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Estriol Production Rates and Breast Cancer*

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Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545 and the Department of Medicine, Boston University, Boston, Massachusetts 02118

ABSTRACT. We have infused [6,7-3H]estrone or [6,7-3H]estradiol and [4,14C]estriol into seven women who had breast cancer and into five normal postmenopausal women. We measured the endogenous concentrations and the metabolic clearance rates of estrone, estradiol, and estriol and calculated the blood production rates for these steroids in each group. There was no significant differences between the respective requirements for each group. Our data does not support the argument that physiological amounts of estriol is a protective against breast cancer development in women (J Clin Endocrinol Metab 48: 44, 1978).

Inherent to the suggested protective action of estriol against breast cancer development is the argument that it inhibits the action of estradiol at the mammary cell level. This argument is based, among other data, on the differing effects on the uterus of estradiol and estradiol when administered acutely to rats (1), the low incidence of dimethylbenzanthracine (DMBA)-induced tumors in rats given estriol before DMBA administration as compared with rats given DMBA alone (2), and the lower ratios of estradiol/estrone and estradiol conjugates in the urine of women with, as compared with the high ratios of estradiol/estrone and estradiol for women without, breast cancer (3).

Were women to develop breast cancer because their levels of estriol were lower than the estradiol levels in women who did not develop breast cancer, then it might be expected that such a difference could be demonstrated between two such groups of women. However, we have looked for such a difference in two studies on such groups of women and now wish to present data to show that the breast production rates of estriol in normal women and in women who have had breast cancer are not dissimilar.

Materials and Methods

All subjects were more than 2 years postmenopausal, were in good health, and were not taking any medication. The mean ± SE age of the normal subjects was 55 ± 5 years and ranged from 48-60-years-old. The mean ± SE age of the breast cancer group was 58 ± 9 years and ranged from 42-70-years-old. These women were at least 10 years, and one was 25 years, postradical mastectomy and had had no evidence of recurrence. Subjects gave their informed consent for the study.

For the studies 20 μCi [6,7-3H]estrone (Sp. C1/micromole) or 20 μCi [6,7-3H]estradiol (Sp. C1/micromole) and 2 μCi [4,14C]estriol (Sp. C1/micromole) were administered as a single pulse of 8 ml of an 8% ethanol in isotonic sodium chloride solution. The same two steroids in 14 ml of the same solution were then infused at a constant rate for 3 1/2 h. A baseline blood sample was obtained before the priming pulse injection and three baseline samples were obtained from the contralateral arm during the last hour of the infusion. All samples were centrifuged when obtained and the plasma was stored frozen until analyzed.

The concentrations of estrone and estradiol and the baseline sample were measured as previously described (4). The estriol radioimmunoassay was carried out as described (5) using 5- to 10-microliter samples. The water blank values were consistently less than 3 pg and the sensitivity of the assay was 3 pg/ml under these conditions.

The plasma samples obtained during the

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ESTRIOL PRODUCTION RATES

The infusions were analyzed for radioactivity as estrone, estriol, and estradiol, and estradiol using non-radioactive estrogens for recovery standards (6, 7). Solvent extraction, and phenolic partition were the initial purification steps and final purification was obtained using multiple thin-layer chromatography and derivative formation for estrone and estriol (8) and multiple thin-layer and Sephadex LH-20 chromatography for estradiol (7). Recoveries through the procedures were monitored by calculating the amount of non-radioactive estrogens present in the purified samples on the basis of UV adsorption at 280 nanometers. Measurements of radioactivity as the free estrogens were done as previously described (9).

Data analysis.

The metabolic clearance rates (MCR) were calculated (10)

$$MCR = \frac{r}{X^*}$$

where $r$ = rate of infusion per day; $X^*$ = concentration of radioactivity of infused precursor per liter of plasma; $e$ = infused precursor; $E_1$ = estrone; $E_2$ = estriol; $E_3$ = estradiol.

The blood production rates, $P_1^*$, were calculated as $P_1^* = i^* \times MCR^*$; where $i^*$ = concentration of the endogenous estrogen e.

The blood production rates are calculated in micrograms per day which will be a maximal figure (11). However, variations that occur during the day in the secretion of steroids, and thus their blood production rates, seem to correlate directly with each other (12) so conclusions based on production rates calculated as micrograms per day would be valid.

All comparisons were done using Student's $t$ test (13).

Results

(All results are given as mean ± SE unless indicated otherwise). We have shown previously (7, 9) that the infusions were carried out long enough to achieve an isotopic steady state.

The results for the women who had had breast cancer are shown in Table 1, and for the normal postmenopausal women in Table 2. [The estriol data for subjects 11–14 were reported previously (7)].

In all categories the respective mean values

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Plasma Conc. (pg/ml)</th>
<th>MCR</th>
<th>$P_1^*$ (µg/day)</th>
<th>Estrone $P_1^*$ (µg/day)</th>
<th>Estradiol $P_1^*$ (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1/day</td>
<td>1/day/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>1,490</td>
<td>890</td>
<td>12</td>
<td>42</td>
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<tr>
<td>2</td>
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<td>1,969</td>
<td>1,250</td>
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<td>53</td>
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<td>6</td>
<td>1,420</td>
<td>770</td>
<td>9</td>
<td>30</td>
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<tr>
<td>4</td>
<td>7</td>
<td>1,160</td>
<td>710</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1,570</td>
<td>900</td>
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<td>45</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1,780</td>
<td>1,150</td>
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<td>—</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>1,800</td>
<td>1,000</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
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<tr>
<td>Mean</td>
<td>7</td>
<td>1,600</td>
<td>950</td>
<td>12</td>
<td>45</td>
</tr>
<tr>
<td>SR ±</td>
<td>2</td>
<td>100</td>
<td>70</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Plasma Conc. (pg/ml)</th>
<th>MCR</th>
<th>$P_1^*$ (µg/day)</th>
<th>Estrone $P_1^*$ (µg/day)</th>
<th>Estradiol $P_1^*$ (µg/day)</th>
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<tr>
<td></td>
<td></td>
<td>1/day</td>
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<td>2,080</td>
<td>1,110</td>
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<tr>
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<td>11</td>
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<tr>
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<td>1,500</td>
<td>15</td>
<td>56</td>
</tr>
<tr>
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<td>6</td>
<td>1,960</td>
<td>1,150</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>SR ±</td>
<td>1</td>
<td>100</td>
<td>90</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

*Estriol data on subjects 11–14 reported previously (7).
for the breast cancer group did not differ significantly from the normal group with $P > 0.1$ for each mean except for the mean values for MCR in 1/day where $0.1 > P > 0.05$.

Discussion

One of the major reasons for postulating that estril exerted a protective influence against the development of breast cancer was the report that women with breast cancer excreted less conjugates of estril with respect to the conjugates of estrone and estradiol compared with the excretory pattern of women without breast cancer (3). We have shown, however, that the ratio of urinary estrogen metabolites does not correlate with the ratio of estrogen blood production rates (14). In the present study, we were not able to demonstrate that the women who had had breast cancer were significantly different from the normal women with respect to the plasma level, MCR, or blood production rates of estril. In addition, the production rates of estrone and estradiol were not significantly different. Thus, in both these groups the tissues were exposed to similar levels of estrogens. It should be noted that the number of women in the groups studied was not large and there was considerable variation of the production rates within the groups. Thus, our data would have detected differences between the groups only if the differences were relatively large.

Our studies were done several years after the breast cancer had been present, and we have no knowledge of estrogen dynamics at the time of development of the breast cancer nor in the years preceding the cancer. It is possible that differences between the groups could have been present at those times, but lacking extensive prospective studies these data are not available. However, our data on urinary ratios and blood production rates in young women (14) suggest that such studies might not reveal any such differences. In that study, we were unable to find differences between estril production rates of women with low urinary estrogen ratios compared with women with high urinary estrogen ratios. Women in both groups ranged from 21-45 years of age.

Clark et al. (15) have reported that estril is an estradiol agonist when it is present continuously; however, if estril were to be protective against breast cancer development, then it should be an estradiol antagonist. When administered acutely in physiological amounts, estril is a partial estradiol antagonist (1, 15) but our data show that estril is present relatively constantly in normal premenopausal and postmenopausal women (6, 7) as well as in women who have had breast cancer, and thus should act as an agonist.

Thus, along with Clark's in vitro data (1), our present in vivo data do not support the argument that estril when present in physiological amounts exerts a protective influence against the development of breast cancer. It is probable that the action of estril in preventing DMBA-induced tumors (2), is a pharmacologic one similar to that described for estradiol (16).

Acknowledgment

We would like to thank Mr. C. Flood and Mr. M. Franz for their excellent technical assistance.

References

8. Longcope, C., D. S. Layne, and J. F. Tait, Metabol

and \( \gamma \) and \( \delta \).