With about 134,000 new cases and 72,800 deaths annually, cancer of the uterine cervix accounts for the most frequent cancer among women in India. Although HPV infection has been shown to play a critical role in the aetiology of cervical cancer, genetic alterations also contribute significantly to the pathogenesis of the disease. The main focus of the study was to understand the role of HPV infection and genetic alterations in a cohort of Indian women with locally advanced cervical carcinoma.

The incidence of HPV as well as different genotypes was determined in 270 pretreatment cervical cancer biopsies using PCR with 3 different primer sets and high-throughput luminex bead array. The overall HPV positivity was 95% and the incidence of HPV16 and/or HPV18 was the highest (72%). We then determined the physical state of the virus as well site of viral integration was in a subset of cases (n=86) positive for HPV16 and/or HPV18 by APOT assay. Integration was observed in 79% cases and was found to be more frequent at chromosomal loci 1p, 3q, 13q, 6q, 11q and 20q. Also, protein coding genes as well as fragile sites were identified as potential hotspots. Comparison with clinical outcome revealed that patients with only episomal form of HPV had a better disease free survival as compared to those with integrated form. We also determined the viral load in the same 86 cases with known physical status by SYBR green based quantitative real time PCR. It was observed that high viral load combined with integration served as a worst prognostic marker.

In order to understand the genetic alterations in the tumour samples, whole exome sequencing of 11 cervical biopsies and 8 matched controls (blood from the same patients) was done. A number of interesting germline (such as RNASEL, PTPRJ, ZFP64, etc.) and somatic (FGF7, SOS2, DIDO1 and MAP3K3, RASA1, etc.) variations were identified and further validated by Sanger sequencing. These might represent predisposing and/or potential disease causing mutations. The data, besides being a source of information on novel variations in the Indian genome (which the dbSNP currently lacks), would mark the beginning of understanding the genomic landscape of cervical cancer.

The significance of the study lies in the fact that we have addressed all the major factors associated with pathogenesis of cervical cancer and assessed the role of each. The genetic analysis of the next generation data would be first of its kind on Indian cervical cancer patients. Such approaches would help in better understanding the fundamental rules of cervical carcinogenesis and be a step forward towards identifying biomarkers and newer treatment modalities for management and cure of the disease.