

Conclusions

Oropharyngeal cancer is the eleventh most common cancer worldwide. In parts of India and South East Asia, it is the most common cancer owing to the use of chewing quid's containing betel nut and tobacco, indicating a strong environmental and cultural influence in the prevalence of this disease. Even though these are important etiological factors, relatively few people exposed to them actually develop cancer, often despite years of exposure. There are also patients who develop oral cancer in the absence of such habits or other identifiable lifestyle or environmental etiological factors. Therefore host susceptibility may also play a role.

Proper recognition and repair of the DNA damage are essential for homeostasis and normal functioning of multicellular organisms. DNA repair activities are maintained by the presence of different DNA damage sensor and repair mechanisms. Defects in the DNA repair pathways are often associated with excessive cell death or transformation of cells and variations in DNA repair genes are hypothesized to modify individual and population cancer risk.

The study looked into seven gene polymorphisms selected from the three important repair gene pathways. The polymorphisms include: XRCC1 *Arg194Trp*, *Arg280His* and *Arg399Gln* of the Base Excision Repair (BER) pathway; XPD *Lys751Gln* polymorphism, ERCC4/XPF *Arg415Gln* and ERCC1 codon 118 polymorphism of the Nucleotide Excision Repair (NER)

pathway and XRCC3 *Thr241Met* polymorphism of the Homologous Recombination Repair (HRR) pathway.

This study analyzed the distribution of XRCC1, XPD, XRCC3, ERCC1 and ERCC4 genotypes in the same set of cases and controls. The frequency of 194Trp and 399Gln of XRCC1 gene, 751Gln of XPD gene and ERCC1 118 variant alleles were more pronounced among cases compared to controls. The codon 280 polymorphic variant as well as ERCC4 and XRCC3 exhibited no statistically significant increase in risk. When individual risk of leukoplakia subjects was studied as against normal population it was seen that only XRCC1 codon 194 and 399 allele and the XPD variants gave significant results. None of the other genotypes exhibited any increase in risk for oral cancer. Lifestyle factors like smoking and betel quid chewing also was observed to influence risk of squamous cell carcinoma of the oral cavity whereas, alcohol and gender did not have any effect on cancer development.

Presence of Micronuclei (MN) in cells indicates the extent of DNA damage in the cell. Abnormally increased number of MN was more prominent in cases than in controls. It was observed that carriers of the variant allele had more number of MN than the normal wild genotype in the case of XRCC 194, XRCC 399, XPD and ERCC1 genes. We observed that increased presence of abnormal MN in cases which were also polymorphic made them more prone to oral cancer.

It was noted that polymorphisms in DNA repair genes had a subtle effect on DNA repair capacity of an individual. The XRCC1 (BER pathway) and XPD and ERCC1 (both NER pathway) gene polymorphisms had a modest risk association with cancer outcome. The results suggested that these *XPD and XRCC1* polymorphisms had a dominant effect on DRC in cases and a smaller effect on DRC in controls. Lifestyle factors like habits, age and gender did not seem to influence risk for cancer significantly. It was seen that as repair capacity diminished, the probability of being a case increased. It could be thus concluded that inefficient repair response or inability to mobilize DRC on tobacco exposure may lead to accumulation of genetic damage. By this assay we could ascertain that DRC indeed plays an important role in increasing risk for oral cancer.

Treatment response to radiation treatment was also studied and it was seen that 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. On the other hand a majority of patients with a wild genotype showed only partial response to RT and number of events like recurrence, after the follow up period was high. Most of the subjects who were categorized in the “normal MN” group and carrying the wild genotype returned to the clinic with various cases of partial response and recurrence. This further emphasizes our hypothesis that genetic susceptibility plays a significant role in DNA damage and

development of cancer. These paradoxical results can pave way for comprehensive research on the use of genetic susceptibility as an investigative tool for deciding treatment options for oral cancer. To the best of our knowledge this is the first study which suggests a link between SNPs and radiation treatment efficacy.

To conclude, our data supports a role for DNA repair gene polymorphisms in increased oral cancer risk. It could be also be concluded that as repair capacity diminished, the probability of being a case increased. Inefficient repair response or inability to mobilize DRC on carcinogen exposure may lead to accumulation of genetic damage and eventually cancer. On the other hand, inability to repair DNA damage could also prove beneficial, when radiation treatment is mandatory. These paradoxical results opens up a whole new arena of personalized medicine, wherein genetic susceptibility can be used as a diagnostic tool in the outpatient clinic in deciding treatment options with an expected favorable response from the patient.

Future perspective

As more and more information about the biological and chemical function of different genes is gathered, the possibilities of identification of the role of different polymorphisms will also increase. It will be then important to consider the possible complexity of interactions between different polymorphisms, especially in different genes at different steps along the cancer pathway.

We now have an extensive set of data on phenotypic and genotypic markers of susceptibility as predictors of oral cancer risk. However, there are many issues that need to be addressed. These issues include selection bias, variability and reliability of the tests, and the retrospective nature of the study designs, raising concerns about the impact of disease status on the assay results. We also need

to know how well these functional data (derived from surrogate lymphocytic tissue) reflect events at the level of the target tissue. Therefore, the logical next step in risk assessment is to correlate these surrogate phenotype/genotype data with tissue specific analyses from oral biopsies and washings, and tumor tissue.

As the need grows for rapid and efficient translation of emerging new technologies and approaches to improved patient management, early detection, and prevention, there will inevitably be a growing emphasis placed on molecular epidemiology research and the application of the approaches intrinsic to epidemiology to other aspects of translational research. Molecular epidemiologists will increasingly be called on to identify high-risk (susceptible) subgroups who might benefit disproportionately from screening or chemoprevention interventions. Additional studies in these high-risk individuals can also provide insight into applying these approaches to the average risk population.