ABSTRACT

Individuals differ in their susceptibility to disease. Some of these differences are attributed to the concept that heritable traits modify the effects of environmental exposures. Cancer of the oral cavity epitomizes this concept. Oral cancer, the eleventh most common malignancy and a major cause of cancer morbidity and mortality worldwide has become a significant social and economic burden in parts of South East Asia, particularly India. More than 80% of oral cancers are attributed to tobacco. However, only a fraction of smokers acquire oral cancer in their lifetime. One of the several cellular processes that could explain this inter-individual variation in risk is DNA Repair Capacity (DRC), which has been the focus of our study. There is a substantial inter-individual variation in DRC within a population. There is a large subgroup with reduced DRC who are likely to be at increased cancer risk, but are phenotypically normal. This at-risk group needs to be identified to intensify screening interventions. Our approach to risk assessment has been multitiered, beginning with a detailed epidemiological assessment in case-control studies, followed by the application of phenotypic and genotypic markers of genetic susceptibility. We first observed that SNPs in major DNA repair genes like XRCC1, XRCC3, ERCC1 and XPD played a major role in predicting genetic susceptibility to oral cancer. We then looked into the actual extent of DNA damage, established by our in vitro studies using the Cytokinesis Block Micronucleus Assay [CBMN]. The significantly higher spontaneous micronuclei levels observed in patients suggest a higher
background level of genetic instability in the cancer patients. The next step was to look into DRC within oral cancer cases and age and habit matched control populations. This was done by the Host Cell Reactivation assay (HCR), which measures the expression level of UV damaged reporter genes. DRC% was also correlated with presence of genetic polymorphisms in the DNA repair genes XRCC1, XRCC3, XPD and ERCC1. A statistically significant lower DRC was observed in case of patients compared to control subjects. This sub optimal DRC was associated with a 2-3 fold increased risk of oral cancer. It was seen that as repair capacity diminished, the probability of being a case increased. In addition to SNPs as cancer susceptibility markers, we also looked into their possible role as biomarkers of radiation treatment (RT) response. Patients with polymorphic variants in their genome responded better to RT as was evident from their complete response [CR] and no evidence of disease [NED] after a follow up period of three years. To the best of our knowledge this is the first study, which suggests a role for repair gene polymorphisms in influencing treatment protocols.