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Plasma sex hormone concentrations and the risk of breast cancer in postmenopausal women: the Multiethnic Cohort Study

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Abstract

To add to the existing evidence, which comes mostly from within White populations, we conducted a nested case-control study within the Multiethnic Cohort to examine the association between circulating sex hormones and breast cancer risk among postmenopausal women. Of the women who had a plasma sample, 129 women developed breast cancer during follow-up. Two controls per case, matched on area (Hawaii, Los Angeles), ethnicity/race (Japanese American, White, Native Hawaiian, African American, Latina), birth year, date of blood draw and time fasting, were selected from the women who had not developed breast cancer. Levels of estradiol, estrone, androstenedione, dehydroepiandrosterone (DHEA) and testosterone were quantified with radioimmunoassay after organic extraction and Celite column chromatography separation. Estrone sulfate, dehydroepiandrosterone sulfate (DHEAS), and sex hormone binding globulin (SHBG) were quantified by direct immunoassays. As estimated with conditional logistic regression, the sex hormones were positively associated and SHBG was negatively associated with breast cancer risk. All associations, except those with DHEAS and testosterone showed a significant linear trend. The odds ratio associated with a doubling of estradiol was 2.29 (95% confidence interval (CI) 1.58–2.35) and the odds ratio associated with a doubling of testosterone was 1.35 (95% CI 0.98–1.82). The associations in Japanese American women, who constituted 54% of our sample, were similar or slightly qualitatively stronger than in those of other ethnicity/race. This study supports previous evidence of an association between sex hormones and breast cancer risk and suggests that the associations are similar in Japanese American women.

Keywords

estrogens; androgens; blood; breast cancer; postmenopausal; nested case-control

Introduction

Many risk factors for postmenopausal breast cancer are thought to be mediated by a hormonal mechanism (Clemons & Goss 2001, Henderson & Feigelson 2000). The investigation of circulating sex hormones has provided more direct evidence. A pooled analysis published in 2002 (Key *et al*. 2002) of nine prospective studies of women not using hormone replacement therapy (HRT) (Barrett-Connor *et al*. 1990, Berrino *et al*. 1996, Cauley *et al*. 1999, Dorgan *et al*. 1997, Dorgan *et al*. 1996, Garland *et al*. 1992, Gordon *et al*. 1990, Hankinson *et al*. 1998, Helzlsouer *et al*. 1994, Kabuto *et al*. 2000, Thomas *et al*. 1997, Toniolo *et al*. 1995, Zeleniuch-Jacquotte *et al*. 1997), found that all estrogenic and androgenic steroid sex hormones examined were associated with increased breast cancer risk, and that sex hormone binding globulin (SHBG) was associated with decreased risk. Since the publication of this pooled analysis, these findings have been supported for the most part by analyses in some of the studies with extended follow-up (Cummings *et al*. 2005, Eliassen *et al*. 2006, Missmer *et al*. 2004, Sieri *et al*. 2009, Zeleniuch-Jacquotte *et al*. 2004) and additional large prospective studies (Beattie *et al*. 2006, Cummings *et al*. 2002, Gunter *et al*. 2009, Kaaks *et al*. 2005, Manjer *et al*. 2003, Onland-Moret *et al*. 2003).

With a single exception, all of these studies were conducted in largely Caucasian populations. Kabuto *et al.* (2000) investigated the association with estradiol, SHBG and dehydroepiandrosterone sulfate (DHEAS) in Japanese women but had only 26 postmenopausal cases and did not investigate testosterone levels. The odds ratio (OR) for the association with a doubling of estradiol was 0.90 (95% confidence interval (CI) 0.42–1.92) (reported in (Key *et al*. 2002)) suggesting that the association may be different in women of Japanese ancestry. Two case-control studies conducted in China, on the other hand, found that breast cancer risk in Asian postmenopausal women was positively associated with estrogen and testosterone levels (Wang *et al*. 2009, Yu *et al*. 2003). This preliminary report examines the association between estrogens (estradiol, estrone, estrone sulfate), androgens (androstenedione, DHEA, DHEAS, testosterone), and SHBG and breast cancer among postmenopausal women not using HRT within the Multiethnic Cohort (MEC) study, in which a large proportion of the participants are Japanese American.

Materials and methods

Study design and population

We conducted a case-control study nested within the MEC. This cohort includes over 215,000 men and women between the ages of 45 and 75 years living in Hawaii and Los Angeles who returned a baseline questionnaire between 1993 and 1996 (Kolonel *et al*. 2000). From information in the questionnaire, participants were assigned to a single ethnic/racial group and if more than one group was reported, assignment was based on the following priority ranking: African American, Native Hawaiian, Latino, Japanese American, and White. More than 95% of all non-Hawaiians reported only one ethnic group. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Diet was assessed with a food frequency questionnaire inquiring about frequency of consumption and portion size for over 180 food items consumed over the past year. Menopausal status was inferred from reported cessation of menstrual periods, oophorectomy, and initiation of HRT.

Between 2001 and 2006, 67,594 MEC participants agreed to donate a biospecimen and complete a short questionnaire that updated information including HRT use and menopausal status. Fasting blood was drawn in the early morning at a clinical laboratory or in the participant's home, processed, and separated. Plasma was divided into 2 mL aliquots and stored at −80 C. The MEC and this study were approved by the Institutional Review Boards of the

University of Southern California and the University of Hawaii. All participants provided informed consent at time of blood collection.

Cases and controls

Cases were women who had contributed a blood specimen before being diagnosed with a first primary breast cancer to the end of follow-up (December, 2006). Diagnoses were identified by linkage with the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries that cover the entire population of the two states. Deaths were identified by linkage with state vital statistics databases and the National Death Index. Two control women per case were randomly selected from a pool of subcohort members alive and not diagnosed with breast cancer at the age of the diagnosis of the case, and matched to the case by area (Hawaii, Los Angeles), ethnicity, birth year (± 1 year), date of blood draw (± 6 months), time of blood draw (± 2 hours), hours fasting before blood draw (0–<6, 6–<8, 8–<10, ≥10), and type of biospecimen (serum, plasma). Some women only had serum available and were excluded because the volume of serum that could be extracted from the 0.5 mL straws in which it was stored was too low to reliably quantify the low hormone levels found in postmenopausal women.

Of the 327 cases who had a fasting blood sample available in the biorepository, 124 were currently using HRT, 70 only had serum samples, and one had been matched to controls with serum samples by mistake. Of the 264 controls matched to the remaining 132 cases, one did not have a plasma sample, and two did not have sufficient sample for assays. Thus, 129 cases with two matched controls and three cases with one matched control had assay results for the analytes of primary interest (estrogens, testosterone, and DHEA). One control did not have sufficient sample to assay SHBG and DHEAS.

Laboratory assays

Assays for sex hormones and SHBG were performed at the Reproductive Endocrine Research Laboratory at the University of Southern California (FZS). Each batch included matched case-control sets and pooled quality control samples, which were in random order and the identity of which were blinded to laboratory personnel, plus laboratory standards. Levels of the unconjugated steroid hormones were determined by radioimmunoassay after organic extraction and partition chromatography on Celite columns (Stanczyk *et al*. 2007). Levels of the conjugated steroid hormones were determined using direct immunoassays (Ranadive *et al*. 1998). Levels of SHBG were determined using a chemiluminescent immunometric assay on an Immulite analyzer (Siemens Medical Solutions, Los Angeles, CA). The limits of detection were 5 pg/mL for estrone, 0.01 ng/mL for estrone sulfate, 2 pg/mL for estradiol, 0.03 ng/mL for androstenedione, 0.04 ng/mL for DHEA, 15 μg/dL for DHEAS, 1.5 ng/dL for testosterone, and 1 nmol/L for SHBG. Seven women were below the limit for estradiol and 57 women were below the limit for DHEAS. These women were assumed to have levels equal to half of the detection limit. Bioavailable testosterone and estradiol were estimated with a validated algorithm using the measured concentrations of the sex hormones and SHBG and an assumed albumin concentration of 43 g/L (Rinaldi *et al*. 2002, Sodergard *et al*. 1982, Vermeulen *et al*. 1999). The intra-batch coefficients of variation were [10%] for estrone, [8.5%] for estrone sulfate, [9%] for estradiol, [6%] for androstenedione, [4%] for DHEA, [4.5%] for DHEAS, [3.5%] for testosterone, and [8%] for SHBG.

Statistical analysis

Because levels of hormones and SHBG were positively skewed, they were logarithmically (base 2) transformed when used as continuous variables. Odds ratios estimating the association between quartiles of hormone concentrations based on the distribution in controls and breast cancer risk were computed using conditional logistic regression. Odds ratios estimating the

association between a doubling of hormone concentrations and breast cancer risk were also computed; these analyses also constituted our test for linear trend. Included in the models were two of the matching factors as continuous variables, age at blood draw and hours fasting, to control for any residual differences in these variables between cases and controls. We also evaluated a number of risk factors as potential confounders (listed in Table 1). None were retained as confounders because when added to the models, they changed the ORs associated with a doubling of hormone concentrations no more than 10%. Analyses stratified by HRT use (past, never) and time between blood collection and diagnosis (<1, ≥1 year) were done. These analyses used hormone levels in tertiles; the product between the stratification variable and hormone levels as continuous variables was introduced into the models to examine the significance of the effect modification. An analysis stratified by ethnicity (Japanese American, other) also used hormone levels in tertiles and as continuous variables. The analyses were done using the LOGISTIC procedure with a STRATA statement in SAS version 9.1 (SAS Institute, Cary, NC). All statistical tests were two-sided with a 0.05 level of significance.

Results

Characteristics of the 132 cases and 261 controls are shown in Table 1. The median age of the participants was 68 years and over half of the women were Japanese American. About half of both cases and controls used HRT in the past. Levels of the sex hormones were higher in cases than controls and level of SHBG was lower in cases than controls (Table 2). Among controls, levels of the analytes were often significantly correlated. For example, the Pearson correlations of estradiol with estrone, testosterone and SHBG were 0.51, 0.33, and −0.27, respectively.

The sex hormones were positively associated with breast cancer risk and SHBG was inversely associated with breast cancer risk (Figure 1). All associations, except those with DHEAS and testosterone, showed a significant trend, the strongest of which were observed for estradiol and free estradiol (Figure 2). Women who had estradiol levels in the highest quartile had an approximately six-fold increase in breast cancer risk relative to women in the lowest quartile (OR 6.42, 95% CI 2.78–14.90). We did not find that past HRT use significantly modified any of these associations (all P for heterogeneity > 0.05). Generally the trends observed in the overall group were reflected in both past and never users of HRT but were qualitatively stronger among the latter group (data not shown). The associations between the estrogens and breast cancer risk were slightly, but nonsignificantly, stronger if blood was taken one year or more before diagnosis whereas the association between SHBG and breast cancer risk was slightly, but nonsignificantly, stronger if blood was taken less than one year before diagnosis (data not shown). As depicted in Figure 2, when the analysis was conducted among Japanese American women, all associations except those with DHEAS and testosterone showed a significant trend and tended to be stronger than those in the group of other ethnicity/race. For example, the OR for a doubling of estradiol was 2.88 (95% CI 1.63–5.10) in Japanese American women whereas it was 1.87 (95% CI 1.17–2.99) in the overall sample.

Discussion

In this study, estrogenic and androgenic hormones were positively associated and SHBG was inversely associated with breast cancer risk. The pooled analysis done in 2002 (Key *et al.* 2002) and four of the five prospective studies of circulating hormones done since then (Cummings *et al.* 2002, Gunter *et al.* 2009, Kaaks *et al.* 2005, Manjer *et al.* 2003) have also found such associations. In the current study, however, stronger associations were observed for some analytes such as estradiol, estrone sulfate, and SHBG. For example, the OR corresponding to a doubling of estradiol was 2.26 (95% CI 1.58–3.25) whereas the summary OR in the pooled analysis was 1.29 (95% CI 1.15–1.44) with ORs ranging from 0.76 to 1.69 in the individual studies.

The impact of the short time between blood collection and diagnosis (median of 1 year), which could be construed as a limitation of our study, should be considered. Because mammary tumors express aromatase, they have the capability of producing estrogens (Pasqualini *et al.* 1996) and reverse causality could be a concern. However, in breast cancer patients, breast tissue estrogens do not reflect circulating estrogens (Geisler 2003). Furthermore, time between blood collection and diagnosis has been assessed in the prospective studies of sex hormones and breast cancer risk studies and most found that less time between blood and diagnosis had little effect on the association between most hormones and breast cancer risk (Dorgan *et al.* 1996, Hankinson *et al.* 1998, Kabuto *et al.* 2000, Key *et al.* 2002, Sieri *et al.* 2009, Zeleniuch-Jacquotte *et al.* 1997), but other studies found some associations to be weaker (Dorgan *et al.* 1997, Hankinson *et al.* 1998, Onland-Moret *et al.* 2003, Toniolo *et al.* 1995) and other studies yet found some associations to be stronger (Dorgan *et al.* 1996, Kabuto *et al.* 2000, Zeleniuch-Jacquotte *et al.* 2004). Finally, in one study that had two blood samples a mean of 31 months apart, the rate of change in hormone levels was not significantly different between cases and controls, although for androstenedione there was a suggestive difference in rates (Zeleniuch-Jacquotte *et al.* 2004).

Some of our associations may have been stronger than in other studies because our indirect assays were quite valid and reliable, perhaps leading to less attenuation of risk estimates due to nondifferential exposure misclassification. Estradiol measurements done in the laboratory in which our assays were performed correlate very well with the gold standard method (GC-MS/MS), as do other indirect assays, whereas direct assays without an extraction step to eliminate cross-reactivity with other hormone metabolites seem to correlate less well (Lee *et al.* 2006). In other reliability studies, however, direct assays correlate well with indirect assays (Rinaldi *et al.* 2001). Furthermore, the coefficients of variation of the assays done in this study are not noticeably lower than what has been reported in other studies that also ensure that case-control sets are in the same batch to eliminate the effect of inter-batch variability. Also possibly contributing to the strength of our associations is that over half of our sample was Japanese American women and in this study, the associations between most sex hormones and breast cancer risk were stronger than in the women in of other ethnicity/race. This difference, however, may not be enough to wholly explain our stronger results in comparison to previous studies. Several factors, including chance, may have contributed to our stronger associations between levels of estradiol, estrone sulfate, and SHBG and breast cancer risk.

The only other prospective study done among postmenopausal Asian women, conducted in Japan, found no significant association between estradiol, DHEAS, and SHBG; the point estimate for estradiol was below 1.0 but the CIs were wide due to a small sample size (Kabuto *et al.* 2000). Two case-control studies conducted in China, however, found a positive association between postmenopausal breast cancer risk and levels of estrogens and testosterone (Wang *et al.* 2009, Yu *et al.* 2003). The null association could have been due to chance or could have been influenced by the population under study having low levels of estradiol. It is difficult to compare the levels of sex hormones between studies due to differences in assay techniques.

The Japanese American women in the current study likely have higher levels of sex hormones than in these other studies of Asian women. Studies directly comparing Eastern and Western Japanese populations with the same assay techniques have observed lower sex hormone levels in former (Shimizu *et al.* 1990). In the MEC, Japanese American women have sex hormone levels similar to Whites but once BMI and other factors are taken into account, their estradiol levels are higher than Whites (Setiawan *et al.* 2006). The adoption of a Westernized lifestyle may be responsible for the sex hormone levels of the women of Japanese ethnicity/race in our study. Ninety-two percent of them were born in the United States and Japanese Americans in the MEC seem to have partially adopted a Westernized lifestyle with respect to dietary patterns although it is still likely to differ from Whites (Park *et al.* 2005). Indicators of a less Westernized

lifestyle, such as a dietary pattern high in vegetable and soy intake, are associated with higher SHBG concentrations (Wu *et al*. 2009) and lower testosterone concentrations (Setiawan *et al*. 2006). Japanese American women in the baseline MEC have similar rates of breast cancer incidence relative to White women and, in fact, once other known risk factors are taken into account, they are at slightly higher risk (Pike *et al*. 2002, Woolcott *et al*. 2009). In Japanese American women, it is possible that hormone levels mediate the association between the adoption of a Westernized lifestyle and breast cancer risk.

Some other limitations of our study should be noted. We had a small sample size; although we had sufficient power to detect associations of the magnitude observed in other studies and had a larger number of women of Asian ancestry than other published prospective studies, our ability to detect differences in effect between subgroups was limited. As follow-up continues, we will be able to pursue analyses in other ethnic/racial groups. We also had blood at only one point in time. Other studies have observed that hormone levels up to five years apart are moderately correlated (Hankinson *et al*. 1998, Kim & Zeleniuch-Jacquotte 1997, Toniolo *et al*. 1995, Zeleniuch-Jacquotte *et al*. 2004). Our covariate information was derived from the baseline questionnaire, which was done an average of 9.3 years before the blood was drawn. This limitation only affects the time-dependent covariates, such as BMI, and are unlikely to change the conclusions in this study because most other studies have found that covariates confound the associations between circulating sex hormones and breast cancer risk very little (Cummings *et al*. 2005, Dorgan *et al*. 1996, Endogenous Hormones and Breast Cancer Collaborative Group 2003, Hankinson *et al*. 1998, Kaaks *et al*. 2005, Kabuto *et al*. 2000, Key *et al*. 2002, Onland-Moret *et al*. 2003, Zeleniuch-Jacquotte *et al*. 2004).

In conclusion, this study supports previous evidence that sex hormone levels are associated with an increased risk of breast cancer, and SHBG levels are associated with a decreased risk among postmenopausal women. It suggests that these associations are similar in Japanese American women; in these women, it is possible that hormone levels mediate the association between the adoption of a Westernized lifestyle and breast cancer risk.

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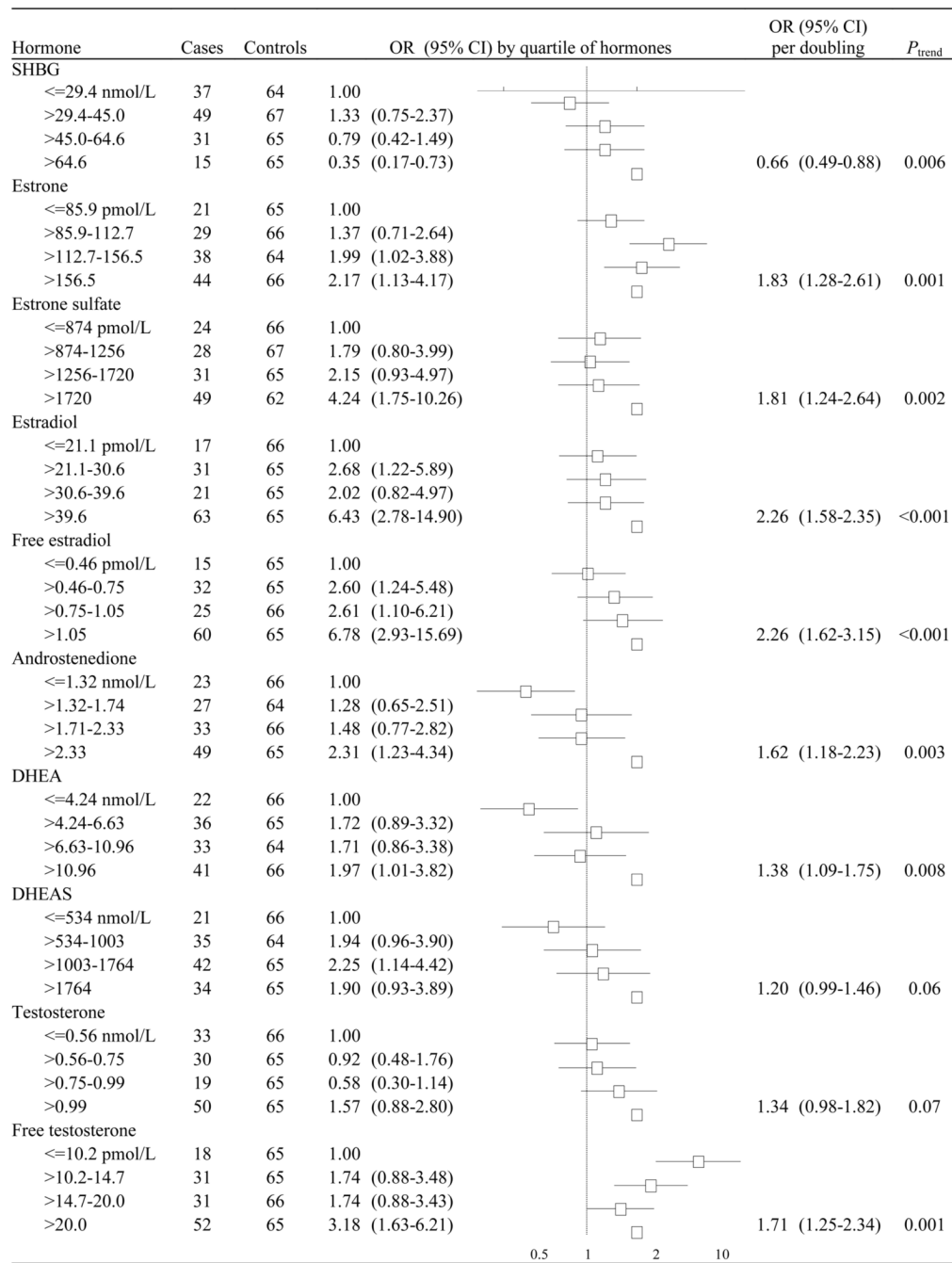| Hormone	Cases	Controls	OR (95% CI) by quartile of hormones	OR (95% CI) per doubling	P_{trend}
SHBG					
<=29.4 nmol/L	37	64	1.00		
>29.4-45.0	49	67	1.33 (0.75-2.37)		
>45.0-64.6	31	65	0.79 (0.42-1.49)		
>64.6	15	65	0.35 (0.17-0.73)	0.66 (0.49-0.88)	0.006
Estrone					
<=85.9 pmol/L	21	65	1.00		
>85.9-112.7	29	66	1.37 (0.71-2.64)		
>112.7-156.5	38	64	1.99 (1.02-3.88)		
>156.5	44	66	2.17 (1.13-4.17)	1.83 (1.28-2.61)	0.001
Estrone sulfate					
<=874 pmol/L	24	66	1.00		
>874-1256	28	67	1.79 (0.80-3.99)		
>1256-1720	31	65	2.15 (0.93-4.97)		
>1720	49	62	4.24 (1.75-10.26)	1.81 (1.24-2.64)	0.002
Estradiol					
<=21.1 pmol/L	17	66	1.00		
>21.1-30.6	31	65	2.68 (1.22-5.89)		
>30.6-39.6	21	65	2.02 (0.82-4.97)		
>39.6	63	65	6.43 (2.78-14.90)	2.26 (1.58-2.35)	<0.001
Free estradiol					
<=0.46 pmol/L	15	65	1.00		
>0.46-0.75	32	65	2.60 (1.24-5.48)		
>0.75-1.05	25	66	2.61 (1.10-6.21)		
>1.05	60	65	6.78 (2.93-15.69)	2.26 (1.62-3.15)	<0.001
Androstenedione					
<=1.32 nmol/L	23	66	1.00		
>1.32-1.74	27	64	1.28 (0.65-2.51)		
>1.71-2.33	33	66	1.48 (0.77-2.82)		
>2.33	49	65	2.31 (1.23-4.34)	1.62 (1.18-2.23)	0.003
DHEA					
<=4.24 nmol/L	22	66	1.00		
>4.24-6.63	36	65	1.72 (0.89-3.32)		
>6.63-10.96	33	64	1.71 (0.86-3.38)		
>10.96	41	66	1.97 (1.01-3.82)	1.38 (1.09-1.75)	0.008
DHEAS					
<=534 nmol/L	21	66	1.00		
>534-1003	35	64	1.94 (0.96-3.90)		
>1003-1764	42	65	2.25 (1.14-4.42)		
>1764	34	65	1.90 (0.93-3.89)	1.20 (0.99-1.46)	0.06
Testosterone					
<=0.56 nmol/L	33	66	1.00		
>0.56-0.75	30	65	0.92 (0.48-1.76)		
>0.75-0.99	19	65	0.58 (0.30-1.14)		
>0.99	50	65	1.57 (0.88-2.80)	1.34 (0.98-1.82)	0.07
Free testosterone					
<=10.2 pmol/L	18	65	1.00		
>10.2-14.7	31	65	1.74 (0.88-3.48)		
>14.7-20.0	31	66	1.74 (0.88-3.43)		
>20.0	52	65	3.18 (1.63-6.21)	1.71 (1.25-2.34)	0.001

0.5   1   2   10

Figure 1.
Odds ratios (OR) and 95% confidence intervals (CI) for the association of hormone concentrations with the risk of breast cancer.

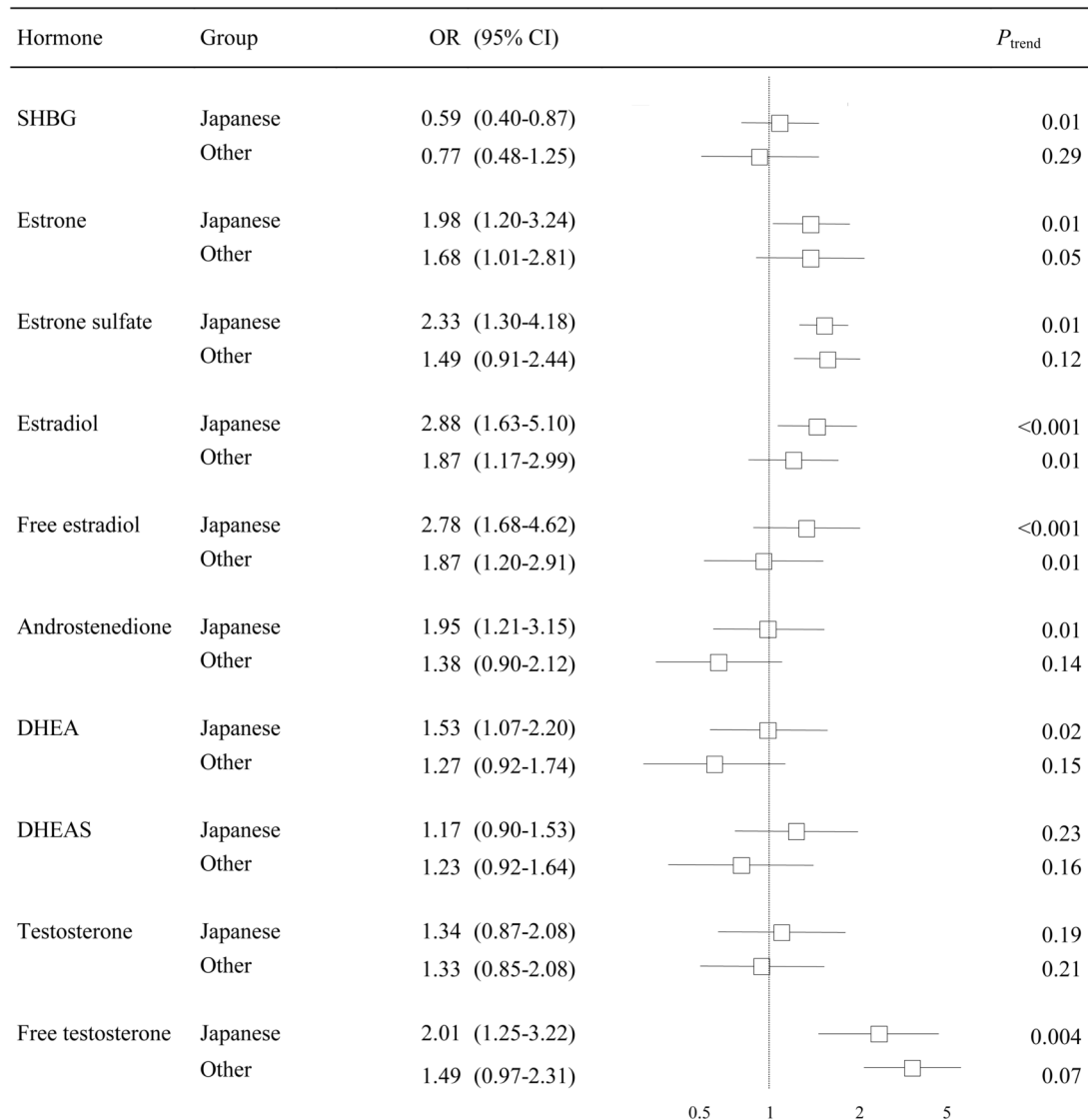| Hormone	Group	OR (95% CI)		P_{trend}
SHBG	Japanese	0.59 (0.40-0.87)		0.01
	Other	0.77 (0.48-1.25)		0.29
Estrone	Japanese	1.98 (1.20-3.24)		0.01
	Other	1.68 (1.01-2.81)		0.05
Estrone sulfate	Japanese	2.33 (1.30-4.18)		0.01
	Other	1.49 (0.91-2.44)		0.12
Estradiol	Japanese	2.88 (1.63-5.10)		<0.001
	Other	1.87 (1.17-2.99)		0.01
Free estradiol	Japanese	2.78 (1.68-4.62)		<0.001
	Other	1.87 (1.20-2.91)		0.01
Androstenedione	Japanese	1.95 (1.21-3.15)		0.01
	Other	1.38 (0.90-2.12)		0.14
DHEA	Japanese	1.53 (1.07-2.20)		0.02
	Other	1.27 (0.92-1.74)		0.15
DHEAS	Japanese	1.17 (0.90-1.53)		0.23
	Other	1.23 (0.92-1.64)		0.16
Testosterone	Japanese	1.34 (0.87-2.08)		0.19
	Other	1.33 (0.85-2.08)		0.21
Free testosterone	Japanese	2.01 (1.25-3.22)		0.004
	Other	1.49 (0.97-2.31)		0.07

0.5   1   2   5

Figure 2.
Odds ratios (OR) and 95% confidence intervals (CI) for the association between a doubling of hormone concentrations and the risk of breast cancer among Japanese American women and women of other race/ethnicity.

Table 1

Characteristics of the cases and controls

Characteristic	Cases	Controls
	N (%)	**N (%)**
Number of subjects	132 (100)	261 (100)
Ethnicity/race[a]		
Japanese American	72 (54.5)	142 (54.4)
White	30 (22.7)	60 (23.0)
Native Hawaiian	17 (12.9)	34 (13.0)
African American	8 (6.1)	15 (5.7)
Latina	5 (3.8)	10 (3.8)
Number of children[b]		
0	17 (12.9)	28 (10.7)
1	7 (5.3)	24 (9.2)
2–3	70 (53.0)	134 (51.3)
>=4	38 (28.8)	74 (28.4)
Aged ≥ 25 years at first birth, parous women[b]	40 (34.8)	65 (27.9)
Hawaii [a]	113 (85.6)	224 (85.8)
>12 years of education[b]	91 (68.9)	172 (65.9)
Aged <13 years at menarche [b]	70 (53.0)	145 (55.6)
Past oral contraceptive use	67 (50.8)	119 (45.6)
Past use of HRT[b]	68 (51.5)	132 (50.6)
1st degree family history of breast cancer	10 (7.6)	34 (13.0)
≥1 alcoholic drink/day	12 (9.1)	23 (8.8)
	Median (IQR)	Median (IQR)
Age at blood draw[a] (years)	68.0(61.4 – 75.7)	68.1 (61.2 – 75.2)
Years between blood draw and diagnosis[a]	0.9(0.5 – 1.9)	1.0 (0.5 – 1.9)
Years between baseline and blood draw	9.2(8.6 – 10.4)	9.4 (8.9 – 10.4)
Hours fasting before blood draw[a]	13.1(12.0 – 14.1)	12.9 (11.8 – 14.1)
Body mass index[b] (kg/m^2)	24.7(22.4 – 27.6)	24.0 (21.5 – 27.5)
Physical activity[b] (MET-hours/week)	4.2(1.4 – 8.9)	3.6 (2.0 – 8.2)

IQR, Interquartile range (25th percentile to 75th percentile); MET, metabolic equivalent.

[a]Matching variables.

[b]Summary statistics based on slightly fewer than 132 cases and 261 controls due to missing values.

Table 2

Geometric mean (95% confidence interval) concentrations of sex hormones and SHBG in cases and controls

Sex hormone/SHBG	Cases	Controls
SHBG (nmol/L)	37.6 (34.7 – 40.9)	43.6 (40.7 – 46.7)
Estrone (pmol/L)	132.0 (121.9 – 142.9)	111.9 (105.7 – 118.4)
Estrone sulfate (pmol/L)	1363 (1218 – 1525)	1168 (1092 – 1250)
Estradiol (pmol/L)	36.7 (33.4 – 40.5)	28.3 (26.4 – 30.4)
Free estradiol (pmol/L)	0.96 (0.87 – 1.07)	0.70 (0.64 – 0.76)
Androstenedione (nmol/L)	2.02 (1.87 – 2.19)	1.73 (1.63 – 1.84)
DHEA (nmol/L)	7.61 (6.82 – 8.49)	6.30 (5.79 – 6.86)
DHEAS (nmol/L)	1068 (927 – 1229)	916 (825 – 1018)
Testosterone (nmol/L)	0.83 (0.76 – 0.90)	0.75 (0.71 – 0.80)
Free testosterone (pmol/L)	17.2 (15.9 – 18.6)	14.4 (13.5 – 15.3)

DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin.