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## STUDY OF SERUM BETA CATENIN LEVELS IN PATIENTS OF BREAST CARCINOMA IN NORTH INDIAN POPULATION

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### **Abstract**

**Background:** Breast cancer is a malignant proliferation of epithelial lining of ducts or lobules of breast and occurs due to hyper estrogenic states. It appears that estrogen and progesterone act through proto-oncogenes and growth factors to affect breast cancer etiology. Beta catenin is a proto-oncogene and the mutation of this gene is found in a variety of cancers including primary hepatocellular carcinoma, colorectal cancer and breast cancer. It may be one of the marker in breast cancer as it is having impact on cyclic D pathway but the precise role is not known. **Aim and Objectives:** To estimate the serum levels of beta catenin in patients of carcinoma breast and to compare with age matched healthy controls. **Methodology:** The present study was conducted in the department of Biochemistry in collaboration with department of Radiotherapy and Surgery in PGIMS Rohtak. Twenty five patients with histopathological proven carcinoma breast were taken for the study and same number of age matched subjects served as controls. Serum beta catenin was assessed by enzyme linked immunosorbent assay (ELISA) along with routine biochemistry of all the subjects. **Results:** The beta catenin levels were found to be increased in the cases as compared to controls. The mean value was  $43.32 \pm 9.39$  pg/mL in cases and  $19.6 \pm 4.17$  pg/mL in control subjects and pvalue was significant. **Conclusion:** Beta catenin may play a role in the pathogenesis of breast cancer and can be used as a prognostic marker.

**Keywords:** Malignant, Breast Carcinoma, Proto-oncogene, Mutation, Beta Catenin.

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### **Introduction and Review of Literature:**

Breast cancer is a malignant proliferation of epithelial lining of ducts or lobules of breast. It is the commonest cause of death in middle aged female in Western world

and occurs more commonly with family history of cancer. Diet low in phyto-oestrogens and high intake of alcohol also contributes to it. It is a hormone dependent disease and occurs due to hyper-

estrogenic states. It occurs both in females and males but it is very rare in males. Epithelial malignancies of the breast are the most common and accounts for about one third of cancer in females world-wide. The highest incidence of carcinoma breast is above the age of 40 years and it is extremely rare before the age of 20.<sup>1</sup> This is a clonal disease in which a single transformed cell due to a series of somatic or germline mutations is able to express full malignant potential. Various genes such as Breast Cancer 1,2 (BRCA-1, BRCA-2) p53 and phosphatase are involved. With BRCA-1 the gene mutation is more profound hence the risk being five times greater than normal.<sup>2</sup>

Obesity has been associated with abnormally high expression of the enzyme aromatase in the breast and increased local estrogen production which causes predisposition to breast hyperplasia and cancer. Increased adiposity in postmenopausal women may trigger the signalling pathway that induce the aromatase expression. Various other factors like early menarche, late menopause, nulliparity, history of previous radiation exposure and food habits like intake of alcohol, fatty acid, oral contraceptives etc. also play an important role in development of carcinoma breast. A palpable mass is the most common symptom of underlying malignancy and the most common lesions are invasive carcinomas, fibroadenomas and cysts.<sup>3</sup>

It appears that estrogen and progesterone act through proto-oncogenes and growth factors to affect breast cell proliferation and breast cancer etiology. Also the metabolic microenvironment of the tumour can influence a range of factors like proliferation rate, cell cycle, growth rate and apoptosis.<sup>4</sup>

Beta catenin is a 90 kD multifunctional protein and is involved in regulation and coordination of cell-cell adhesion and gene transcription. It was identified as a component of mammalian

cell adhesion complex, a protein responsible for cytoplasmic anchoring. Beta catenin has been shown to play a critical role in cell proliferation, differentiation and apoptosis of different malignant entities. It has been identified as proto-oncogene and the mutation of this gene is found in a variety of cancers including primary hepatocellular carcinoma, colorectal cancer, ovarian carcinoma, lung cancer, breast cancer and glioblastoma.<sup>5</sup>

Wnt/beta catenin signalling plays a critical role in regulating the self renewal, proliferation and differentiation of cells in several stem cell niches, including the skin and hair follicle, the mammary glands, the intestinal crypt and the bone marrow. Consistent with this role constitutive activation of beta catenin signalling has been associated with tumorigenesis as a result of mutations in beta catenin and other components of the Wnt signalling pathway including the axin and T-cell factor.<sup>6</sup>

It may be one of the marker in breast cancer as it is having impact on cyclic D pathway but the precise role is not known. Nuclear accumulation of beta catenin resulting from aberrant Wnt signalling or mutation of beta catenin results in breast cancer. Therefore the subcellular distribution of beta catenin remarkably affects the phenotype and behaviour of tumor cells. Over accumulated cytoplasmic beta catenin might also be a malignant marker for breast cancer because of certain relationship between cytoplasmic and nuclear beta catenin in adenocarcinomas.<sup>7</sup>

The reports of Beta catenin expression in breast carcinoma and its association with outcome are limited and controversial. Some authors have reported that beta catenin expression is associated with poor prognosis but others have failed to demonstrate a correlation between beta catenin expression and outcome.<sup>8</sup> The current study was planned to gain a better

insight into the correlation between beta catenin expression, survival and prognosis of patients with breast carcinoma and aimed at estimation of the levels of serum Beta catenin in patients of carcinoma breast and to compare with age matched healthy controls.

## MATERIAL AND METHODS

The present study was conducted in the department of Biochemistry in collaboration with department of Surgery and Radiotherapy in PGIMS Rohtak. Twenty five patients with histopathological proven carcinoma breast were taken for the study and twenty five age matched subjects served as control. Out of total 25 patients, 11 were in stage III of breast carcinoma while 13 were in stage II and one patient was in stage I of the disease.

**Inclusion criteria:** The patients with histopathological proven carcinoma breast irrespective of the stage and given consent were enrolled in the study.

**Exclusion criteria:** Patients having any systemic disease, pregnant females, on

supplements were excluded from the study.

All the patients were subjected to routine haematological and biochemical investigations. The routine biochemistry of all the subjects was done on the Randox auto analyzer in the department. Serum beta catenin was assessed by enzyme linked immunosorbent assay (ELISA) using the commercial kit. The results were compared with twenty five age matched healthy controls and the data was compiled. As there was unequal variance unpaired t- test was applied for analysing the data.

**Results:** In the present study the following results were observed. For the routine haematological tests like Haemoglobin, WBC count and platelets the values were within their respective reference range in cases and controls. The mean blood sugar, serum creatinine and serum uric acid also were within the reference range and comparable in cases and controls and there was no significant change. However mean levels of blood urea was significantly higher in cases as compared to controls (Table-I)

Table I: Mean  $\pm$ SD of routine haematological and biochemical tests

Parameter	Cases (n=25)	Controls (n=25)	p value
Haemoglobin(g/dL)	10.5 $\pm$ 0.77	10.8 $\pm$ 1.07	>0.05
WBC	8308 $\pm$ 1261.25	8236 $\pm$ 1310.49	>0.05
Platelets( in lakhs)	3.38 $\pm$ 0.82	3.42 $\pm$ 0.58	>0.05
Blood glucose (mg/dL)	124.64 $\pm$ 5.49	121.04 $\pm$ 6.24	>0.05
Blood urea(mg/dL)	34.24 $\pm$ 6.11	28.04 $\pm$ 6.49	<0.01
Serum creatinine (mg/dL)	0.93 $\pm$ 0.19	0.97 $\pm$ 0.17	>0.05
Serum uric acid (mg/dL)	5.68 $\pm$ 1.31	5.38 $\pm$ 0.73	>0.05

Table II: Mean  $\pm$ SD of serum beta catenin levels in cases and controls

Parameter	Cases (n=25)	Controls (n=25)	p value
Beta catenin (pg/mL)	43.32 $\pm$ 9.39	19.6 $\pm$ 4.17	<0.01

The serum beta catenin levels were increased in cases as compared to controls and found to be statistically significant (Table-II).

**Discussion:** Breast cancers is a clinically heterogeneous disease and can be linked to various type of germ line mutations, excessive estrogen state, increased expression of growth factors and some disruption of the signalling pathways. Consequently, much effort has been focused on the clinical significance, interrelationships and discovery of biomarkers which aim at optimal utilization of available therapies. However various types of breast cell proliferation in relation to breast cancer also needs a molecular explanation in detail.<sup>9</sup>

Beta catenin has many functions including the regulation of cell-cell adhesion and transcription. Because its stability and abundance is regulated by the Wnt pathway, it can be considered an ideal molecule for determining the molecular basis of malignancy. Beta catenin accumulates in many malignant cancers in breast, ovarian, glioma and prostate and a related abnormal activation of the Wnt pathway occurs frequently in these cancer.<sup>10</sup>

In our study the blood urea levels were increased in cases that may be attributed to increased protein catabolism in the patients as a result of various cytokines in response to tumors that are responsible for cancer cachexia. Also there is increased whole body protein turnover rate in cancer patients.<sup>11</sup>

In our study the levels of beta catenin were also found to be significantly raised in cases that may be due to aberrant activation of beta catenin mediated transcriptional signalling and disruption of

balance between cell proliferation and differentiation thus paving the way for tumorigenesis. There are evidences of increased cytoplasmic and nuclear expression of beta catenin in cancer cells. Hence the prominent expression of beta catenin in breast cancer strongly implicate the role of this protein molecule in tumor promotion.<sup>12</sup>

Some studies have demonstrated that activated Beta catenin may lead to cyclin D1 over expression thus causing increased, uncontrolled cell growth and tumorigenesis. The cyclins turn on different cyclin dependent protein kinases (CDKs) that phosphorylates the essential substrates for progression through the cell cycle. Cyclin D level rise in the late G1 phase and allow progression in the S phase. These D cyclins activate CDK4 and CDK6 which are also synthesized during G1phase of cells undergoing active division. The D cyclins and CDK4and CDK6 are nuclear proteins that assemble as a complex in the G1 phase. Excessive production of the cyclin or production at an inappropriate time might result in abnormal and unrestricted cell division.<sup>13</sup>

Studies have shown abnormal beta catenin expression in the most of the high clinical grade adenocarcinomas where increase in beta catenin expression in the nucleus was accompanied by diffuse cytoplasmic expression of beta catenin. Nuclear beta catenin also up regulates the expression of preinvasive proteins. It is possible that abnormal accumulation of beta catenin in the nucleus resulted in the loss of E-cadherin and consequent cell polarity and cell adhesion. In combination with T cell factor nuclear beta catenin transactivates

the gene encoding cyclin D which in turn induces mammary hyperplasia.<sup>14</sup>

Our results are in consistent with the study done by López-Knowles et al, they found that the cytoplasmic beta catenin expression was not only associated with high-grade tumors and high proliferation rates, but also with estrogen receptor and human epidermal growth factor 2 expression and lymph node metastasis.<sup>15</sup>

Hence over accumulated cytoplasmic beta catenin can be considered a malignant marker for breast cancer Our studies demonstrated that beta catenin was a poor prognostic marker in human cancer and was implicated in human breast cancer.

**Conclusion:** Beta catenin can be a potential prognostic marker in breast carcinoma as it has role both in cancer formation and progression and provide an opportunity for development of potential therapy by blocking the beta catenin pathway in breast cancer cells. It is possible that through further characterization of the role of Wnt beta catenin signaling in tumors, it will emerge as a valuable therapeutic target for breast cancer. But as the sample size is small, large numbers need to be studied before the definitive conclusions can be drawn.

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