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Topic: Methylation and Expression of FHIT gene in Indian Female Breast Cancer Patients

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## ABSTRACT

Breast cancer is one of the leading causes of death In Indian females. Majority of patients affected by the disease are above 40 years of age and breast cancer is detected in higher clinical stages. There are various genetic as well as environmental risk factors associated with breast cancer which Include age at the time of first child, parity, menstrual status, exposure to radiation and family history. Various changes at the genetic level involving oncogenes, tumor suppressor genes as well as DNA repair genes are responsible for the development of breast carcimoma.

*FHIT* is a candidate tumor suppressor gene. Loss of heterozygosity, deletions at the *FHIT* gene, hypermethylation, abnormal transcripts and reduced mRNA expression are the possible reasons for the loss of expression of *FHIT* gene in breast cancer. This favours the candidancy of *FHIT* gene as a prognostic factor of breast cancer.

The present study was therefore designed to study the methylation as well as expression of *FHIT* gene In Indian female breast cancer pateints.115 breast carcinoma samples as well as 30 normal control samples were included in the study. Majority of patients were in the age group 40-49 years. According to menstrual status 53% of the women were in pre-menopausal stage. Out of 115 breast carcinoma patients 90.43% were Hindu, 5.21% were Muslim and 4.34% belonged to the Sikh community. All the 59.13% vegetarian patients belonged to the Hindu community. More than 90% of the patients belong to clinical stage II and III. Lack of awareness regarding the disease as well as hesitation to discuss the same has lead to an increase in the number of cases belonging to higher clinical stages in our country.

On methylation analysis 45 (39%) out of 115 breast carcinoma samples are found to be methylated. Hypermethylation leads to either monoallelic or biallelic Inactivation of *FHIT* gene. There is no statistically significant correlation between methylation status of *FHIT* gene as well as clinico-epidemiological characteristics such as clinical stage (p=O.52) as well as histological grade (p=O.55).

We studied the expression of *FHIT* gene by Immunohistochemistry. Out of 115 samples, 49 had either low or nil expression. This loss of expression could be attributed majorly to hypermethylation of the gene apart from other mechanisms of gene inactivation such as loss of heterozygosity, gene deletions etc.. However, there is no statistically significant correlation between *FHIT* gene expression as well as clinico-epidemiological characteristics such as clinical stage (p=O.97) as well as histological grade (p=O.93).

We further found a highly significant (p<O.0001) positive correlation between *FHIT* methylation and expression. This finding demonstrates that methylation of *FHIT* is an important mechanism for silencing this gene in breast cancer and can be used as a marker for risk assessment.

Finally, our findings of a frequent acquired tumor-related epigenetic alteration favor the candidacy of *FHIT* as a TSG. Fhit protein may play a crucial role in development and progression of breast cancers and may act as a prognostic factor in patients with breast carcinoma. Moreover, knowledge of the *FHIT* methylation state in primary breast cancers may be useful to identify tumors that are more likely to respond to FHJT-demethylating therapy. However, further research is needed to study the exact mechanism of the Fhit inactivation in Indian breast carcinoma and larger studies will be required to elucidate whether Fhit loss is a useful prognostic biomarker of breast carcinoma.