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Endogenous Sex Steroid Hormone Levels In Women With Breast Malignancy

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Abstract : *Hormones play a critical role in breast carcinogenesis. Serum endogeneous sex steroid hormone levels (estradiol, progesterone and testosterone) of 30 confirmed cases of women with breast cancer and 40 healthy controls were analysed using the Enzyme Linked Immunofluoresence Assay (ELFA) method. Serum levels of estradiol were raised in the premenopausal and postmenopausal phases with statistically significant association of $p<0.05$. Serum values of progesterone and testosterone were statistically insignificant with $p>0.05$. Concentration of serum estradiol may predict the risk for breast malignancy and hence may help the clinicians to decide further management to decrease breast cancer risk.*

Keywords : *Serum estradiol, progesterone, testosterone, breast malignancy*

I. Introduction

The breasts are hormonally regulated tissues that respond to a number of hormones circulating within the body. Postnatal development of normal mammary gland from puberty to menopause is critically dependent upon two steroid hormones, estrogen and progesterone.

Estrogen is the hormone that controls breast cell proliferation and division. Estrogen is released during the first half of the menstrual cycle, which enlarges the breast glands in preparation for pregnancy. Once estrogen levels decrease following ovulation, the breast returns to its normal state. Estradiol which is most abundant in women of reproductive age, is the strongest of the estrogen hormones and the one most responsible for breast development.

Progesterone levels are low during the first half of the menstrual cycle, but contribute to breast development during the second half of the cycle, once estrogen levels are lowered. Estrogen first induces enlargement of tissues within the breast, and progesterone ensures these tissues develop proper functioning within the breast to aid in breast development.

Hormones play a critical role in breast carcinogenesis. In the recent past there has been extensive focus on the role of estrogen as a growth regulator of normal breast tissue and breast cancer. However, progesterone is also a potent breast mitogen and recent epidemiological studies suggest that progesterone may play a greater role than estrogen in breast cancer.[1] Serum levels of testosterone have been suspected in the etiology of breast cancer.[2] Testosterone or its metabolites might play a role in breast cancer etiology by altering the availability of estrogens or by acting as an estrogen precursor.[3]

II. Materials and methods

The study was carried out after Institute Ethics Committee clearance. Blood samples of 70 postpubertal females, willing to give sample for sex hormone evaluation were collected of which 30 were cases and 40 were controls. The cases were of breast malignancy who were diagnosed on cytology and confirmed by histopathology. The menstrual history of all the females was recorded. Those on oral contraceptives, hormone replacement therapy and pregnant or lactating women were excluded. Also those with ovarian pathology, women with bilateral oophorectomy and chronic or acute liver disease were excluded. For cases the sample for hormonal assessment was drawn at the time of presentation of breast lump.

Blood was drawn from the antecubital vein under aseptic precautions. Serum was separated by centrifugation at 1500 rpm for 10 mins and stored at -20 degrees until further evaluation. Serum was analysed for serum estradiol, progesterone and testosterone using the Enzyme Linked Immunofluorescence Assay (ELFA) method. Controls were women without any breast pathology, not on oral contraceptives, hormone replacement therapy, non pregnant and non lactating.

Statistical Analysis - The software used was OpenEpi Version 3.01. Unpaired ‘t’ test with equal variance was applied. A p value of less than 0.05 was considered significant.

III. Results

Out of the 30 cases, 12 were premenopausal and 18 were postmenopausal women. Most of the cases were in the age group of 41-50 years (47%), followed by 31-40 years. 79% of the patients presented with complaint of breast lump. 17% presented with pain in the breast. Other symptoms included nipple discharge, excoriation/eczema and ulcerating or fungating growth. Upper outer quadrant was most commonly involved followed by the upper inner quadrant. 73% of the cases were of infiltrating ductal carcinoma. Other cases included were of infiltrating lobular carcinoma, medullary carcinoma, mucinous carcinoma, apocrine carcinoma, metaplastic carcinoma, spindle cell sarcoma and malignant phyllodes.

Table 1: Descriptive characteristics of cases and controls

Characteristic	Cases mean±SD	Controls mean±SD
Age in years	46.3±10.48	44.7±16.24
Body mass index in Kg/m^2	23.4±2.53	23.8±2.81
Age at menarche in years	13.23±1.85	13.75±1.63
Parity (only in married women)	2.1±0.81	2.02±0.9
Age at first childbirth in years (only in parous women)	26.7±2.76	26.19±2.73

Table 2: Mean serum estradiol levels in cases and controls

Parameter	n = 30		n = 40		p value
	Cases	mean(pg/ml)±S.E	Controls	mean(pg/ml)±S.E	
Follicular phase	6	132.80±36.36	12	49.42±5.88	0.004
Luteal phase	6	185.17±40.08	11	113.55±8.05	0.03
Post menopausal	18	29.37±2.83	17	18.41±1.08	0.001

The cases showed significantly higher levels of serum estradiol ($p < 0.05$) as compared to controls.

Table 3: Mean serum progesterone levels in cases and controls

Parameter	n = 30		n = 40		p value
	Cases	Mean(ng/ml)±S.E	Controls	mean(ng/ml)±S.E	
Follicular phase	6	0.79±0.23	12	0.68±0.11	0.65
Luteal phase	6	13.67±2.09	11	13.75±2.00	0.97
Post menopausal	18	0.42±0.06	17	0.34±0.01	0.20

There was no significant association ($p > 0.05$) in the serum levels of progesterone between the two groups.

Table 4: Mean serum testosterone levels in cases and controls

Parameter	n = 30		n = 40		p value
	Cases	mean(ng/ml)±S.E	Controls	mean(ng/ml)±S.E	
Follicular phase	6	0.42±0.06	12	0.40±0.02	0.81
Luteal phase	6	0.37±0.06	11	0.35±0.07	0.81
Post menopausal	18	0.24±0.02	17	0.25±0.01	0.66

There was no significant association ($p > 0.05$) in the serum levels of testosterone between the two groups

IV. Disscussion

Sex steroid hormones play an important role in the etiology of breast cancer. In our study significant association with endogenous serum estradiol was found in the premenopausal and postmenopausal women. Similar findings were seen in Arora et al in the luteal phase and in Eliassen et al in the follicular phase.[1,4] Similar findings in the postmenopausal women were seen in Sieri et al, Schairer et al and Missmer et al.[5,6,7]

Estrogens contribute to tumor growth by promoting the proliferation of cells with existing mutations or perhaps by increasing the opportunity for mutations.[8] Eliassen et al found a positive association between follicular estradiol but not with luteal estradiol, reflecting the fact that luteal estradiol is derived primarily from ovarian production whereas a greater proportion of early follicular estradiol is derived from non ovarian sources (eg. adipose tissue). Another possible explanation given is that women who are close to menopause have longer follicular and slightly shorter luteal phases. Also estrogen receptor expression in breast tissue is higher in follicular phase than in luteal phase.[1]

In our study no association was found with endogenous progesterone levels in breast cancer cases compared to controls. Similar findings in the premenopausal women were seen in Eliassen et al and Herbert Yu et al and in Missmer et al in postmenopausal women. Significant association was seen in Arora et al, while some studies have got inverse associations.[1,4,7,9] It has been hypothesized that progesterone may either decrease breast cancer risk, by mitigating the estrogen induced proliferation or increase the risk because of the higher breast cell proliferation in the luteal phase.[1,8]

In our study we have found no association between endogenous serum testosterone and breast cancer. Similar findings were seen in premenopausal women in Eliassen et al and in post menopausal women in Adly et

al.[1,10] However Sieri et al, Missmer et al and Herbert Yu et al have found significant association in postmenopausal women.[5,7,9]

Testosterone increases the breast cancer risk either directly by increasing cellular growth and proliferation or indirectly by acting as a precursor to estradiol.[8] It is converted to estradiol by the enzyme aromatase in the peripheral adipose tissues. Evidence against the risk of breast cancer and endogenous serum testosterone are that there is no stimulatory effect on mammary epithelial cells in cell culture experiments with testosterone. Studies claiming an association have not adjusted for the increased estradiol levels, whereas those studies adjusted for estradiol levels did not show any association. Also aromatase inhibitors used in the treatment of breast cancer block the conversion of testosterone to estradiol thus increasing the testosterone levels, however these women did not have increased incidence of contralateral breast cancer nor did they experience increased tumour growth.[11]

V. Conclusion

Higher circulating levels of serum estradiol were associated with breast malignancy. Concentration of serum estradiol may predict the risk for breast malignancy and hence may help the clinicians to decide further management to decrease breast cancer risk. However more studies are required to find an association between endogenous sex steroid hormones and breast diseases.

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