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Estrogen Production and Metabolism in Normal Postmenopausal Women and Postmenopausal Women with Breast or Endometrial Cancer*

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Abstract—*The metabolic clearance rates of estradiol in postmenopausal women with breast cancer* (1269 ± 370 1/24 hr, *mean* ± *S.D.*) *or endometrial cancer* (1320 ± 238 1/24 hr) *were significantly higher than in normal postmenopausal women* (922 ± 238 1/24 hr). *The metabolic clearance rates of estrone were elevated in women with endometrial cancer* (2012 ± 749 1/24 hr) *or with conditions associated with an increased risk for breast or endometrial cancer* (1830 ± 413 1/24 hr) *compared with values for normal postmenopausal women* (1321 ± 301 1/24 hr). *The production rate of estradiol was only increased in women with breast cancer. Significant correlations were found between subjects' percentage of ideal body wt and the metabolic clearance rates of estrone and estradiol and also the production rate of estrone. The increased clearance rates may reflect differences in either the binding of estrogens to plasma proteins or the tissue metabolism of estrogens in cancer patients.*

INTRODUCTION

ENDOMETRIAL and breast cancer occur most commonly in postmenopausal women when production of estrogens, which have been implicated in the development of tumours in these endocrine sensitive tissues [1], is greatly reduced. In postmenopausal women it is now established that estrone is derived almost exclusively from androstenedione [2] although the origin of estradiol remains unresolved. Increased production of estrone was suggested as a factor in the development of endometrial cancer [2] but more recent studies showed that when cancer and control subjects were weight-matched, there was no difference in estrone production rates [3, 4].

In postmenopausal women plasma levels of estrone exceed those of estradiol [5]. This excess of estrone may not be as great at the tissue level since there is now evidence that this steriod serves as a pre-hormone for the formation of estradiol [6]. No consistent abnormality in plasma estrogen concentrations has been found in cancer patients [1, 7] but as the plasma concentration of a hormone represents a balance between its production and clearance rate it is possible that differences could exist between cancer and normal subjects. In the present study, therefore, production rates of estrone and estradiol and their metabolic clearance rates (MCR) were measured in normal postmenopausal women and in postmenopausal women with breast or endometrial cancer. A group of postmenopausal women with benign breast disease or endometrial hyperplasia, conditions associated with increased risks for development of cancer, were also studied. The conversion of estrone to estradiol was also measured to investigate the possibility of increased conversion to estradiol in cancer subjects.

A preliminary account of some of the results obtained in this study has been presented [8].

SUBJECTS

Details of subjects' ages, their number of years postmenopausal (YPM), body wt and percentage of ideal body wt (IBW) are shown in Table 1. Subjects per cent IBWs were calculated by comparison of a subject's weight with tables of the average weights of women of the same age and height. There were no significant differences between the body wts or IBWs of the cancer and normal women. Values for IBW were only obtained for four of the six patients with endo-

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Table 1. *Subjects ages, years postmenopausal, weights and percentage of ideal body wt*

	n	Age (yr)	YPM‡ (yr)	Weight (Kg)	IBW3§ (%)
Breast cancer	9	64.4 ± 9.0‖	14.8 ± 12.0	76.4 ± 18.0	115.9 ± 25.0
Endometrial cancer	6	68.7 ± 11.0	15.2 ± 10.8	66.0 ± 6.9	99.5 ± 16.9
B.B.D.* + E.H.†	5	58.6 ± 7.8	7.8 ± 9.6	78.6 ± 22.6	125.0 ± 29.3
Normals	8	62.3 ± 9.9	14.3 ± 12.5	60.5 ± 12.7	98.9 ± 22.4

* Benign breast disease. † Endometrial hyperplasia. ‡ Years post menopause. § Ideal body weight ‖ Mean ± S.D. ¶ $n = 4$.

metrial cancer. The women were only included in this study if at least 1 yr had elapsed since their menopause. Patients had not received any hormonal therapy during the 3 months preceding investigation. Patients had histologically proven endometrial cancer or breast cancer (Stage III). Two women were also investigated whose breast tumours proved to be benign and three women who had either cystic and atypical or moderate cystic glandular endometrial hyperplasia. Control subjects were in hospital awaiting surgery for varicose veins, haemorrhoids or a hernia. All subjects were investigated 2–3 days before operation after obtaining their informed consent to the study.

MATERIALS AND METHODS

MCRs for estrone and estradiol and the conversion of estrone to estradiol were measured using a double isotope technique as previously described [8]. Briefly, MCRs were measured by the infusion of approx. 30 μCi [6, 7,-^{3}H) estrone (44 Ci/mmol, New England Nuclear, Southampton, U.K.) and 3 μCi (4−^{14}C) estradiol (59 mCi/mmol, New England Nuclear) in 5% ethanol in physiological saline. A priming dose of 40% of the total amount of radioactive steriods used was injected i.v. immediately before the start of the infusion and the remaining dose infused over a 3.5 hr period at 5.1 ml/hr. After 2.5, 3 and 3.5 hr of tracer infusion blood samples (50 ml) were taken. Plasma was separated from the red blood cells and stored at −20° C until analysed.

The extraction of steriods from plasma, purification by Sephadex LH 20 column chromatography and thin layer chromatography and counting procedures were as previously described [9], with the exception that in the present study non-radioactive estrone (200 μg) and estradiol (200 μg), obtained from Sigma, Poole, Dorset, U.K., were added to the plasma samples to monitor recoveries. MCRs were calculated from the rate of steroid infusion divided by the steady-state concentration of the infused steriod [10]. Production rates (PR) of estrone and estradiol were calculated as the product of the MCR and plasma concentration of estrone and estradiol, measured in samples of plasma obtained before isotope infusion, by methods previously described [11]. Transfer constants (ρ) for the conversion of estrone to estradiol were calculated as described by Baird *et al.* [10]

$$\rho^{E1\ E2} = CR^{E1\ E2} \times \frac{MCR\text{-}E2}{MCR\text{-}E1}$$

where $CR^{E1\ E2}$ is the conversion ratio of infused tracers.

Data were analysed using Student's *t*-test and linear regression, using the method of least squares.

RESULTS

Significant correlations were found between MCR−E_1 and %IBW ($r = 0.75$, $P < 0.001$) and also MCR−E_2 and %IBW (r 0 0.72, $P < 0.001$) (Figs. 1 and 2). MCRs−E_1 were significantly higher in women with endometrial cancer or with benign breast disease or endometrial hyperplasia compared with those for normal postmenopausal women (Table 2). MCRs−E_2 were significantly elevated in the breast cancer ($P < 0.05$) and endometrial cancer ($P < 0.01$) patients but not in women with benign breast disease or endometrial hyperplasia.

The mean plasma concentration of estrone was significantly higher in women with benign breast disease or endometrial hyperplasia and the mean plasma concentration of estradiol was significantly elevated in women with breast cancer (Table 3). Also shown in Table 3 are the production rates of estrone and estradiol. The production rate of estrone was elevated in women with benign breast disease or endometrial cancer compared with normal postmenopausal women whereas estradiol production was only significantly increased in women with breast cancer. While the production rate of estrone (Fig. 3) showed a significant correlation with %IBW ($r = 0.63$, $P < 0.001$) no such correlation (Fig. 4) was found between the production rates of estradiol and %IBW ($r = 0.29$, N.S.).

The extent to which estrone was converted to estradiol was similar in the patients and normal postmenopausal women (Table 4). The percentages of estradiol derived from estrone are also shown in Table 4. For most subjects less than 30% of the estradiol appeared to derive from estrone.

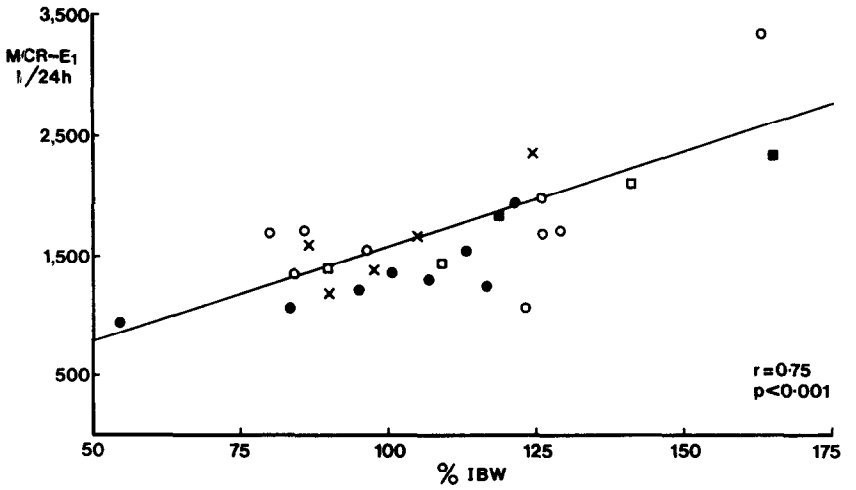

Fig. 1. Correlation between metabolic clearance rate of estrone ($MCR-E_1$) and percentage of ideal body wt (% IBW) in normal postmenopausal women (●) and postmenopausal women with breast cancer (○), benign breast disease (■), endometrial cancer (×) or endometrial hyperplasia (□).

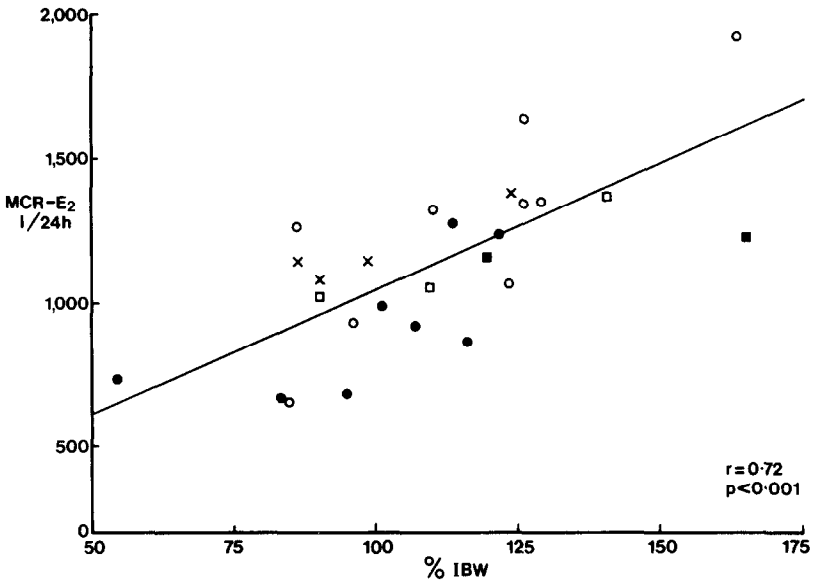

Fig. 2. Correlation between metabolic clearance rate of estradiol ($MCR-E_2$) and percentage of ideal body wt (% IBW) in normal postmenopausal women (●) and postmenopausal women with breast cancer (○), benign breast disease (■), endometrial cancer (×) or endometrial hyperplasia (□).

Table 2. $MCR-E_1$ and $MCR-E_2$

	n	$MCR-E_1$ (1/24 hr)	$MCR-E_2$ (1/24 hr)
Breast cancer	9	1834 ± 645‡	1269 ± 3703§
Endometrial cancer	6	2012 ± 7493§	1320 ± 238‖
BBD* + EH†	5	1830 ± 413§	1168 ± 149
Normals	8	1321 ± 301	922 ± 238

* Benign breast disease. † Endometrial hyperplasia. ‡Mean ± S.D. § $P < 0.05$. ‖ $P < 0.01$.

However, for one subject with endometrial cancer 77% of estradiol was calculated to originate from estrone.

DISCUSSION

The results of the present study demonstrate that there are differences between normal postmenopausal women and postmenopausal women with breast cancer who have increased plasma levels, clearance and production rates of estradiol. These findings are consistent with the recent results obtained by other groups who have found increased plasma levels of estradiol and an increase in the free estradiol fraction in postmenopausal

Table 3. Plasma concentrations of estrone and estradiol and production rates of estrone and estradiol

	n	Pc E_1 (ng/100ml)	Pc E_2 (ng/100ml)	PR−E_1 (μg/24h)	PR−E_2 (μg/24h)
Breast cancer	9	3.7 ±1.4‡	2.4 ± 0.5§	65.2 ± 39.5	30.2 ± 9.7‖
Endometrial cancer	6	4.5 ± 1.9	1.9 ± 0.7	94.2 ± 62.6§	34.9 ± 30.9
B.B.D.* and EH†	5	4.7 ± 0.3‖	1.8 ± 0.7	85.4 ± 15.0¶	20.4 ± 7.7
Normal	8	3.3 ± 0.7	1.8 ± 0.5	44.2 ± 15.7	16.1 ± 5.5

* Benign breast disease. † Endometrial hyperplasia. ‡ Mean ± S.D. § $P < 0.05$. ‖ $P < 0.01$. ¶ $P < 0.001$.

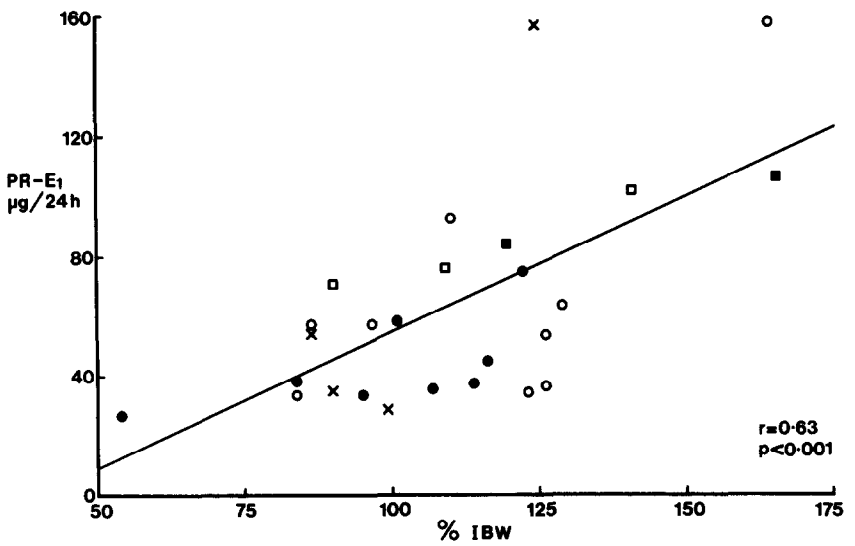

Fig. 3. Correlation between production rate of estrone ($PR-E_1$) and percentage of ideal body wt (% IBW) in normal postmenopausal women (●) and postmenopausal women with breast cancer (○), benign breast disease (■), endometrial cancer (×) or endometrial hyperplasia (□).

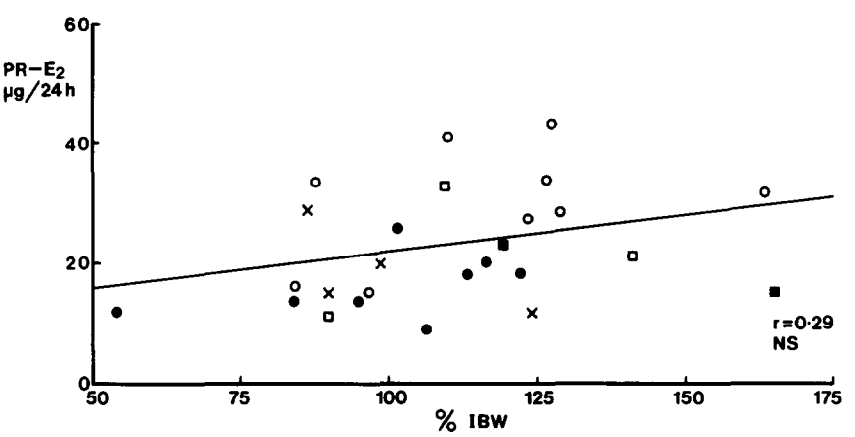

Fig. 4. Correlation between production rate of estradiol ($PR-E_2$) and percentage of ideal body wt (% IBW) in normal postmenopausal women (●) and postmenopausal women with breast cancer (○), benign breast disease (■), endometrial cancer (×) or endometrial hyperplasia (□).

women with breast cancer [12, 13]. In contrast to the results obtained for breast cancer patients, although the MCR−E_2 was increased in women with endometrial cancer, there was no increase in plasma levels or production rates of estradiol. For women with benign breast disease or endometrial hyperplasia, a group considered to have an increased risk of developing endocrine cancers, no differences were detected in plasma levels, clearance or production of estradiol. However, plasma levels, clearance and production rates of estrone were increased. The elevation in production and clearance rates of estrone in these subjects may lead to an increase in the availability of estrone to

Table 4. Transfer constants for the conversion of estrone to estradiol and percentage of estradiol derived from estrone

	n	$[\rho]^{E1E2}_{B\ B}$ %	Percentage of E2‡ derived from E1
Breast cancer	(9)	4.3 ± 0.3§	9.4 ± 1.6
Endometrial cancer	(6)	6.3 ± 1.13	27.9 ± 10.9
BBD* and EH†	(5)	4.6 ± 0.5	17.3 ± 7.4
Normals	(8)	4.6 ± 0.4	10.4 ± 1.6

* Benign breast disease. † Endometrial hyperplasia. ‡ Calculated as [ρ] E1 E2 x $PR-E_1/PR-E_2 \times 100$.
§ Mean ± S.E.

tissues, where estrone can be converted to estradiol.

Few previous studies have been carried out to measure MCRs or production rates of estrone or estradiol in postmenopausal women with breast cancer, and no previous studies appear to have been carried out to measure estradiol production rates in postmenopausal women with endometrial cancer. Increased clearance rates of estrone in some women with breast cancer were found by Kirschner *et al.* [14]. These authors did not relate clearance rates to body weight but did note that there was more obesity in women with higher MCRs estrone. In the present investigation we have shown that the metabolic clearance rates of estrone and estradiol are related to %IBW. Although the mean values for the weight and %IBW of subjects with breast cancer were higher than for the control group, the differences were not statistically significant.

An important factor that influences steriod clearance rates is the degree and nature of its protein binding [15]. The binding capacity of sex hormone binding globulin is inversely related to %IBW [16] and this could account, in part, for the correlation found in the present study between $MCR-E_2$ and %IBW.

The finding of a significant difference in plasma levels of estradiol between breast cancer and normal subjects is in contrast to the results of our previous study [17] where a greater number of subjects were studied but no significant difference was found. In the present study, however, plasma estradiol concentrations were measured in women who currently had breast cancer, whereas the majority of women previously investigated had had breast cancer 4 months to 18 yr before investigations. Others have also reported higher plasma levels of estradiol in postmenopausal women with breast cancer [12, 13]. No increase was detected in the plasma level of estradiol of women with endometrial cancer in the present study, thus confirming the results of Davidson *et al.* [18].

Production rates of estrone and estradiol measured in the normal postmenopausal women are similar to values previously reported [20]. The higher plasma levels of estradiol and increased metabolic clearance rates of estradiol for women with breast cancer resulted in a significant elevation in the production rate of estradiol. As previously found by Kirschner *et al.* [14], no increase in the production rate of estrone by postmenopausal women with breast cancer was detected.

Production rates of estrone have been measured in postmenopausal women with endometrial cancer but were calculated from the specific activity of urinary estrogen metabolites after the administration of a dose of radiolabelled estrone; when allowance was made for weight no increase was found in the production rate of estrone [3, 4]. In the present study the production rate of estrone was higher in women with endometrial cancer. However, if the two subjects for whom IBWs were not obtained are excluded, the mean value for the production rate of estrone does not differ from normal.

The significant correlation found beween the production rate of estrone and %IBW supports the results of previous studies in which plasma levels of estrone [20] and the extent of conversion of androstenedione to estrone [2, 21] were found to be related to body wt. As estrone is thought to be the main precursor for estradiol formation in postmenopausal women [2, 22] it was surprising that a similar correlation was not found between the production rate of estradiol and %IBW. However, Poortman *et al.* [20] found no relationship between plasma levels of estradiol and body weight. In our study, and those by others [19, 22], conversion of estrone to estradiol only accounted for part of the total production rate of estradiol by postmenopausal women.

Previous investigations did not reveal any increase in the conversion of androstenedione to estrone in women with endometrial cancer [3, 4],

and we have found no increase in the conversion of estrone to estradiol in women with breast or endometrial cancer.

In conclusion, this study has shown that while plasma concentrations, clearance rates and production rates of estradiol are all increased in postmenopausal women with breast cancer, only the clearance rate of estradiol was elevated in women with endometrial cancer. This suggests that if estrogens are involved in the development of endocrine cancers their effect on the breast and endometrium may differ. It is possible that changes in estrogen metabolism at the cellular level may be of greater importance in the development of endometrial cancer, and we are currently examining the factors involved in regulating the tissue metabolism of oestrogens.

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