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Circulating Levels of 17β-Estradiol, Testosterone and Progesterone in Postmenopausal Breast Cancer Patients Receiving Anticancer Chemotherapy

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Abstract.- Plasma levels of steroid hormones (17β-estradiol, testosterone and progesterone were determined in postmenopausal women suffering from breast cancer, cancers other than breast and normal healthy subjects. The levels of all steroids were considerably higher in breast cancer patients than the other two groups. During the five month sampling period, estradiol levels decreased in breast cancer patients after CMF (cyclophosphamide, methotrexate, 5-flourouracil) therapy, but there was no significant change in the concentration of testosterone and progesterone. In the patients suffering from cancers other than breast and healthy controls, the levels of all the three steroids remained steady throughout the sampling period. Knowledge of the hormonal status of postmenopausal women facilitates the choice and timing of chemotherapy for controlling the disease.

Key words: Breast cancer, steroid, anti-cancer chemotherapy, estradiol, testosterone, progesterone.

INTRODUCTION

Cancer is a leading cause of death for women aged 35 to 50 and breast cancer is the most common malignancy in this age group. Various treatments have been used but the annual mortality rate has remained unchanged (Haskel, 1985).

The breast cancer can be controlled upto some extent by the chemotherapy and or endocrine therapy if detected early (Bonadonna *et al.*, 1983). Adjuvant chemotherapy is used after mastectomy for advanced or metastatic disease. But this strategy has proved less effective in postmenopausal patients (Bonadonna *et al.*, 1988). The role of these and other therapies in postmenopausal patients appear to be palliative rather than curative and results in an increase in disease free interval (Bonadonna *et al.*, 1983). Breast cancer is an endocrine related disorder in which various hormones are involved in the pathogenesis (Rowlands, 1987). In postmenopausal women, the amount of sex hormones produced by ovaries is insignificant and the androgens produced by the adrenals are converted into estrogen in peripheral tissues such as muscle and adipose tissues. Furthermore the breast tumor cells themselves can produce estrogens ectopically (Santner *et al.*, 1986). Several studies have been carried out on urinary excretion of steroid hormones by women with and without breast cancer (Zumoff, 1981) but few investigations have been carried out to measure their plasma levels. As blood levels of hormones are considered to be representative of their direct influence on target cells, more sensitive and direct immunological assay methods have been utilized in the present study to measure circulating hormonal steroids in various patient groups and controls.

MATERIALS AND METHODS

Eighty six postmenopausal women were selected for the present investigation and were divided into three groups. 26 women (Group I) were without any endocrinological disorder, were healthy and were postmenopausal for over a year (aged between 46-71 years). Group II comprised of postmenopausal women suffering from cancers (lung, thyroid, gastrointestinal tract) other than breast. These women did not have any gynaecological disorder in the past and were aged between 48-68 years. Group III consisted of 30 advanced stage breast cancer patients aged 47-65 years. This group was receiving adjuvant chemotherapy with Cyclophosphamide, Methotrexate and 5-flourouracil (CMF).

Blood sampling was carried out in all three groups overlapping with the drug regimen to group III individuals between 9-10 a.m. on day 0, 8, 20 and 28 of each month for five months. Blood was allowed to clot,

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centrifuged and serum was collected and stored at -20°C until used. The concentration of hormones was determined by using highly sensitive and specific Coat-A-Count radioimmunoassay kits (Diagnostic Products Corp. USA). The sensitivity of the assays were 8 pg/ml for estradiol, 0.4 ng/ml for progesterone and 0.4 nmol/ml for testosterone. The inter and intra assay coefficients of variation were 10.5 and 9.3% for estradiol, 7.3 and 9.5% for testosterone and 6.9 and 11% for progesterone respectively. Comparisons of hormone levels between groups were performed by Duncan's multiple ranged test. Three way ANOVA was used to determine P-values and these P-values were used for all statistical analyses.

RESULTS

The serum concentration of estradiol, testosterone and progesterone in the three groups (I-III) at day 0 of the regimen is presented in Fig. 1. Circulating levels of estradiol were highest among the breast cancer patients compared with the normal controls and patients with cancers other than breast. The same pattern was observed with testosterone and progesterone. The levels of testosterone were considerably high in breast cancer patients compared to the other two groups.

There was no significant difference in the estradiol levels at various intervals of the sampling regimen in group I and group II subjects (Table I). In contrast to these groups, estradiol concentration dropped considerably among group III patients at day 28 of the therapy (Table I).

Circulating levels of testosterone in breast cancer patients (group III) were much higher (Table I) than those in group I (normal controls) and group II (patients with cancers other than breast). The levels of testosterone in group III patients did not show any significant variation following the administration of chemotherapy (Table I).

The mean values for circulating progesterone concentration in the three groups studied are presented in Table I. The values remained steady throughout the sampling regimen in group I and II subjects. However in group III, there was a slight increase in progesterone concentration at day 28 of the regimen (Table III).

DISCUSSION

Our results show higher estradiol levels in breast cancer patients compared to normal controls and patients with cancers other than breast. The circulating

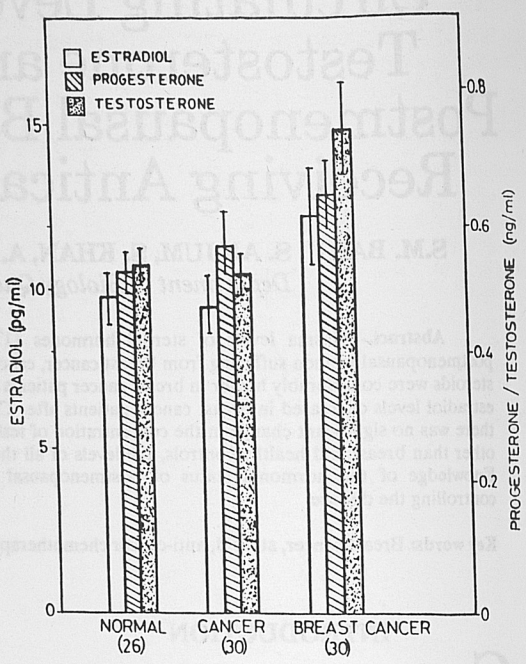

Fig. 1. Plasma levels of estradiol, progesterone and testosterone in normal healthy postmenopausal women, those suffering from cancers other than breast and breast cancer at day 0 of the sampling regimen. The numbers in paren-theses show the number of subjects included in each group.

levels of testosterone and progesterone were also higher in breast cancer patients compared with normal controls and patients with cancers other than breast. These findings are best explained in the light of the finding that after menopause, the ovary produces only minimal amounts of either estrone or estradiol, and the adrenal becomes the major source of estrogen precursors (Rizkallah *et al.*, 1975; Judd *et al.*, 1976). While the adrenal gland do not secrete estrogens directly, it releases the prehormone androstenedione which is then converted into estrone in peripheral tissues via enzyme aromatase. Extraglandular aromatase is present in fat, liver, hair follicles, brain, muscle and other tissues (Longcope *et al.*, 1978; Smuk *et al.*, 1977). A variety of data supports the concept that estrogens can be made in breast cancer tissue *in situ* from plasma precursors in postmenopausal women (Edery *et al.*, 1981; Fishman *et al.*, 1977; Millington, 1975).

There have been conflicting data regarding the circulating estradiol levels. Secreto *et al.* (1983) have reported subnormal estradiol levels in postmenopausal

TABLE I.- **Mean values (±SEM) of circulating steroid hormones in various groups of postmenopausal women.**

Groups of subjects/steroid hormones	Sampling/drug regimen (days)			
	0	8	20	28
Estradiol 17-β				
I. Normal women	8.4±2.00 (n=26)	8.6±0.8 (n=21)	9.8±1.2 (n=21)	8.2±.9 (n=20)
II. Women with cancer other than breast	8.23±0.98 (n=30)	8.0±1.2 (n=25)	8.5±0.8 (n=24)	7.8±1.1 (n=22)
III. Women with breast cancer*	11.6±1.69 (n=30)	11.7±1.5 (n=28)	10.8±1.3 (n=25)	98.6±1.47 (n=25)
Testosterone (ng/ml)				
I. Normal women	0.54±0.062 (n=26)	0.57±0.05 (n=21)	0.5±0.08 (n=21)	0.52±0.05 (n=20)
II. Women with cancer other than breast	0.52±0.06 (n=30)	0.54±0.09 (n=25)	0.51±0.04 (n=24)	0.48±0.09 (n=22)
III. Women with breast cancer*	0.74±0.07 (n=30)	0.71±0.05 (n=28)	0.71±0.06 (n=25)	0.75±0.06 (n=25)
Progesterone (ng/ml)				
I. Normal women	0.53±0.08 (n=26)	0.49±0.07 (n=21)	0.48±0.1 (n=21)	0.5±0.09 (n=20)
II. Women with cancer other than breast	0.57±0.10 (n=30)	0.59±0.07 (n=25)	0.59±0.09 (n=24)	0.54±0.1 (n=22)
III Women with breast cancer*	0.62±0.01 (n=30)	0.60±0.07 (n=28)	0.65±0.12 (n=25)	0.67±0.08 (n=25)

*Breast cancer partients receiving CMF therapy.

patients, however, Mcfarlane *et al.*, 1976 and Bird *et al.*, 1981 found estradiol levels to be higher in postmenopausal breast cancer patients. Our data support the later and the elevated estradiol levels in our studies most probably represent *in situ* or peripheral conversion of precursors from hyperactive adrenals. This receives further support from the finding that testosterone levels are high in postmenopausal breast cancer patients and remain unaffected by the anticancer chemotherapy. The anticancer drugs used in this study reduced estradiol levels but had no effect on testosterone levels. In contrast to premenopausal breast cancer patients where the primary site of action is the functional ovary and its steroidogenesis, the postmenopausal subjects did not have functional ovaries and the reduced estradiol levels reflected an inhibition of the estrone-estradiol conversion step either in the tumor itself or in the peripheral tissues. However, another explanation may be a general cytotoxic response in the tumor resulting in reduced overall conversion of estradiol precursors. Since more than forty percent breast tumors are estradiol responsive/dependent, the management of disease in postmenopausal women is more complicated because of different endocrine status compared with premenopausal patients, where endocrine/chemotherapy have been found successful. Although there was a small increase in progesterone concentration following chemotherapy, these values are not different statistically. The control of advanced breast cancer in postmenopausal breast cancer patients can be best achieved by interfering at the aromatization step which involves the conversion of estrone into estradiol.

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