Twenty-four-Hour Preoperative Endocrine Profiles in Women with Benign and Malignant Breast Disease

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SUMMARY

Mean 24-hr growth hormone, luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations determined preoperatively in 16 women with benign breast masses and 17 patients with breast cancer were similar to those levels found in 25 age- and weight-matched control subjects. Mean 24-hr testosterone levels, however, were significantly elevated in women with breast cancer evaluated in the luteal phase of their cycles and were normal in postmenopausal breast cancer women. In addition, serum thyroid-stimulating hormone, thyroxine, cholesterol, and triglyceride levels were normal in these subjects. Plasma cortisols and urinary 17-hydroxysteroid excretion tended to be higher in both the benign and malignant breast disease group and probably reflected preoperative anxiety. Hence, we have found normal concentrations of a variety of endocrine and other biochemical agents that can stimulate breast tissue growth and/or have been previously reported to be disordered in women with breast cancer.

INTRODUCTION

In recent years there have been conflicting reports of both normal and abnormal concentrations of a variety of peptide and steroid hormones in women with breast cancer. These breast cancer patients were usually evaluated after the breast mass had been removed and, in addition, many subjects had received ablative endocrine and/or chemotheraphy, all of which could significantly modify endocrine secretion (33, 34). Frequently factors such as age, weight, and phase of the menstrual cycle when the patients were studied were not adequately controlled. In addition, most studies evaluated only 1 or a few hormones, and until recently (1, 20) no effort had been made to measure several hormones in the same cancer patient. A variety of peptide and steroid hormones have marked diurnal variation (18), and therefore conclusions about endocrine secretion based on a single fasting sample may not accurately reflect the 24-hr mean hormonal concentration.

In an attempt to determine whether abnormal endocrine secretion is present in patients with benign and malignant breast lesions evaluated prior to surgery, we determined the mean 24-hr serum hormonal concentrations and patterns of endocrine secretion of a variety of peptide and steroid hormones in these women. In addition, we have performed other endocrine and biochemical assays that have been previously reported to be disordered in patients with breast cancer. This study suggests that many of the endocrine and biochemical parameters previously reported as being abnormal in women with breast cancer show no significant deviation from normal when compared with age- and weight-matched control subjects.

MATERIALS AND METHODS

Protocol. For determination of the mean 24-hr concentration of a variety of hormones in patients with breast cancer, 33 women with breast masses were evaluated on the clinical research unit several days prior to breast surgery. Initial study included a history, a physical examination, and routine clinical and endocrine laboratory tests. Patients ate and slept at their usual times, but their activity was restricted to the hospital room and was observed constantly by the nursing staff. No patient was on any form of endocrine medication, and drugs were not given during the study. Blood samples were obtained through an indwelling heparinized scalp vein needle placed in a forearm vein to permit hourly sampling for GH and every-4-hr sampling for the other hormones without repeated venipuncture. The patients were able to sleep throughout the night, and a sleep record was maintained on each patient throughout the 24-hr study period. Serum samples were stored at −20°C until assayed for the various hormones.

Patients. Eight of 12 postmenopausal breast cancer patients had infiltrating ductal carcinomas, and 4 subjects had infiltrating lobular carcinomas. Only 1 subject, a patient with an intraductal carcinoma, had more than 4 lymph nodes that contained metastases. The 5 premenopausal patients with breast cancer had the following pathological diagnoses: 2 subjects had infiltrating ductal carcinomas, 2 patients had infiltrating lobular carcinomas, and 1 subject had a comedocarcinoma. None of these patients had more than 4 axillary nodes with metastases. These 5 patients were evaluated in the luteal phase of their menstrual cycles. Fifty % of the patients with benign disease of the breast

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The abbreviations used are: GH, growth hormone; IACV, interassay coefficient of variation; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone.
had pathologically confirmed benign adenomas, and the other half had cystic disease of the breast. We also evaluated in the Clinical Research Center, 16 premenopausal and 9 postmenopausal women whose ages, heights, and weights (Table 1) were similar to those of the breast mass subjects. Many of these women were nonpaid volunteers who were recruited through the efforts of the Columbus Cancer Clinic. They were studied under the same conditions imposed on the breast mass patients in the Clinical Research Center. A control subject or premenopausal breast mass patient was assigned to the luteal-phase group if she was in the second half of her menstrual cycle and if her serum progesterone levels were compatible with ovulation. Conversely, follicular-phase individuals were, by history and serum progesterone levels, in the first half of their cycles.

**Assays and Statistical Analysis.** Radioimmunoassay of the polypeptide and steroid hormones were performed with the following methods and precision: GH (11) was assayed with an IACV of 10 to 13%; estradiol and progesterone (26) were measured with IACV’s of 6 and 7%, respectively; the testosterone (26) assay had an IACV of 7%; and LH and FSH (31) both had IACV’s of 12 to 15%. The standard for pituitary LH and FSH was the international reference preparation, LER-907. GH standard was obtained from the NIH Pituitary Hormone Program. Plasma triglyceride (6), cholesterol (17), cortisol (19), 24-hr urine for 17-hydroxysteroids (17) and 17-ketosteroids (16) were also assayed in these patients. Radioimmunoassays for serum TSH were performed with the use of the reagent system of Beckman (Fullerton, Calif.), and serum thyroxine was measured with reagents from Nuclear-Medical Laboratories, Inc. (Dallas, Texas).

In tests for differences between groups, a series of 1-way analyses of variance were utilized. When significant differences (p < 0.05) were found by analysis of variance, the post hoc test for differences between means was performed. In addition, height and weight data from all groups were converted to a Quetelet index (weight/height²) which was then subjected to a 1-way analysis of variance (15), and no differences were found.

**RESULTS**

**24-hr Profiles of GH, LH, FSH, Estradiol, Progesterone, and Testosterone in Control Subjects and Patients with Breast Masses.** Serum GH concentrations and the patterns of GH secretion were similar in all patient groups evaluated (Table 2). Although serum GH levels were slightly decreased in the postmenopausal women, this difference was not significant. In addition, the expected sleep-related augmentation of GH secretion (32) occurred at approximately the same time and was of the same magnitude in all patient groups. There was no significant difference in serum LH and FSH concentrations or in patterns of secretion between control subjects and those with breast masses (Table 2). An appropriately elevated concentration of serum gonadotropins was noted in all postmenopausal subjects. Serum concentrations and patterns of secretion of estradiol and progesterone in the patients with breast masses were similar to those in the control groups (Table 2). Mean 24-hr testosterone levels, however, were significantly elevated (p < 0.05) in the breast cancer subjects evaluated in the luteal phase of their cycles (Table 2) and were normal in the postmenopausal breast cancer patients. The serum estradiol levels were appropriate for the menopausal status of the normal females and the pre- and postmenopausal women with breast cancer. The elevated serum progesterone levels in the luteal-phase women appropriately reflected recent ovulatory events (Table 2).

**Adrenal, Thyroid, and Lipid Levels in Control Subjects and Patients with Breast Masses.** Significantly elevated 24-hr urinary 17-hydroxysteroids were found in the luteal-phase benign (p < 0.02) and malignant (p < 0.05) disease subjects (Table 1). A significantly elevated (p < 0.05) 4-pm plasma cortisol level with normal diurnal variation was also found in the postmenopausal breast cancer patients (Table 1). There were no significant differences between groups in the 24-hr urinary 17-ketosteroid levels. The nonsignificant elevation in the urinary 17-ketosteroid level of the benign

<table>
<thead>
<tr>
<th>Phase of menstrual cycle</th>
<th>n</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Wt (kg)</th>
<th>Cortisol (µg/100 ml)</th>
<th>17-Hydroxysteroids (mg/24 hr)</th>
<th>17-Ketosteroids (mg/24 hr)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a.m.</td>
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<td></td>
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<tr>
<td>Follicular</td>
<td>7</td>
<td>33.6 ± 4.5ₐ</td>
<td>169 ± 3</td>
<td>66 ± 7</td>
<td>13.3 ± 2.1</td>
<td>6.1 ± 1.0</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Control</td>
<td>5</td>
<td>33.6 ± 2.7</td>
<td>162 ± 4</td>
<td>64 ± 2</td>
<td>15.7 ± 2.0</td>
<td>9.5 ± 1.7</td>
<td>4.3 ± 0.6</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal</td>
<td>9</td>
<td>38.6 ± 3.3</td>
<td>165 ± 1</td>
<td>64 ± 3</td>
<td>15.6 ± 1.6</td>
<td>8.0 ± 0.6</td>
<td>2.8 ± 1.9</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>32.6 ± 3.1ₐ</td>
<td>165 ± 2</td>
<td>58 ± 2</td>
<td>18.5 ± 1.6</td>
<td>10.7 ± 1.3</td>
<td>6.2 ± 1.1</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>46.4 ± 1.7</td>
<td>167 ± 2</td>
<td>76 ± 8</td>
<td>18.3 ± 1.3</td>
<td>10.1 ± 2.4</td>
<td>5.2 ± 0.7</td>
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<td>Cancer</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Postmenopausal</td>
<td>9</td>
<td>61.8 ± 3.1</td>
<td>162 ± 2</td>
<td>69 ± 5</td>
<td>16.7 ± 2.0</td>
<td>8.5 ± 0.9</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>54.8 ± 3.4</td>
<td>163 ± 2</td>
<td>56 ± 3</td>
<td>21.4 ± 2.7</td>
<td>10.6 ± 2.1</td>
<td>3.7 ± 1.6</td>
</tr>
<tr>
<td>Benign</td>
<td>12</td>
<td>65.2 ± 3.0</td>
<td>165 ± 2</td>
<td>67 ± 4</td>
<td>19.9 ± 1.4</td>
<td>11.0 ± 0.7ₐ</td>
<td>4.6 ± 0.5</td>
</tr>
</tbody>
</table>

ₐ Mean ± S.E.

ₐ p < 0.01 between benign and cancer.

ₐ p < 0.02 between benign and control.

ₐ p < 0.05 between cancer and control.
Table 2
Mean 24-hr hormonal concentrations in normal women and those with benign and malignant breast disease

<table>
<thead>
<tr>
<th>Phase of menstrual cycle</th>
<th>n</th>
<th>GH (ng/ml)</th>
<th>LH (mIU/ml)</th>
<th>FSH (mIU/ml)</th>
<th>Estradiol (pg/ml)</th>
<th>Progesterone (ng/ml)</th>
<th>Testosterone (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>2.9 ± 0.6*</td>
<td>6.1 ± 2.1</td>
<td>3.6 ± 1.1</td>
<td>91.1 ± 38.0</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.05</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>2.9 ± 0.8</td>
<td>7.4 ± 1.6</td>
<td>4.4 ± 1.4</td>
<td>99.8 ± 30.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.09</td>
</tr>
<tr>
<td>Luteal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>2.7 ± 0.4</td>
<td>16.0 ± 11.5</td>
<td>4.6 ± 1.0</td>
<td>138.5 ± 25.7</td>
<td>7.9 ± 3.5</td>
<td>0.2 ± 0.04</td>
</tr>
<tr>
<td>Benign</td>
<td>7</td>
<td>2.4 ± 0.2</td>
<td>10.2 ± 2.6</td>
<td>6.0 ± 29.0</td>
<td>107 ± 29.0</td>
<td>8.0 ± 3.1</td>
<td>0.2 ± 0.02</td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
<td>2.7 ± 0.4</td>
<td>7.7 ± 2.8</td>
<td>5.4 ± 1.2</td>
<td>126.0 ± 25.1</td>
<td>6.6 ± 2.8</td>
<td>0.4 ± 0.10*</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>2.2 ± 0.2</td>
<td>48.5 ± 33.3</td>
<td>84.7 ± 45.6</td>
<td>23.7 ± 8.0</td>
<td>0.3 ± 0.1</td>
<td>0.2 ± 0.09</td>
</tr>
<tr>
<td>Benign</td>
<td>12</td>
<td>1.9 ± 0.2</td>
<td>49.0 ± 10.7</td>
<td>72.8 ± 21.8</td>
<td>23.0 ± 4.0</td>
<td>0.4 ± 0.1</td>
<td>0.2 ± 0.03</td>
</tr>
</tbody>
</table>

*p < 0.05 between control and cancer and between benign and cancer.

Previous reports, however, have suggested that many of these hormones are found in abnormal concentrations in women with breast cancer.

Serum levels of estradiol, a potent stimulator of metabolic processes in normal (25) and malignant (21) breast tissue, have been reported to be elevated in women with malignant breast disease (7) and in daughters of patients with breast cancer (12). In addition, 1 group has found diminished urinary estrone levels in premenopausal breast cancer patients and elevated levels in postmenopausal breast cancer patients (1). In contrast, we found normal mean 24-hr serum estradiol concentrations in pre- and postmenopausal women with breast cancer (Table 2). Our findings are supported by the recent study by McFayden et al. (20) that demonstrated normal 8-hr mean serum estradiol concentrations in 6 postmenopausal women with breast cancer.

Progesterone also influences normal (25) and malignant (13) breast tissue metabolism, and it has been recently postulated that estrogen-progesterone imbalance may play a role in breast cancer (28). Abnormally elevated serum progesterone levels in postmenopausal women with breast cancer have been reported (30). Our 24-hr mean progesterone concentrations, however, did not reveal any significant differences between controls and pre- and postmenopausal breast mass patients (Table 2).

**DISCUSSION**

We have demonstrated that the 24-hr mean hormonal concentrations of a variety of peptide and steroid hormones in women with benign and malignant disease of the breast evaluated preoperatively are not significantly different from levels found in age- and weight-matched control subjects.
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The physiological role of testosterone on normal and malignant breast tissue metabolism is not clear. Grattarola et al. (9, 10), however, have reported that women with endometrial hyperplasia and breast cancer have elevated urinary testosterone levels and that these levels remain elevated in those patients with metastatic disease. A recent report suggests that malignant breast tissue can convert testosterone to the potent androgen 5α-dihydrotestosterone (14), a finding that is not supported by the recent work of Rose et al. (27). Also, McFayden et al. (20) described an increased 8-hr mean plasma testosterone level in 6 postmenopausal breast cancer patients. The 24-hr mean serum testosterone concentrations in our study demonstrated a significant elevation in the luteal-phase breast cancer patients, whereas the postmenopausal breast cancer subjects had serum testosterone levels similar to those of the control subjects (Table 2). The reason for the difference in serum testosterone results between the 2 studies is not clear but may reflect differences in study design. Four of the 6 subjects evaluated by McFayden et al. (20) had metastatic disease and were evaluated following therapy, whereas only 1 of our breast cancer patients had metastatic disease at the time of the study, and all were evaluated preoperatively.

Twenty-four-hr mean LH and FSH concentrations were normal in the breast cancer patients, similar to those previously noted in subjects with breast tumors evaluated during an 8-hr interval (20). GH has previously been shown to produce benign mammary tumors in rats (23), and abnormal GH stimulation following glucose ingestion has been demonstrated in women with breast cancer (4, 24). In this study we found a normal pattern of GH secretion as well as similar 24-hr mean GH concentrations in the control and breast mass patients (Table 2). Hence, normal mean 24-hr concentrations of a variety of polypeptides and steroid hormones that could directly or indirectly effect breast tissue growth were demonstrated in these patients. In addition, the pattern of secretion of the various hormones was not different between the control and breast mass patients.

Previous studies have reported increased (3) and decreased (2) plasma cortisol levels in breast cancer subjects. Elevated urinary 17-hydroxy steroids were found in our luteal-phase benign breast mass subjects. An elevation in 4 p.m. plasma cortisol levels with normal diurnal variation was also found in the postmenopausal breast cancer patients (Table 1). Although these alterations may have an etiological relationship to the neoplastic breast disease, we favor the explanation that the elevated levels that occurred in subjects with either benign or malignant disease reflect the patients’ preoperative anxiety. This hypothesis is supported by another study that reported normal plasma cortisol levels in breast cancer patients who were also studied postoperatively (20).

Abnormally elevated serum TSH levels (22) and depressed serum protein bound iodine concentrations (1) have been described previously in patients with breast cancer. The breast cancer patients in this study, however, had normal serum TSH and thyroxine concentrations (Table 3). The depressed protein bound iodine levels of the previous report (1) may have reflected the influence of chronic illness that has now been demonstrated to depress serum thyroxine concentrations (5).

Previous reports have suggested that serum cholesterol was both elevated (2) and depressed (8) in women with breast cancer, whereas serum triglyceride levels have been reported to be normal (8). Normal serum cholesterol and triglyceride levels were found in our control and breast cancer subjects (Table 3).

Thus, our study suggests that a variety of endocrine and biochemical parameters are normal in women with benign and malignant disease of the breast if they are evaluated preoperatively. These findings, however, do not exclude the possibility that significant endocrine dysfunction occurs at some earlier period in the development of the neoplasm.

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