Plasma Hormone Levels in Different Ethnic Populations of Women

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SUMMARY

It has been suggested that the urinary hormone profile is subject to environmental changes, such as urbanization and Westernization, and that the composition of the hormones can be used as a discriminate in determining the patient at risk for breast cancer.

In this study, a comparison of the plasma hormone levels in Bantu and Japanese women, low-risk populations, and Caucasian women, a high-risk population, showed a higher level of 17β-estradiol in prepubertal girls and young Bantu and Japanese women. The higher estrogen level in the Bantu was evident in the early luteal and late follicular phases of the menstrual cycle. The difference in the dehydroepiandrosterone and testosterone levels in Bantu young women and prepubertal girls, together with the higher estrogen levels in prepubertal Bantu girls, suggests differences in adrenal activity between Bantu and Caucasian women. A fall in the plasma androstenedione was evident in postmenopausal Bantu and Japanese women but not Caucasian women.

Data suggest that the hormone profile is different among the 3 ethnic groups in both the pre- and postmenopausal patients. Since the daily life-style of the women is comparable, it is suggested that the composition of the hormone profile is partially dependent on dietary factors.

INTRODUCTION

Although the incidence of breast cancer varies markedly in different populations and is affected by environmental factors (43), no comparative studies of the plasma hormone profiles or dietary habits of different populations of healthy women at risk for breast cancer are available.

Many studies have reported the plasma hormone levels in the umbilical cord blood (35, 39), in prepubertal girls (17, 22), and in pre- (28) and postmenopausal (24) healthy Caucasian women, but few comparative studies of the hormone profiles of different races are available. Saxena et al. (40) reported the menstrual pattern of LH, estradiol, and progesterone secretion to be similar in Caucasian and Thai women, whereas comparable levels of plasma testosterone were found in Japanese and Occidental women (25). Kuo

maoka et al. (27) in a preliminary study reported comparable levels of plasma estradiol in the luteal phase of premature Japanese and British women.

However, in these studies, little detail is available as to the time or the day of the menstrual cycle or to the matching age of the subjects (25, 27, 35).

Urinary analysis of androgens, androsterone, ET, and estrogens, estradiol, estrone, and estriol of Asians, Africans, and Occidentals further suggests differences in hormone metabolism between races (7, 30). Such differences are more evident in young menstruating women. Although such differences may be partly genetic, changes in the urinary estrogens on migration or urinary differences between rural and urban populations (26) suggest that hormone metabolism is also partly controlled by environmental factors, such as diet (12).

This investigation reports a comparison of the hormone profiles of 2 populations, Bantu and North American Caucasian women, whose life-style and diet are markedly different. Analysis of the hormone profiles in healthy premenopausal Japanese women and in healthy postmenopausal women is also reported.

MATERIALS AND METHODS

Patient Selection and Blood Sampling. A sample of umbilical venous cord blood was taken before severance. Healthy prepubertal 9-year-old school girls, without physical signs of sexual development and healthy nonobese young women, nurses or nursing aides between 20 and 30 years of age with normal 28-day menstrual cycles were selected. Women between 2 and 5 years postmenopause, free of overt signs of endocrine abnormalities, were selected. Postmenopausal women with any history of diabetes, thyroid, hypertension, or coronary disease were excluded.

Blood was taken between 9 and 10 a.m. For prepubertal girls, 2 blood samples were obtained on separate visits. Two blood samples taken on the 20th day of 2 successive menstrual cycles were obtained from 20- to 30-year-old menstruating women. Blood was also sampled on alternate days during the menstrual cycle of healthy volunteers, whereas in several cases 2 complete menstrual cycles were obtained from the same subject.

Peripheral blood was obtained from an antecubital vein using a heparinized syringe, whereas blood from the umbilical cord was obtained under free circulation before severance. The plasma was separated immediately by centrifuga-

1 This work was supported by National Cancer Institute Grant CA-012376.
2 To whom requests for reprints should be addressed, at the American Health Foundation, Dana Road, Valhalla, N. Y. 10595.
3 The abbreviations used are: LH, luteinizing hormone; ET, etiocholanolone; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone.

Received November 14, 1975; accepted March 23, 1976.
tion at 4° and frozen at -20°. The samples from Cape Town, Montreal, and Tokyo were flown in a frozen state to our laboratory.

**Hormone Samples.** All samples were run in duplicate except the estrogen determinations which were run in quadruplicate using duplicate assays at 2 dilutions. Estradiol and estrone were separated on Sephadex LH-20 columns according to the method of Hertogh (19) and were assayed by the cytosol protein binding method of Nagai and Longcope (36). The sensitivity of the assay was 5 pg/ml with an interassay variation of less than 5% between 4 and 300 pg and an intraassay variation of 5%. Recovery of estradiol was 84 to 87% and that of estrone was 95%.

Androstenedione, DHEA, and testosterone were also separated on Sephadex LH-20 and assayed by radioimmunoassays according to the method of Furuyoma et al. (16) and Chen et al. (10). Within the 10- to 150-pg range of the standard curves, the variation between assays was less than 5%, with recovery of the 3 androgens greater than 98%.

LH and FSH were determined by the double antibody radioimmunoassay of Midgley (33, 34). Purified LH, FSH, and antibodies were obtained from the Hormone Distribution Division, Endocrinology Section of the National Institute of Arthritic and Metabolic Diseases, Bethesda, Md. All solvents were of analytical grade, whereas the diethyl ether was further purified by redistillation. All glassware was washed with acid and rinsed thoroughly with deionized distilled water.

**RESULTS**

In the umbilical vein of Bantu infants, there was a significantly higher DHEA content and higher ratio of DHEA to androstenedione. Comparable levels of estrogens were present, but the level of testosterone was higher in Bantu than in Caucasian cord blood (Table 1).

In 9-year-old prepubertal Bantu girls, the estradiol level was significantly higher, whereas the estrone levels were similar to those in Caucasian girls. The level of androstenedione and DHEA was lower in 9-year-old children than in cord blood, and the testosterone content was markedly lower in Caucasian than in Bantu girls (Table 1).

The plasma estradiol increased in both groups during puberty, but the estradiol level continued to be significantly higher in young, menstruating Bantu women. Little change occurred in the estrone level during puberty in either group. The estradiol level was also significantly higher in young Japanese as compared with Caucasian women (Table 2).

Since diurnal and cyclic fluctuations occur in the plasma hormones in young women, sampling was carried out under standardized conditions, between 9 and 10 a.m. on the 20th day of 2 menstrual cycles to increase the reliability of the data presented. For example, levels of estradiol and androstenedione varied less than 10% between menstrual cycles in individual subjects in this study, whereas the difference in the hormone levels between samplings obtained from prepubertal girls with the exception of testosterone was less than 5%.

A marked increase occurred in the testosterone, androstenedione, and DHEA during puberty, with a significantly greater increase in DHEA in Bantu women. The DHEA levels in Japanese and Caucasian women were similar, whereas the androstenedione levels tended to be higher in the former. Although the estradiol/testosterone ratio in young Caucasian women was comparable to that reported by Gupta et al. (17), both the Bantu and Japanese women had a higher estradiol/testosterone ratio, which increased during puberty in Bantu (0.44/0.70) but decreased in Caucasians (0.66/0.52).

<table>
<thead>
<tr>
<th>Androgen and estrogen in the umbilical cord plasma in female offspring and in 9-year-old girls</th>
<th>Estradiol</th>
<th>Estrone</th>
<th>Androstenedione</th>
<th>DHEA</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bantu (28)</td>
<td>7.8 ± 1.3</td>
<td>13.6 ± 1.6</td>
<td>584 ± 32</td>
<td>714 ± 51</td>
<td>156 ± 13</td>
</tr>
<tr>
<td>Caucasian (30)</td>
<td>9.1 ± 1.2</td>
<td>17.0 ± 1.7</td>
<td>619 ± 33</td>
<td>419 ± 24</td>
<td>120 ± 7 (49)</td>
</tr>
<tr>
<td>9-year-old girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bantu (94)</td>
<td>9.0 ± 0.3</td>
<td>25.2 ± 0.9</td>
<td>157 ± 6.4 (73)</td>
<td>156 ± 10 (73)</td>
<td>16.8 ± 0.9</td>
</tr>
<tr>
<td>Caucasian (20)</td>
<td>5.7 ± 0.7</td>
<td>24.5 ± 3.1</td>
<td>194 ± 20</td>
<td>151 ± 16</td>
<td>9.6 ± 2.4</td>
</tr>
</tbody>
</table>

* Result expressed as ng/100 ml plasma.
* Number of subjects given in parentheses.
* Mean ± S.E.
* p < 0.01.
* p < 0.05.

<table>
<thead>
<tr>
<th>Estrogen and androgen levels in young menstruating Bantu, Caucasian, and Japanese women</th>
<th>Estradiol</th>
<th>Estrone</th>
<th>Testosterone</th>
<th>DHEA</th>
<th>Androstenedione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bantu (83)</td>
<td>30.8 ± 1.9</td>
<td>29.8 ± 1.4</td>
<td>43.8 ± 1.8</td>
<td>452 ± 26</td>
<td>282 ± 11</td>
</tr>
<tr>
<td>Caucasian (21)</td>
<td>23.8 ± 1.0</td>
<td>24.6 ± 2.5</td>
<td>45.4 ± 3.5</td>
<td>352 ± 25</td>
<td>285 ± 22</td>
</tr>
<tr>
<td>Japanese (12)</td>
<td>29.8 ± 1.9</td>
<td>30.4 ± 3.3</td>
<td>49.0 ± 5.1</td>
<td>294 ± 42</td>
<td>358 ± 44</td>
</tr>
</tbody>
</table>

* Results given as ng per 100 ml plasma.
* Number of subjects given in parentheses.
* Mean ± S.E.
* p < 0.01; significantly different from Caucasians.
Comparison of the estradiol content in Bantu and Caucasian women sampled on alternate days during the menstrual cycle suggested that the Bantu women tended to maintain a higher estradiol level in the early follicular and late luteal phases of the cycle (Chart 1). No cyclic changes in the androstenedione or DHEA were evident throughout the menstrual cycle.

No significant difference was evident between the LH and FSH in the 3 groups of young women or between the prepubertal Bantu and Caucasian girls (Table 3). In the postmenopausal women, compared with the premenopausal women from the 3 ethnic groups, both the estradiol and androstenedione levels were reduced, whereas the LH and FSH were increased (Table 4). Interestingly, the androstenedione levels were significantly lower in the Bantu and Japanese versus the Caucasian women.

DISCUSSION

Epidemiological evidence suggests that environmental factors, such as life-style (14) and/or dietary habits (37), can alter the incidence of breast cancer and that diets, especially those with a high animal protein content (15, 42), can initiate earlier menarche, the latter factor also being associated with an increased risk of breast cancer. Furthermore, evidence is available that diet can alter the release of gonadotrophins (3, 6) and adrenal activity (13, 18, 41).

This study was undertaken as part of a program to determine why higher rates of breast cancer occur in Caucasian as compared to Bantu and Japanese women and why this disease is increasing in young Caucasian women (38).

In regard to the socioeconomic differences of the urban Bantu and Caucasian populations, a marked difference is evident in their dietary patterns and habits. Nurses and nursing aides from the different populations were selected in order to obtain comparable life-styles, while subjects were not taking or had taken contraceptives. With the exception of 5 Caucasians the subjects had been pregnant at least once but were not presently pregnant or lactating. The Bantu maintain a diet high in carbohydrate predominantly with vegetable protein and a low fat content, the latter being derived mainly from highly unsaturated sunflower oil (Table 5; Ref. 29). Urban Japanese, although consuming the same percentage of the daily calories from fat as the Bantu, consume 32% of their total protein as animal protein and 70% of their carbohydrate as rice (20).

Although the levels of estrogens in the umbilical cord of Bantu and Caucasian neonates in this study are similar, the higher level of DHEA and testosterone suggests an increased biosynthesis of DHEA in the fetal adrenals in late pregnancy (11) and conversion of DHEA to testosterone (5) in the Bantu. To what extent these differences are due to maternal nutrition altering the hormone production of the fetal adrenals or liver aromatization of androgens is unclear. The significance of the higher levels of androstenedione in both races at birth than in prepubertal children, previously reported by Mizuno et al. (35), is unknown.

A difference in adrenal function and interconversion of androgens in prepubertal Bantu girls is suggested by the higher estradiol and testosterone levels. Comparable but more marked changes in the plasma hormones, such as

![Chart 1. Plasma 17β-estradiol in 6 healthy Bantu (---) and 6 Caucasian women (——) during the menstrual cycle. Blood samples were taken every 2 days. Vertical bars, mean ± S.E.](image-url)

### Table 3

<table>
<thead>
<tr>
<th>Gonadotrophin levels in prepubertal girls and in Bantu, Caucasian, and Japanese women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotrophin levels (mIU/ml)</td>
</tr>
<tr>
<td>9-yr-old girls</td>
</tr>
<tr>
<td>Caucasian (20)</td>
</tr>
<tr>
<td>LH</td>
</tr>
<tr>
<td>FSH</td>
</tr>
</tbody>
</table>

* Mean ± S.E.

### Table 4

<table>
<thead>
<tr>
<th>The plasma estrogen, androgen, and gonadotrophin levels in Bantu, Japanese, and Caucasian postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (ng/100 ml)</td>
</tr>
<tr>
<td>Bantu (27)</td>
</tr>
<tr>
<td>Japanese (16)</td>
</tr>
<tr>
<td>Caucasian (27)</td>
</tr>
</tbody>
</table>

* Number of subjects given in parentheses.

* Significantly different from Caucasian level; p < 0.01.
increases in plasma estrogens (23) and testosterone and delayed menarche, occur in girls with congenital adrenal hyperplasia (4). That the higher level of estradiol in Bantu girls arises from the adrenals by increased excretion of androgen precursors and/or peripheral conversion is indicated since menarche is reached 1 to 2 years later in Bantu as compared with Caucasian girls (31) and as the plasma estrogens are suppressed by dexamethasone in prepubertal children (8). Furthermore, comparison of the androstenedione/estradiol ratio in prepubertal girls and young women (17/9) implies an adrenal origin of the plasma estrogens (2) in these prepubertal girls.

The higher level of estrogens in the Bantu and Japanese found on the 20th day of the menstrual cycle and which is evident during the early follicular and luteal phases may imply either a different ovarian production, delayed clearance, or a higher secretion from the adrenals especially in the luteal phase (1).

Judd et al. (24) have reported estradiol and androgens to be present in the ovarian vein of postmenopausal women. In this study low plasma levels of estradiol were present in the postmenopausal women. The marked fall in androstenedione in Bantu and Japanese postmenopausal women versus Caucasian women could suggest that a greater proportion of the plasma androstenedione is of ovarian origin in the Bantu and Japanese women.

Concerning the relative changes in the plasma and urinary hormone profiles, comparative studies show an increase in the urinary androsterone and ET in Japanese women on urbanization (26). Japanese migrants to Hawaii show an increased excretion of estradiol and estrone (12), whereas Caucasians have been reported to excrete more androsterone and ET than do Japanese women (Table 6). It is evident, therefore, that urbanization and Westernization may produce changes in the hormone excretion in women. Furthermore, Metcalf (32) reported that loss of ovarian function diminished the excretion of androsterone and ET, whereas increased adrenal activity was accompanied by a rise in androsterone and ET excretion. The fact that young Bantu and Japanese women have a higher plasma estrogen content than Caucasians yet excrete less estrogens than Caucasian women suggests differences in metabolism or rates of clearance, whereas the higher rate of excretion of androsterone and ET in menopausal Caucasian versus Japanese women may be related to the significantly lower plasma level of androstenedione in the latter.

To what extent the differences in androgen and estrogen levels in the Bantu and Caucasian women are associated with dietary factors can only be proved by dietary modification and by studies in progress to correlate dietary and hormonal factors in rural and urban populations with early and late menarche. The smaller stature and later menarche of Bantu girls, however, would substantiate the fact that diet can alter stature as well as the age of menarche (21) and that their low incidence of breast cancer may be associated with their low intake of fat and animal protein (9).

Table 5

<table>
<thead>
<tr>
<th>Age of menarche</th>
<th>Fat (% calories)</th>
<th>Carbohydrate (% calories)</th>
<th>Protein (% calories)</th>
<th>Daily calorie intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bantu.a</td>
<td>14.9</td>
<td>19.7</td>
<td>68.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.8</td>
<td>34.0</td>
<td>54.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Japanese.b</td>
<td>13.4</td>
<td>18.0</td>
<td>68.5</td>
<td>13.5</td>
</tr>
</tbody>
</table>

a Data from Louw and Du Plessis (29).

b Data from Insull et al. (20).

Table 6

| Urinary levels of androgens and estrogens in premenopausal Caucasian and Japanese women |
|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Japanese                               | Japan                                  | Caucasian                               |
| Rural                                  | Urban                                  | (urban)                                |
| Androsterone (A)                       | 0.77a                                  | 1.03a 1.2a                              | 2.4a                                  |
| Etocholanolone (B)                     | 1.13                                   | 1.56 1.0                                | 2.2                                   |
| Ratio A/B                              | 0.68                                   | 0.68 1.2                                | 1.09                                  |
| 17 β-estradiol (E₂)                    | 2.5a                                   | 3.3a                                    | 3.4a/3.7a                             |
| Estone (E₁)                            | 5.3                                    | 6.1                                     | 7.0/8.0                               |
| Estriol (E₃)                           | 8.2                                    | 9.6                                     | 8.3/7.1                               |
| E₃/E₁ + E₂                             | 1.27                                   | 0.76                                    | 0.83/0.62                             |

a Japanese women, 58 urban; 63 rural. Age adjusted to 35 years. Results given as mg/24 hr. Data from Kodama et al. (26).

b Values taken from regression plot for subjects at 30 years of age. Results given as mg/24 hr. Data from Bulbrook et al. (7).

c Follicular phase, 18 subjects, 15 to 39 years of age. Results given as mg/liter. Data from MacMahon et al. (30).

d Follicular phase, 42 Japanese, 37 Caucasian, 20 to 24 years of age. Results given as mg/liter. Data from Dickinson et al. (12).
ACKNOWLEDGMENTS

We thank R. McNeil and E. Regan for patient care and L. Garbaczewski, A. De Pace, H. Kunnar, and M. Gardere for their skilled assistance.

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