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Abstract

Worldwide, breast cancer (BC) is the most frequently diagnosed type of cancer with a high mortality rate in women and India is facing a growing epidemic. Estrogen is inextricably linked to BC and estrogen levels influence disease risk and its prognosis. Endocrine therapeutic strategies targeting the growth-promoting activity of estrogen remain the most preferred choice of treatment for BC. Therefore, it is pertinent to understand how estrogen pathways are associated with breast tumor development. However, there is a void with regard to the role of estrogen pathway genes in Indian BC population. This work has attempted to address the role of *ESR1*, *ESR2*, *CYP17A1* and *CYP19A1* genes in North Indian population and the combinatorial presence of promoter methylation status of ERα and ERβ and its correlation with protein expression in clinical relevance.

The present population based case–control study comprised of 360 sporadic female BC cases and an equivalent number of genetically unrelated healthy controls (sex matched) from North Indian ethnicity. Prior ethical approval of the study protocol was obtained, along with a written informed consent from all participants. Statistical analysis with Bonferroni correction for multiple testing corrections was performed. Genotype and allele frequencies were found to be significantly associated with BC susceptibility in North Indian population and strong correlations with various clinical parameters such as menopausal status, ER status, PR status, HER2 status,

clinical stage and histological grade were observed. To our knowledge, this study is the first attempt to examine the association of *ESR2* (rs2987983) and *CYP19A1* (rs700519) polymorphisms with BC risk in North Indian population. This study is far more comprehensive than previous ones in terms of larger sample size and multi-analytic approach to correlate BC risk with various clinical parameters.

The methylation status of *ESR1* and *ESR2* and its correlation with respective protein expression was also analyzed. A high frequency of methylation in ERα (68.75%) and ERβ (64.17%) in BC tumor tissues was observed and seems to be a mechanism of gene silencing in our population. Strong associations between ERα/ERβ methylation and ERα status, PR status, tumor size, clinical stage and triple negative tumors were observed. In our knowledge, this study revealed for the first time the role of combinatorial presence of promoter methylation of ERα and ERβ in BC in our population. The observation of correlation between ERα and ERβ methylation with small tumor size and early stages of BC, suggests that methylation is an early event occurring in BC in our population.

In summary, this work provides evidence that estrogen pathway related genes indeed contribute independently towards BC susceptibility and highlight their importance in North Indian population. It is anticipated that concurrent methylation of ERα and ERβ and their associated loss of protein expression could be used as a promising diagnostic/prognostic biomarker in our population. Consistent with the clinical relevance of endocrine therapies, results of this work strongly emphasize that estrogen signaling pathway remains important while treating and developing new drugs to combat BC.