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Estriol Production Rates and Breast Cancer*

J. HOWARD PRATT† AND CHRISTOPHER LONGCOPE‡

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

ABSTRACT. We have infused [6,7-^{3}H]estrone or [6,7-^{3}H]estradiol and [4-^{14}C]estriol into seven women who had 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 were no significant differences between the respective measurements for each group. Our data does not support the argument that physiological amounts of estriol are protective against breast cancer development in women. (*J Clin Endocrinol Metab* **46:** 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 estriol 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 estriol/estrone and estradiol conjugates in the urine of women with, as compared with the high ratios of estriol/estrone and estradiol for women without, breast cancer (3).

Were women to develop breast cancer because their levels of estriol were lower than the estriol 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 blo production rates of estriol in normal wom and in women who have had breast canc are not dissimilar.

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† Present address: Department of Medicine, University of Indiana, Indianapolis, Indiana.

‡ Address reprint requests to Dr. C. Longcope, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545.

Materials and Methods

All subjects were more than 2 years postmen pausal, were in good health, and were not taki any medication. The mean ± SE age of the norm subjects was 55 ± 5 years and ranged from 46- 60-years-old. The mean ± SD age of the brea cancer group was 58 ± 9 years and ranged fr 42- to 70-years-old. These women were at leas years, and one was 25 years, postradical maste tomy and had had no evidence of recurrence. A subjects gave their informed consent for the studies

For the studies 20 μCi [6,7-^{3}H]estrone (SA Ci/mmol) or 20 μCi [6,7-^{3}H]estradiol (SA Ci/mmol) and 2 μCi [4-^{14}C]estriol (SA mCi/mmol) were administered as a single pulse 8 ml of an 8% ethanol in isotonic sodium chlori solution. The same two steroids in 14 ml of th same solution were then infused at a constant ra for 3½ h. A base-line blood sample was obtain before the priming pulse injection and three blo samples were obtained from the contralateral ar during the last hour of the infusion. All sampl were centrifuged when obtained and the plasm was stored frozen until analyzed.

The concentrations of estrone and estradiol the base-line sample were measured as previous described (4). The estriol radioimmunoassay w carried out as described (5) using 5- to 10-ml plasm samples. The water blank values were consistent less than 3 pg and the sensitivity of the assay w 3 pg/ml under these conditions.

The plasma samples obtained during the in

sions were analyzed for radioactivity as estrone, estradiol, and estriol 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 estradiol (8) and multiple thin-layer and Sephadex LH-20 chromatography for estriol (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)

$$MCR^e = r^e / X^e$$

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 = estradiol; E_3 = estradiol.

The blood production rates, $P_B{}^e$, were calculated as $P_B{}^e = i^e \times MCR^e$; where i^e = 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 1. Estrogen production rates in breast cancer women

Patient No.	Plasma Conc. (pg/ml)	Estriol MCR 1/day	Estriol MCR 1/day/m²	Estriol P_B (μg/day)	Estrone P_B (μg/day)	Estradiol P_B (μg/day)
1	8	1,490	890	12	42	—
2	5	1,960	1,250	10	—	—
3	6	1,420	770	9	63	25
4	7	1,160	710	8	30	8
5	3	1,570	900	5	45	18
6	3	1,780	1,150	5	—	14
7	18	1,800	1,000	32	—	—
Mean	7	1,600	950	12	45	16
SE ±	2	100	70	3	7	4

TABLE 2. Estrogen production in normal women[a]

Patient No.	Plasma Conc. (pg/ml)	Estriol MCR 1/day	Estriol MCR 1/day/m²	Estriol P_B (μg/day)	Estrone P_B (μg/day)	Estradiol P_B (μg/day)
11	3	2,080	1,110	7	36	11
12	7	1,900	1,110	13	25	17
13	11	1,960	1,080	22	34	25
14	3	1,630	960	5	—	—
15	7	2,240	1,500	15	56	20
Mean	6	1,960	1,150	12	38	18
SE ±	1	100	90	3	7	3

[a] 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 estriol exerted a protective influence against the development of breast cancer was the report that women with breast cancer excreted less conjugates of estriol 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 estriol. 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 estriol 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 estriol is an estradiol agonist when it is present continuously; however, if estriol were to be protective against breast cancer development then it should be an estradiol antagonist. When administered acutely in physiological amounts, estriol is a partial estradiol antagonist (1, 15) but our data show that estriol is present relatively constantly in normal premenopausal and postmenopausal women (5, 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 (15), our present *in vivo* data do not support the argument that estriol when present in physiological amounts exerts a protective influence against the development of breast cancer. It is probable that the action of estriol in preventing DMBA-induced tumors (2), is a pharmacologic one similar to that described for estradiol (16).

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