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Research Article

Comparative Analysis of Serum Prolactin in Postmenopausal Females with Breast Cancer before and After Treatment -A Pilot Study in Southern Districts of Haryana

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Abstract: Breast cancer is usually present for many years (as long as 5-10 years) before it can be clinically diagnosed (theory of the 'dormant malignant cell'). This implies that breast cancer cells, during their subclinical period, are likely to have been exposed for a considerable period of time to endogenous prolactin. So, we planned this study to evaluate the role of endogenous prolactin hormone, if any, in postmenopausal females excluding the patients on hormone replacement therapy to know whether there is any relationship between breast cancers and if there is any relation – whether it is a positive or negative? Is there any effect on serum prolactin after the treatment? Hormone therapy is known to affect these hormone levels but whether treatment of breast cancer per se also decreases the serum prolactin levels is not known. We planned the present study to determine serum prolactin levels in patients before and after 4 months of treatment (chemotherapy/surgery and radiotherapy). Circulating hormone levels were measured using a chemiluminescence method. Their results were compared with a group of 25 age matched healthy controls. We found that serum prolactin levels were very significantly higher in patients before treatment (Group I) as compared to controls (Group III). Serum prolactin levels were significantly higher in patients before treatment (Group I) when compared after 4 months of treatment (Group II). We concluded that postmenopausal females with breast cancer have abnormalities in serum prolactin levels. These abnormalities may be considered in the pathogenesis of the disease and should be taken into account in the treatment of patients of breast cancer. It might also be helpful to delay the onset of cancer by normalizing the levels of these hormones and in deciding the treatment modality for the patients once breast cancer has been diagnosed but further studies are required to prove the benefit of measuring serum hormone levels as a screening test.
Keywords: Breast cancer, prolactin, chemiluminescence, menopause

INTRODUCTION

Breast cancer is the most common malignancy and most common cause of cancer deaths among women world-wide. Among females breast cancer incidence rates are higher in postmenopausal than in pre-menopausal women. It accounts for 3-5% of deaths in the developed countries while it is 1-3% in the developing countries. Carcinoma of breast is extremely rare before 20 years of age but thereafter the incidence rises steadily. Early menarche and late menopause, nulliparous females and elderly primigravida are predisposed to breast carcinoma. At the age of 30 years the incidence is 1: 622 females, at the age of 60 it is 1: 24 females and by the age of 90, 1: 8 females are affected [1].The average age of diagnosis of breast carcinoma is 64 years [2].

Most breast carcinomas are epithelial tumors that develop in ducts or lobules; less commonly are non-epithelial cancers of supporting stroma. 95% of all breast malignancies are adenocarcinomas and less than 5% are other type's eg squamous cell carcinoma, phylloid's tumor, sarcoma and lymphoma. In situ carcinoma accounts for 15-30% of all breast cancers whereas invasive breast carcinoma accounts for 70-85% of breast carcinoma, in which ductal carcinoma accounts for 79% of cases. Traditionally, there are two systems of classification of breast carcinoma based on the clinical staging of disease - the Manchester System and TNM (Tumor, Nodes, and Metastasis) staging [1].

The etiological factors implicated are – Caucasian race, family history of breast carcinoma, history of prior breast disease, mutation of BRCA1 and BRCA2 gene, post menopausal females on hormone

replacement therapy (HRT), radiation exposure, increased fat intake, moderate to heavy alcohol intake, obesity and less breast feeding.

Various biological factors associated with aging are likely to contribute to the increased incidence and prevalence of cancer with age i.e. the duration of carcinogenesis, the increased susceptibility of aging cells and tissues to environmental carcinogens and physiological alterations that favor tumor growth and metastasis (e.g. immune senescence and proliferative senescence) [3].

Prolactin (PRL) is 23kDa hormone produced primarily by lactotrophs of the anterior pituitary and extrapituitary sites. Among the extra pituitary sites, prolactin expression is seen in the placental decidua (richest source), dermal fibroblasts, brain, myometrium and lymphocytes. The breast cancer cells also produce prolactin locally. Biological activities of PRL are mediated by specific membrane receptors (PRL-R). PRL affects cellular growth, angiogenesis, proliferation and differentiation, initiation and maintenance of milk production [4]. Human prolactin (hPRL) undergoes several post translational modifications such as glycosylation; phosphorylation and cleavage that contribute towards its pleotropic action [5].

Metoclopramide (dopaminergic antagonist) has a high capacity to induce hyperprolactinemia in rats and also accelerate tumour growth. Estrogen, progesterone, growth hormone, and Prolactin is responsible in the development of breast cancer [5].

In humans, prolactin secretion is increased by stimulation of the nipple, estrogen, breast suckling (activates neural afferent pathways in the hypothalamus that induce PRL release), exercise, meals, sexual intercourse, minor surgical procedures, general anesthesia, chest wall stimulation or trauma (invoke the reflex suckling arc), chronic renal failure (decreasing peripheral clearance of PRL), hypothyroidism (because of compensatory TRH secretion), acute myocardial infarction, and other forms of acute stress. Certain medications such as reserpine, haloperidol, cimetidine and phenothiazine increase plasma prolactin level whereas levodopa decreases it. Secretion of prolactin is topically inhibited by the hypothalamus; the primary inhibitor being dopamine [6]. It has been shown that administration of exogenous prolactin increases the rate of mammary tumor formation and suppression of prolactin level has the opposite effect [7]. Studies on postmenopausal cases have shown that higher prolactin is associated with increased risk of breast cancer [8,9]. Majority of the breast cancer cells have been shown to express the prolactin receptor (PRL-R) [10]. Studies on humans have demonstrated the correlation between high prolactin receptor levels & shorter survival in breast cancer patients [11]. The use of anti prolactin agents can block in-vitro growth of human breast cancer cell lines [12]. Meng and coworkers found that receptor concentrations were higher in malignant breast tissue with 95% breast tumors staining positively [13]. Studies have also shown that there is significant positive correlation between serum prolactin and pathogenesis of human breast carcinoma [14].

However, the role of prolactin in human breast carcinoma has been controversial. Clevenger et al. studied the role of prolactin and prolactin-receptors in mammary carcinoma and found positive correlation between elevated levels of serum prolactin and carcinoma breast [15]. In vitro studies have also indicated that the antiprolactin agents can block human breast cell lines [16]. Holtkamp et al reported that as many as 44% of patients with metastatic breast disease were hyperprolactinemic during the course of disease [17]. In a subset of women at risk for familial breast cancer, basal serum PRL levels were significantly elevated [18]. Vanderhaar and Biswas demonstrated that human breast cells respond to PRL growth signal when grown as solid tumors in nude mice [19].

Reduction of human prolactin with bromocriptine does not alter the progression of the disease [20]. Surgical intervention such as hypophysectomy has also not been successful in the treatment of breast carcinoma.

On the other hand; RIA based studies have detected that specific receptor based binding of prolactin in established cases of breast carcinoma is seen only in 20-60% of human breast carcinoma [21, 22]. Pearson et al. observed that treating patients with prolactin inhibiting ergot drugs in order to diminish the levels of circulating prolactin results in no change in disease over time [23].

Wang et al. and Ingram et al. showed that there is no clear cut correlation between circulating pro-lactin levels and the etiology or progression of breast carcinoma [24, 25].

Studies have demonstrated that prolactin mRNA is produced in normal human breast epithelium and that breast cancer cells can synthesize appreciable quantities of prolactin in vitro. Little is known about the relationship between blood and breast tissue prolactin concentrations; however prolactin staining in breast tumors was significantly correlated with plasma prolactin concentrations at the time of diagnosis in one report. Moreover limited evidence suggests that prolactin is associated with higher cellular motility and angiogenesis [6].

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with the Department of Radiotherapy, Pt. B. D. Sharma,

University of Health Sciences, Rohtak. The patients were randomly selected and divided into two groups; twenty five postmenopausal females with breast carcinoma at the time of diagnosis were taken as the study group. These patients were subjected to serum prolactin estimation before treatment (Group I) and after 4 months of treatment (Group II). All patients were either surgically managed (Modified Radical Mastectomy) and/or given anticancer regimen - 5-FU, Epirubicin, Cy-clophosphamide (FEC) for six cycles and radiotherapy locally or generalized depending upon the site and ex-tent of metastasis, general condition of the patient, side effects of therapy and the staging of the cancer. Staging of breast carcinoma was done according to TNM staging by the Department of Radiotherapy. Their results were compared with a group of 25 age matched healthy controls (Group III).

In-formed consent was taken from all patients and healthy controls. This study was approved by the review board of the institute. Females on oral contraceptive pills / hormone therapy or drugs affecting serum prolactin levels were excluded from the study. Females with BMI ≥30 kg/m2 were also excluded. Staging of breast carcinoma was done according to TNM staging [26].

METHODS

Five ml of venous blood was collected aseptically from anticubital vein. Serum was separated by centrifugation (2000 rpm for 15 minutes) and subjected to analysis of serum hormones.

Serum Prolactin levels were measured using direct chemiluminescent technology on an ADVIA Centaur CP (Siemens). Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays [27]. Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Standard curves for hormones were plotted using increasing concentrations of hormone on the X-axis and relative light units (RLU) on the Y-axis. Two levels of controls were used for all the hormones. Samples were run only when levels were within range.

Quality control charts were prepared by plotting observed values on the Y-axis and time when the observa-tions were made on the X-axis. The control limits were calculateed from the mean (x) and standard deviations (s). 95% to 99.7% control values correspond to mean ±2 or 3 SD.

The ADVIA Centaur CP Prolactin assay is a two-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of two antibodies. The first antibody, in the Lite Reagent, is a polyclonal goat anti-prolactin antibody labeled with acridinium ester. The second antibody, in the Solid Phase, is a monoclonal mouse antiprolactin antibody, which is covalently coupled to paramagnetic particles. A direct relationship exists between the amount of pro-lactin present in the patient sample and the amount of RLUs detected by the system.

RESULTS

In the present study, we found that serum prolactin levels were higher in patients before treatment (Group I) and the difference was statistically highly significant when compared to the control group (Group III).After treatment (Group II) the serum prolactin levels were decreased significantly compared to pretreatment levels (Group I) and became non significant compared to the controls (Group III).

The age in the study group (Gp I and II) varied from 45 - 75 years having the mean age ± SD as 51.76 ± 9.01 years as compared to 50.72 ± 6.04 years in the control group (Gp III) were also the age varied from 45 - 75 years (Table-1).

Out of 25 patients in the study group (Gp I and II), 4 (16%) patients gave the family history of carcinoma breast in one of their close relatives whereas none in the control group (Gp I) gave such history (Table-2)

16% of the subjects in the study group (Gp I and II) gave the history of smoking compared to 8% in the control group (Gp III) (Table-3).

In the study group (Gp I and II), 7 cases were of type IIB stage, 6 cases were type IV stage, 4 cases were IIIB stage, 3 were type IIIA stage, 2 cases of type IIA stage, 2 cases of type IIIC stage and 1 case of type I stage accounting for 28%, 24%, 16%, 12%, 8%, 8% and 4% respectively (Table-4).

Table-1: Distribution of age of subjects in control group vs study group according to mean age ± SD

	Control Group (III) n=25	**Study Group (I and II) n=25**
Mean Age ± SD (years)	50.72 ± 6.04	51.76 ± 9.01

Table-2: Distribution of subjects in control group vs study group according to family history

Group	Positive Family History	Negative Family History	% Positivity
Control Group (III) n = 25	Nil	25	Nil
Study Group (I and II) n = 25	4	21	16%

Table-3: Distribution of subjects in control group vs study group according to history of smoking

Group	Positive Smoking History	Negative Smoking History	% Positivity
Control Group (III) n = 25	2	23	8%
Study Group (I and II) n = 25	4	21	16%

Table-4: Distribution of subjects according to tnm (ajcc) staging

TNM Staging	Total Cases	% of Total Cases
I	1	4
IIA	2	8
IIB	7	28
IIIA	3	12
IIIB	4	16
IIIC	2	8
IV	6	24

Table- 5: Comparative analysis of serum hormone levels between patients and healthy controls

Group	Control Group (III) n = 25	Study Group (I) n = 25	Study Group (II) n = 25	p Value$	p Value#	p Value¥
Serum Prolactin (1.8- 20.3ng/mL)	10.16 ± 5.08	28.49 ± 15.82	15.51 ± 12.98	<0.001***	>0.05*	<0.05**

p Value$: p value calculated using unpaired 't' test between Group III and Group I
p Value#: p value calculated using unpaired 't' test between Group III and Group II
p Value¥: p value calculated using paired 't' test between Group I and Group II
*: not significant
**: significant
***: very significant

The study group's (Gp I) pretreatment Serum Prolactin Mean ± SD value was 28.49 ± 15.82 having the range between 5.64- 56.34 ng/mL and the range in control group (Gp III) being 1.93- 18.83 ng/mL having Mean ± SD 10.16 ± 5.08. The p value < 0.001, was statistically highly significant (Table-5).

The study group's (Gp II) post treatment Serum Prolactin Mean ± SD value was 15.51 ± 12.98 having the range between 6.40- 70.12 ng/mL and the range in control group (Gp III) being 1.93- 18.83 ng/mL having Mean ± SD 10.16 ± 5.08. The p value > 0.05 and was statistically nonsignificant.

The study group's (Gp I) pretreatment Serum Prolactin Mean ± SD value was 28.49 ± 15.82 and the post treatment (Gp II) Serum Prolactin Mean ± SD value being 15.51 ±12.98. The p value < 0.05 and was statistically significant.

DISCUSSION

The mean age of breast cancer patients was 51.76 ±9.01 years and that of healthy controls was 50.72 ±6.04 years. There was family history of breast cancer in 16% of patients whereas no family history was found in healthy controls (Table III). A woman's risk of breast cancer is higher if her mother, sister, or daughter had breast cancer. The risk increases if a family member gets breast cancer before 40 years of age. The increased risk is because of the inheritance of the breast cancer susceptibility gene, BRCA l, which is linked to both breast and ovarian cancer. Individuals with a mutated form of BRCA l have an 80 - 85% chance of developing breast cancer during their lifetime[1].

16% of patients indicated a history of smoking com-pared to 8% in the control group (Table III). Smoking leads to formation of benzo [*a*] pyrene guanine adducts which result in damage to DNA in the S phase of the cell cycle and thereby increasing chances of cancer [28].

In our study, 28% of the females with breast cancer be-longed to a higher income group. Increased incidence in females in the higher income group is probably because of lower birth parity (parity <3), early detection, altered lifestyle, dietary habits (increased fat intake), and better access to breast cancer screening procedures [1].

Females with a sedentary life style are more prone to breast cancer. In our study we found that 72% of patients have a sedentary life style as compared to only 25% of controls had sedentary life style. The effect of physical activity on the incidence of breast cancer is mediated by an increased capacity for glucose transport into the muscle and adipose tissue in response to insulin stimulation. Lack of exercise leads to decreased insulin sensitivity and increased insulin concentration. Hyper insulinemia amplifies the bioavailability of IGF-I. IGF-I and insulin together have been shown to stimulate motility of cells in human breast cancer cell lines, an effect that could enhance migration and invasion of the tissues. IGF-I also promotes angiogenesis in breast tissue [29]. The role of estrogen is clear in breast cancer but the role of other hormones like prolactin, progesterone, and testosterone is not very certain. Hormone therapy is known to affect these hormone levels whether does treatment of breast cancer per se also decreases the hormone levels is not known. We planned the present study to determine hormone levels in patients before and after 4 months of treatment (chemotherapy/surgery and radiotherapy). These levels were compared to controls to elucidate the role of endogenous serum prolactin in breast cancer.

Prolactin is produced by anterior pituitary, placenta, skin fibroblasts, brain, myometrium, lymphocytes[30] and also by the local productionfrom the mitotic breast cancer cell lines. The malignant breast tissue respond to endogenous (usual sites of production), exogenous and locally produced prolactin. Prolactin has been shown to increase the growth of both normal and malignant cell lines in vitro[31]. Prolactin affects cellular growth, angiogenesis, proliferation and differentiation of the normal and mitotic breast cancer cell lines through the PRL-R. The prolactin receptor may be associated with the estrogen (ER) and progesterone (PR) receptor expression. Several in vitro studies have reported that long-term prolactin or estrogen exposure can increase both PRL-R and ER expression. Increased prolactin positivity has been significantly associated with increased tumor size, higher stage, nodal involvement, and a worse overall survival inunivariate analyses [32- 34].(122,23,24)

Prolactin may lead to breast cancer by promoting cell proliferation and growth by altering the expression of cyclin D1 (an important cell cycle regulator) causing increased cell motility, and supporting tumor vascularization. It has a mitogenic action in breast cells. Prolactin also appears to inhibit apoptosis of breast cancer cell lines. One study reported that endogenous prolactin expression in breast cancer cell lines was negatively correlated with C2 ceramide induced apoptosis. Introduction of a prolactin antibody was associated with a three to seven fold increase in cell death in the same model system [35].

Females with breast cancer have abnormalities in serum prolactin levels which may be considered in the pathogenesis of the disease and should be taken into account in the treatment of such patients. Reduction of serum prolactin levels might prove to be helpful in preventing breast cancer and evaluating its levels might be helpful to screen the risk of breast cancer. This might also be helpful to delay the onset of cancer by normalizing the level of serum prolactin and in deciding the treatment modality for the patients once breast cancer has been diagnosed. Serial monitoring of serum levels of prolactin must be done but the sample size of study group was small so further studies are required to prove this.

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