



**EPIDEMIOLOGICAL AND ETIOLOGICAL FACTORS ASSOCIATED WITH
NASOPHARYNGEAL CARCINOMA**

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most part of the world and it is one of the most confusing, commonly misdiagnosed, and poorly understood disease. NPC has a remarkable racial and geographical distribution. In recent decades, it has attracted world-wide attention because of complex interactions of genetic, viral, environmental and dietary factors, which might be associated with the etiology of this disease. Nasopharyngeal carcinoma has a well-defined geographical distribution, primarily affecting individuals from southern China and South East Asia¹. It has been reported to be prevalent in three widely different populations, *viz.* Chinese in South East Asia, Arabs in North Africa and Eskimos in the Arctic². In spite of very high incidence of oral cancer in the Indian sub-continent, NPC has a low incidence which is comparable to other parts of the world except in some ethnic groups in the North East (NE) Region of India. It seems there are some significant geographical and ethnic variables within the country, which predispose people for high incidence of NPC in NE region of India. Ho³ suggested that at least three etiological factors are possibly contributing for the high incidence of NPC in various Chinese populations. These are ubiquitous Epstein-Barr virus (EBV), genetically determined susceptibility and associated environmental factors. Environmental factors

are numerous and appear to have a secondary role, mainly in the promotion of the neoplastic process¹. The present article is an attempt to provide a hypothesis for the higher incidences of NPC in different parts of the world including NE region of India based on the available information mainly on the etiology and epidemiology of this disease in India as well as other parts of the world.

Epidemiology of Nasopharyngeal Carcinoma

The incidence of NPC is low in most part of the world (an age-adjusted incidence of less than 1 per 100,000 people). The rates are twice as high in males as in females⁴. However, the incidence of the disease is higher in certain population and geographical regions of the world. It mainly affects people from southern China. Higher incidence of the disease is also reported in some other population of South East Asian countries especially among admixture of Chinese population. Moderately higher incidence of NPC is reported in some other population groups also such as Eskimos in the Arctic, Arabs in North Africa and few other population groups of South East Asia. Chinese of southern origin have a uniquely high risk, the incidence per 100,000 population being 10-20 in males and 5-10 in females⁵. Highest incidence has been reported among people of

Guangdong province and Guangxi region of China where the incidence of NPC reaches 50 or more 100000 people per year⁶. The incidence pattern revealed the higher prevalence of NPC among Chinese wherever they have migrated⁷. Sudan has also reported higher incidence of NPC. NPC forms 5.8% of all cancer cases in the Sudan Cancer Registry and 7.2% at the Radiation and Isotope Centre, Khartoum, Sudan⁸.

In spite of the high incidence of cancer of the oral cavity and other parts of pharynx, cancer of nasopharynx is uncommon in Indian sub-continent except for NE region of the country. There are some significant geographical variations within the country with respect to the distribution of nasopharyngeal carcinoma reflecting ethnic susceptibility for the disease. Studies based on NPC cases registered in most of the cancer diagnosis and treatment centres in NE Region of India during 1988-89 and computed with the population structure of the region indicated that the incidence of NPC is quite high in Nagaland (about 4.3 per 100,000 people/year). Taking into consideration the 1981 census figure for the population structure of Nagaland, the incidence of NPC was nearly 6.2 and 2.1/ 100,000 male and female, respectively^{9,10}. Further, hospital based studies on the pattern of cancer incidence in Nagaland revealed that out of 149 biopsies of suspected cancer cases, 37 were histopathologically positive for malignancies and about two third of them were with cancer of nasopharynx¹¹. These studies show that the Naga community is more vulnerable to this diseases. These Naga tribes belong to the mongoloid group of people. Thus it can be inferred that NPC is relatively higher among the Mongoloid group of people in the NE region of India compared to Caucasian population residing in other parts of the country. These studies further suggested that the Mongoloid populations, particularly the Nagas are having intermediate risk for nasopharyngeal carcinoma as the incidence is about 4.3/100,000 people/year. Other populations under the intermediate risk are Malays of South East Asia, Polynesians in New Zealand and some population of North Africa and Arctic Circle.

Another important characteristic of NPC epidemiology is sex distribution. In most of the studies male preponderance over the female was reported from different parts of the world. Studies from NE region of India¹¹ also indicate different age peak groups and male preponderance over the female and the ratio was about 3:1. The pattern of age distribution of NPC varies in

different parts of the world. Hirayama⁴ reported that the incidence in both the sexes starts rising after the age of 20-24 and reaches a plateau between 45 and 54 years of age. Earlier, Commun *et al*¹² reported a younger age peak at 10- 19 years in addition to the main peak at 50-59 years in Tunisia, an area of intermediate risk for nasopharyngeal carcinoma. This relatively high frequency of NPC among younger population seems to be a characteristic feature in areas of intermediate incidence *ie.* Uganda, Kenya, Sudan and Tunisia. Hirayama⁴ reported that the additional peak in adolescence appears to be lacking among Chinese in the USA. Balakrishnan *et al*¹³ also observed a bimodal age distribution with peaks in age group of 15-24 and 45-54 years from India. However, no specific bimodal age peaks were observed in a study from NE region of India¹⁰.

Etiological Factors

It is believed that a number of etiological environmental factors along with genetic/host factors might be responsible for the causation of this cancer as the incidence is confined mainly to some population/ethnic groups or certain geographical region of the world. Ho³ suggested that at least three etiological factors *ie.* ubiquitous Epstein Barr virus (EBV) infection, genetically determined susceptibility, and associated environmental factors are possibly contributing for the high incidence of NPC in various Chinese populations. In India it is observed that most of the Naga people live in ill-ventilated houses without separate kitchen, particularly in rural area. They use to keep the firewood (mainly oak and pine tree wood which produces thick smoke) burning during day and night for heating, lighting and cooking purposes. A bamboo shelf hanging over the fireplace is used for smoke drying of meat and vegetables for preservations. They consume this smoke dried foodstuffs. The people living in ill ventilated houses are inhaling smoke continuously for longer duration compared to those living in well-ventilated houses. Such living and dietary habits might have some role in the etiology of this cancer¹⁰.

Some other dietary habits are also reported to be associated with the increased risk of NPC. Cantonese salted fish had been suspected as a possible aetiological factor in development of NPC¹⁴. This was supported by the demonstration of nitrosamines in cantonese salted dried fish^{15,16}. An experimental support for this theory has also been provided and it was demonstrated that three out of twenty treated rats developed carcinoma of

the nasal or para nasal cavities when fed on diet of cantonese salted fish¹⁷. Yu *et al*¹⁸ supported this finding, using large sample size in an experimental study. They reported four malignant tumours of the nasal cavity among rats fed with Chinese salted fish. The consumption of salted fish during weaning periods is reported to be an independent risk factor for NPC in Hongkong¹⁹. Case control studies in Hong Kong²⁰ and Malaysia among Malaysian Chinese²¹, and in China among Chinese²² also showed strong association with salted fish consumption in early childhood and nasopharyngeal carcinoma. Poirier *et al*,²³ detected relatively high levels of volatile nitrosamine in common food items consumed frequently by populations at high risk for NPC in Tunisia, South-China and Greenland. Similarly Zou *et al*²⁴ demonstrated appreciable levels of nitrosamine in the salted fishes consumed by residents in high-risk area of NPC in China. Further, a strong EBV activation was observed in aqueous extracts of cantonese salted dried fish from China, and to a lesser extent in Qaddid (dry mutton preserved in olive oil) from Tunisia²⁵.

The acetone extract of smoke dried meat tested to document the genotoxic potential using sperm head shape abnormality test revealed a significant dose responsive mutagenic effect²⁶. Mutagenic effect of smoke dried meat was also revealed in *Salmonella typhimurium* using TA 98 strains by Ames's test¹⁰. Sarkar *et al*²⁷, reported that smoke meat extract (SME) was mutagenic in *Salmonella typhimurium* with or without S9 mixture, and was clastogenic in mammalian test system. They further reported that SME has the potential to induce skin papilloma as well as systemic tumour in Swiss albino mice and chemical analysis of SME revealed the presence of nitrosodimethylamine (NDMA), nitrosodiethyl amine (NDEA), nitrosopyrrolidine (NYPR) and benzo (a) pyrene (BaP). The presence of NDEA in smoke dried meat strengthens the view that consumption of smoked meat may be one of the risk factors associated with higher prevalence of NPC in Nagaland. In an earlier study three out of fourteen NDEA treated rats developed adeno carcinoma in the nasal cavities but none of the animals treated with NDMA developed nasal or paranasal tumours. A recent case control study on NPC in NE region of India strengthens this hypothesis which indicated that consumption of smoke dried meat and use of herbal nasal medicine were the significant risk factors for the nasopharyngeal carcinoma²⁸. The available data suggest that preserved foodstuffs might be one of the important etiological factors for high incidence of NPC in different geographical region of the world²⁹.

Inhaled substances has been also attributed as responsible factors in the etiology of NPC and epidemiological evidence are equivocal. Studies carried out on soots collected from different villages of Nagaland revealed clastogenic and mutagenic potential in plant³⁰ and bacterial¹⁰ cells assay, respectively. Thus it is presumed that inhalation of smoke continuously may also play an important role in the high incidence of nasopharyngeal carcinoma in this part of the world. However, recent case control study carried out in NE region of India did not find significant association between exposures to smoky atmosphere and nasopharyngeal carcinoma²⁸.

A number of environmental inhalants have been reported to be associated with NPC. Hu and Huang³¹, reported a positive association with the use of fossil fuels for cooking and NPC. Clifford and Bulbrook³² stated that many African in Kenya including those who have high incidence of NPC live in ill-ventilated houses from which smoke and fume from cooking can hardly escape through the heavily thatched roof. They reported that smoke, particularly from wood, containing carcinogen might get deposited on the posterior and lateral nasopharyngeal walls for several hours in a day for years together. Analysis of soots taken from the roof of these huts showed that it contained significant quantities of benzopyrene, benzanthracene, poly-nuclear aromatic hydrocarbons³³. Lin *et al*³⁴ also found that working under poorly ventilated conditions was associated with NPC and the risk was more than twice compared to those working under ventilated conditions. Zheng *et al*³⁵ also provided unequivocal evidence for two other factors implicated in enhancing the risk of NPC in China. These are consumption of traditional medicines (herbal tea) and exposure to domestic wood fumes.

It has been reported that persons who had smoked cigarettes for ten years or more had a higher risk for NPC³⁶. A study conducted in India also observed significantly high relative risk among the smokers, particularly for the well differentiated nasopharyngeal carcinoma¹³. Lin *et al*³⁴ compared the surrounding environments of NPC patient with those of neighbourhood controls in Taiwan and found that smoking of cigarettes and working in poorly ventilated places were strongly associated with NPC. Another study suggested that long term cigarette smoking is associated with NPC but low levels of exposure to cigarette smoke via passive smoking exposure and alcohol consumption are not associated with disease risk³⁷.

Formaldehyde vapours have been found to induce cancer of the nasal passage in laboratory animals. Formaldehyde related occupation in the printing industry also appeared to be associated with nasal cancer (either sinonasal cancer or nasopharyngeal cancer)³⁸. An association was also reported between cancer of the nasal cavity and sinuses and the textile work³⁹. Besides, some other non-dietary risk factors have been implicated in nasopharyngeal carcinoma⁴⁰. It was reported that occupational exposure to products of combustion and cotton dust was independently related to risk of NPC. Similarly occupational exposure to formaldehyde, but not the wood dust, also increases the risk of NPC⁴¹. However, this association seems to be specific to squamous cell carcinomas. Further, the intake of preserved foods at an early age has been linked to NPC risk in all population groups⁴². The data on inhalation of various types of smokes/fumes/dust suggest that inhalants may play an important role, though might be secondary as a promoter, for the high incidence of NPC in different geographical region of the world. The inhalants may differ from one region to another depending upon the living environment of the high-risk groups of people.

Viral Etiology

Epstein Barr virus is a member of the large herpes virus family and distributed ubiquitously. It is found throughout all human populations, with a prevalence of over 90% in adults⁴³. It is believed that environmental, genetic or chemical co-factors might be responsible for the high incidence of certain cancers such as NPC and Burkitt' lymphoma in different geographical region of the world. Evidence are accumulating that Epstein-Barr virus also plays an important causative role in the etiology of this cancer. Epstein *et al*⁴⁴ first detected the Epstein-Barr virus (EBV), by electron microscopy in a small percentage of cells cultured from Burkitt lymphomas (BL). A preliminary study on EB virus serology carried out in North-eastern region of India also indicated higher level of EBV IgG VCA antibody in the sera of patients with nasopharyngeal carcinoma compared to control or patients with oesophageal malignancy⁴⁵. Further, activation of EBV by the consumption of smoke dried meat by the Naga people cannot be ruled out as there are reports that some of the food stuff used in NPC prone area have the potential to induce EB virus activity.

An association between nasopharyngeal carcinoma and EBV was suggested by the results of

seroepidemiological studies from different parts of the world⁴⁶⁻⁴⁹. It was confirmed subsequently by the demonstration of the persistence of EBV DNA and / or virus determined nuclear antigen (EBNA) in NPC tumour cells^{17, 50,51}. Henle and Henle, first described that Serum IgA antibodies to the virus capsid antigen (VCA) and early antigen (EA) were significantly associated with NPC⁴⁸. de The in 1984 reported that though the role of EBV in the causation of NPC is not well understood, the viral capsid antigen IgA test allows both early detection of NPC in high incidence area and differential diagnosis in low incidence area⁵². It has been reported that the EBV is intimately related to carcinoma of nasopharynx and elicits the formation of antibodies that are useful for diagnosis and follow up study⁵³. Lavine *et al*⁵⁴, also reported that antibodies to EBV antigens have been used in the early detection of NPC and serological assays are being utilized in mass screening of high risk populations. They mentioned that EBV serology is of value in the detection of early relapse.

Lin *et al*⁵⁵ assessed the relative importance of various risk factors of nasopharyngeal carcinoma, which included antibodies to EBV capsid antigen (anti VCA) and early antigen (anti EA) as well as other environmental factors using a multivariate logistic regression method and reported that anti VCA and anti EA titers were significantly associated with NPC. The relative risk increased with the increase of antibody titers⁵⁴. It has been demonstrated that infection of normal nasopharyngeal epithelial cells with EBV takes place in patients with nasopharyngitis⁵⁰. Further, genotype of EBV has been reported for Chinese NPC⁵⁶. Two major polymorphisms have been described based on a heterogeneous sequence of the EBNA2 gene and the restriction enzyme polymorphisms observed on several parts of the viral genome from highly divergent sequences encoding the EBNA2 gene. The types have been termed as A and B. The A type EBV has more efficient transforming activity than the B type virus and there was a significant difference between the EBV variants common in Chinese NPC and those in North African NPC⁵⁷.

Very scanty data are available on detailed genotypes and EBV serology in NPC patients from India. It has been reported that geographically A type EBV was far more prevalent in Western India, while in Eastern India particularly Assam, all five cases were positive for B type EBV. Thus, a significant variation in the type of EBV infection was observed in nasopharyngeal carcinoma

in different ethnic populations in India⁵⁸. Earlier, a wide spread early and persistent EBV infection was reported in Indian population⁵⁹. A study on EB virus serology carried out in NE region of India also indicated high EB virus IgG VCA antibody in the sera of patients with nasopharyngeal carcinoma. Further, the EVB titre was slightly higher among mongoloid group of people than non-mongloid group⁴⁵. Zheng *et al*⁶⁰ reported that the combination of salted fish and EBV was strongly associated with NPC, compared to EBV or salted fish alone. They reported that the IgA-VCA was the most important predictor of NPC, followed by fish. Scientists have studied the correlation of herbal medicine use and EBV in NPC and suggested that herbal medicines have a direct proliferative effect on EBV – transformed cell and thus there is a stronger association of EBV with the development of NPC⁶¹. EBV has been also classified as a group I carcinogen by the International Agency on Research on Cancer, because of its association with NPC⁴³.

Genetic or Host Factors

The high incidence of NPC among Southern Chinese both in China and Chinese migrated abroad and the intermediate rates among population admixed with Chinese and also in certain other ethnic groups have suggested a strong genetic control over expression of the disease. A number of reports have suggested the role of histocompatibility locus antigens (HLA) association with NPC especially among the Chinese. The marked differences in the incidence pattern among different ethnic and dialect groups, migrants retaining the high incidence pattern even in subsequent generation and family clustering suggest a very strong genetic etiology of NPC. Simons *et al*⁶² first described the association of HLA antigens with NPC in Southern Chinese. The genetic factors, mainly HLA antigens' association with NPC was suggested in 1990 for the Chinese population and to a lesser extent in other Asian ethnic groups⁶. Though there were differences between NPC patients and control in several genetic system tested⁷, the only one strongly associated with NPC is HLA, which is situated on the short arm of chromosome six⁶. It was reported that two different haplotypes are associated with the newly diagnosed NPC-A2, Cw11, Bw46 and Aw33, Cw3, Bw58, DR3. There are consistent negative association with the alleles A11 and B13. The relative risk associated with A2, Cw11 Bw46 haplotype is 3.4 and with Aw33, Cw3, Bw58, DR3, is 2.2⁶³. However, no such data on genetic

aspects are available from NE region of India. Simons *et al*⁶⁴ demonstrated that HLA antigens play a role in determining both susceptibility for NPC and survival after diagnosis. Later Chan⁶, also suggested that though there is no bimodal peak in age incidence curve among Chinese NPC, the HLA data reveal that the younger and older onset patients are genetically different and may involve different mechanism. He further reported that the Aw33, Cw3, Bw58, DR3 haplotypes are also associated with poor survival. A2 without Bw46 or Bw58 and A2, B13 appears to be associated with long-term survival⁶⁵. He concluded that HLA association with NPC has been well established in the Chinese⁶.

Studies are in progress in different laboratories to elucidate exact location and function of these genes. Very recently it was reported that since the HLA association with NPC remains the strongest among common cancers, it is to be hoped that this enigma, as well as the fine map location of one or more HLA- linked NPC risk loci, will soon be achieved (Simon, M.J. Unpublished observation).

In addition to the association between EBV, HLA and NPC, recently enzyme cytochrome P450 2E1 (CYP2 E1), is also implicated in the etiology of this cancer. The cytochrome P450 2E1 which is involved in the metabolic activation of procarcinogens into reactive intermediate capable of forming adducts and damaging DNA, is believed to play an essential role in chemical carcinogenesis⁶⁶. It was reported that chemical carcinogenesis involves metabolism in the body, of the carcinogen and its interaction with DNA. The activation mechanism is particularly related to the cytochromes P-450s (CYPs), and four of these known to activate carcinogens are CYP1A1, CYP1A2, CYP2E1 and CYP3A4. Nitrosamine is a substrate of CYP2 E1⁶⁷. Gervasi *et al*⁶⁸ demonstrated that the respiratory section of human nose contains a wide array of oxidative and non-oxidative enzymes, which could play a crucial role in the bioactivation or detoxication *in situ* of inhaled xenobiotics. Thus consumption of foodstuffs containing nitrosamines or inhalation of carcinogenic smoke might have adverse effects on nasal epithelium. Further, CYP2 E₁ is one of the several NPC susceptible gene and is believed to render the nasopharyngeal epithelium susceptible to NPC developments⁶⁸. Earlier studies carried out in Taiwan also showed a relationship between this enzyme and NPC among various Asian ethnic groups, including Chinese in Taiwan^{69, 70}. These studies point towards the significant

role played by CYP2 E1 enzyme in the etiology of nasopharyngeal carcinoma along with other environmental and dietary factors.

Review of data on NPC suggested that EBV infection and genetic susceptibility are the constant etiological factors responsible for the higher incidence of NPC among various ethnic groups while other factors such as ingestants and inhalants may depend on the distinct dietary practices and living environment adopted by various ethnic groups in different geographical region of the world⁷¹.

Conclusions

On the basis of available current information and work experience, it is suspected that NPC is a consequence of four interacting factors. The EBV and genetic susceptibility are the constant factors for various ethnic groups. The other factors such as inhalation or dietary factors are different for one region to another or different to one or another ethnic groups (Fig.). In the

place of salted fish in China along with other factors. Thus people who are at the risk should consider the risk factors associated with NPC especially dietary and environmental factors which could be avoided by adopting the healthy life style in order to minimize the risk. The data available also point to the importance of information and education programme on the food habits for the population at risk, residing in the high or intermediate risk prone area of NPC of the world as it is speculated that epithelial cells might become susceptible to EBV infection as a result of exposure to environmental carcinogens eg. the dietary factors such as salted fish⁶² or other foodstuffs containing carcinogens including smoke dried foodstuffs.

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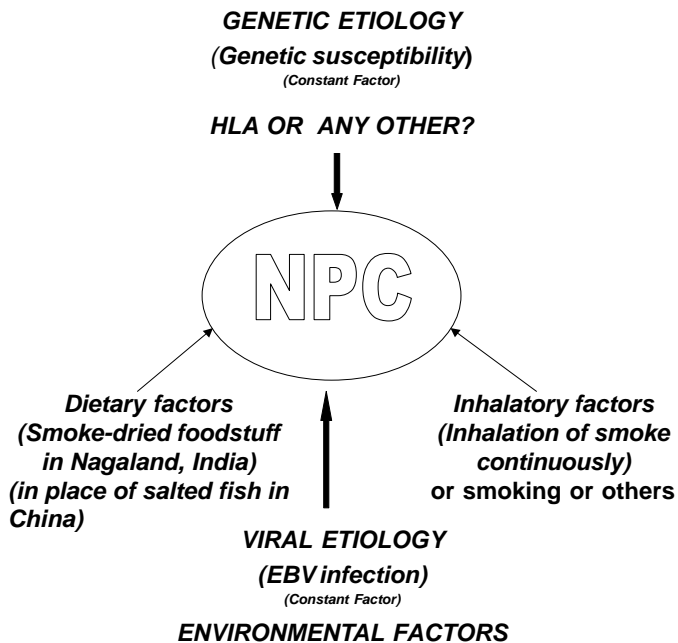


Fig. Possible etiological factors associated with nasopharyngeal carcinoma in NE region of India.

case of Chinese population consumption of salted dried fish has been reported to be associated with nasopharyngeal carcinoma. However, the high incidence of this cancer in Nagaland (NE region of India) may be due to the consumption of smoke dried food stuffs in

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Printed and Published by Shri J.N. Mathur for the Indian Council of Medical Research, New Delhi
at the ICMR Offset Press, New Delhi-110 029

R.N. 21813/71