CHAPTER - IV

GENERAL DISCUSSION
General Discussion:

India is a developing country with one of the most diverse populations and diets in the world. Cancer rates in India are lower than those seen in Western countries, but are rising with increasing migration of rural population to the cities, increase in life expectancy and changes in lifestyles. In India, rates for the cancers of UADT (mainly oral and oesophageal cancers) are some of the highest in the world (Sinha et al., 2003).

The burden of cancer is still increasing worldwide despite of the good advances made by the medical science. Epidemiological studies have shown that many cancers may be avoidable. It is widely held that 80-90% of human cancers may be attributable to environmental and life style factors such as tobacco, alcohol and dietary habits (WHO, 1997). Cancer prevention includes primary, and secondary prevention methods. Primary prevention refers to avoiding cancer causing substances in the environment or dietary elements associated with increased risk; dietary supplementation with putative protective agents. Secondary prevention aims at early detection and removal of benign tumors of oral, cervical and breast (Osborn et al., 1997). It was estimated that in the year 2000, worldwide over 10 million new cases of cancer occurred (approximately 5.3 million men and 4.7 million women) and over 6 million people died for cancer (Parkin et al., 2001).

Urbanization, industrialization, changes in lifestyles, population growth and aging all have contributed for epidemiological transition in the country. The absolute number of new cancer cases is increasing rapidly, due to growth in size of the population and increase in the proportion of elderly persons as a result of improved life expectancy following control of communicable diseases. In India, the life expectancy at birth has steadily risen from 45 years in 1971 to 62 years in 1991, indicating a shift in demographic profile (SRS, 1998). It is estimated that life expectancy of Indian population will increase to 70 years by 2021-25 (NCCP, 1996). Such changes in the age structure would automatically alter the disease
pattern associated with aging and increase the burden of problems such as cancer.

UADT cancers predominantly affect men. All most all the UADT cancers are much higher in male than in female (Murthy & Mathew, 2004). This is borne out by the sex distribution of the patients in some of the large series and also from the higher incidence rates among men (Fahmy et al., 1983; Fleming et al., 1982). The sex differences in some population groups could be a direct consequence of the sex distribution of tobacco habits. For instance, in an epidemiological study in India, it was found that the male:female ratio of oral cancer patients was proportional to the prevalence of tobacco habits among men and women in the general population (Mehta et al., 1982). In a study of 498 oral cancers among South African Blacks, Fleming et al. (1982) observed a high male:female ratio (7:1) which they related to the differences in tobacco usage between the sexes. Oral cancer, like most other cancers, affects the individuals in the higher age group, most of the patients being over the age of 40. The peak occurrence, however, varies in different population groups. In Western countries the peak occurrence is in the sixth and seventh decade, whereas in Asia it is generally earlier (Paymaster, 1962). In Iran and India, the peak occurrence appears to be in the fifth and sixth decades (Fahmy et al., 1983). There are some variations in the age distribution with regard to race and sex. In South Africa, the peak occurrence of oral cancer for two races combined was in the sixth and seventh decades. However, the disease occurred in the lower age groups among Blacks. In India, 1977 oral cancers were recorded in six registry areas and the peak occurrence for man was in the 50-59 year age group while for woman it was in the 60-69 year age group (Sanghvi et al., 1986). The present study projected the high incidence of UADT cancers in between the age group 56-60 years (Table-1.10). Moreover, this study has attempted for the first time to project district wise occurrence of the UADT cancers in Assam, India (Table-1.11).

Cancers of the upper aero-digestive tract (UATD) are the most prevalent cancers globally. In India the NCRP (National Cancer Registry Program) data has revealed a very high incidence of the disease across the country with special
reference to the northeastern region. Case-control and cohort studies have established that the high incidence of the disease in India is due to widespread habits of tobacco consumption (Gupta et al., 1999). Excessive promotion of new form of tobacco products has substantially increased the prevalence of the disease in India and there is apprehension that the incidence of the disease would further increase. In northeastern region of country the prevalence of the disease is even much higher than the national average and has been attributed to the extensive use of the betel quid and tobacco (NCRP, 2002). This investigation has been able to highlight the occurrence of 94% of the UADT cancers with the habit of betel nut and tobacco chewing as risk factors (Table-1.14) and the rest 6% (Table-1.13) without these habits.

Tobacco consumption remains the most important avoidable cancer risk. Between 25% and 30% of all cancers in developed countries are tobacco-related (WHO, 1995). India is the third largest producer and consumer of tobacco. The country has a long history of tobacco use in a variety of ways of chewing and smoking. The habit of chewing (15-70%) and smoking (23-77%) vary considerably from area to area (WHO, 1995). It has been estimated that in 1996, 184 million persons used tobacco in the country in one or other forms (MoHFW, 2001)). The cancer risk of tobacco use has been extensively investigated (Nandakumar et al. & Sankaranarayanan et al., 1990). Tobacco-related cancers account for nearly 50% of all cancers among men and 25% of all cancers among women. Burden of tobacco-related cancer in India by 2001 has been estimated to be nearly 0.33 million cases annually (Murthy et al., 1998). There are predictions of incidence of 7-fold increase in tobacco-related cancer morbidity between 1995 and 2025. Further there will be an overall increase by 220% of cancer death simply related to tobacco use by the year 2025 (NCRP, 1996).

A variety of tobacco habits are prevalent in India and they differ from region to region (Bhonsle et al., 1992). The use of tobacco in many forms increases the risk of UADT cancers. The most widespread is the chewing of betel quid with tobacco and this has been demonstrated as one of the major risk factors for the cancers of UADT. A dose response relationship as measured by the duration of
chewing, frequency of chewing per day, period of time chewed and retention of chewing quid overnight while asleep has also been demonstrated (Jussawalla & Deshpande, 1971; Sankarnarayanan et al., 1989; Akhtar, 1998). It has been shown that the risk of chewing betel quid with tobacco is much higher compared to the risk without tobacco (Fig-1.17), which is either insignificant or much lower (Gupta et al., 1982). In addition, there is a site-specific relationship, for example, in areas where tobacco-containing quid is kept in the lower labial groove, cancers at those sites are common.

Tobacco consumption has decreased in many developed countries while in most developing countries it is still increasing. This may largely be due to the fact that relatively fewer studies have been reported from developing countries, including India, on the risk of cancer at different cancer sites due to the use of various forms of tobacco (Dikshit et al., 2000). In a study conducted in Bhopal, India showed the attributable risk for those who chewed tobacco was 84.4% for development of oral cavity cancer. This suggests that the high percentage of lung, oropharyngeal and oral cavity cancers in Bhopal could be prevented if tobacco habits were not started (Dikshit et al., 2000).

An earlier study conducted in India reported that 30% of the population of 15 years or older - 47% men and 14% of women - either smoked or chewed tobacco, which translates to almost 195 million people - 154 million men and 41 million women in India. The prevalence may be underestimated by almost 11% and 1.5% for chewing tobacco among men and women, respectively, and by 5% and 0.5% for smoking among men and women, respectively, because of use of household informants (Rani et al., 2003). Tobacco consumption was significantly higher in poor, less educated, scheduled castes and scheduled tribe populations. The prevalence of tobacco consumption increased up to the age of 50 years and then leveled or declined. The prevalence of smoking and chewing also varied widely between different states and had a strong association with individual’s socio-cultural characteristics as reported by the study (Rani et al., 2003).

Persons who use chewing tobacco and snuff are reported to be experiencing an increased risk of oral cancer. Because of the pharmacologic
properties of nicotine and other constituents of smokeless tobacco, there is also concern that smokeless tobacco products may lead to cardiovascular diseases as well (Winn, 1997). Hemoglobin adducts to carcinogens present in smokeless tobacco products are measurable in the blood of smokeless tobacco users, indicating that smokeless-tobacco-related carcinogens circulate throughout the body. This prompts a concern that smokeless tobacco may increase risks of other cancers as well. The evidence to date from epidemiologic studies indicates no relationship between smokeless tobacco and bladder cancer, but there is suggestive evidence linking smokeless tobacco use to prostate cancer risk. Molecular epidemiologic studies may help to identify markers of malignant transformation in smokeless tobacco users that may help in early intervention to prevent or ameliorate the consequence of oral cancer. Further studies are needed to determine more clearly the non-oral cancer risks potentially associated with smokeless tobacco use (Winn, 1997).

Like many other studies reported in India and elsewhere, the present study also indicated very high incidence of the UADT cancers in northeastern region of India. About 60% of the total cases were represented by the cancers of the UADT during the study period of the present investigation, revealing the highest occurrence of the disease in oesophagus in the region in comparison to the other parts of India (Table-1.15a & 1.15B). The study also showed the possible association of chewing betel quid, both with and without tobacco, with the risk of cancers of the UADT (Fig-1.17).

There have been several endeavors to understand the aetiology of UADT cancers all over the world, but no definite results could be established so far though epidemiologic studies suggested strong correlation of the disease with tobacco and betel quid chewing habits (Fig-1.14, 1.15, 1.16). Review of previous literatures unearths about the extensive investigations carried out to study the role of certain elements on causation of cancers. Study of trace elements has been an area of interest for last 3 decades to find out their possible role in the various biological processes and malignancy is the major among them. But most of the studies so far been carried on the possible role played by trace elements on
causation of cancer are mostly on the concentration levels of these elements in
the cancerous tissues and most of the studies reported elevated levels of many of
these elements in cancerous tissues. But there has been very little endeavor to
study the probable sources of these trace elements entering the biological
systems, i.e. the cancer affected organisms. The present study for the first time
exposed the presence of significant quantity of Pb, Cr, Ni, As which may attribute
as the risk factors for the high incidence of the UADT cancers in the northeast
region of India. Therefore, tobacco and betel nut are considered as the most likely
sources of risk containing factors as revealed in the epidemiological study.

In an epidemiologic data on the average daily human dietary intake of the
trace elements like Zn, Cu, Fe, Cd, Ni, Mo, Si, Se etc. from different foods by
using food samples collected from 232 villages in China suggests an association
between the elements and oesophageal cancer (Chen et al., 1996). This views
help to establish a relationship with the present finding on the significant
amount of S, K, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Br, Rb, Sr, Mo, Pb, As,
Ba and Ga, in the habituated materials like tobacco and betel nut samples (Table
- 2.14).

A characteristic pattern of trace element concentration in several
carcinomas was extensively observed by Ranade and Panday (1983;1984;1985).
It was observed that copper concentration varies from organ to organ (Owen,
1964) and with age (Everett et al., 1964; Evans et al., 1970). It was established
that in cancer patient serum copper concentrations are of considerable
importance in assessing the activity and prognosis of the disease (Hrgovicic et al.,
1973; Roguljic et al., 1980). Elevated serum copper and decreased serum zinc
concentrations have been detected in patients with sarcoma (Breiter et al., 1978)
and carcinoma of the digestive system. Variations of Cu concentration in human
breast tissue were reported (Ranade et al., 1989; Rizk and Sky-peck, 1984). Zinc
and copper are two important trace elements of the tissue. Zinc is necessary for
growth, appetite, testicular maturation, skin integrity, mental activity, wound
healing, prevention of lipid peroxidation and immunocompetence (Burch et al.,
1978). Zinc is involved in the activity of at least 90 enzymes. Andronikashvili et al.,
(1972) concluded that zinc is rather important in some forms of neoplastic growth. Reports of Fujioka and Liberman (1964) and Weser et al. (1969) have established that zinc alone is responsible for nucleic acid biosynthesis in regenerating liver, while Rubin (1972) observed a correlation of zinc content with Rous sarcoma development.

Sufficient experimental data also have been accumulated about chromium, nickel, arsenic, and beryllium to indicate that they are human carcinogens also evident in this experiment (Table-2.13, 2.14) and exhibit genetic toxicity in a number of test systems which suggest that mutagenesis is involved in the initiation of cancer by these metals. While arsenic has not been shown to induce tumors in experimental animals, it has been shown that arsenic depresses that level of DNA polymerase in human epidermal cells, inducing a reduction of the DNA repair mechanism, which in turn renders human cells vulnerable to DNA damage by secondary factors; i.e., exposure to arsenic and cigarette smoking significantly increased the incidence of chromosomal aberrations in lymphocytes, suggesting that arsenic may have acted as a cocarcinogen (Chakravarty, 1994; Linder, 1977).

The levels of vanadium and selenium were significantly elevated in breast cancers compared to normal tissue. Vanadium is a ubiquitous essential trace metal experimentally linked to the membrane bound Na-K ATPase pump system (Becker, 1980; Cantley, 1979). High levels of vanadium (12.4 μg/g, Table-2.9) reversibly inhibit the pump system and adenylkinase while stimulating adenylcyclase, glucose oxidation, and transfer. While selenium in large concentrations (77.6 μg/g, Table-2.9) is toxic, it is also an essential trace metal at low concentrations (Clayton, 1980; Thomsen, 1980). Deficiencies of selenium have been related to a cause of muscular dystrophy, pancreatic fibrosis, hepatosis dietetica, cancer, and certain disorders attributed to prostaglandin and vitamin E deficiency. Selenium and vitamin E protect membranes from oxidative degradation and prevent exudative diathesis. Selenium functions as a metalloenzyme glutathione peroxidase to reduce peroxides before they can attack the cell membrane. There have been numerous reports that geographical areas,
low in selenium have higher incidences of various cancers, heart disease, and muscular dystrophy (Thomsen, 1980).

Although the various findings presented here generate more questions than answers, they do give guidelines for future study into the possible roles and interactions of essential trace elements in the carcinogenic process. For example, vanadium, selenium, and zinc each appear to play an important role in various membrane functions. Selenium and zinc have also been shown to be antagonistic to each other in a number of metabolic systems (Sigel, 1980; Underwood, 1977). A better understanding of the interrelationships of trace metals is obviously needed to better understand their role in regulating tumor growth.

The bulk of trace element investigations associate elemental concentrations with the study of tumour pathogeneses, course of disease and efficiency of medical therapy. Several factors are known to be responsible for promoting the development of a lung cancer. Between risk factors one can find smoking occupation, environment, chronic bronchitis and scars in the lung (Kubala-Kukus, 1999).

This increased awareness of the role of trace elements, their interactions in metabolism and disease suggested the need for a multi-element micromethod of analysis which could provide data quickly and efficiently for several elements in the same biological sample. The present study has shown the applicability of a Particle Induced X-ray emission spectroscopy for the simultaneous determination of trace element's in micro-samples of human tissues. This makes practical the gathering of needed base-line data of large populations.

Thus this study presented an account about the predominance and possible aetiology of the UADT cancers in the northeastern region of India by carrying out a detail investigation during a three years period (2000-2001). The present study, the first of its kind in the region, unearth about the predominance of the disease as compared to the other parts of the country and elsewhere in the world, supporting the several claims made by various other workers till date as
discussed above. Thousands of studies and articles have already been put forwarded across the globe demonstrating a strong correlation of the cancer of the UADT with the prevalence of use of the tobacco and betel but in various forms, which has again been confirmed by the present findings with additional inputs, facilitating further characterization of the subject. The etiological clues being provided by the present study about the source of risk factors for the UADT cancers, in the light of the probable of role of various elements in carcinogenesis, has so far been the first of its kind, which reveal shocking evidence of the presence of high concentration of certain elements with carcinogenic properties in the habituated materials like tobacco and betel nut in various forms. This piece of evidence strongly supports a significant correlation between the wide spread habit of betel nut and tobacco chewing with the very high incidence of the UADT cancers in the northeastern region of India in general and the state of Assam in particular, strengthening the similar findings of other workers elsewhere.

This is the first clue towards this subject that frequent and prolonged habits of chewing betel nut and tobacco perhaps elevate the level of certain elements directly or indirectly responsible for the process of carcinogenesis, opens a new era for further research, which in turn will largely help in prevention of the disease by presenting strong evidence to the society about the deadly role of betel nut and tobacco consumption.

"Let's make the society free from tobacco and betel nut use and help the future generation to live without the UADT cancers."
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