Plasma Hormone Profiles in Populations at Different Risk for Breast Cancer

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SUMMARY

Evidence suggests that the reliability of urinary androgens or estrogens as prognostic discriminants for breast cancer may vary with different populations and may bear little relation to changes in plasma hormone levels. In this study the plasma estradiol level was significantly lower in Bantu, but not in Caucasian, women with breast cancer, while the proportion of plasma androstenedione to dehydroepiandrosterone increased in Bantu patients. These changes in the plasma hormone profile in Bantu patients, a low-risk population for breast cancer, imply a change in ovarian and/or adrenal activity. Lack of similar hormone changes in Caucasian patients may be due to the initial differences in the hormone profile between healthy Caucasian and Bantu women and to the different environmental factors that promote the breast disease in Western women.

INTRODUCTION

An association of changes in hormone metabolism and the development of breast cancer have been suggested by epidemiological data where early menarche (30), pregnancy, or surgical castration (11) decrease, and late pregnancy (27), menopause (34), or ovarian failure (12) increase the incidence of breast disease.

Concerning the relation of hormones to breast cancer, a large-scale prospective study of premenopausal Caucasian women reported a change in the urinary ratio of androsterone to etiocholanolone in women subsequently developing breast disease (16). Changes in the excretion of estrogens have also been reported in premenopausal breast cancer patients (3, 33). As urinary hormones may be altered both by urbanization (23) and Westernization (10) and as migratory studies of Kobei Nisei clearly show the age of menarche, a risk factor for breast cancer, to be modulated by environmental factors (22), it is of interest whether the development of breast disease in low- and high-risk populations shows similar changes in the hormone profile and is related to the preexisting hormone levels in healthy women.

The decreased risk of breast cancer in populations with a late menarche or an early pregnancy implies that the hormone levels established at puberty and during the early reproductive years are of prime importance. This study reports the plasma androgen, estrogen, and gonadotropin levels in young premenopausal Bantu women at low risk for breast cancer in comparison with a high-risk population of Caucasian women.

MATERIALS AND METHODS

Patients consisted of young premenopausal Bantu and Caucasian women under 30 years of age with locally advanced breast cancer, but without associated diseases such as diabetes or thyroid diseases, admitted to the Groote Schuur Hospital, Cape Town, South Africa. Blood was obtained prior to surgery on the 20 to 22nd day of the menstrual cycle.

Healthy young women between 20 and 30 years of age with a normal 28-day menstrual cycle and without any history of diabetes, thyroid, or cardiovascular disease were selected. Blood was obtained between 9 and 10 a.m. on the 20th day of 2 or more menstrual cycles from the same individual and the plasma was separated by centrifugation at 4°. The plasma was then stored at −20° and shipped airmail in freezing containers to this laboratory.

Plasma estradiol and estrone were separated on Sephadex LH-20 columns while the estrogen determinations were made in quadrupled, duplicate samples at 2 dilutions as described previously (21). The sensitivity of the assay was 5 pg/ml with an interassay variation of less than 5% between 4 to 300 pg and an intraassay variation of 5%. Recovery of estradiol was 84 to 87% and of estrone was 95%. Plasma androstenedione DHEA2 and testosterone were separated on Sephadex LH-20 columns and assayed by radioimmunoassays, according to the method of Chen et al. (6) and of Furoyama et al. (14), respectively. Recovery of the 3 androgens was greater than 98%; variation between assays was less than 5%. LH and FSH levels were determined by the method of Midgley (25, 26).

RESULTS

As shown in Table 1, the plasma estradiol and estrone levels were significantly decreased in young Bantu women with breast cancer, while the estrogen levels were unaltered in Caucasian patients. The LH content tended to increase in

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2 The abbreviations used are: DHEA, dehydroepiandrosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.
Bantu and Caucasian patients. An increase in the plasma level of FSH was evident in Caucasian and Bantu patients; the latter being increased significantly.

Comparison of the plasma androgen levels showed a significant increase in androstenedione and a decrease in DHEA in Bantu, but not in Caucasian, patients. In Bantu and Caucasian women with breast cancer, no significant change occurred in the plasma testosterone levels.

DISCUSSION

Epidemiological data (17, 35) suggest that dietary factors may initiate or promote the development of breast cancer, but it is unclear whether dietary factors can directly affect adrenal and/or ovarian activity leading to a hormone balance-modulating ovarian dysfunction or neoplastic growth in mammary tissue. Adrenal function, as reflected by excretion of androsterone and etiocholanolone, is affected by food deprivation, hirsutism, and absence of functional ovaries (24). Furthermore, urbanization of Japanese women also results in an increased excretion of etiocholanolone and androsterone (23).

In regard to the plasma hormone levels in breast cancer patients, only a few preliminary studies are available (4, 29, 32). Whether changes in hormone levels are related to the initiation of the disease or are associated with the disease is often unclear (13). Specific changes may be evident in young but not menopausal woman and may vary with the stage of the disease. Previous reports of lower plasma levels of DHEA (15, 29) and DHEA sulfate (4, 5) and of decreased conversion of pregnenolone to DHEA (7) imply a decreased adrenal synthesis in some breast cancer patients. Furthermore, Deshpande et al. (8), using in vivo perfusion of human adrenals, reported a correlation between the biosynthesis of DHEA and its urinary excretion. The fall in plasma DHEA and increase in androstenedione in premenopausal Bantu patients with breast cancer suggest either an increased conversion to androstenedione, decreased synthesis (7), and/or more rapid excretion may occur (29, 33).

Results of in vitro studies by Deshpande and Yates (9) show that the interconversion of DHEA to androstenedione by the 3-hydroxysteroid dehydrogenase and the 3-ketosteroid 5',4-isomerase can be inhibited by physiological levels of estradiol and estrone. Accordingly, the decrease in plasma estradiol and estrone in Bantu patients may thus permit an increase of enzymatic conversion of DHEA to androstenedione. The effect of estrogens on the DHEA-androstenedione metabolism has been recently supported by Abraham and Maroulis (2) who reported that estrogen administered to postmenopausal women elevated serum DHEA but did not alter the level of androstenedione.

Although about 60% of the plasma androstenedione in the luteal phase is of ovarian origin (1), no evidence is available that an increased ovarian secretion of androstenedione occurs in breast cancer patients. The decrease in urinary androgens in precancer Caucasian cases (16) and in young patients (4) would argue against such a change.

As the estrogen level can control the level of release of pituitary hormones (36), elevated LH and FSH levels in these

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Plasma levels of estrogens and gonadotropins in healthy young women and women with breast cancer</th>
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</thead>
<tbody>
<tr>
<td>Units</td>
<td>Bantu (Healthy subjects (83))</td>
</tr>
<tr>
<td>Estradiol ng/100 ml</td>
<td>30.8 ± 1.3(^a)</td>
</tr>
<tr>
<td>Estrone ng/100 ml</td>
<td>29.8 ± 1.4</td>
</tr>
<tr>
<td>LH mIU/ml</td>
<td>3.8 ± 0.26</td>
</tr>
<tr>
<td>FSH mIU/ml</td>
<td>4.69 ± 0.26</td>
</tr>
</tbody>
</table>

\(^a\) Number in parentheses, number of subjects or patients per group.
\(^b\) Mean ± S.E.
\(^c\) Significantly reduced in patients, \(p < 0.01\).
\(^d\) Significantly reduced in patients, \(p < 0.05\).
\(^e\) Significantly increased in patients, \(p < 0.05\).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Plasma levels of androgens in healthy young women and young women with breast cancer</th>
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<tbody>
<tr>
<td>Units</td>
<td>Bantu (Healthy subjects (83))</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>282 ± 11(^a)</td>
</tr>
<tr>
<td>DHEA</td>
<td>452 ± 26</td>
</tr>
<tr>
<td>Testosterone</td>
<td>43.8 ± 1.3</td>
</tr>
</tbody>
</table>

\(^a\) Numbers in parentheses, number of subjects or patients per group.
\(^b\) Expressed as ng per 100 ml plasma and given as mean ± S.E.
\(^c\) Significantly increased from healthy subject, \(p < 0.01\).
\(^d\) Significantly decreased from healthy subject, \(p < 0.01\).
patients may reflect the decreased level of plasma estrogen. The lower plasma levels of estradiol in Bantu and also Japanese premenopausal patients (20) may result from a failure to establish the menstrual cycle at puberty or later ovarian dysfunction; a factor associated with breast cancer (31). Comparison of the urinary androgens and estrogens from low and high risk populations, although showing similar changes in healthy women on urbanization and migration, fails to show comparable trends in breast cancer patients (3, 29, 33).

Although urinary estrogens or urinary androsterone and etiocholanolone and DHEA may be discriminant functions in Caucasian (16), Japanese (33), and Bantu women, respectively, it remains to be determined whether a change in ovarian function, in adrenal metabolism, or in ovarian dysfunction, together with altered adrenal metabolism, is associated with the development of breast cancer. In view of the differences in the plasma hormone profile in the Bantu versus Caucasian women and the lower incidence of breast cancer in the former (5:1:19.0/100,000 women; 25 to 35 years of age) (19), evidence would suggest that Bantu women are either protected by genetic factors and/or are not subject to adverse environmental factors as are Western women.

As adrenal activity may be subject to diet control (18, 28) and other environmental factors (24), evidence would suggest that the Bantu diet, which is low in fat and animal protein, may maintain a hormone profile that renders the Bantu women less sensitive to the development of breast disease. Further studies of the dietary composition and plasma hormone profiles of healthy women in different populations and of women with breast cancer are necessary to determine the relation of diet to hormone profile and breast cancer.

ACKNOWLEDGMENTS

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