

## The Risk Factor: Nasopharyngeal Carcinoma

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### ABSTRACT

Nasopharyngeal carcinoma (NPC) is a tumor arising from the epithelial cells that cover the surface and line the Nasopharynx. Although NPC is a rare malignancy in the world, it is endemic in a few well-defined populations. In 2002, ~80,000 incident cases of nasopharyngeal cancer were diagnosed worldwide and the estimated number of deaths exceeded 50,000 and recorded as the 23rd most common new cancer in the world. Well-established risk factors for NPC include elevated antibody titers against the Epstein-Barr virus, consumption of salt-preserved fish, a family history of NPC and certain *human leukocyte antigen* class I genotypes. Consumption of other preserved foods, tobacco smoking and a history of chronic respiratory tract conditions may be associated with elevated NPC risk however, consumption of fresh fruits and vegetables and other *human leukocyte antigen* genotypes may be associated with decreased risk. Evidence for a causal role of various inhalants, herbal medicines and occupational exposures is inconsistent. Other than dietary modification, there are no concrete preventive measures for NPC exist. Unresolved gaps given in understanding of NPC, there is a clear need for large-scale, population-based molecular epidemiologic studies to elucidate how environmental, viral, and genetic factors interact in both the development and the prevention of this disease.

**Keywords:** Nasopharyngeal carcinoma, Risk Factors, NPC, salt-preserved fish.

### INTRODUCTION

NPC was the fourth most common new malignancy in Hong Kong, primarily affecting individuals from southern China and South East Asia<sup>1</sup>. 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 Arctic. The annual incidence of NPC in the UK is 0.3 per million at age 0–14 years, and 1 to 2 per million at age 15–19 years. Incidence is higher in the Chinese and Tunisian population.<sup>[1]</sup> In spite of very high incidence of oral cancer in the Indian subcontinent, 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. There are three etiological factors 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. The WHO classifies NPC into three histological types: keratinizing squamous cell carcinoma (type I); and non keratinizing carcinoma, characterized as differentiated (type II) or undifferentiated

(type III). Type III NPC comprises over 95% of NPC in high-incidence areas and most of the remaining 5% is type II NPC<sup>[2]</sup>; in contrast, type I NPC is predominant in low-incidence regions and may have an etiology distinct from that of the other two histological types. Cervical lymph adenopathy is the initial presentation in many patients and the diagnosis of NPC is often made by lymph node biopsy. Symptoms related to the primary tumor include trismus, pain, otitis media, nasal regurgitation due to paresis of the soft palate, hearing loss and cranial nerve palsies. Larger growths may produce nasal obstruction or bleeding. Etiological factors include Epstein-Barr virus (EBV), genetic susceptibility and consumption of food with possible carcinogens – volatile nitrosamines. The recommended treatment schedule consists of three courses of neoadjuvant chemotherapy, irradiation and adjuvant interferon (IFN)-beta therapy.<sup>[3]</sup>

### DEFINITION

Nasopharyngeal carcinoma (NPC) is a tumor arising from the epithelial cells that cover the surface and line the nasopharynx. NPC was first described as a separate entity by Regaud and Schmincke in 1921.

### RISK FACTORS

#### 1, Epstein-Barr virus

The ubiquitous EBV infects and persists latently in over 90% of the world population. In Hong Kong, 80% of children have been infected by 6 years of age; almost 100% have

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seroconverted by age of 10 years. Although primary EBV infection is typically subclinical, the virus is associated with later development of several malignancies including NPC. [4] Transmission, mainly through saliva occurs earlier in life in developing countries where living conditions are crowded and less hygienic. B lymphocytes are the primary target of EBV infection and the route of EBV entry into epithelial cells is unclear; nevertheless, EBV replication can occur in pharyngeal epithelial cells as well as in B lymphocytes in both normal and malignant nasopharyngeal tissue. [5-8]

EBV is further linked to the development of NPC through EBV DNA, RNA, and/or gene products in tumor cells of virtually all cases, regardless of geographic origin NPC may originate from a single progenitor cell infected with EBV before clonal expansion. Clonal EBV has also been detected in severe dysplasia or carcinoma *in situ* of the nasopharynx indicating a role for the virus in the early stages of tumor progression. Therefore, it is apparent that environmental and/or genetic cofactors also contribute to NPC risk. [9-14]

## 2, Salt-Preserved Fish and Other Foods

The nonviral exposure most consistently and strongly associated with risk of NPC is consumption of salt-preserved fish, a traditional staple food in several NPC-endemic areas. In studies of Chinese populations, the relative risk of NPC associated with weekly consumption, compared with no or rare consumption, generally ranged from 1.4 to 3.2, whereas that for daily consumption ranged from 1.8 to 7.5. [15-16] NPC risk is also elevated in association with other preserved food items including meats, eggs, fruits and vegetables in southern Chinese, Southeast Asians, North Africans/Middle Easterners and Arctic natives as well as in low-incidence northern Chinese and the U.S. population. In southern China, intake of salted fish and other preserved foods is particularly high among boat-dwelling fishermen and their families, known as Tankas-the population subgroup at highest risk of developing NPC. Furthermore, salted fish is a traditional weaning food resulting in early and frequent feeding of infants- especially in the Cantonese population and in families of lower socioeconomic status. Childhood exposure especially at weaning seems more strongly related to NPC risk than adulthood exposure. Further, increasing duration and frequency of consumption are independently associated with elevated risk of NPC. [17]

The carcinogenic potential of salt-preserved fish is supported by experiments in rats, which develop malignant nasal and nasopharyngeal tumors after salted fish consumption. The process of salt preservation is inefficient, allowing fish and other foods to become partially putrefied. As a result, these foods accumulate significant levels of nitrosamines which are known carcinogens in animals. Salt-preserved fish also contains bacterial mutagens, direct genotoxins and EBV-reactivating substances, any or all of which could also contribute to the observed association. [18]

## 3, Tobacco, Other Smoke, and Alcohol

The majority of case-control studies examining cigarette smoking and risk of NPC in a variety of populations reported as an increased risk of 2- to 6-fold, establishing tobacco smoke as a consensus risk factor for NPC. [19]

Some researchers have suggested that the high incidence of NPC in southern Chinese and North Africans is caused by smoke from wood fires in chimneyless homes. However, chimneyless homes are also found in regions with a low incidence of NPC. In two studies in China, NPC cases were

up to five times more likely to be exposed to domestic wood fire than controls, but others found no such association. Studies examining burning incense or antimosquito coils have been similarly equivocal, with two studies finding up to a 6-fold excess risk of NPC with use of antimosquito coils [20-21] and one finding a higher risk among individuals with religious altars at home, but most studies finding no association. [22-23]

Alcohol consumption also seems not to be associated with NPC risk, because most case-control studies were negative. Again, inconsistent findings may be due to differences in study characteristics as well as chance or confounding. [21, 24-27]

## 4, Herbal Medicines

In Asian populations, several case-control studies reported a 2- to 4-fold excess risk of NPC in association with use of traditional herbal medicines, although three studies in southern China found no association. Any association with use of herbal drugs may be difficult to disentangle from other aspects of a traditional lifestyle such as diet. A role of Chinese herbal plants in NPC development is, however, biologically plausible because several such commonly used plants can induce viral lytic antigen expression by activating EBV *in vitro*. [28-29] In addition, EBV inducers were detected in extracts of soils, as well as some vegetables grown in these soils, from areas in southern China where NPC is endemic. Although use of certain EBV-inducing herbs of the Euphorbiaceae family was not associated with risk in southern China, use of other specific EBV-inducing herbal drugs has not been examined in relation to NPC risk. In the Philippines, use of any herbal medicines was associated with elevated NPC risk, especially among those who used herbal drugs and had high anti-EBNA antibody titers, suggesting a direct proliferative effect of herbal medicines on EBV-transformed cells. [30]

## 5, Occupational Exposures

Because specific occupational exposures tend to be uncommon in the general population, they are unlikely to account for a substantial proportion of NPC, especially in endemic areas. Occupational exposure to fumes, smokes, dusts, or chemicals overall was associated with a 2- to 6-fold higher risk of NPC in some but not all studies. [21, 31]

An increased risk of NPC following workplace exposure to formaldehyde is supported by experimental observations in rodents.

Specific types of dust have also been examined in association with NPC risk. Several studies, with some exceptions, found that risk of NPC was elevated among wood workers and other individuals potentially exposed to wood dust, with positive dose-response trends corresponding to longer duration and higher average or cumulative exposure. Chronic airway stimulation and inflammation, reduced mucociliary clearance and epithelial cell changes following deposition of wood dust particles in the nasopharynx may promote the development of NPC; exposure to wood solvents and preservatives, such as chlorophenols may also be involved. In three studies from China, textile workers who typically have heavy exposure to cotton dust were at significantly increased NPC risk which could be attributable to irritation and inflammation of the nasopharynx, either directly or via bacterial endotoxins in cotton dust. [32] In contrast, investigators who found that NPC risk was 70% lower in workers exposed to cotton dust suggested that endotoxins

could have a protective effect by potentiating an antitumor immune response. [23]

Occupational exposure to industrial heat or combustion products more than doubled the risk of NPC, although these categories may encompass different exposures. Similarly, the excess of NPC incidence or mortality observed among welders, furnacemen, boiler firemen, smiths and forging-press operators, bakers, metal workers, and restaurant wait staff may be due to shared exposure to heat and fumes or to disparate exposures. Three studies reported an excess risk of NPC among printing workers, but did not identify specific inks, solvents or other substances that could be responsible for the association. Although an excess risk of NPC has been observed among agricultural workers studies assessing overall use of pesticides found no association with NPC risk. [23, 33]

## 6, Other Exposures

Most studies investigating prior chronic ear, nose, throat and lower respiratory tract conditions found that they approximately doubled the risk of NPC. These findings suggest that benign inflammation and infection of the respiratory tract may render the nasopharyngeal mucosa more susceptible to development of NPC. In addition, some bacteria can reduce nitrate to nitrite, which can then form carcinogenic *N*-nitroso compounds. In Taiwan, habitual chewing of betel nut (*Areca catechu*) for  $\geq 20$  years was associated with 70% higher risk of NPC in families with  $\geq 2$  affected members. [34]

An ecologic study in southern China found 2- to 3-fold higher trace levels of nickel in the rice, drinking water and hairs of individuals living in a county with high NPC incidence compared with those in a low-incidence county. Furthermore, nickel levels were higher in NPC cases than controls in the high-incidence country. Likewise, nickel, zinc and cadmium content in the drinking water of another high-incidence region was higher than that in the water of a low-incidence area and nickel levels in drinking water were correlated with NPC mortality. [35]

A map-based ecologic study in China showed a geographic correlation between NPC mortality and low soil levels of the alkaline elements magnesium, calcium and strontium as well as high soil levels of radioactive thorium and uranium. All of these findings regarding a possible role of trace elements in NPC incidence or mortality remain to be confirmed in analytic epidemiologic studies.

## 7, Familial Clustering

Familial aggregation of NPC has been widely documented in high-incidence, [36] intermediate-incidence and low-incidence populations. Such clustering can result from shared genetic susceptibility, shared environmental risk factors or both. In the case of NPC, genes and environmental exposures likely play a combined role.

Environmental risk factors such as salted fish, smoking and exposure to wood products as well as elevated anti-EBV antibody levels and some genetic polymorphisms seem to increase risk of both familial and nonfamilial NPC. [37]

## 8, Human Leukocyte Antigen Genes

Searches for genes conferring susceptibility to NPC have focused on the *human leukocyte antigen (HLA)* genes. These genes encode proteins required for the presentation of foreign antigens including viral peptides to the immune system for targeted lysis. Because virtually all NPC tumors contain EBV, individuals who inherit *HLA* alleles with a reduced

ability to present EBV antigens may have an increased risk of developing NPC, whereas individuals with *HLA* alleles that present EBV efficiently may have a lower risk. [38]

## 9, Other Genetic Variation

Several genetic polymorphisms and chromosomal abnormalities have been identified by epidemiology studies searching for NPC susceptibility loci. A few studies examined genetic variation in genes involved in metabolism of nitrosamines, tobacco and other contaminants. In general, large genetic association studies using comparable tools and analytic methods will likely be needed to allow results to be validated and synthesized and a consensus to be reached. [39]

**Table 1: Summary of some possible risk factors for NPC**

Factor	Strength of association	Consistency of association	Subgroup-specific associations
EBV	Strong	Consistent	More consistent association with types II and III NPC
Salt-preserved fish	Moderate to strong	Consistent	Stronger association with consumption at weaning
Other preserved foods	Moderate	Fairly consistent	
Lack of fresh fruits and vegetables	Moderate	Fairly consistent	
Tobacco smoke	Weak to moderate	Fairly consistent	Stronger association with type I NPC
Other inhalants	Weak to moderate	Inconsistent	
Herbal medicines	Weak to moderate	Inconsistent	
Formaldehyde	Weak to moderate	Inconsistent	
Occupational dusts	Weak to moderate	Inconsistent	More consistent association with wood dust exposure
Chronic respiratory tract conditions	Moderate	Fairly consistent	
Family history of NPC	Strong	Consistent	
<i>HLA</i> class I genotypes	Moderate to strong	Consistent	Inconsistent associations with <i>HLA</i> class II genotypes

## CONCLUSION

Currently, the most feasible means of lowering one's risk of NPC seems to be dietary modification, especially reduced consumption of and weaning with salt-preserved fish and perhaps increased intake of fresh fruits and vegetables. Further research including more thorough nutritional epidemiologic studies should seek to identify the particular compounds in preserved foods that contribute to the pathogenesis of NPC as well as the properties of fruits and vegetables that may prevent it. Factors that reduce the risk of NPC after migration may serve as the basis for effective preventive measures.

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