

Cancer in North-East Regions of India

A very high incidence of cancers of all sites in general and tobacco and pesticide-related cancers in particular has been reported in North-East region of India. However, the available data on tobacco usage and pesticide exposure alone is not sufficient to explain the high incidence.

North-East region of India has different customs, food habits, life-style, diverse ethnic groups, and type and pattern of tobacco use in as compared to the rest of the country. It is very well known that the carcinogenicity of tobacco is attributed to nitrosamines, PAHs, benzene, Benzo(a)pyrene etc. Moreover there is extensive use of pesticides in tea gardens in North-East which can lead to widespread occupational and environmental exposures.

ICMR has set up Cancer Registries in the North-East under the NCRP (National Cancer Registry Programme). These centers have good working relationship with the populations harboring the cases of cancers and have earlier provided data showing the high prevalence of certain types of cancers in these regions. Multicentric studies have been initiated by ICMR to find out the genetic factors, in addition to common environmental exposures, tobacco smoking, alcohol consumption, pesticide exposure and dietary habits which could possibly explain the high prevalence of certain cancers in North-East India which forms the basis of the current studies.

Studies on Esophageal cancer started in 2004. Interesting leads have been obtained from the ongoing multicentric project on esophageal cancer at ICPO, Institute of Pathology, New Delhi, Regional Medical Research Centre, Dibrugarh and BB Barooah Cancer Institute, Guwahati. In 2005, this study was extended to include other tobacco and pesticide-related cancers such as oral cancer, stomach cancer, lung cancer, breast cancer and malignant lymphoma. These multi-centric studies will investigate the link between carcinogenic contents of tobacco and pesticides used in North-East and genetic variation including polymorphism/mutations associated with ethnic variation. The study will be carried out in six population-based cancer Registry area of North-East with a case control epidemiological design. National Institute of Occupational Health, Ahmedabad will be doing pesticide and chemical residue analysis of tobacco that present in micro-quantities in environmental and biological samples while the genetic studies on blood samples and gene expression analysis in tissue samples will be done at ICPO in collaboration with IOP.



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Comprehensive Study of Carcinoma Esophagus at North-East India—a Multidiscipline Approach

(An ICMR-Taskforce Multicentric Collaborative Study)

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CANCER incidence data generated from six hospital-based Cancer Registries under National Cancer Control Program (NCRP) has revealed that in India, Assam has the highest incidence of esophageal cancer. In Assam, aggregation of esophageal cancer in families is a long-observed and well documented phenomenon. Epidemiological studies indicate that tobacco smoking and alcohol consumption are two major factors contributing to development of esophageal cancer. However, the role of genetic factors for familial aggregation has not yet been elucidated.

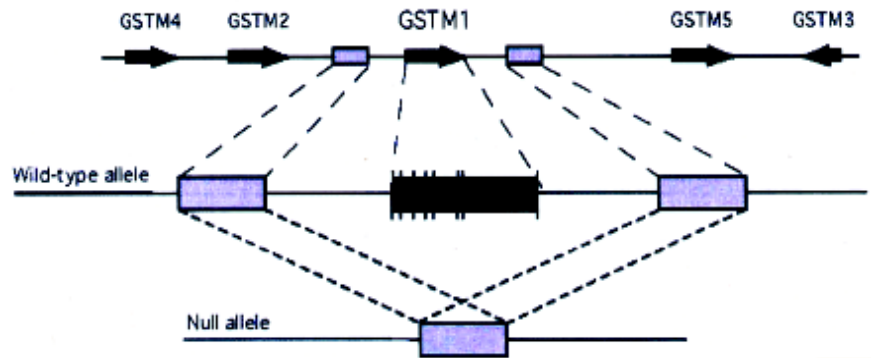
Recent studies have addressed this issue by studying genetic factors in the etiology of esophageal cancer by attempting to identify genes associated with its development and progression. Chromosomal regions with frequent allelic loss may point to major susceptibility genes that will assist in understanding the molecular event involved in esophageal carcinogenesis and may serve as the basis for the development of markers for genetic susceptibility and screening for early detection of this cancer. Identifying the genes up-regulated and down-regulated in esophageal cancer and their association with familial aggregation and tobacco use may help in identifying targets for therapy and understanding the carcinogenic mechanisms. With this background, the current study has been planned to investigate the role of genetic factors and tobacco smoking in the etiology of esophageal cancer. ICPO has received 43 blood samples and 59 tissue biopsies and have analyzed p53 and GST μ (GSTM) mutation and polymorphism in esophageal pre-cancer and cancer cases by PCR-SSCP and direct DNA sequencing.

ICPO being the national referral centre for HPV has been assign to determine the status of HPV in these patients to create a baseline data and to correlate genetic changes and environmental factors like HPV infection, tobacco chewing and food habits with development of esophageal cancer. Out of 36 case and control biopsies analyzed none was found positive for HPV DNA. Several studies have reported presence of HPV DNA in esophageal cancer but in this study we have not found any HPV DNA so far. This may indicate a different etiological factor in this region for the development of esophageal cancer.



Endoscopic photograph showing esophageal lesion

GSTM1 null allele—GSTM cluster at 1p13.3 arranged as 5'- GSTM4-GSTM2-GSTM1-GSTM5-GSTM3-3 (top of the diagram). The *GSTM1* is embedded in a region with extensive homologies and flanked by two almost identical 4.2-kb regions (light boxes). The *GSTM1* null allele arises by homologous recombination of the left and right 4.2 kb repeats, which results in a 16 kb deletion containing the entire *GSTM1* gene. Due to this mechanism and absence of no known evidence of selection of wild type allele it is expected that null allele has got very good chances of increasing in the population over the wild type allele



Mutation in *p53* gene in exon 5 and exon 7 were checked. Out of 18 cases mutation is detected in exon 5 in two cases (11.1%) and one in exon 7 (7.6%). Work is in progress and samples will be analyzed for other exons also.

Polymorphism of *GSTM1* gene was done to detect homozygous null and non-null genotypes. We have reported homozygous *GSTM1* null genotype in Indian population in general is around 36%. Interestingly, in North-East population samples we found a much higher percentage of *GSTM1* null genotype (26 out of 43 cases i.e. 60.5%). The work to increase the sample size and to validate the observation is in progress.

Cancer in North-East India— Understanding the Role of Tobacco

(An ICMR-Taskforce Multicentric Collaborative Study)

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THE burden of tobacco related cancer is increasing alarmingly throughout the world. Tobacco is the second most major cause of death in the world. Nearly 5 million people die due to tobacco use every year and this figure will increase to 10 million by the end of 2020. It is not only causes lung cancer; but it also increases the risk of other cancers like esophageal, oral cavity, hypopharynx, larynx, urinary bladder, colon, rectum, pancreas and cervix. In North-East region very high incidence of all sites of cancers in general and tobacco related cancers in particular have been reported. Both Mizoram and Assam states have reported very high incidence of esophageal cancer in both sexes. The proportion of tobacco-related cancers relative to all sites is highest in Assam and Meghalaya. These proportions are relatively higher than those reported elsewhere in the country. Pattern of tobacco use is different in North-East region where bidis and cigarettes available locally are different from main land.

The genetic susceptibility of cancer due to ethnic variation related to polymorphism and mutation in autosomal recessive genes has been suspected. Certain dietary and tobacco-related carcinogens act as co-factors to bring out genetic changes such as activation of oncogenes and mutation in tumor suppressor genes. In view of these facts, ICPO will be studying tobacco-related malignancies such as oral and oro-pharangeal, esophageal, stomach and lung cancers for mutations in cancer specific gene such as *p16*, *p53*, and



People of North-East India consume tobacco in different forms apart from smoking which is being correlated with increased incidence of a set of cancers of specific organ sites

DNA methyltransferase 3B (DNMT3B) whereas gene polymorphism studies for *APE1*, *XRCC1*, *CXP2A6*, *CYP1A1*, and *GSTμ* genes and gene expression studies for p16, CyclinD1, CyclinE, p53, Bcl-2, Bax, Cox-2, HPV, E-catherin will be performed. ICPO will be receiving samples from 3 centres in North-East which are Silchar Medical College, Silchar, Regional institute of Medical Sciences, Imphal and Assam Medical college, Dibrugarh.

Effect of Pesticide Exposure in Causation of Cancer in North-East India

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THERE is an extensive use of pesticides in tea gardens in North-East which can lead to widespread occupational and environmental exposures. According to the study conducted by IARC, 50% of the pesticide found to possess carcinogenic potential. High incidence of certain cancers like cancer of breast with higher serum DDE levels have been reported from North-East districts by ICMR. The incidence of breast cancer in Aizawl district was 36.2/100,000 which is higher than that reported by any of the population based cancer registry of NCRP. The present study is designed to investigate the link between exposure to pesticides and genetic variation including polymorphism/mutations associated with ethnic variation. The study will be carried out in the six population based cancer registry area of the North-East with a case control epidemiologic design similar to project on Tobacco-related cancers.

Development of breast cancer involves genetic, hormonal and environmental factors. Two major genes known to confer susceptibility are BRCA 1 and BRCA 2, explain only 5-10% of the total incidence. The other genes which are related to endogenous hormone exposure and also plausible candidates for susceptibility include estrogen receptor, progesterone receptor and vitamin D receptor which are members of nuclear receptor super family. ICPO will, therefore, perform the mutation and polymorphism studies of ER, CYP17, AR, Vitamin D Receptor, BRCA1, BRCA2, p53, p16, Her2-Neu to establish any propensity of occurrence of certain mutation in ethnic groups which renders the North-East population more susceptible to development of breast cancer.



Large-scale usage of pesticides in the tea gardens of the North-East region leads to heavy contamination of water and environment resulting in exposure of pesticides to local population