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

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## 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 ($E_1$), estradiol ($E_2$), 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 $\leq$ 0.004). Across racial/ethnic groups, Native Hawaiians had the highest mean levels of androstenedione, 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), $E_1$ ($\geq$21%; $P$ = 0.009), total $E_2$ (+26%, $P$ = 0.001), bioavailable $E_2$ (+31%, $P$ < 0.001), and lower SHBG (−12% $P$ = 0.07) levels. Compared with Whites, Japanese Americans had higher $E_2$ (+15%, $P$ = 0.036) and bioavailable $E_2$ (+18%, $P$ = 0.024) levels. African Americans also had higher $E_1$ (+21%, $P$ = 0.004), $E_2$ (+20%, $P$ = 0.007), and bioavailable $E_2$ (+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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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 ≤14%, ≤12%, and ≤13% at low, medium, and high levels, respectively. The interassay coefficients of variation for SHBG were all ≤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 $\leq$ 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 Stated. 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, $E_1$, $E_2$, bio $E_2$, and SHBG), age at menarche (for $E_1$, $E_2$, and bio $E_2$), 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 $E_2$ 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 $E_1$ and $E_2$ 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 $E_2$ 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 $E_2$ 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 $E_2$ 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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## References

1. Ghafoor A, Jemal A, Ward E, Cokkinides V, Smith R, Thun M. Trends in breast cancer by race and ethnicity. CA Cancer J Clin 2003;53:342–55.
2. Research Group for Population-Based Cancer Registries in Japan. Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. Jpn J Clin Oncol 2003;33:241–5.
3. Minami Y, Tsubono Y, Nishino Y, Ohuchi N, Shibuya D, Hisamichi S. The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. Int J Cancer 2004;108:901–6.
4. Tamakoshi K, Yatsuya H, Wakai K, et al. Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. Cancer Sci 2005;96:57–62.
5. Deapen D, Liu L, Perkins C, Bernstein L, Ross RK. Rapidly rising breast cancer incidence rates among Asian-American women. Int J Cancer 2002;99:747–50.
6. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 1993;85:1819–27.
7. Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in Whites. Cancer Epidemiol Biomarkers Prev 2002;11:795–800.
8. Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000;21:427–33.
9. Endogenous Hormone and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
10. Pinheiro SP, Holmes MD, Pollak MN, Barbieri RL, Hankinson SE. Racial differences in premenopausal endogenous hormones. Cancer Epidemiol Biomarkers Prev 2005;14:2147–53.
11. Probst-Hensch NM, Pike MC, McKean-Cowdin R, Stanczyk FZ, Kolonel LN, Henderson BE. Ethnic differences in post-menopausal plasma oestrogen levels: high oestrone levels in Japanese-American women despite low weight. Br J Cancer 2000;82:1867–70.
12. Shimizu H, Ross RK, Bernstein L, Pike MC, Henderson BE. Serum oestrogen levels in postmenopausal women: comparison of American Whites and Japanese in Japan. Br J Cancer 1990;62:451–3.
13. Henderson BE, Bernstein L, Ross RK, Depue RH, Judd HL. The early *in utero* oestrogen and testosterone environment of Blacks and Whites: potential effects on male offspring. Br J Cancer 1988;57:216–8.
14. Bernstein L, Yuan JM, Ross RK, et al. Serum hormone levels in premenopausal Chinese women in Shanghai and White women in Los Angeles: results from two breast cancer case-control studies. Cancer Causes Control 1990;1:51–8.
15. Haiman CA, Pike MC, Bernstein L, et al. Ethnic differences in ovulatory function in nulliparous women. Br J Cancer 2002;86:367–71.
16. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346–57.
17. Haiman CA, Stram DO, Pike MC, et al. A comprehensive haplotype analysis of CYP19 and breast cancer risk: the Multiethnic Cohort. Hum Mol Genet 2003;12:2679–92.
18. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72.
19. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 β to human plasma proteins at body temperature. J Steroid Biochem 1982;16:801–10.
20. Rinaldi S, Dechaud H, Toniolo P, Kaaks R. Reliability and validity of direct radioimmunoassays for measurement of postmenopausal serum androgens and estrogens. IARC Sci Publ 2002;156:323–5.
21. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A. Associations between reproductive and menstrual factors and postmenopausal sex hormone concentrations. Cancer Epidemiol Biomarkers Prev 2004;13:1296–301.
22. Chubak J, Tworoger SS, Yasui Y, Ulrich CM, Stanczyk FZ, McTiernan A. Associations between reproductive and menstrual factors and postmenopausal androgen concentrations. J Womens Health (Larchmt) 2005;14:704–12.
23. Hankinson SE, Colditz GA, Hunter DJ, et al. Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in postmenopausal women in the Nurses' Health Study (United States). Cancer Causes Control 1995;6:217–24.
24. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995;87:1297–302.
25. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003;95:1218–26.
26. Key TJ, Pike MC, Baron JA, et al. Cigarette smoking and steroid hormones in women. J Steroid Biochem Mol Biol 1991;39:529–34.
27. Madigan MP, Troisi R, Potischman N, Dorgan JF, Brinton LA, Hoover RN. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998;9:199–207.
28. McTiernan A, Tworoger SS, Rajan KB, et al. Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial. Cancer Epidemiol Biomarkers Prev 2004;13:1099–105.
29. McTiernan A, Tworoger SS, Ulrich CM, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64:2923–8.
30. Nagata C, Kabuto M, Takatsuka N, Shimizu H. Associations of alcohol, height, and reproductive factors with serum hormone concentrations in postmenopausal Japanese women. Steroid hormones in Japanese postmenopausal women. Breast Cancer Res Treat 1997;44:235–41.
31. Newcomb PA, Klein R, Klein BE, et al. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318–21.
32. 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.
33. Prentice R, Thompson D, Clifford C, Gorbach S, Goldin B, Byar D; The Women's Health Trial Study Group. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. J Natl Cancer Inst 1990;82:129–34.
34. Wu AH, Stanczyk FZ, Seow A, Lee HP, Yu MC. Soy intake and other lifestyle determinants of serum estrogen levels among postmenopausal Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 2002;11:844–51.
35. Wu AH, Pike MC, Stram DO. Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J Natl Cancer Inst 1999;91:529–34.
36. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control 2001;12:47–59.
37. SEER. Surveillance, Epidemiology, and End Results. Available from: http://www.seer.cancer.gov.
38. Pathak DR, Osuch JR, He J. Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in Black and White populations. Cancer 2000;88:1230–8.
39. Woods MN, Barnett JB, Spiegelman D, et al. Hormone levels during dietary changes in premenopausal African-American women. J Natl Cancer Inst 1996;88:1369–74.
40. Lamon-Fava S, Barnett JB, Woods MN, et al. Differences in serum sex hormone and plasma lipid levels in Caucasian and African-American premenopausal women. J Clin Endocrinol Metab 2005;90:4516–20.
41. Randolph JF, Jr., Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88:1516–22.

42. Feigelson HS, Shames LS, Pike MC, Coetzee GA, Stanczyk FZ, Henderson BE. Cytochrome P450c17α gene (CYP17) polymorphism is associated with serum estrogen and progesterone concentrations. Cancer Res 1998;58:585–7.
43. Haiman CA, Hankinson SE, Spiegelman D, et al. The relationship between a polymorphism in CYP17 with plasma hormone levels and breast cancer. Cancer Res 1999;59:1015–20.
44. Haiman CA, Riley SE, Freedman ML, Setiawan VW, Conti DV, Le Marchand L. Common genetic variation in the sex steroid hormone-binding globulin (SHBG) gene and circulating shbg levels among post-menopausal women: the Multiethnic Cohort. J Clin Endocrinol Metab 2005; 90:2198–204.
45. Setiawan VW, Hankinson SE, Colditz GA, Hunter DJ, De Vivo I. HSD17B1 gene polymorphisms and risk of endometrial and breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:213–9.
46. Small CM, Marcus M, Sherman SL, Sullivan AK, Manatunga AK, Feigelson HS. CYP17 genotype predicts serum hormone levels among pre-menopausal women. Hum Reprod 2005;20:2162–7.
47. Tworoger SS, Chubak J, Aiello EJ, et al. Association of CYP17, CYP19, CYP1B1, and COMT polymorphisms with serum and urinary sex hormone concentrations in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2004;13:94–101.
48. Dunning AM, Dowsett M, Healey CS, et al. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. J Natl Cancer Inst 2004;96:936–45.
49. Lurie G, Maskarinec G, Kaaks R, Stanczyk FZ, Le Marchand L. Association of genetic polymorphisms with serum estrogens measured multiple times during a 2-year period in premenopausal women. Cancer Epidemiol Biomarkers Prev 2005;14:1521–7.