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TITLE OF THE THESIS**: MOLECULAR ANALYSIS OF *PTEN* GENE IN BREAST CANCER PATEINTS.**

Abstract

Cancer is medically neoplasm where cells divide and grow uncontrollably, forming malignant tumors, which invade nearby parts of the body. One of the most common malignancies in women is the breast cancer. PTEN was characterized as tumor suppressor gene in 1997 on the long arm of chromosome 10, it is a phosphoinositide 3-phosphatase which can inhibit cellular proliferation, by deactivating PI 3-kinase-dependent signaling. Keeping the above in view we designed our studies which determine the expression and significance of *PTEN* in breast carcinomas, to detect the mutation frequency of *PTEN* in sporadic breast carcinoma tissues and to determine the association between *PTEN* promoter methylation and gene expression.

Methods: Immunohistochemical methods were used to determine the expression of the *PTEN* gene in breast carcinoma, staining with an Anti-PTEN protein antibody was performed on formalin fixed paraffin embedded tissue. We evaluated the methylation status of the CpG islands of PTEN using Methylation Specific PCR (MS-PCR) breast carcinoma tissues. The mutational analysis of *PTEN* gene was performed by Single Stranded Conformational Polymorphism (SSCP). We evaluate allelic losses in microsatellites of the 10q23 region

Results and Conclusion: total 181 cases of breast carcinoma in which the frequency of loss of PTEN protein expression in breast carcinoma was found to be 54% (97/181). Loss of PTEN expression was significantly associated with tumor size, stage and grade ($p<0.001$). The promoter methylation frequency of PTEN was found to be present in 49% (88/181) of cases

examined. Out of these 88 cases showing promoter methylation of PTEN in breast cancer tissues, 54 cases showed loss of PTEN expression. A significant correlation existed between promoter hypermethylation and loss of PTEN expression ($p<0.05$). We therefore conclude that promoter hypermethylation of PTEN gene occurs frequently in human breast cancer and is a crucial and major mechanism of epigenetics silencing of the PTEN gene. Among 105 breast cancer patients analysed, we detected seven (7%) cases with PTEN mutation were detected our finding on PTEN mutation are much lower in breast cancer compared with that of the other tumors. Point mutations in exon 9 of were identified in 2/105 breast cancer cases. TG→GT resulted in a codogenic amino acid change from Valine to Glycine. Exon 9 is a functional domain of PTEN and mutation in codon 343 at exon 9 can therefore affect the function of this gene**.** From the pattern of our findings we can very well say that PTEN promoter methylation may have been the main contributer which leads to decreased expression of PTEN gene. Allelic loss for of the PTEN region was found in 35% (36/103) of tumors. The relationship between *PTEN* and promoter hypermethylation and the existence of LOH at *PTEN* locus was found to demonstrate a bizarre pattern, 10 cases were found todemonstrate loss of *PTEN* expression, promoter hypermethylation and LOH at the same time and another 16% showed LOH and loss of *PTEN* expression but were not hypermethylated. Both events occurred simultaneously, leading to biallelic inactivation and a complete lack of function of the *PTEN* gene.