Pathological Profile of the Carcinoma Breast Patients with Relation to Serum Prolactin Levels in an Apex Institute of Uttar Pradesh

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ABSTRACT

Introduction: Breast cancer is most common cancer on females worldwide with high mortality. PRL (prolactin) has a role in mammary gland growth, differentiation and lactation. It has been revealed that PRL may be involved in pathogenesis and progression of breast cancer malignancy. This study was designed to find out any association between serum Prolactin level with breast cancer and in its various stages. In this article a comparative cross sectional study with 30 cases and 28 controls conducted in apex institute of Varanasi, U.P. from July 2016 to July 2018 has been done. The serum prolactin levels were determined by AxSYM system which is a micro-particle enzyme immunoassay (MEIA) technology.
RESULTS: Early menarche and post-menopausal status are significantly more associated with Carcinoma breast. Most common associated history with carcinoma breast was anorexia and weight loss. Mean prolactin level was significantly higher in carcinoma breast patients (39.67 ± 7.71) in comparison to controls (28.72 ± 1.63).
CONCLUSIONS: All high risk postmenopausal women with early age of menarche and not having breastfed should be made aware about breast cancer and train Self Breast Examination. Prolactin can be a potential target for primary prevention and intervention in breast cancer, especially in high risk females.

KEYWORDS: breast cancer; prolactin; post-menopause;

INTRODUCTION

Breast cancer is the most frequent female cancer in both more developed and less developing countries (Ferlay et al., 2015) [1]. India has one of the highest mortality rates for breast cancer. Fifty percent of Indian women diagnosed with breast cancer will die due to the disease. India is facing challenging situation due to 11.54% increases in incidence and 13.82% increase in mortality due to breast cancer during 2008–2012. The main reasons for this observed hike in mortality are due to lack of adequate breast cancer screening, diagnosis of disease at advanced stage and unavailability of appropriate medical facilities.

In addition to genetic abnormalities, there are several other factors that may increase the risk of breast cancer such as environmental changes, age, geographical location, age at pregnancy, nulliparity, hormones and growth factors. Estrogens, progesterones, androgens and insulin are some of the hormones that have been shown to stimulate tumorogenesis in breast cancer. Many of these hormones facilitate tumor growth in autocrine/paracrine pathway [2].

Prolactin is a 198-amino acid polypeptide that is secreted by lactotroph cells in the anterior pituitary and is the main trophic factor for milk production by the breast [3]. Prolactin does a lot of works in the body including the effects on Reproductive behavior and Homeostasis by regulating solar and humoral immune responses, regulating water and salt and regulating angiogenesis. PRL has a role in mammary gland development, differentiation and lactation. It has been shown that PRL may be involved in pathogenesis and progression of breast cancer malignancy (Tworoger et al. 2007)[4]. Furthermore it is shown that PRL acts on mammary epithelial cells directly to increase cell proliferation and accelerate invasion to carcinoma [5].

A study shows that in post-menopausal women, as breast cancer risk increases serum PRL levels also increase. Higher serum PRL levels are known to be associated with higher risk of developing metastatic breast cancer due to their correlation with tumor size, stage and lymph node status of the carcinoma [6]. Also three quarters of the tumors in this study are shown to express PRL which confirms the idea that PRL may play a role through autocrine/paracrine pathway.

This study was designed to find out any association between serum Prolactin level with breast cancer and in its various stages.

METHODS AND MATERIAL

An apex care center based comparative cross sectional study was conducted between July 2016 to June 2018 in Department of General Surgery and Endocrinology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh on histologically proven breast cancer subjects who gave consent excluding Pregnant / lactating women, who have received chemo / radiotherapy prior to presentation and subjects who have earlier history of cancer or any calcium metabolism affecting disorder. Data collection was done for six months period during which 30 patients gave consent. 28 female attendants of the 30 patients gave consent for study to be used as controls.

The serum prolactin levels were determined by the help of department of Endocrinology by AxSYM system which is a micro-particle enzyme immunoassay (MEIA) technology with a commercial kit from Abbott. Data was entered and cleaned using Microsoft Excel version 2010 and other statistical test was calculated using SPSS (Statistical Package for Social sciences) version 16.0 software.

RESULTS AND OBSERVATION

Mean age of the patients in breast cancer was 48.70 years with standard deviation of 10.8 years, majority belonging to 35-50 years age group. Half of the patients were illiterate. 10% subjects presented with cyclical pain while about 23% presented with nipple discharge.

Table 1: Distribution of the patients according to related clinical history

	Carcinoma Breast (n=30)		Controls (n=28)		p-value
	No.	%.	No.	%.	
Age menarche Early (before age 12 years) Late (after age 12 years)	21 9	70.0 30.0	7 21	25.0 75.0	<0.001
Menopausal status					

Pre	3		33.33	22	78.57	<0.001
Post	27		66.67	6	21.42	
Parity						
Nulliparous	5		16.67	2	7.14	0.031
1-2	10		33.33	19	67.86	
>2	15		50.00	7	31.80	
Breast feeding						
Yes	20		66.67	24	85.72	0.090
No	10		33.33	4	14.28	

Early menarche and post-menopausal status is significantly more associated with Carcinoma breast. Though controls have more breastfed than the cases, the difference is not significant.

Table 2: Distribution of the Carcinoma Breast patients according to associated history (n=30)

	No.	Percent (%)
Anorexia	22	73.3
Weight loss	20	66.7
Signs of metastasis	2	6.7
History of biopsy from involved breast	5	16.7
History of previous treatment	8	26.7
History of Previous surgery	2	6.7
Hypertension	5	16.7
Diabetes	2	6.7
Family history of breast cancer	1	3.3

Most common associated history with carcinoma breast was anorexia and weight loss.

Table 3: Distribution of the patients according to size of the lump, NAC involvement and management

	Carcinoma Breast (n=30)	
	No.	%.
Size		
< 2	0	0.0
2.1-5	10	33.3
>5	13	43.4
Chest wall involvement	3	10.0
Skin involvement	4	13.3
Nipple areola complex (NAC)		
Yes	4	13.33
No	26	86.67
Nipple retraction		
Yes	9	30.0
No	21	70.0
Surgery		
Non surgical management	0	0.0
Excision	0	0.0
MRM	30	100

In our study, most of the patients with carcinoma breast have lump size more than 5 cm. All cases were managed by modified radical mastectomy.

Table 4: Distribution of examination finding in Carcinoma Breast patients (n=30)

Variable	No of case	Percentage
Lump in breast	30	100
Ulceration breast	3	10.0
Axillary swelling	15	50.0
Peau'd orange	3	10.0
Satellite Nodule	0	0.0
Inflammatory carcinoma	1	3.33
Fixity chest wall	3	10.0
Edema arm	2	6.67
Axillary involvement	18	60.00
Supraclavicular	4	13.33
Infraclavicular	2	6.67
Internal mammary	1	3.33

Above table tells that all patients presented with breast lump with other sign and symptoms of varying frequency.

Table 5: Distribution of Mean Lipid profile in groups

	Carcinoma Breast Mean±SD	Controls Mean±SD	t-value	p-value
TC	178.73±52.538	147.55±49.070	-2.331	0.023
TG	152.57±86.723	141.30±61.186	-0.545	0.588
HDL	45.920±17.162	39.000±10.392	-1.841	0.070
LDL	105.50±33.009	90.15±36.022	-1.693	0.100
VLDL	31.640±18.816	29.880±15.155	-0.391	0.698

Values of all lipid parameters were higher in patients in comparison to control though only value of total cholesterol comes out to be significant.

Table 6: Distribution of clinical staging in Breast cancer patients

Stage	Number
$T_1N_0M_0$	0
$T_2N_0M_0$	5
$T_2N_1M_0$	5
$T_3N_0M_0$	5
$T_3N_1M_0$	6
$T_3N_2M_0$	2
$T_{4a}N_1M_0$	3
$T_{4b}N_2M_0$	2
$T_{4c}N_1M_1$	1
$T_{4d}N_2M_1$	1

On clinical staging of disease majority of cases were of $T_3N_1M_0$ (n=6) followed by T_2N_0M0 (n=5). None of case was T1N0M0 stage in our study.

Table 7: Distribution of mean prolactin level among breast cancer, benign breast diseases and healthy controls

	Mean±SD	f-value	p-value
Carcinoma Breast (n=30)	39.67±7.71		<0.001
Controls (n=28)	28.72±1.63		

Mean prolactin level was significantly higher in carcinoma breast patients in comparison to controls.

Table 8: Distribution of prolactin level of the patients with clinic-pathological profile of the carcinoma breast patients

Variable	No of case	Prolactin (Mean±SD)	P- value
T stage			
T1	0	0	
T2	4	33.400±4.0075	T2 Vs T3: p=1.00
T3	15	36.316±6.1354	T2 Vs T4 : p=0.002
T4(a, b)	11	46.542±5.5387	T3 Vs T4 : p<0.001
N-stage			
N0	14	36.289±6.3660	N0 Vs N1 : p=0.211
N1	11	41.751±8.8794	N0 Vs N2 : p= 0.106
N2	5	44.600±4.5519	N1 Vs N2 : p=1.000
M stage			
M0	28	39.912±7.9224	0.542
M1	2	36.385±3.0901	
Histological grade			
High	26	39.770±8.1942	0.869
Low	4	39.068±3.9605	

Mean prolactin levels increase as the stage increases in T-stage and N-stage. No trend found in M-stage neither histological grade of the cancer shows any significant difference.

Table 9: Distribution of prolactin level of the patients with receptor status

Variable	No of case	Prolactin (Mean±SD)	P- value
ER (estrogen receptor)			
Positive	15	43.291±7.8814	0.008
Negative	15	36.062±5.7680	
PR (prolactin receptor)			
Positive	16	43.648±8.2626	0.001
Negative	14	35.138±3.5361	
Her-2/neu			
Over expressed	13	43.989±8.0046	0.005
Not over expressed	17	36.379±5.7655	
TNBC	14	35.138±3.5361	

In the above table we can see that all receptor positive status has significantly higher mean prolactin level.

DISCUSSION

Women who have early menarche and late menopause have a slightly higher risk of breast cancer. This may be related to a higher lifetime exposure to the hormones (Arriagada et al, 2006 and Fisher et al, 2001) [7, 8], which is similar to this study.

Study conducted by Dixit et al., 2016 [9], age of subjects enrolled in the study ranged from 16 to 58 years with the mean age of subjects in malignant and control group was 48.70 ± 10.04, and 35.60 ± 12.42 years, respectively which coincides with our study having 48.70 ± 10.81 and 34.60 ± 7.528 years respectively. The reason for difference among all groups could be the fact that as the age increases the risk of breast cancer increases.

In our study carcinoma breast was more associated with post-menopausal females as compared to controls, which is similar to Raina *et al* (2008) [10] which showed 70% and belong to clinically advanced disease, Wang M. *et al* (2016) [11] and Tikk et al (2015)[12].

Ray and Hussain et al (2001) [13] examined the association between lipids, lipoproteins, vitamins and it was found that Breast cancer patients had a higher level of serum cholesterol, triglycerides and LDL-C than healthy controls. Similarly higher levels of all components of lipid profile were found among breast cancer patients compared to healthy control subjects in our study as well.

In comparison with controls, carcinoma breast cases have higher levels of lipid profile.

Higher level of serum triglycerides and lower level of HDL-C among Breast cancer patients compared to healthy control shown by Chang et al. (2007); Furberg et al. (2004); Kucharska-Newton et al. (2008) [14,15,16] in contrast to our study in which levels of HDL was also high. In the study of (Hasija K. et al 2005) [18] reported that HDL-C level was either elevated or depressed in women with Breast Cancer.

A meta-analysis (2016) [11] shows that serum prolactin level is significantly associated with breast cancer with risk ratio of 1.16. Our finding is similar to the finding of meta-analysis as serum prolactin level is significantly higher in patients than controls.

Serum prolactin level is significantly related to the receptor status of the patient i.e. ER, PR and Her2neu status as well as histological grade of the disease. Our result replicates the finding from NHS I and II where the association with PRL was stronger among ERþ/PRþ tumours (Tworoger et al, 2007) [4].

Mean serum prolactin level in premenopausal patients is less than the post menopausal patients and is significantly related to menopausal status which is coherent with many studies. PRL levels among parous premenopausal women were lower than those among nulliparous women [4].

However, we did not find an association between parity and PRL concentrations among postmenopausal, which contrasts with some reports (Wang et al, 1988; Eliassen et al, 2007) [18,17]. Lowered PRL levels have been suggested as one of several possible

mechanisms that mediate this risk while other analyses have shown null (Tworoger et al, 2007) [19] or positive associations (Wang et al, 1988; McTiernan et al, 2006) [18,20].

Among breast cancer patients Nicol M et al (2002) [21] found a higher level of prolactin in patients with DCIS. They could not be found any correlation between prolactin levels and histological grade of tumor. Similar finding was found in our study also with no statistical variation of prolactin as per stage and grade of breast cancer.

Tikk K et al (2015) [12] have reported a moderate positive association between circulating prolactin level and invasive breast cancer risk among postmenopausal women. They also found a higher circulatory level of prolactin to be associated with increased risk of in situ breast cancer, similar tour study

CONCLUSION AND RECOMMENDATION

All high risk postmenopausal women with early age of menarche and not having breastfed should be compulsorily educated about breast cancer and taught Self Breast Examination.

Rice et al. in post-menopausal women (2015) [22] reported that higher prolactin levels and higher mammographic density which is consistent with prolactin mitogenic properties and the association between prolactin and breast tumor promotion. They have suggested that prolactin deserves investigation as a target for breast cancer risk reduction.

Our study has demonstrated a higher level of prolactin among breast cancer patients compared to healthy control (p <0.005). This suggests that prolactin level plays a role in pathogenesis of breast disease both benign and malignant. Whether it can be a possible target for primary prevention of breast cancer among high risk women or a therapeutic target in women suffering from breast cancer needs to be studied in large randomized multi centric trials.

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