

## Impact of Serum Thyroid Hormones and Estrogen Status on the Risk of Breast Cancer in Kashmiri Women

Athar Ali\*, Manzoor R Mir, Sumira Bashir and Tehseen Hassan

Division of Veterinary Biochemistry, Faculty of Veterinary Sciences & Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences & Technology, Jammu & Kashmir, India

### Abstract

Estrogen involvement in breast cancer has been established; however, the association between breast cancer and thyroid diseases is controversial. Estrogen-like effects of thyroid hormone on breast cancer cell growth in culture have been reported. The aim of our study was to investigate a possible correlation between the genesis of breast cancer and the levels of serum thyroid hormones. We measured the percentage of free estradiol ( $E_2$ ) and the amounts of sex hormone-binding globulin (SHBG) and thyroid hormones in serum samples from Kashmiri patients with breast cancer ( $n=50$ ) and normal controls ( $n=25$ ). The patients were found to have significantly higher free  $E_2$  and significantly lower SHBG than controls. Moreover, the serum levels of free triiodothyronine ( $FT_3$ ) and free thyroxine ( $FT_4$ ) were lower in the patients than in controls, while the serum levels of TSH and TBG in the patients were not significantly different from those in controls. These results suggest that the reduction in the serum  $FT_3$  and  $FT_4$  levels, which is independent of changes in the serum level of free  $E_2$ , may be one of the risk factors for breast cancer in Kashmir.

**Keywords:** Estradiol ( $E_2$ ), Free thyroxine ( $FT_4$ ); Free triiodothyronine ( $FT_3$ ); Thyrotropin (TSH); Sex hormone binding globulin (SHBG); Thyroxine-binding globulin (TBG)

### Introduction

Breast cancer is a hormone-dependent neoplasm. It is the most common malignancy in women in Western countries and accounts for 18.4% of all cancers in female patients [1]. Qualitative changes in the lifestyle of women in developed countries that can influence risk factors for breast cancer, such as age at menarche, menopause, or first pregnancy, may partially explain this phenomenon [2]. Growing and developing breasts require the coordinated action of several hormones such as prolactin, estrogen ( $E_2$ ), progesterone, adrenal steroids, insulin, and thyroid hormones [3]. Among the above stated hormones,  $E_2$  is considered to be a potent mitogen for the normal mammary gland, whereas thyroid hormones appear to stimulate lobular development, contributing to the differentiation of normal breast tissue [4]. The biological activity of thyroid hormones and  $E_2$  is only manifested in cells expressing thyroid receptor (TR) and estrogen receptors (ER), respectively, that overall belong to the nuclear receptor superfamily. These receptors share a common mechanism of action whereby hormone-receptor complexes bound to cis acting DNA elements enhance or repress transcription of target genes [5]. The involvement of  $E_2$  in breast cancer growth has been established. About one third of breast cancers maintain  $E_2$  dependence for growth and the concentration of ER in malignant breast tissues is an indicator of their hormonal dependence [5]. We compared the serum levels of thyroid hormones in patients with breast cancer and those in normal Kashmiri women. Moreover, the correlation between the estrogen status, which is one of the risk factors for breast cancer, and the serum levels of each thyroid hormone in Kashmiri women was also examined.

### Subjects and Methods

#### Subjects

The study was carried out in Faculty of Veterinary Biochemistry (SKUAST-K) association with Govt. Medical College Srinagar located in North India. The Study included 50 patients with Breast Cancer and

25 Controls (healthy volunteers). Breast cancer patients were 38–80 years old and were without any known thyroid disease. The patients and controls were differentiated in to premenopausal and postmenopausal types. All patients were studied before any Radio or Chemo Therapy and did not take ant contraceptive steroids (Table 1).

A serum sample (2 ml) was collected from each subject, frozen quickly, and stored at  $-20^{\circ}\text{C}$  until analysis. In the case of premenopausal women, serum samples were collected in the follicular phase, i.e., within 10 days after the end of menstruation, to minimize as much as possible the influence of cycle changes in hormone levels

### Methods

Radio Immuno Assay (RIA) described below was carried out on a pair of approximately same numbers of serum specimens from patients

	Premenopausal		Postmenopausal	
	Patients	Controls	Patients	Controls
No of subjects	30	15	20	10
Age (years)	35 + 9	25 ± 15	51 + 9	46 ± 15
Height (cm)	Variable Height			
Weight (kg)	50 ± 15	45 ± 20	60 ± 6	50 ± 5

**Table 1:** Background data of normal controls and patients with breast cancer.

**\*Corresponding author:** Athar Ali, Division of Veterinary Biochemistry, Faculty of Veterinary Sciences & Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences & Technology, Jammu & Kashmir, India, E-mail: [atherali15@gmail.com](mailto:atherali15@gmail.com)

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Specification	Premenopausal			Postmenopausal		
	Controls (n=15)	Patients (n=30)	P	Controls (n=10)	Patients (n=20)	P
Free E <sub>2</sub> %	1.75±0.25	2.4±0.2	<0.00003	2.0 ±0.7	2.5±0.5	<0.005
SHBG (nmol/litre)	60.3±25.0	50.2±21.0	<0.001	60.9±18.9	45.1±9.1	<0.005
Free T <sub>3</sub> (pg/ml)	6.9±0.5	5.1±0.7	<0.00015	6.4±2.1	4.9±1.5	<0.025
Free T <sub>4</sub> (pg/dl)	1.2 ±0.27	0.9±0.2	<0.037	1.2±0.85	1.0±0.5	<0.05
TSH (µunits/ml)	1.08 ± 0.6	1.02±0.8	Not Significant	1.22±0.5	1.11±0.7	NS
TBG (µg/ml)Controls	20.7±3.2	19.0±2.8	Not significant	20.7±3	18.2±4.7	NS

**Table 2:** Free E<sub>2</sub>, SHBG, and thyroid functions in normal controls and patients with breast cancer.

and controls. Serum aliquots were analyzed for T<sub>3</sub>, free thyroxine (T<sub>4</sub>F), thyroid-stimulating hormone (TSH), E<sub>2</sub> using commercially available kits (DPC, Los Angeles, CA, USA). and serum TBG was by using the TBG <sup>125</sup>IRIA kit (Midori Juji, Chiba, Japan). The amount of SHBG in serum was measured by the SHBG IRMA (<sup>125</sup>I)kit (FarnosDiagnostica, Finland).

### Statistical analysis

The results were analyzed statistically using the Student's *t*-test for unpaired variables to evaluate the significance of differences between the mean values of the two studied groups.

### Results

We found that the mean percentage of free E<sub>2</sub> in serum in this study was found to be significantly (P <0.00003) higher in patients with breast cancer than that in normal controls, which was independent of menstrual status. The mean concentration of SHBG was significantly (P <0.005) lower in both premenopausal and postmenopausal patient groups than in corresponding control groups. The mean level of serum FT<sub>3</sub> was consistently lower in patients regardless of menstrual status as shown in Table 2, namely, 6.9±0.5 pg/ml for premenopausal controls (n=15) and 6.4±2.1 pg/ml for premenopausal patients (n=30) (P <0.0001); and 6.4±2.1 pg/ml for postmenopausal controls (n=10) and 4.9±1.5 pg/ml for postmenopausal patients (n=20) (P=0.002). The mean levels of serum FT<sub>4</sub> is 1.2 ±0.27 pg/ml for premenopausal controls (n=15) and 0.9±0.2 pg/ml for premenopausal patients (n=30) (P <0.03); and 1.2±0.85 pg/ml for postmenopausal controls (n=10) and 1.0±0.5 pg/ml (P <0.05) for postmenopausal patients (n=20). Thus it shows that the values of T<sub>3</sub> and T<sub>4</sub> were found to be significantly lower in patients than those in corresponding controls. while levels of TSH were not significantly different between the patient and the control group regardless of menopausal status.

### Discussion

To investigate pathological changes in thyroid hormones in the serum of patients with breast cancer, the full biochemical spectra of thyroid functions must be examined using very sensitive assay methods such as radioimmunoassay. Although the levels of FT<sub>4</sub> in the serum of breast cancer patients have been measured by several investigators, the results reported so far were normal [6-9], lower [10-11] or higher [12] than the control level, and no unanimous conclusion has yet been reached about this inconsistency. In this connection, other factors affecting the serum level of thyroid hormones, including concerns about assay procedures as described above, might be taken into account. It should be noted in particular that even if the serum levels of thyroid hormones are increased or decreased in breast cancer patients

[9-12], these changes are still within normal ranges. In addition, serum specimens from patients and controls should be assayed simultaneously because of possible intra-assay variations, and laboratory workers must be blinded to the study status of all specimens. In the present study, serum sample collection from patients was carried out immediately after their admission to our hospital, namely preoperatively on the first visit for cancer screening, and control serum samples were collected from the normal women. Both breast cancer patients and normal women studied in the present study were judged not to be under any unusual conditions such as hormone therapy. The mean levels of FT<sub>3</sub> and FT<sub>4</sub> in the serum of Kashmiri patients with breast cancer were found to be significantly lower than those in corresponding age-matched controls in the present study. Thomas et al. [13] have found in seven different ethnic groups that the serum level of FT<sub>4</sub> is significantly and inversely correlated with the risk of breast cancer. It has also been reported that women with early breast cancer are associated with reduced thyroid function [10-11]. On the other hand, Vorherr [14] has stated that thyroid hormones may influence metabolism of estrogen and carcinogens, and hyperthyroidism may be protective against breast cancer genesis. Our present results and the discussion made by Thomas et al. [13] and Vorherr [14] strongly suggest that the levels of free thyroid hormones in serum may be crucial for the risk of breast cancer, and the high serum levels of free thyroid hormones may be protective against carcinogenesis. Elevated levels of serum TSH have been reported in breast cancer patients by several investigators [6-8,10,15-17]. However, we did not find any significant difference in the serum level of TSH and SHBG between the patient and control groups in the present study. Our results suggest that the reduction in the serum FT<sub>3</sub> and FT<sub>4</sub> levels, which is independent of changes in the serum level of free E<sub>2</sub>, may be one of the risk factors for breast cancer in Kashmir.

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