



## **ASSOCIATION OF SERUM PROGESTERONE AND RISK FACTORS IN BREAST CANCER PATIENTS**

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### **ABSTRACT**

Evaluation of the association of serum progesterone and risk factors in breast cancer patients so as to provide indirect evidences to assess the Sherman and Korenman hypothesis (Bulbrook et al., 1978) regarding the protective effect of progesterone in breast cancer. Thirty nine patients were included in the study, blood samples were collected from breast cancer patients and RIA technique was used to determine progesterone in these samples. Progesterone was found to increase (statistically insignificant) in relation to the presence of risk factors like early menarche, late marriage, absence of feeding, late menopause, nulliparity, low parity and late pregnancy. Sherman and Korenman hypothesis does not seem to be valid and progesterone probably does not play a protective role in breast cancer.

### **INTRODUCTION**

Ovarian ablation requires an extensive research as yet to establish its role in cancer treatment (1992). This unstability in relation to hormonal treatment of this disease is a part of confusion which exist due to lack of evidence about the definite role of important steroidal hormones in this malignancy (Zumoff 1981; Henderson et al., 1975; Bulbrook et al., 1978; Fishman et al., 1978; Morgan et al., 1978; Dewaard 1975; Mirra et al., 1971 and Wynder et al., 1978). Many studies present the important role of estrogenic stimulation (Bonadonna 1988; Fasal & Paffenbarger 1975; Fishser et al., 1974 and Nevinny et al., 1969), while other studies show the significant role of progesterone in this regard (Sherman & Korenman 1974). Some workers have proved direct evidences by determining the important hormones in breast cancer patients but their results are still conflicting (Kelsey et al., 1981; Thomas 1978). In this study we have tried to provide an indirect evidence by determining the progesterone level in association to different risk factors in breast cancer patients.

### **PATIENTS AND METHODS**

This study was conducted in the Department of Radiotherapy JPMC Karachi in

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1997. The breast cancer patients who came for treatment were randomly selected. They were 40 in number and fulfill the following criteria:

- a) Female of different age groups (after Menopause).
- b) Biopsy proven breast cancer.
- c) Without any Radiotherapy, chemotherapy or hormonal therapy.
- d) Absence of clinically demonstrable metastasis.

5 cc blood was taken from the prominent cubital vein of each patient. No anticoagulant was added. The sample was centrifuged. Serum was separated and frozen for measurement of progesterone by RIA technique.

A detailed examination of the patient was done after selection. A structured interview containing different direct and indirect questions and confirmations about different life mile stones and reproductive life (Age at Menarche, Age at marriage, Age at 1st delivery, Age at menopause, Breast feeding, and Family history) was taken by the patient. Different questions contained different details of risk factors of breast cancer. All these details were collected on printed proforma. A registration number was issued to each patient. This number was marked on the sample for further processing. Student 't' test was used for the assessment of statistical significance.

## RESULTS

Table 1 reveals the characteristics of recruited patients in the study. This comprises Sex, Average age, pathology and location of lesion and Karnfsky range.

Serum progesterone is expressed in ng/ml.

Table 2 reflects progesterone level in breast cancer patients with respect to their Age at Menarche. Patients with early menarche had  $0.201 \pm 0.03$  of progesterone content whereas with late menarche it is found to be  $0.18 \pm 0.02$ . Although the difference is statistically insignificant ( $P > 0.05$ ), but progesterone shows an increase in high risky group as compared to others.

Table 3 depicts progesterone level in breast cancer patients with respect to their age at Marriage. Progesterone factor is found to be  $0.15 \pm 0.01$  in early marriage group whereas in late marriage group and very late marriage group it is found to be  $0.18 \pm 0.02$  and  $0.23 \pm 0.05$  respectively. Although these findings are statistically insignificant ( $P > 0.05$ ) but progesterone level seems to be highest in more risky groups as compared to other groups.

Table 4 exhibits the status of progesterone in breast cancer patients according to parity. Progesterone content was found to be  $0.31 \pm 0.11$  in nulliparous women whereas in low and medium para it is found to be  $0.19 \pm 0.04$  and  $0.19 \pm 0.02$  respectively.

In polyparous progesterone level is found to be  $0.13 \pm 0.01$  no statistically significant difference was found ( $P > 0.05$ ) in these groups. It is to be noted that progesterone level is relatively high in more risky groups as compared to other groups i.e. it is less in intermediate and less risky groups.

Table 5 indicates progesterone level in breast cancer patients with reference to their age at pregnancy. Progesterone level is shown to be  $0.16 \pm 0.01$  and  $0.18 \pm 0.11$  in early pregnancy and late pregnancy. The difference is statistically insignificant ( $P > 0.05$ ) but the point worth mentioning is the increased progesterone level in highly prone group i.e. in late pregnancy.

Table 6 shows progesterone factor in breast cancer patients with respect to the duration of breast feeding. In non-feeding group, progesterone is found to be  $0.24 \pm 0.07$  whereas in long and short feeding group it is found to be  $0.19 \pm 0.03$  and  $0.16 \pm 0.01$  respectively having statistically insignificant difference ( $P > 0.05$ ). Progesterone content seems to be high in more risky groups as compared to other groups.

Table 7 shows progesterone level in breast cancer patients with reference to the occurrence of Menopause.  $0.16 \pm 0.01$  and  $0.19 \pm 0.05$  are the progesterone factor in early menopausal and late menopausal group respectively. The difference between the two groups is statistically insignificant ( $P > 0.05$ ). One point which is evident from the table is the increased level of progesterone in high risk group i.e. at late menopausal state.

## DISCUSSION

Even after collecting great amount of data, and having the detailed knowledge of its behaviour, we are still not in a position to decide role of steroidal hormones in breast cancer (1992). Many studies advocate the role of estrogen (Bonadonna 1988; Fasal & Paffenbarger 1975; Fishser et al., 1974 and Nevinny et al., 1969) while others highlight the significance of progesterone (Sherman & Korenman 1974). "An ovulation-luteal inadequacy hypothesis" proposed by Sherman and Koreman (1974) requires to be mentioned here. According to this hypothesis a woman with variety of risk factors for cancer have in common with chronic anovulation or luteal inadequacy and therefore subnormal progesterone estrogen ratio. The existence of an increased incidence of anovulation or luteal inadequacy in women with breast cancer has been

supported by anatomical findings of Sommer (1974) Grattarola (1964) and the hormonal data of Kodama et al. (1977) Bulbrook et al (1992) and Cowan et al (1981) but has been put in doubt by the hormonal data of England et al. (1975), Swain et al (1975) and Makarkey et al. (1977). All this leads to conclusion that the role of estrogen and especially of progesterone is still vague in breast cancer. However most of the studies are based on the estimation of progesterone and estrogen in patients but contain insufficient information about the ultrachanges either in estrogen or progesterone to understand the behaviour of these hormones in these patients.

In previous results we have tried to link estrogen to different risk factors in breast cancer and found that estradiol decreases in association to various risk factors (Paper sent to Royal Society of Medicine, England). We concluded that either some factors of estrogen are responsible for malignant changes in breast, which was in accordance with Siiteri et al. (1974), Dilman et al (1968) and Lemon et al (1966) or progesterone may be the culprit. In this study, we are highlighting the association of progesterone to these risk factors.

Although our results do not present statistically significant changes in progesterone in association with various risk factors, but most important alteration is the same change i.e. increase in progesterone with increase in magnitude of a risk factor; for example, progesterone is high in those women who had early menarche as compared to those who had late menarche. Similarly it is high in nullipara, intermediate in low and median para and least in high para; as the nullipara come into the high risk group, low and median para in intermediate risk group and highpara in small risk group, according to the studies conducted by many researchers (1979). In the same way high progesterone is seen in women with late pregnancy, those who have not done breast feeding and those who have experienced late menopause, i.e. in all those groups who are high risk groups as shown by found in breast cancer patients (Sherman & Korenman 1974) but relatively high serum progesterone is present in association to risk factors. At this stage we are not in a position to support or contradict our findings, by other studies because there is lack of data which is collected in this way "An ovulation-luteal inadequacy hypothesis" or "protective role of progesterone in breast cancer" proposed by Sherman and Korenman (1974) is not supported by our results, because they do not show a protective effect of progesterone, which was designed in this hypothesis. However "Estrogen window hypothesis" proposed by Korenman (1980) is not supported or contradicted buys, because there maybe low progesterone during these periods which have been mentioned in this hypothesis. However this already been weakened by several evidences, already published (Zumoff 1981; Henderson et al., 1975 and Bulbrook et al., 1978). On the part of our study, "Estrogenic stimulation" proposed in many research articles (Bonadonna 1988; Fasal & Paffenbarger 1975; Fishser et al., 1974

and Nevinny et al., 1969) as a cause of malignant changes in breast cancer, perhaps this does not retain its validity. This is because of reciprocal relation which exists between estrogen and progesterone in endocrine milieu of woman, so one can expect that as an indirect evidence, our data represent a reduction in estradiol in our patients. However as suggested by Siiteri (1974), Dilman (1968) and Lemon (1966) and their colleagues, that some other estrogen fraction or metabolite or estradiol is supported by our present study.

Table 1  
Patients characteristics

|                            |                                            |
|----------------------------|--------------------------------------------|
| Mode of recruitment        | Random-Diagnosis based                     |
| Total number of patients   | 40                                         |
| Number of patients dropped | 1*                                         |
| Sex                        | Female                                     |
| Status                     | Post-Menopausal                            |
| Age (Years)                | 55.61 (Average)                            |
| Nature of Disease          | Biopsy proven                              |
| Pathology of Lesion        | Various malignant breast tumors            |
| Location of Lesion         | Different quadrants of breast-unilaterally |
| Criteria of Selection      | Already mentioned                          |
| Karnofsky range            | > /80                                      |

\*Insufficient serum was obtained from her sample.

Table 2  
Serum progesterone in breast cancer patients according to age at menarche

| Group          | Serum progesterone (ng/ml) | Significance |
|----------------|----------------------------|--------------|
| Early Menarche | 0.201 $\pm$ 0.03 (20)*     | P > 0.05     |
| Late Menarche  | 0.18 $\pm$ 0.02 (19)       | P > 0.05     |

\*Average  $\pm$  S.E. (No. of patients)

**Table 3**  
Serum progesterone in breast cancer patients according to age at marriage

| Group              | Serum progesterone (ng/ml) | Significance |
|--------------------|----------------------------|--------------|
| Early Marriage     | 0.15 ± 0.01 (13)*          | P > 0.05     |
| Late Marriage      | 0.181 ± 0.02 (15)          | P > 0.05     |
| Very Late Marriage | 0.23 ± 0.05 (11)           | P > 0.05     |

\*Average ± S.E. (No. of patients)

**Table 4**  
Serum progesterone in breast cancer patients according to parity of patients

| Parity                             | Serum progesterone (ng/ml) | Significance |
|------------------------------------|----------------------------|--------------|
| Nulliparous                        | 0.31 ± 0.11 (04)*          | P > 0.05     |
| Low Parity<br>(Upto 2 children)    | 0.19 ± 0.04 (08)           | P > 0.05     |
| Median Parity<br>(Upto 5 children) | 0.19 ± 0.02 (12)           | P > 0.05     |
| High Parity<br>( > 5 children)     | 0.13 ± 0.01 (11)           | P > 0.05     |

\*Average ± S.E. (No. of Patients)

4 patients were unmarried.

**Table 5**  
Serum progesterone in breast cancer patients according to age at first delivery

| Group           | Serum progesterone (ng/ml) | Significance |
|-----------------|----------------------------|--------------|
| Early pregnancy | 0.16 ± 0.01 (18)*          | P > 0.05     |
| Late pregnancy  | 0.18 ± 0.11 (14)           | P > 0.05     |

\*Average ± S.E. (No. of patients)

7 patients were unmarried or never get pregnant after marriage.

**Table 6**  
Serum progesterone in breast cancer patients according to duration of breast feeding

| Group                                               | Serum progesterone (ng/ml) | Significance |
|-----------------------------------------------------|----------------------------|--------------|
| Absence of feeding                                  | 0.24 ± 0.07 (07)*          | P > 0.05     |
| Short period of feeding<br>(upto 16 months)         | 0.19 ± 0.03 (10)           | P > 0.05     |
| Long period of feeding<br>( > 16 months of feeding) | 0.16 ± 0.01 (22)           | P > 0.05     |

\*Average ± S.E. (No. of patients)

**Table7**  
Serum progesterone in breast cancer patients according to menopause

| Group           | Serum progesterone (ng/ml) | Significance |
|-----------------|----------------------------|--------------|
| Early Menopause | 0.16 ± 0.01 (18)*          | P > 0.05     |
| Late Menopause  | 0.191 ± 0.05 (19)          | P > 0.05     |

\*Average ± S.E. (No. of patients)

2 patients had indeterminable menopause i.e. suffered an abnormally long period of paramenopause and could not tell about the clear cut age at menopause.

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