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*Original Research Article*

# Study on Dietary and Environmental Risk Factors for Nasopharyngeal Cancer in Manipur

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## ABSTRACT

**Background:** Nasopharyngeal carcinoma (NPC) is a rare cancer worldwide except in South East Asia, Southern China and North Africa. In spite of the high incidence of cancer of the oral cavity and other parts of pharynx, NPC is uncommon in the Indian subcontinent except in the Northeastern part of the country.
**Objective:** To evaluate the dietary and environmental risk factors for Nasopharyngeal cancer in Manipur, India.
**Materials & Methods:** A total of 30 qualified controls were included in the study. Interviews were conducted face-to-face by investigators employing a structured questionnaire for demographic data, information including dietary habit, smoking, consumption of tobacco in any form,invironmental factors and family history of NPC among first degree relatives. All NPC were regrouped into three histopathological types according to the WHO 1991 classification.
**Result:** Our result shows that consumption of smoked meat, and living in smoky houses, were found to be risk factors for NPC, with elevated ORs (5.5;p=<0.001),and 16.0 2;p=<0.001 respectively. Fresh fruit consumption was inversely associated with NPC risk with ORs of 0.25;p=<0.05 and found significantly the possibility of affecting NPC among peoples with lack of fresh fruit intake.
**Conclusion:** It is concluded that history of taking smoked meat, living in poor ventilated smoky house and lack of fruit intake are major risk factors of nasopharyngeal cancer.

***Key Words:*** Nasopharyngeal cancer, Dietary, Environmental.

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare cancer worldwide except in South East Asia, Southern China and North Africa. In spite of the high incidence of cancer of the oral cavity and other parts of pharynx, NPC is uncommon in the Indian subcontinent except in the Northeastern part of the country.[1] The mongoloid race in this region has shown an increase in NPC incidence. [2,3] The latest National Cancer Registry programme (NCRP),2006 -2008 has reported the highest

age-adjusted incidence rates (AARs) of NPC in Aizawl district(6/100000) followed by Manipur State(5/100000 ) excluding Imphal West district and Nagaland state in males in Northeastern India. As per earlier report of NCRP 2002, Nagaland state had the highest AARs followed by Manipur and Mizoram in this region. The district-wise distribution of the Age-adjusted incidence rates(AARs) of NPC in Kohima district in Nagaland states was 19.4/100000,among the highest AARs reported in the world. In our departmental cancer registry report, total cases of NPC accounts for approximately 6.5% of all malignancies over the 5 years. NPC has been the 2nd most common malignancy in males for the past decade contributing approximately 11 % of all malignancies in the same sex. NPC has a remarkable racial and geographical distribution with complex interaction of genetic, viral(Epstein Barr Virus), environmental and dietary factors which may be associated with the etiology of these disease. The significant difference in geographical, ethnicity and dietary habits within our country could predispose people of Northeastern India for high incidence of NPC. One study from this region reveals an association of this cancer with consumption of smoked meat and herbal nasal medicine.[4] Another study on smoked meat of this region has shown the presence of volatile nitrosamine which is already known as strong carcinogen[5,6]. NPC has a tendency to affect the relatively young population more than most other cancers; the loss of working life due to NPC is substantial. Neck mass, nasal obstruction ,epistaxis and diplopia are the common presenting symptoms. In endemic region of the world like Southern China, Hong Kong, Taiwan etc, non-keratinizing carcinoma (Type III, WHO) particularly the undifferentiated type is the commonest type[7]. Nasopharynx being not easily accessible, diagnosis is often delayed and the disease is in advanced stage at the time of presentation. A concrete study on risk factors of NPC with dietary, smoking and tobacco consumption history with clinico-pathology from Manipur has not been reported till date to the best of our knowledge. The purpose of this study was to re-evaluation of previously reported risk factors and attempts to find new potential factors of NPC in Manipur.

## MATERIALS AND METHODS

This is a hospital-based case-control study in Regional Cancer Centre(RCC), Regional Institute of Medical Sciences (RIMS), Manipur. It is the biggest referral Centre in Manipur.

Eligibility criteria included the following:1)histological confirmed case of NPC 2) age less than 70 years,3)no previous diagnosis of or treatment for NPC 4)residence in Manipur. Exclusion criteria are; 1).Synchronous malignancies 2). pregnant or lactating female 3). Psychosis. 30 eligible cases during the period from January 2010 to June 2011 were recruited. Controls were frequency-matched to cases by age, sex, dialect, geographical location. The controls were recruited from people who requested health examination in RIMS for non-neoplasm causes. A total of 30 qualified controls were included in the study. Interviews were conducted face-to-face by investigators employing a structured questionnaire for demographic data, information including dietary habit, smoking, consumption of tobacco in any form, environmental factors and family history of NPC among first degree relatives. All NPC were regrouped into three histopathological types according to the WHO 1991 classification. This classification consisted of Type I (Keratinizing squamous cell carcinoma), Type II (Differentiated non-keratinizing carcinoma) and Type III (Undifferentiated non-keratinizing carcinoma). The data were analyzed using SPSS14. Odds ratios (ORs) and tests of

significance applied.

## RESULTS

The demographic characteristics of the study population are shown in Table I. As expected, the distribution by age, sex, ethnicity and geographical residence were comparable between cases and controls. Table II presents the relationship between dietary and environmental factors and NPC risk in the case-control dataset. Consumption of smoked meat, and living in smoky houses, were found to be risk factors for NPC, with elevated ORs (5.5;p=<0.001), and 16.0 2;p=<0.001 respectively. Fresh fruit consumption was inversely associated with NPC risk with ORs of 0.25;p=<0.05 and found significantly the possibility of affecting NPC among peoples with lack of fresh fruit intake.

In majority of cases (48.2%), presentation was within 3 months from onset of symptoms. The frequency of different presenting symptoms is listed in Table III. The commonest presenting symptoms were neck swelling (80.0%) followed by nasal obstruction (33.3) and epistaxis (26.6%). The neck swellings were unilateral in 45% and bilateral in 42% of patients. Other symptoms were impairment of hearing (23.3%), headache (23.3%), dysphagia (10.0%) and nasal discharge (6.6%) respectively. The commonest histopathology observed was undifferentiated carcinoma (Type III, WHO) accounting for approximately 73.3 % of all histological types affecting both young and elderly patients. 7 cases ( 23.3% of total patients) had cranial nerve(CN) lesions. One of 7 cases had bilateral VI and VII CNs involvement. Commonly the cranial nerve V was affected upto 28.5% followed VI ( 28.5%) and X (14.2%) cranial nerves respectively. The patients were staged according to the Tumor, Node, Metastasis (TNM) staging system. Only 28.5% of total patients presented in early stages and remaining patients (71.5%) in advanced stages.

**Table I – Presenting Symptoms and their Frequencies(n = 30)**

| Symptoms | | No (%) |
|---|---|---|
| Neck Swelling | | 24 (80.0) |
| Nose | Bleeding | 8(26.6) |
| | Obstruction | 10(33.3) |
| | Discharge | 2(6.6) |
| Aural | Impairment of hearing | 7(23.3) |
| | Tinnitus | 2(6.6) |
| Headache | | 7(23.3) |
| Eye | Blindness | 2(6.6) |
| | Diplopia | 1(3.3) |
| | Squint | 1(3.3) |
| Facial Pain | | 2(6.6) |
| Dysphagia | | 3(10.0) |
| Hoarseness | | 1(3.3) |
| Others | | 3(10.0) |

**Table II – Age and Histopathology (WHO Classification)**

| Age(yrs) | Type I (Keratinizing squamous cell carcinoma) No(%) | Type II (Differentiated non keratinizing carcinoma) No(%) | Type III (Undifferentiated non keratinizing carcinoma) No(%) |
|---|---|---|---|
| <30 | 0 | 1(20.0 ) | 1(4.5 ) |
| 30 – 39 | 0 | 1(20.0 ) | 3(13.6 ) |
| 40 – 49 | 1( 33.3 ) | 1(20.0 ) | 6 (27.2 ) |
| 50 - 59 | 2(66.7 ) | 2(40.0 ) | 7(31.8 ) |
| 60 – 69 | 0 | 0 | 3 (13.6 ) |
| 70 – 79 | 0 | 0 | 2(9.0 ) |
| | 3 | 5 | 22 |

**Table III Demographic characteristics status of the study populations**

| Variables | cases(%) | Control(%) | p-value |
|---|---|---|---|
| Sex | | | |
| Male | 20 | 23 | 0.390 |
| Female | 10 | 7 | |
| Age(yrs) | | | |
| Mean | 49.66 | 49.70 | |
| (SD) | 11.24 | 9.48 | |
| <30 | 2 | 0 | 0.581 |
| 30-40 | 4 | 6 | |
| 41-50 | 8 | 10 | |
| 51-60 | 13 | 12 | |
| >60 | 3 | 2 | |
| Ethnicity | | | |
| Tangkhul | 21 | 19 | 0.871 |
| Kuki | 4 | 3 | |
| Hmar | 2 | 2 | |
| Paite | 2 | 4 | |
| Meitei | 1 | 2 | |
| Geographical distribution(District) | | | |
| Ukhrul | 10 | 8 | 0.903 |
| Churachandpur | 6 | 5 | |
| Tamenglong | 5 | 5 | |
| Imphal | 2 | 4 | |
| Senapati | 7 | 8 | |

**Table IV – Risk factors for NPC**

| Factor | | Cases | Controls | Odds ratio | One-sided P value |
|---|---|---|---|---|---|
| Tobacco consumption | | 14 | 16 | 0.76 | 0.606 |
| Ever eaten | Yes | 16 | 14 | | |
| | No | 6 | 9 | 0.58 | >0.10 |
| Frequency | <daily | 8 | 7 | 1.00 | |
| | Daily | | | | |
| Cigarette | | | | | |
| Ever taken | Yes | 16 | 18 | 1.00 | >1.00 |
| | No | 14 | 12 | | |
| Frequency | 1-10/day | 10 | 14 | 0.57 | >0.10 |
| | 11-20/day | 4 | 3 | 1.38 | |
| | >21/day | 2 | 1 | 2.07 | |
| Smoke meat | | | | | |
| Ever eaten | Yes | 22 | 10 | 5.5 | <0.001 |
| | No | 8 | 20 | | |
| Frequency | <daily | 14 | 7 | 0.34 | <0.001 |
| | Daily | 8 | 3 | 3.27 | |
| Fermented foods | | 24 | 18 | 2.6 | >0.05 |
| Ever eaten | Yes | 6 | 12 | | |
| | No | 8 | 5 | 1.8 | >0.10 |
| Frequency | <monthly | 10 | 7 | 1.37 | |
| | Monthly | 6 | 6 | 0.42 | |
| | ≥weekly | | | | |
| Fresh fruits | | | | | |
| Ever eaten | Yes | 10 | 20 | 0.25 | <0.05 |
| | No | 20 | 10 | | |
| Frequency | <monthly | 3 | 5 | 0.55 | <0.01 |
| | Monthly | 5 | 10 | 0.40 | |
| | ≥weekly | 2 | 5 | 0.76 | |
| Smoky house | Yes | 25 | 6 | 16.0 | <0.001 |
| | No | 5 | 24 | | |
| Dust exposure | Yes | 18 | 16 | 1.31 | >0.10 |
| | No | 12 | 14 | | |

## DISCUSSION

Linguistically, the Northeastern region is distinguished by a preponderance of the Tibeto-Burman language, by variable mongoloid features among peoples of the region and the population here is thought to comprise migrating people from east and south-east Asia who are presumed to have brought with them the risk for NPC to this region.

From the environmental aspect, Manipur is a hill state of Northeastern India, and experience predominantly humid sub-tropical climate with hot humid summer, severe monsoons and mild winter.

The pattern of Bimodal age distribution with peaks in age groups of 15-24yrs and 65-74yrs has been reported in low-risk populations.[8] .However, the pattern of age distribution in our study doesn't show any such bimodal pattern like earlier studies in this region.[9] Number of patients begins to increase after age of 30years, reaches a peak between 50 and 59 years, then begins to decline after 60 years in our present study similarly with studies in high-incidence areas in China. [10,11] One intriguing characteristic of North African NPC, concerning its bimodal age distribution with a secondary peak of incidence in the range of 15-25 years ,is not observed in Asian NPC.[12]

In different parts of the world, male preponderance over the females in most studies has been reported.[7] Likewise, our study gives a male to female ratio of 2.0:1 similarly to those observations in Northeast states population based cancer registries 2006-2008 of National Cancer Registry programe, India.

The mean duration of symptomatology before presentation was 6 months (range:15 days – 36 months) in our patients. Neck swelling (80.0%) followed by nasal obstruction (33.3%) were the common presenting symptoms in our patients. Percentages of neck swelling (80.0%) and epistaxis (26.6%) were similar to those findings of one study in Malaysia.[13] In that study, 17.0% and 36.0% of the patients had nasal block and hearing loss whereas in our present study, 33.3% and 23.3% of the patients presented the symptoms.[12] Less number of our patients(10.0%) had neuro-ophthalmic manifestation compared to findings of a study in Nigeria where 60.0% of the patients presented the same manifestation.[14]

Non-keratinizing type particularly undifferentiated squamous cell type was the most common histopathological type in 73.3% of our patients which agrees with findings from high - incidence region of China where 84.6% of all histopathological types was non-keratinizing and keratinizing type was only in 5.8% of all NPC.[7] The non-

keratinizing type particularly undifferentiated histopathological type has the strongest association with EBV infection[15,16,17] and it is the dominant type found in children and adolescent. But, none of our patient is adolescent despite evidence reveals the association of EBV infection with NPC in patients of this region.[18]

More number of our patients ( 23.3% ) had cranial nerve(CN) involvement in contrast to findings of one study by Huang W et al where involvement was in few patients (9.6%).[19] Cranial nerves V(28.5 %), VI (28.5%) and X (14.2%) were commonly found to be affected respectively in our patients which are different from findings of one study from China where cranial nerves V, VI and XII were involved in 38.0%,26.0%, and 11.0% respectively[20]. The poorer neurologic outcome associated with a longer duration of CN symptoms may be related to a more severe long term CN compression that results in irreversible damage. Timely diagnosis and treatment are therefore critical to improving the neurologic outcome .Periods of cranial nerve involvement and the level of the recovery of cranial nerve involvement were significantly correlated with prognosis.[19]

20.0% of our patients had family history of cancer. The primary sites were nasopharynx (42.8%), nasalcavity (33.3%), paranasalsinus (16.6 %), respectively. The proportion of our patients with a family history of NPC is higher compared to those findings in the high-incidence areas Hong Kong(7.2 %) and Guangzhou(5.9 %)[21,22]

Results from the present study indicate that consumption of smoked meat, living in smoky house are risk factors for NPC, while consumption of fresh fruit is inversely associated with NPC risk. In Northeastern India, smoked meat and smoked fish are widely eaten as main source of protein like salted fish in South East Asia. Few studies already shown the carcinogenicity of smoked meat which contains nitrosamines like in salted fish21 and consumption of smoked meat has been validated as a significant risk factor for NPC in few studies.4

Besides consumption of smoked meat, exposure to smoke from burning wood fires were also found to be associated with an increase risk of NPC in our present study. 25 patients (83.3%) compared with 6 control subjects were found living in poorly ventilated overcrowded houses and they used firewood for cooking and warming the room thereby leads to daily exposure to smokes. Significant association of occupational exposure to smoke with NPC has already been reported.[23].Consumption of tobacco (Khain /zarda pan) were significantly associated with NPC in few study[24]unlike in our study. Our data demonstrate that many NPC patients had ingested poorly preserved fermented food, but statistically insignificant. Regular intake of fermented foods being a risk factor of NPC has been shown in one study by Mimi C. Yu etal.[25] The inefficiency of the preservation method might result in putrefaction accumulating carcinogens like nitrosamines, bacterial mutagens and EBV-reacting substances. Our study confirmed poor intake of fresh fruit among cases (ORs,0.25, p=<0.05) than controls which was consistent with previous several reports on how consumption of fresh fruit can significantly reduce the risk of NPC with a dose-dependent relationship[26,27]. The limitations of our study was small sample size and a preliminary report. More studies are needed to confirm more risk factors in this region with large sample size.

## CONCLUSION

This case-control study highlighted high-incidence of NPC in Northeastern India and possibility of conducting more research work on this disease. Age distribution, sex ratio, presenting symptoms and pattern of histopathology in our patients is similar to

those findings in high-incidence areas of world .History of taking smoked meat, living in poor ventilated smoky house and lack of fruit intake are major risk factors of NPC. By improving the awareness of this leading cancer, any further delay in presentation could be minimized. Early detection and early treatment to reduce the morbidity and mortality associated with NPC in addition to imparting awareness on how to prevent the disease from the view of dietary and environmental risk factors to general population is the need of this region.

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