We know very little, and yet it is astonishing that we know so much, and still more astonishing that so little knowledge can give us so much power.

Bertrand Russell
Worldwide, the increasing incidence and prevalence of various types of non-communicable diseases are responsible for "modern epidemics". Among these, cancer is the second commonest cause of mortality in the developed countries and the tenth commonest cause of mortality in the developing countries. Cancer is an abnormal growth of cell that can affect any tissue or organ of the body and constitute one of the deadliest scourges of the modern era. It continues to be a menace despite advances in diagnosis and treatment modalities.

India is a country which is presently in transition from developing to a developed nation. It has a population of more than one billion people with an increasing middle class population. In the population, the head and neck squamous cell carcinomas (HNSCC), that originate mostly from the squamous cells, have been identified as one of the commonest malignancies that account for 23% of all cancers in males and 6% in females. They mostly occur in patients older than 50 years of age. These are mainly malignant growths arising in the mucous membranes of oral cavity, pharynx, and larynx that constitute the upper aerodigestive tract (UADT) cancers. Among these cancers, malignancy of the oral cavity is the leading type in the country and ranks first in men and third in women among all the cancers.

Epidemiological studies have shown that habitual tobacco use and alcohol consumption are the two major strongly implicated risk factors responsible for the high incidence of UADT cancers. Nevertheless, only a minor proportion of the exposed individuals develop these cancers. Hence, it was presumed that incidence of these cancers could be influenced by both exogenous exposure and genetic predisposition. Cancer genes can be classified as caretaker genes and gatekeeper genes. While the caretaker genes affect DNA repair, metabolic activation and detoxification of carcinogens, the gatekeeper genes affect cell cycle control and DNA replication.
The inherited differences in the capacity of xenobiotic metabolizing enzymes have been found to be an important factor that determines the genetic susceptibility to UADT cancer. Majority of the environmental procarcinogens require metabolic activation to get converted into their respective reactive electrophilic intermediates by the cytochrome P-450 superfamily of Phase I enzymes. Subsequently, the Phase II enzymes detoxify these intermediates by conjugation reactions. The metabolic activation and detoxification of xenobiotics express significant interindividual differences in humans which is a key factor that regulates the genetic predisposition or host susceptibility to various carcinogens. The cytochrome P450 (CYP) dependent mono-oxygenases play an important role in the metabolism of environmental carcinogens. The metabolic activation of procarcinogens to reactive metabolites is mediated by these polymorphically distributed CYP enzymes in humans. Among these, CYP1A1, CYP2D6 and CYP2E1 have been reported to be involved in the pathogenesis of UADT cancers. The activated carcinogens are detoxified by phase II [(glutathione-S-transferases (GST), N-acetyl transferases (NAT))] enzymes to protect the body from the toxic effects of carcinogens. Besides, the phase III transporter system consists of antiporter activity that is associated with P-glycoprotein (P-gp). The genetic polymorphisms in drug transporters that are involved in the transmembrane efflux of xenobiotics may also result in susceptibility of normal tissues to neoplastic transformation by various carcinogens. The ABCB1 gene, that belongs to Adenosine triphosphate binding cassette (ABC) superfamily encodes P-gp which is an energy dependent efflux pump that reduces the intracellular accumulation of a wide range of xenobiotics.

Cytochrome P-450 (CYP) 1A1 is a key enzyme in the phase I bioactivation of xenobiotics. It contributes to the aryl hydrocarbon hydroxylase activity, catalyzing the first step in the metabolism of a number of polycyclic aromatic hydrocarbons. These include tobacco carcinogen, benzo (a) pyrene and several other tobacco related procarcinogens such as nitrosamines and aromatic amines. They are metabolized to
their ultimate DNA-binding forms\textsuperscript{19,20}. \textit{CYP1A1} gene is expressed in many epithelial tissues especially in buccal mucosa, which is responsible for the \textit{in situ} activation of tobacco carcinogens\textsuperscript{21}. The important genetic polymorphisms of \textit{CYP1A1} are \textit{CYP1A1*2A} and \textit{CYP1A1*2C}. There are conflicting results regarding the association between these polymorphic genotypes and risk of different cancers in various ethnic groups.

\textit{CYP2E1} is a well known ethanol-inducible form of cytochrome P-450. It is responsible for the metabolic activation of procarcinogens such as N-nitrosamines and various other low-molecular-weight compounds into reactive intermediates that play an essential role in chemical carcinogenesis\textsuperscript{22,23}. Thus, \textit{CYP2E1} activity is an important determinant of human susceptibility to toxicity and carcinogenicity of industrial and environmental chemicals. There are studies that described significant associations between \textit{CYP2E1} polymorphisms and the incidence of various malignancies in different ethnic populations\textsuperscript{24,25,26}. The commonly investigated genetic polymorphisms of \textit{CYP2E1} are \textit{CYP2E1*5B} and \textit{CYP2E1*6}. There is only limited information available on the association between \textit{CYP2E1} polymorphisms and risk of UADT cancers among Indians till date.

The glutathione S-transferases are known to protect the cells from cytotoxic agents which catalyze the conjugation of glutathione with electrophilic compounds. The \textit{GST} genes exhibit polymorphisms which are potentially important modifiers of the individual risk for environmentally induced UADT cancers. The homozygous deletion of \textit{GSTM1} and \textit{GSTT1} genes results in complete lack of enzymatic activity\textsuperscript{27}. Hence, carriers of null genotypes are at increased risk of UADT cancers due to the reduced ability to detoxify carcinogens. Another GST isoenzyme, \textit{GSTP1} is widely expressed in tumour cells and is responsible for the detoxification of benzo (a) pyrene diol epoxide and acrolein present in cigarette smoke\textsuperscript{28}. The \textit{GSTM1} null genotype is present in about 50% of
Caucasians, 33% of African Americans and 45% of Japanese whereas the GSTTI null genotype is present in 64% of Chinese, 60% of Koreans, 20.4% of Caucasians, 22% of African Americans, and 9.7% of Mexican Americans.\textsuperscript{29}

Human ABCB1 was identified due to its over expression in cultured cancer cells.\textsuperscript{30} P-gp, the product of ABCB1 gene, is an ATP dependent membrane efflux transporter that protects the body from environmental toxins and xenobiotics. The ABCB1 gene exhibits polymorphisms, resulting in interindividual variations in the activity of P-gp.\textsuperscript{18} Among the numerous polymorphisms in human ABCB1, the 3435C>T polymorphism in exon 26 has been associated with reduced mRNA expression in the liver.\textsuperscript{31} In vitro studies in human breast cancer MCF-7 cells have shown that expression of P-gp and the modulation of its function may affect the susceptibility of normal tissues to neoplastic transformation by carcinogens.\textsuperscript{32}

Earlier studies in our laboratory among Tamilian population of south India have shown that the genotype frequencies of CYP2E1*1B, CYP2E1*5B and CYP2E1*6 were significantly different from Caucasians and Chinese Orientals.\textsuperscript{33} The frequency of GSTM1 null in south Indians was significantly lower than that in Caucasians while the frequencies of combined GSTM1 and GSTTI null genotypes in south Indians were significantly lower than in the Japanese.\textsuperscript{34} The GSTP1 genotype distribution in Tamilian population varied significantly from Chinese Orientals but not significantly differed from the Caucasians.\textsuperscript{33} In another study on ABCB1 3435C>T polymorphism, the distribution of 3435TT in Tamilians was found to be greater than Africans and almost similar to Caucasians and Orientals. The frequency distribution of the CC genotype in Tamilians was lower when compared with Chinese and Africans whereas CT genotype was higher in comparison with all the major ethnic groups.\textsuperscript{35} Therefore, the genotype data revealed that the Tamilian population of south India differs significantly from other major ethnic groups.
Gene-gene interaction or epistasis is a unique component of the genetic architecture of common diseases, such as cancer. Generally, the effect of single nucleotide polymorphism (SNP) might be less compared to the genetic effect of combinations of functionally relevant SNPs that may additively or synergistically contribute to the increased cancer risk. These interactions might determine the functional outcomes over the independent effects of any one susceptibility gene. In the complex polygenic diseases such as UADT cancers, the genetic susceptibility is dependent on the action of several gene polymorphisms. Since, single gene polymorphisms contribute only to a small extent to the pathogenesis of UADT cancer, it is likely that the cumulative effect of many polymorphisms will be more important in its pathogenesis.

In addition to studying the disease etiology in relation to multiple genes and their variants, it is also essential to investigate the gene-environment interactions that explain the combined influence of genetic and environmental factors on the risk of developing a human disease. On exposure to environmental carcinogens, progression of cancer is facilitated by a cumulative effect of mutations or polymorphisms in these genes. Therefore, analyzing the interactions of genes that are involved in the metabolic activation, detoxification and the xenobiotic transport with the environmental factors could provide fundamental insights into the development of cancer.

Cancer prognosis could be determined by various factors such as patient's age at diagnosis, gender, tumor (size and site) characteristics, as well as treatment response (chemotherapy, radiotherapy and surgery). Traditionally it is considered that, large lesions with metastatic spread have a worse prognosis than small, locally restricted tumors. However, the cancer outcome can vary markedly between patients with tumors from the same site and comparable stage, nodal status, and histological grade. Hence it is essential to investigate the association of genes with tumour characteristics as well as the remission and recurrence related to cancer outcome.
There are conflicting data showing the relationship between genetic polymorphisms of xenobiotic metabolic activating, detoxifying enzymes and transporter proteins and the prevalence of UADT cancers among different ethnic and racial groups. Till date, there is no information available on the role of CYP1A1, CYP2E1, GST and ABCB1 gene polymorphisms towards the risk of UADT cancers in the Tamilian population of south India. As this population was found to be distinct from the other ethnic groups, we investigated the role of these polymorphisms as genetic risk modifiers in the etiology of UADT cancers. We also investigated the potential influence of gene-gene and gene-environment interactions on the UADT cancer risk. The inter-individual genetic variations in relation to the tumour outcome parameters and response to various treatment modalities were also analyzed in the present study.

Tamilnadu is on the east coast of southern India. Tamilians are an ethnic group of Indian origin from south Asia and they are ethnically, linguistically and culturally related to the other Dravidian population. Dravidian race is the name given to the inhabitants of southern and central India and northern Sri Lanka. It is reported that this population had common ethnic origin during the Indus Valley civilization.40.