SUMMARY

The basal plasma concentration of prolactin was determined by radioimmunoassay in Caucasian women at different risk for breast cancer and in three races of women at risk for breast cancer. Samples taken under comparable conditions showed similar basal levels at birth and in prepubertal Bantu and Caucasian girls, or in healthy pre- and postmenopausal Bantu, Caucasian, or Japanese women. Elevated plasma prolactin levels were found in women castrated prior to 35 years of age and in women whose first pregnancy occurred after 35 years. Evidence indicates that the prolactin/estrogen relationship may not be similar in women 35 to 45 years of age as compared to young women and suggests that elevation of serum prolactin per se does not appear to be related to an increased risk of breast cancer. The prolactin level was increased only in Caucasian women with breast cancer. If a high prolactin/estriol ratio increases the susceptibility of the mammary epithelium to neoplastic growth, the lack of changes in prolactin levels in premenopausal Japanese patients and in postmenopausal patients of the three ethnic groups indicates that other factors are involved. Further study of the effects of life-style and diet on the basal level and stimulated release of prolactin is required to resolve the relationship of prolactin to breast cancer.

INTRODUCTION

During the life-span of a woman, high levels of prolactin are found in the amniotic fluid, the umbilical cord (38), and in the serum during pregnancy and lactation. A daily circadian rhythm of prolactin release occurs in both men and women and is present in both pre- and postmenopausal women (30). Prolactin release does not appear to show any consistent relationship with the menstrual cycle (8, 22); the effect of exogenous estrogens on prolactin release is dose dependent (2, 5) and inconsistent (19, 22). Apart from environmental factors such as stress, exercise, and sexual activity, which increase the circulating level of prolactin, changes in prolactin levels have been reported in women with a familial history of breast cancer (11, 17), but the correlation between prolactin and this disease in the general population remains equivocal (5).

In regard to the relationship of prolactin to risk factors for breast cancer, Kwa et al. (17) failed to find any relationship between factors such as age of menarche or 1st pregnancy and the plasma prolactin levels. The relationship of other factors influencing breast cancer such as early castration or late pregnancy or the relationship of perimenopausal symptoms to prolactin changes remains unknown. Furthermore, no comparative studies of basal prolactin levels in healthy women or in women with breast cancer of different races at different risk for breast cancer are available.

This study reports the serum prolactin levels in several groups of healthy, North American Caucasians at different risk for breast cancer and compares prolactin levels in young Caucasian girls and women to those in South African Bantu girls and women. The prolactin level in both pre- and postmenopausal women with breast cancer from the Bantu and Japanese, low-risk populations versus the North American Caucasians, a high-risk population for breast cancer, are also reported.

MATERIALS AND METHODS

Patients. Healthy subjects were free from overt signs of endocrine abnormalities. Nonobese Caucasian women between 35 and 45 years of age were divided into 4 groups: Group 1 consisted of healthy menstruating women; Group 2 consisted of women with perimenopausal symptoms, irregular menses, hot flushes, etc.; Group 3 consisted of women surgically castrated prior to 35 years of age; and Group 4 consisted of women whose 1st pregnancy occurred after 35 years of age but who had not been pregnant during the last year or who were lactating. The young women, nurses or nursing aides, from the 3 ethnic groups, all between 20 and 30 years of age with normal menstrual cycles, and healthy postmenopausal women, at least 2 years postmenopausal and who had had no history of diabetes, thyroid, or coronary heart disease were selected. Patients with locally advanced breast cancer included both pre- and postmenopausal Bantu and Caucasian women admitted to the Groote Schuur Hospital and Japanese women admitted to the Cancer Institute Hospital with locally advanced tumors. None of the patients had received prior hormone therapy or had undergone surgery for at least 8 weeks previously.

Blood Sampling. Venous umbilical cord blood was obtained under free circulation before severance. Blood was drawn in the morning from the antecubital vein of 9-year-old school girls. Since prolactin levels show a circadian rhythm that is dependent on sleep patterns (25), blood samples were always drawn between 9 and 9:30 a.m. In most cases, 2 samples were taken at different visits. Blood was drawn from young Bantu, Caucasian, and Japanese women, 20 to
Prolactin in Women at Risk for Breast Cancer

found; the daily variation was comparable to that reported by McNeilly et al. (23). Comparable plasma prolactin levels were found during the menstrual cycles of Caucasian and Japanese women (Chart 2). The daily mean level of prolactin in 4 Bantu women during their menstrual cycle was \(13.8 \pm 1.2\) ng/ml plasma.

Radioimmunoassay of human prolactin was carried out by the method of Sinha et al. (33), using Lewis HPRL V-L-5 No. 2 (National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Md.), which gives results comparable to those of other radioimmunoassay methods. The interassay reproducibility of the prolactin level in reference to plasma samples was approximately 10%. Precision of the prolactin standard at a concentration of 624 pg and 2.5 ng was 1 and 1.4%, respectively. The lower limit of the sensitivity of the assay was 1.56 ng human prolactin per ml of plasma. The human prolactin (HPRL V-L-5 No. 2) and rabbit antiserum to human prolactin were kindly supplied by the National Institute of Arthritis, Metabolism, and Digestive Diseases. Plasma estradiol and estrone were assayed by a modification of the cytosol-binding protein method of Nagai and Longcope as described previously (14).

RESULTS

The level of prolactin in cord blood from Bantu and Caucasian infants was comparable: Bantu, 28 infants, 153.5 \(\pm 19.1\) ng/ml; Caucasians, 54 infants, 156 \(\pm 11.9\) ng/ml plasma (Mean \(\pm\) S.E.). In 9-year-old Bantu and Caucasian girls the prolactin levels were also similar: Bantu, 102 girls, 10.2 \(\pm 0.8\) ng/ml; Caucasian, 20 girls, 12.9 \(\pm 3.7\) ng/ml plasma. Little increase in prolactin occurred during puberty, resulting in comparable levels in young Bantu, Caucasian, and Japanese women (Chart 1).

To determine the daily variability in healthy menstruating women, samples were taken at 9:00 a.m. from 5 healthy Caucasians 20 to 30 years of age for 5 consecutive days. A mean daily basal value of 20.1 \(\pm 1.6\) ng/ml plasma was found; the daily variation was comparable to that reported by McNeilly et al. (23). Comparable plasma prolactin levels were found during the menstrual cycles of Caucasian and Japanese women (Chart 2). The daily mean level of prolactin in 4 Bantu women during their menstrual cycle was \(13.8 \pm 1.2\) ng/ml plasma.

Chart 1. Plasma prolactin levels in healthy premenopausal Bantu, Caucasian, and Japanese women and in women with breast cancer. —— and ---, mean \(\pm\) S.E.

Chart 2. Daily variation in the plasma prolactin in 8 Caucasian (——) and 5 Japanese (---) women during the menstrual cycle. Results given as mean \(\pm\) S.E.
As shown in Table 1, the plasma prolactin level was elevated in women whose 1st pregnancy occurred after 35 years of age as compared either to women of comparable age or parous women, 20 to 35 years of age. Plasma estradiol levels were similar in both groups of women. Castration prior to 35 years of age caused a significant increase in plasma prolactin and a fall in plasma estradiol. In women with perimenopausal symptoms, the plasma prolactin was reduced, but the estradiol content was unaltered.

As shown in Chart 1, the prolactin level was significantly increased in premenopausal Caucasian (p < 0.01), but not Bantu or Japanese patients. A similar increase (p < 0.05) in plasma prolactin was evident in postmenopausal Caucasian patients. In healthy postmenopausal Bantu, Caucasian, and Japanese women, the prolactin levels were comparable to those in premenopausal women from the 3 ethnic groups (Chart 3). In postmenopausal patients, the prolactin level was higher only in Caucasian patients (Chart 3). In 7 postmenopausal Japanese patients, an increase in the prolactin level occurred after oophorectomy and adrenalectomy (prolactin control: 12 ± 0.7 ng/ml; treated: 23 ± 2.3 ng/ml plasma).

Comparison of the P/E ratio was lower in healthy premenopausal Bantu than in Caucasian and Japanese women and was significantly increased in Bantu and Caucasian patients (Table 2). The P/E ratio increased in healthy postmenopausal as compared to premenopausal women; the lowest ratio occurred in Bantu women. No significant change in the P/E ratio occurred in postmenopausal patients in either population.

**DISCUSSION**

Epidemiological evidence suggests that premature castration before the age of 35 years decreases the risk of breast cancer by 60 to 75% (9, 35), whereas pregnancy after 35 years of age doubles the risk of this disease (31).

In regard to the changes in the plasma hormone profile, it has been suggested, on the basis of mammary tumorigenesis in experimental animals (26), mammary cell development (36), and remission of breast cancer following the control of the release of prolactin (34), that changes in prolactin may be associated with the development of breast cancer.

It is therefore of interest that the plasma prolactin was
increased in women pregnant after 35 years of age and in prematurely castrated women. In the latter, this increase occurred in spite of a lower plasma estradiol level. The latter is of importance since estrogen administration, at least at high levels, increases plasma prolactin (24, 42). Elevation of prolactin, however, does not occur in all women given estrogens (23) and appears to depend on the estrogen administered (30, 42). Estradiol has been reported previously in castrated women (2, 29), and this estrogen may arise in part from peripheral conversion from estrone (20) and from conversion of adrenal androgens (28).

Data suggest, therefore, that other hormones, apart from estrogens, affect the release of prolactin.

Dussault (7) reported that dexamethasone suppression of adrenal activity depressed plasma prolactin, while Seppala and Hirvonen (32) and others (21) have reported raised prolactin levels in women with hirsutism and/or amenorrhea.

In women pregnant after 35 years, the plasma testosterone level was increased (13). This increase is of interest since prolactin may synergize with LH to increase testosterone synthesis (10) and to promote adrenal steroidogenesis (4).

Little is known of the hormone changes in women 35 to 45 years of age. Adamopoulos et al. (1) reported changes in LH levels of perimenopausal women and suggested that as yet unknown changes probably occur in the hypothalamic-ovarian axis in this period prior to menopause.

Studies of Wide et al. (41) further indicate changes in LH and follicular-stimulating hormone in women between 35 and 45 years of age, while Bohnet et al. (3) have suggested a relationship between prolactin levels and LH activity; Stoll (34) has postulated that the sensitivity of the hypothalamic centers falls with age. Elevated levels of LH and follicular-stimulating hormone occur in women with pregnancy after 35 years and in prematurely castrated women, respectively (13). Response of the endocrine system to conception during this period of gonadotrophin increase (i.e., 35 to 45 years of age) and fall in adrenal and ovarian hormones may be different from that occurring after the establishment of the menstrual cycle.

Concerning the relationship of prolactin and breast cancer, Kwa et al. (18) and Henderson et al. (11) have reported that the basal level of prolactin is increased in women from families with a history of breast cancer, although such a change is not evident in the general population.

In regard to the establishment of the release of prolactin, Jacobs et al. (15) reported that the thyrotropin-stimulated prolactin release was modulated by estrogens at puberty, while Vekemans and Robyn (39) reported the nocturnal release to be also affected by estrogens. Since the diurnal release of prolactin in the adult is established at puberty (43) and is related to rapid eye movement-non-rapid eye movement sleep (25), and since diet can alter sleep patterns (27), dietary and hormonal factors at puberty may partly establish the control of the prolactin release.

Higher levels of estradiol reported in daughters of breast cancer patients (11) or altered hormone levels in girls with precocious puberty (16) may increase the susceptibility of mammary epithelial tissue for unbalanced growth.

In this study, the plasma prolactin levels were elevated only in pre- and postmenopausal Caucasian patients. Although social status, stress, and sleep affect the release of prolactin (40), no evidence is available that the Caucasian patients differed from Bantu or Japanese patients with regard to these factors on admission for surgery.

Furthermore, in spite of the fact that factors such as age of menarche and 1st pregnancy differ in the 3 ethnic groups, the recent report of Kwa et al. (17), which failed to find any relationship between prolactin levels and these risk factors, would exclude these differences as an explanation for the changes in Caucasian patients. In this regard, although remission of breast cancer is often related to suppression of prolactin release (34), little evidence is available to suggest that high prolactin level per se is harmful (37).

Chan and Cohen (6) have postulated on the basis of in vivo and in vitro studies of the Huggins dimethylbenz(a)anthracene rat mammary carcinoma model, that a high P/E ratio promotes the development of mammary tumors. The higher P/E ratio in premenopausal but not postmenopausal Bantu and Caucasian patients versus healthy subjects and lack of a similar change in Japanese patients indicate that other factors are involved in these races or that a different control of prolactin release may occur in these patients.

Preliminary evidence suggests that lower plasma prolactin levels occur in vegetarians (12). If the pattern of prolactin release is established by genetic and environmental factors at puberty, and if the subsequent development of breast tissue is related to the hormonal pattern at puberty, further study of the factors controlling prolactin release in young women may give leads to the involvement of prolactin in breast cancer.

REFERENCES


Table 2

<table>
<thead>
<tr>
<th></th>
<th>Healthy Patients</th>
<th>Postmenopausal Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>29.9 ± 3.4 (37)*</td>
<td>52.7 ± 5.3 (23)</td>
</tr>
<tr>
<td>Japanese</td>
<td>24.8 ± 2.9 (12)</td>
<td>46.4 ± 4.3 (16)</td>
</tr>
<tr>
<td>African Bantu</td>
<td>16.8 ± 1.6 (79)</td>
<td>39.2 ± 4.5 (27)*</td>
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</tbody>
</table>

* Numbers in parentheses, number of subjects.

Significantly increased compared to healthy subjects (p < 0.01).

Significantly lower in healthy Bantu versus Caucasian women (p < 0.01).


Prolactin Levels in Populations at Risk for Breast Cancer

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