivariate [§]	38.0	0.004	37.8	0.009	33.9	0.24	31.6	0.86	31.3	<0.001
E ₂ (pg/mL)										
Age adjusted	13.1	0.002	13.8	<0.001	10.9	0.61	11.3	0.31	10.5	<0.001
Multivariate [§]	12.5	0.007	13.1	0.001	12.0	0.036	11.1	0.37	10.4	<0.001
Bio E ₂ (pg/mL)										
Age adjusted	8.44	0.005	9.23	<0.001	6.97	0.66	7.44	0.23	6.72	<0.001
Multivariate [§]	7.93	0.015	8.68	<0.001	7.82	0.024	7.21	0.27	6.62	0.002
SHBG (nmol/L)										
Age adjusted	42.5	0.74	35.5	0.033	40.3	0.62	39.9	0.46	41.7	0.07
Multivariate [§]	43.8	0.22	35.8	0.07	36.8	0.14	40.4	0.85	40.8	0.004

*P comparing with Whites.

†P for testing homogeneity of means across race/ethnicity derived from analysis of covariance.

‡Rates among women ages ≥55 years old at baseline through December 31, 2002. Rates were truncated to aged 55 to 79 and age adjusted to the U.S. 1970 standard population.

§Adjusted for age at blood draw, assay batch, BMI (for bio testosterone, E₁, E₂, bio E₂, and SHBG), age at menarche (for E₁, E₂, and bio E₂), age and type of menopause (for testosterone and bio testosterone), smoking status (for testosterone and bio testosterone), and soy intake (for testosterone and bio testosterone).

higher levels of SHBG; but these differences were not statistically significant (data not shown). U.S. born and foreign-born Latina women had similar hormone profiles. Adjusting for birthplace in the multivariate models did not alter our results (data not shown).

Discussion

In this study conducted among postmenopausal women in the MEC, after adjusting for risk/lifestyle factors, we found significant differences in the endogenous hormonal milieu across five racial/ethnic groups. Native Hawaiian women, who have the highest risk of breast cancer in our cohort, had the highest levels of androgens, estrogens and lowest levels of SHBG. We also found African Americans and Japanese Americans to have higher estrogen levels than White women, whereas levels among Latinas were similar to those of Whites.

Compared with Whites, Native Hawaiians were found to have higher circulating levels of androgens and estrogens; differences that were not accounted for by the racial/ethnic differences in the prevalence of breast cancer risk factors and other lifestyle factors. We have previously shown that after adjustment for seven known breast risk factors (age at menarche and first birth, parity, age and type of menopause, weight, postmenopausal hormone use, and alcohol intake), the breast cancer risk for Native Hawaiians was 65% greater than that of Whites (7). The Native Hawaiians' "high-risk" hormonal profile is consistent with their high rates of breast cancer and suggests that the excess breast cancer risk in Native Hawaiians may be due to their having high plasma androgen and estrogen levels and low SHBG levels.

The low postmenopausal estrogen levels of Japanese women living in Japan (12) were not observed in the Japanese-American women in this study, most of whom (87%) were U.S. born. In our study, Japanese Americans had adjusted mean levels of E₂ that were significantly higher than those of Whites. In a previous smaller study conducted among 193 postmenopausal women in the MEC, Japanese-American women (*n* = 30), despite their low body weight, had 32%

higher E₁ and E₂ levels as high as White women (*n* = 39; ref. 11). Although the magnitude of mean differences in hormone levels between these two ethnic groups was much smaller in the current study, our findings provide support for the previous observation in the initial report. In the MEC, the risk factor adjusted incidence of breast cancer among Japanese Americans was slightly higher than Whites (7). The elevated E₂ levels in Japanese Americans may provide an explanation for their increase in incidence of breast cancer, and that increases in estrogen levels and breast cancer rates may both be determined by long-term exposure to a western diet and other lifestyle factors.

It is well documented that African-American women have higher premenopausal breast cancer rates and lower postmenopausal rates relative to White women (38). Most (10, 13, 15, 39) but not all (40, 41) studies in premenopausal women have reported that African Americans had higher E₂ levels than Whites. In the MEC, the incidence of postmenopausal breast cancer in African Americans was also lower than in Whites; however, their endogenous estrogen levels were found to be significantly higher than those of Whites, confirming findings from an earlier and smaller study in the MEC (11). If having elevated estrogen levels contribute to their higher rates during the premenopausal period, then it is interesting to find out why this elevation does not persist into the postmenopausal period when their estrogen levels are also elevated. Clearly, more work is needed to identify the factors that contribute to these racial/ethnic differences in risk that exist in the premenopausal and postmenopausal periods.

Latinas had sex steroid hormone profiles that were very similar to Whites, in accord with our previous results from a smaller study of 58 Latina postmenopausal women (11). In the MEC, postmenopausal breast cancer risk among U.S. born Latinas was found to be similar to Whites (relative risk, 0.95; 95% confidence interval, 0.75-1.20), whereas migrant Latinas had 16% lower risk than Whites (relative risk, 0.84; 95% confidence interval, 0.64-1.10; ref. 7). We observed that U.S. born and migrant Latinas had similar hormone profiles.

The factors underlying racial/ethnic variation in postmenopausal sex steroid hormone levels are largely unknown; other

than body weight or BMI, little is known about their determinants. Variation in key genes involved in estrogen biosynthesis pathway have been associated with differences in circulating hormone levels (42-49); thus, some of the observed ethnic differences in hormone levels may be ascribed to the differences in the distributions of polymorphisms in these genes. Additional research, however, will be needed to test this hypothesis.

Low response rates in certain ethnic groups may affect generalizability of our results to the general population. The response rates in our cohort ranged from 20% in Latinos to 49% in Japanese Americans. As previously shown, however, the distributions of education level in our cohort generally resemble those reported by the U.S. Census in Hawaii and Los Angeles County for the same ethnic and age groups; thus, we believe that findings from this cohort can be compared across ethnic and social strata and are broadly generalizable (16).

In summary, this study confirms the existence of racial/ethnic differences in endogenous sex hormone levels and adds to the sparse data available in the Latino and Native Hawaiian population. Future research should be aimed to elucidate the determinants of Native Hawaiians' high-risk hormonal profiles and increasing E₂ levels in Japanese Americans and to clarify the relationship between sex steroid hormones and breast cancer risk in postmenopausal African-American women.

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