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Ethnic differences in post-menopausal plasma oestrogen levels: high oestrone levels in Japanese-American women despite low weight

NM Probst-Hensch[1,3], MC Pike[1], R McKean-Cowdin[1], FZ Stanczyk[2], LN Kolonel[4] and BE Henderson[1]

[1]Department of Preventive Medicine, USC/Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90033, USA; [2]Department of Obstetrics and Gynecology, University of Southern California, Los Angeles, CA 90033, USA; [3]Institute of Social and Preventive Medicine, University of Basel, Basel, Switzerland; [4]Cancer Research Center, University of Hawaii, Honolulu, HI 96816, USA

Summary Breast cancer incidence in Japanese-American women is approaching that of US Whites. We investigated whether this shift is paralleled by similar post-menopausal plasma hormone levels in the two ethnic groups. We also included African-American and Latina women to further our understanding of possible ethnic differences in oestrogen metabolism. We measured androstenedione (A), oestrone (E1) and oestradiol (E2) in 30 Japanese-American, 39 non-Latina White ('White'), 66 African-American and 58 Latina women. The (age-adjusted) geometric mean E1 levels were 34 pg ml^{-1} in Japanese-Americans, 28 pg ml^{-1} in Whites, 35 pg ml^{-1} in African-Americans and 31 pg ml^{-1} in Latinas. After adjustment for body mass index, Japanese-Americans had the highest mean E1 value of all groups and this was statistically significantly greater than the value for Whites ($P_{\text{t-test}} = 0.05$). The geometric mean A concentrations were also highest in Japanese-Americans. There was little ethnic difference in E2 levels. In conclusion, post-menopausal plasma oestrogen levels in Japanese-American women are at least as high as those in Whites. © 2000 Cancer Research Campaign

Keywords: oestrogen; androstenedione; Japanese-American; breast cancer

Until recently women in Japan were at very low risk of breast cancer (Ursin et al, 1994), particularly in the post-menopausal period when age-specific breast cancer rates remained essentially constant in contrast to the rates in the USA which continue to steadily increase in the post-menopausal period (Pike et al, 1983). Studies of plasma oestrogen concentrations in 'traditional' Asians (living in Asia) compared with Whites have found lower concentrations in the Asians (Goldin et al, 1986; Key et al, 1990; Shimizu et al, 1990). In particular, a study of post-menopausal Japanese women in Miyagi and non-Latina White women in Southern California found a 32% lower level of plasma oestrone (E1) and a 27% lower level of plasma oestradiol (E2) in the Japanese women (Shimizu et al, 1990).

Breast cancer incidence rates in Japanese-American women now approach those of non-Latina White women (Ziegler et al, 1993). We therefore investigated whether post-menopausal plasma oestrogen and androstenedione (A; precursor of E1) levels in Japanese-American women were accordingly similar to those in (non-Latina) White women. The main comparison group was White women, as this group had been used as the comparison group in previous studies. We also included African-American women and Latina women to further our understanding of possible ethnic differences in estrogen metabolism.

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Correspondence to: NM Probst-Hensch, Institute of Social and Preventive Medicine, Steinengraben 49, CH-4051 Basel, Switzerland

SUBJECTS AND METHODS

Subjects

Subjects are part of a multi-ethnic cohort with an emphasis on studying diet and lifestyle characteristics in the aetiology of cancer. Details of this study are described elsewhere (Kolonel et al, 1999). The cohort included 215 251 subjects aged 40–75 years from Hawaii and Los Angeles county. These subjects had responded to a questionnaire mailed between 1993 and 1996. The response rates to the questionnaire were 25.5% in African-Americans, 51.3% in Japanese-Americans, 21.3% in Latinas and 47.0% in Whites. The distributions of educational level and marital status of the cohort broadly resemble those reported by the US Census.

Blood was collected from a random sample of healthy cohort members after receipt of informed consent. Participation in the blood collection phase has been over 70% in all ethnic groups. Eligible controls for this analysis included women who self-reported no history of cancer and in addition must either have experienced a natural menopause, or had both ovaries removed, or had a simple hysterectomy and be at least 55 years of age. Women who reported any hormone use in the 2 weeks before the blood draw were excluded. Sixty-six African-Americans, 30 Japanese-Americans, 58 Latinas and 39 Whites were included in the study. Characteristics of these subjects are described in Table 1.

Laboratory methods

Plasma aliquots from study subjects were stored in liquid nitrogen until analysis. Plasma levels of A, E1 and E2 were measured by radioimmunoassays previously validated in our laboratory

Table 1 Characteristics of the study subjects by racial/ethnic group

Variable	Japanese-Americans	Whites	African-Americans	Latinas
No. subjects	30.0	39.0	66.0	58.0
Mean age, years	67.2	67.9	63.6	64.8
Mean height, cm	153.0	159.0	164.0	159.0
Mean weight, kg	54.6	67.3	79.0	71.2
Mean BMI, kg m^{-2}	23.3	26.7	29.4	28.2
Nulliparous, %	6.9	5.1	4.5	7.0
Median age at first birth, years	26.7	26.0	22.4	24.0
Median age at menarche, years	13.3	13.0	13.2	13.1
Bilateral oophorectomy, %	3.3	5.1	15.2	10.4

Table 2 Geometric mean plasma hormone levels by racial/ethnic group[a]

Hormone	Japanese-Americans	Whites	African-Americans	Latinas
Androstenedione (A)				
Age-adjusted	417	330	380	319
	(336–517)	(273–399)	(328–439)	(273–371)
Estrone (E1)				
Age-adjusted	34	28	35	31
	(29–39)	(24–32)	(31–39)	(28–35)
Age- and BMI-adjusted	37	28	34	31
	(32–43)	(25–32)	(30–37)	(27–34)
Age-, BMI- and A-adjusted	36	28	33	31
	(31–41)	(25–32)	(30–37)	(28–35)
Oestradiol (E2)				
Age-adjusted	15	16	17	16
	(14–17)	(15–17)	(16–18)	(15–17)
Age- and BMI-adjusted	16	16	16	16
	(15–18)	(15–17)	(15–17)	(15–17)
Age-, BMI- and A-adjusted	16	16	16	16
	(15–18)	(15–17)	(15–17)	(15–17)

[a]All values are given in pg ml^{-1}. The associated 95% confidence intervals are given in parentheses.

(Goebelsmann et al, 1973, 1979; Stanczyk et al, 1988; Cassidenti et al, 1992). Prior to quantification, the hormones were first extracted with hexane:ethyl acetate (3:2) and then separated from interfering metabolites by use of Celite column partition chromatography. The assays were each completed in a single run utilizing appropriate quality control samples. The interassay coefficients of variation for A, E1 and E2 were at low levels: 12.2%, 14.5%, 16.3%; at medium levels 8.0%, 8.2%, 8.4%; and at high levels 12.7%, 12.7%, 7.3%.

Statistical analysis

Statistical analysis was performed on logarithmically transformed values, and geometric mean values are presented. The analysis of covariance (ANCOVA) method was used to assess the impact of ethnicity on hormone concentrations while adjusting for age, body mass index (BMI; weight height^{-2}; adjustment for weight or weight/height had similar effects), and, in the case of E1 and E2 analysis, for A. Adjustment for BMI and age were made as continous variables; adjustment for these factors as categorical variables gave similar results. Age was adjusted for as it has previously been reported to be associated with hormone levels (Madigan et al, 1998). Similar results were obtained, though, in the absence of age adjustment. Confounding by oophorectomy, parity, age at first birth, age at menarche, as well as age at and type of menopause, was not observed for any hormone measurement as judged from entering these variables into the ANCOVA models as categorical variables.

Ninety-five per cent confidence intervals, as presented in Table 2, are based on standard errors for ethnic-specific geometric means derived from the ANCOVA models. Two-sided *P*-values presented for the comparison between Japanese-American and White women are based on ANCOVA models only including Japanese-American and White women. Calculations were performed using the PROC GLM procedure for analysis of covariance in the SAS statistical software system (SAS Institute, Cary, NC, USA).

RESULTS

Age-adjusted geometric mean A levels were highest in Japanese-American women (417 pg ml^{-1}), followed by African-Americans, Whites and Latinas (Table 2). These results were not confounded by ethnic differences in BMI or weight. The higher level in Japanese-Americans compared to White women was not statistically significant ($P = 0.08$).

The high Japanese-American plasma A levels were reflected in their high age-adjusted geometric mean plasma E1 level (34 pg ml^{-1}), only slightly lower than that of the much heavier African-American women (35 pg ml^{-1}), and higher than that of Latina (31 pg ml^{-1}) and White women (28 pg ml^{-1}). The higher level in Japanese-American compared to White women was not statistically significant ($P = 0.13$). After adjustment for ethnic

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group, the effect of BMI on plasma E1 levels was an increase in $\log_e$ (E1, pg ml^{-1}) of 0.023 per 1 kg m^{-2} increase in BMI. After adjustment for BMI, the Japanese-American women had the highest geometric mean E1 levels (37 pg ml^{-1}), followed by African-American women, Latinas, and Whites. The higher level in Japanese-American compared to White women became statistically significant after BMI adjustment ($P = 0.05$). The ethnic-specific differences were diminished slightly after adjustment for A levels in addition to BMI.

The age-adjusted plasma E2 concentrations were very similar in the different ethnic groups.

DISCUSSION

The low oestrogen levels of post-menopausal women living a traditional lifestyle in Japan (Shimizu et al, 1990) were not observed in the Japanese-American women we studied, most of whom (27 of 30) were born in the USA. Geometric mean plasma E1 levels were in fact highest in Japanese-American women, and their geometric mean plasma E2 levels were very close to those of Whites. An increase in blood oestrogen levels in Japanese-American women may provide an explanation for the increase in incidence of breast cancer in Japanese-American women compared to rates in Japan, and, in particular, to the very low rates seen in Japan 30 years ago. The shift in the distribution of menstrual and reproductive factors in Asian-American women towards that in US Whites did not explain much of the increase in breast cancer incidence in Asian-American women (Wu et al, 1996). Causes for the increase in blood estrogen levels in Japanese women living in the USA remain to be elucidated.

Weight and/or obesity are important determinants of plasma oestrogen levels (Potischman et al, 1996; Thomas et al, 1997), as well as of breast cancer risk (Hunter and Willett, 1993; Huang et al, 1997), possibly mediated in part by the increasing extra-glandular aromatization of A to E1 with increasing weight (MacDonald et al, 1978; Simpson et al, 1994). However Japanese-American women in our study, although some 10 kg heavier than 'traditional' post-menopausal women in Japan (Hoel et al, 1983), are still considerably lighter than other American women. In this study they had a 13% lower BMI than Whites. Part of the explanation for their higher E1 levels are the unexpected much higher A levels in Japanese-American women. Genetic variation in the cytochrome P450c17α gene (*CYP17*) has been associated with blood oestrogen levels (Feigelson et al, 1998; Haiman et al, 1999) and may have a role in these high A levels. Ethnic variation in the conversion of A to E1, possibly due to genetic variation in the aromatase gene (Probst-Hensch et al, 1999; Siegelman-Danieli and Buetow, 1999) may further contribute to high E1 levels in Japanese-American women, given that ethnic differences in E1 levels remained after adjustment for A.

Little is known about environmental determinants of endogenous oestrogen and A levels. Some epidemiological evidence found blood oestrogen levels to be positively associated with alcohol intake (Madigan et al, 1998), but Japanese-American women in our cohort consumed much less alcohol than White women (Kolonel et al, 1999). A recent meta-analysis of dietary fat intervention studies found a positive association between dietary fat intake and postmenopausal serum E2 levels (Wu et al, 1999). Yet, Japanese-American women in the multiethnic cohort had the lowest proportion of calories from fat (Kolonel et al, 1999). The effect of soy isoflavones and of soymilk on blood oestrogen levels was investigated in experimental studies (Nagata et al, 1998; Duncan et al, 1999). Results of these studies are only weakly suggestive of a negative association between soy intake and blood oestrogen levels. Soy intake in the Japanese-American women in this study, albeit lower than in Asian women living a traditional lifestyle, was higher than in women of other ethnic backgrounds (Kolonel et al, 1999).

The order of postmenopausal oestrogen and A levels in different ethnic groups did not correlate with the order of increase in the average annual incidence of breast cancer from age 50 to age 70, which was 100% for Latinas, 85% for Whites, 58% for African-Americans and 11% in Japanese-Americans in Los Angeles County between 1988 and 1992 (Parkin et al, 1997). Future studies need to assess more recent changes in age-specific breast cancer rates in different ethnic groups and must investigate the role of genetic and environmental factors in determining ethnic differences in blood oestrogen and A levels. We will be able to address a number of these issues as data accumulate in the Multiethnic Cohort.

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