



Epidemiology of nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world, with an incidence well under 1 per 100 000 person-years. Exceptions are the Chinese, especially the Cantonese living in the central region of Guangdong Province in Southern China. Other populations with elevated rates include the natives of Southeast Asia, the natives of the Arctic region, and the Arabs of North Africa and parts of the Middle East. Intake of preserved foods at an early age has been linked to NPC risk in all population groups with increased NPC rates. Other recognized risk factors for NPC are cigarette smoking, and occupational exposure to formaldehyde and wood dust.

Key words: formaldehyde / nasopharyngeal carcinoma / preserved foods / salted fish / wood dust

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Introduction

Cancer of the nasopharynx is a disease with a remarkable geographic and racial distribution worldwide. Except for a handful of populations, this is a rare human malignancy with an incidence well under 1 per 100 000 population per year. Regardless of race and geography, the commonest form of nasopharyngeal cancers are those arising from the epithelial cells lining the nasopharynx. These carcinomas (commonly referred to as NPC) constitute 75–95% of nasopharyngeal cancers in low-risk populations and virtually all nasopharyngeal cancers in high-risk populations.¹

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Hereditary and viral risk factors for NPC are discussed separately in this issue of the journal. Therefore, this paper will focus primarily on the demographic patterns of NPC and its nonviral environmental risk or protective factors.

Demographic patterns

International variation

Most cancer registries only present incidence data for cancer of the nasopharynx as a whole. Therefore, rates for nasopharyngeal cancer, which, for most populations, are indistinguishable from their respective NPC rates, are used to compare worldwide incidence of NPC. In most parts of the world, annual incidence of NPC is below 1 per 100 000 for both men and women. For example, in the United States, the age-standardized (world population) incidence rates in white (including Hispanic white) men and women are 0.5 and 0.2 per 100 000 person-years, respectively.¹ Table 1 lists the handful of populations that deviate from this low-risk pattern. Highest rates are noted among the Cantonese who inhabit the central region of Guangdong Province in Southern China, of which Hong Kong is a part (Figure 1). Although all Chinese possess increased risk of NPC, rates generally decline as one travels from south to north China (Figure 1). High rates comparable to the Hokkien-speaking Chinese in Taiwan are seen in natives of the Arctic region. Intermediate rates are observed among many indigenous people of Southeast Asia, including Thais, Vietnamese, Malays, and Filipinos. Finally, rates comparable to natives of Southeast Asia are seen among Arabs of North Africa and parts of the Middle East (Table 1).

There is a common feature across the populations demonstrating an elevated risk of NPC; consumption of preserved foods beginning at an early age is frequent among these peoples. Epidemiological studies have linked childhood intake of locally consumed preserved foods to NPC development in all four groups of populations exhibiting increased risk

Table 1. Populations at increased risk for nasopharyngeal cancer

Population	Age-standardized (world) incidence ^a		Reference
	Males	Females	
Chinese, Hong Kong	24.3	9.5	1
Chinese, Taipei	8.1	3.2	2
Chinese, Shanghai	4.5	1.8	1
Chinese, Tianjin	1.8	0.6	1
Inuits, Greenland	12.7	9.2	3
Inuits, Athabascans, and Aleuts, Alaska	11.9	5.6	4
Thais, Chiang Mai	2.6	1.5	1
Vietnamese, Hanoi	10.3	4.8	1
Malays, Singapore	6.5	2.0	1
Filipinos, Manila	7.6	3.7	1
Kuwaitis, Kuwait	2.3	0.6	1
Algerians, Setif	8.0	2.7	1
Israeli Jews born in Morocco, Algeria or Tunisia	2.8	1.3	5

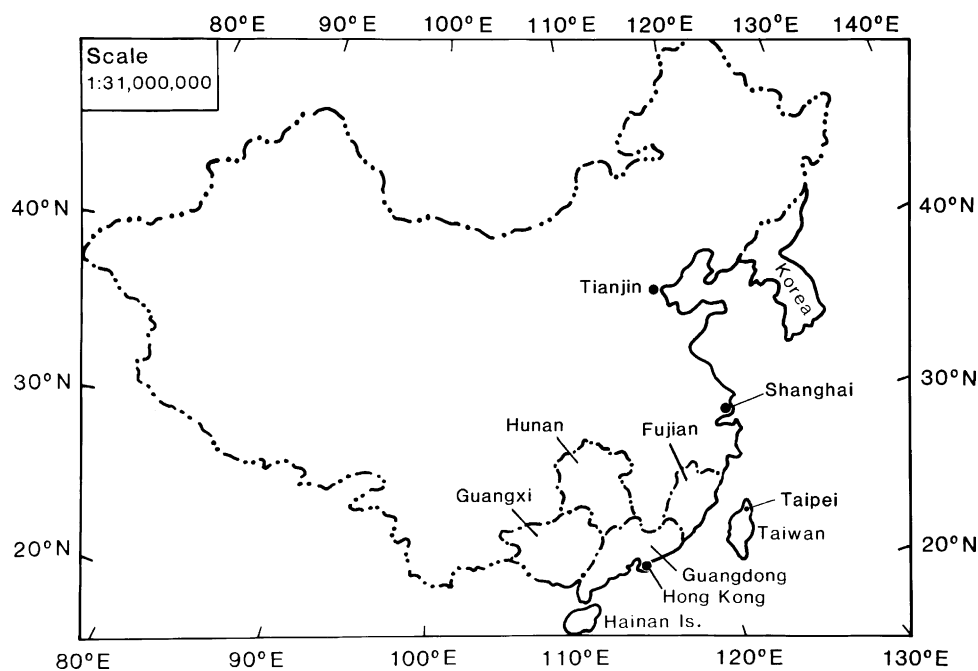
^a Per 100 000 person-years.

of NPC—Chinese, natives of Southeast Asia, natives of Arctic region, and Arabs of North Africa (see the following discussion). It is quite likely that the diverse group of preserved foods from the different cultures actually share common carcinogenic constituents, or their precursors. It is interesting to note that nitrosamines/precursors and Epstein-Barr virus (EBV)-activating substances have been detected in a

number of these preserved foods (see the following discussion).

Gender and age

Independent of race-ethnicity, rates of NPC are higher in men than women. For most populations, the male:female ratio is roughly 2–3:1.¹

**Figure 1.** Map of China showing provinces with high incidence of NPC.

Distributions of age-specific rates of NPC show distinct features across different populations. For most low-risk populations, NPC incidence rises monotonically with age, similar to the age distributions of most epithelial cancers. In contrast, among high-risk Southern Chinese of both sexes, incidence of NPC increases with age until it peaks between 45 and 54 years, and shows a definite decline at older ages.^{1,6} Several populations at low to moderate risk for NPC exhibit a minor peak in incidence among adolescents and young adults (early teens to early twenties); these include United States blacks and whites,⁷ Malaysian Kadazans,⁸ and Indians.⁹

The early age incidence peak noted among Southern Chinese suggests that exposure to the putative carcinogens occur very early in life. All Southern Chinese, irrespective of dialect group, share a popular practice of weaning their babies on preserved foods. Epidemiological studies conducted in these populations have implicated higher risk with earlier age at exposure (see the following discussion), thus offering an explanation for the observed decline in NPC incidence following the middle-age peak.

Race-ethnicity

The high risk for NPC among Chinese is mainly confined to those residing in the southern provinces of Guangdong, Guangxi, Hunan, and Fujian¹⁰ (Figure 1). Several distinct dialect groups inhabit this high-risk region, and these groups have been shown to exhibit varying rates of NPC. Specifically, the Cantonese men and women from central Guangdong show rates that are twice those of their counterparts in other dialect groups, including the Hakka, Hokkien, and Chiu Chau peoples.^{6,11} Even after migration to Southeast Asia, the Cantonese continue to exhibit a twofold higher risk of NPC than the other dialect groups of South China.¹²

Southern Chinese migrants, irrespective of their country of migration, continue to exhibit high rates of NPC.^{1,6,12} However, successive generations of Southern Chinese living in low-risk countries, including the United States⁶ and Australia,¹³ show continually declining rates. There is no evidence that China-born Chinese living in Southeast Asia experience higher rates of NPC relative to their Southeast Asian-born counterparts.¹²

Consumption of a number of preserved food items is an integral part of a traditional Southern Chinese diet. As stated earlier, some of the preserved foods have been linked to NPC development (see the following

discussion). Chinese living in Southeast Asia tend to retain their traditional ways of life while their counterparts in the United States and other western countries are inclined to gradually adopt the lifestyles of their host countries. In other words, intake of preserved foods is likely to diminish over time with overseas Chinese living in western communities, but this trend would be absent from their Asian counterparts. The dialect groups of south China are distinct not only in their languages, but also in their dietary patterns, including the consumption of various preserved foods. Thus, the differential rates of NPC across the dialect groups are likely to be diet related.

Socioeconomic status

Among populations with elevated risk of NPC, including Southern Chinese, indigenous people of Southeast Asia, and Arab of North Africa, lower social class is associated with a higher risk for NPC.^{6,14,15} Consumption of preserved foods was found to be a major risk factor for NPC in these people (see the following discussion). Given that the NPC-associated preserved foods are among the least expensive foods available in those local populations, the observed inverse social class gradients with NPC risk should not be surprising.

In Los Angeles, the population-based cancer registry classifies cancer patients according to social class characteristics of their places of residence. Specifically, census information on income and/or educational levels of residents in the neighborhoods where cancer patients reside is used to rank cancer cases into one of five social class groupings. Figure 2 shows that in Asians, lower social class is related to higher NPC incidence in both men and women, although the trend is more distinct in men. Among non-Hispanic whites, an association between social class and disease risk is apparent only in men. Occupational exposure to dust and smoke has been found to be a risk factor for NPC in the United States (see the following discussion), and is likely one of the reasons for the observed inverse social class–NPC association that is confined to non-Hispanic white men.

Urbanization

No difference in risk of NPC was found between urban and rural Southern Chinese populations, including those residing in Southeast Asia.^{6,16} In contrast, in the United States, non-Hispanic white residents of urban counties experience higher mortality rates of NPC relative to their counterparts in rural counties.

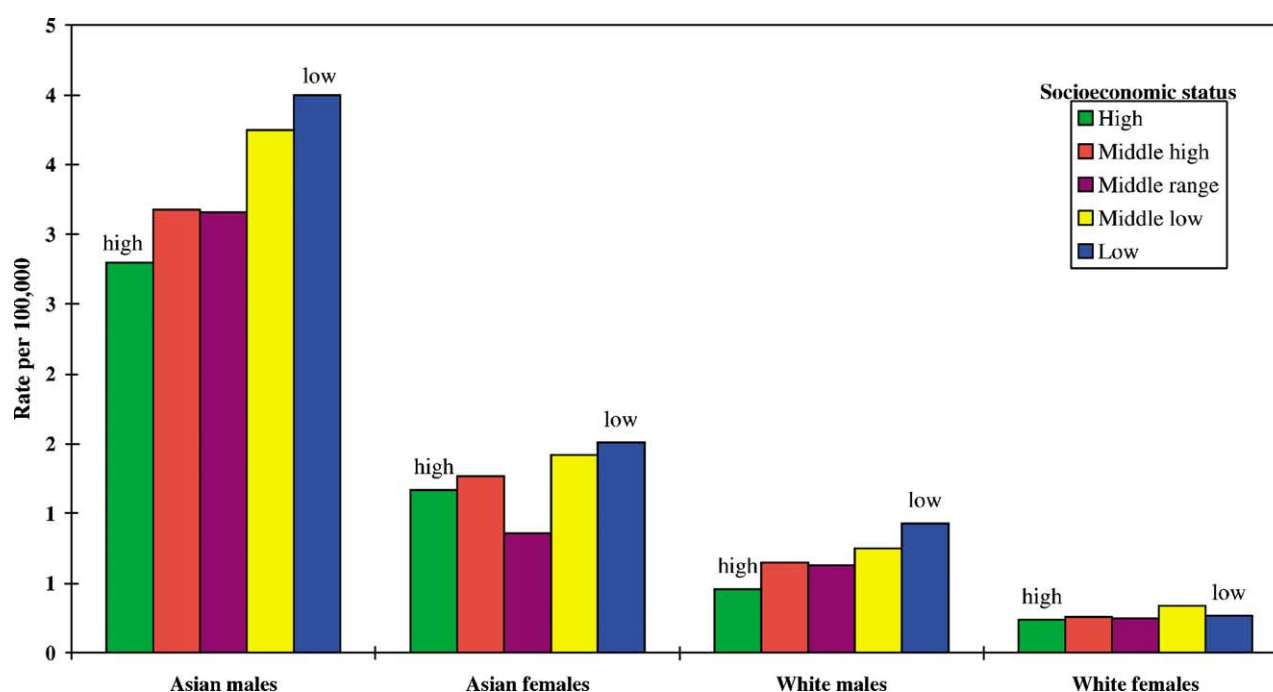


Figure 2. Age-standardized (world population) incidence rates of nasopharyngeal cancer (per 100 000 person-years) in Asian and non-Hispanic white men and women of Los Angeles County, CA, by socioeconomic status, 1972–1999.

For men, the urban:rural ratio of age-adjusted NPC mortality rate was 2.2, while the corresponding figure for women was 1.7.¹⁷

Time trends

Table 2 presents the time trends in average annual incidence rates of nasopharyngeal cancer (per 100 000 person-years) in Hong Kong and Singapore Chinese between 1973 and 1997. In Hong Kong Chinese, there is a monotonic decrease in NPC incidence over this 25-year period in both sexes. Rates during 1993–1997

were 35–40% lower than the corresponding figures during 1973–1977. In contrast, rates of NPC were relatively stable among Singapore Chinese of both sexes over the 20-year period between 1973 and 1992. However, there is a visible drop in incidence for 1993–1997 relative to all previous 5-year periods, suggesting that rates in Singapore Chinese may follow the time trend noted in Hong Kong Chinese, after a lag time of 20 years. Use of salted fish to feed young children, a major risk factor for NPC in Hong Kong Chinese (see the following discussion), has been declining since the end of the Pacific War, as Hong Kong underwent

Table 2. Time trends in average annual age-standardized (world population) incidence rates of nasopharyngeal cancer (per 100 000 person-years) in Hong Kong and Singapore Chinese^a

Period	Average annual incidence			
	Hong Kong Chinese		Singapore Chinese	
	Males	Females	Males	Females
1973–1977	32.9	14.4	19.4	7.5
1978–1982	30.0	12.9	18.1	7.9
1983–1987	28.5	11.2	18.1	7.4
1988–1992	24.3	9.5	18.5	7.3
1993–1997	21.5	8.3	16.7	5.5

^a Data from Cancer Incidence in Five Continents Series.^{1,18–21}

rapid economic development.^{22,23} The economic transformation of Singapore, on the other hand, began around the time of its independence in the 1960s, some 20 years behind Hong Kong.

Nonviral environmental risk factors

Cantonese-style salted fish and other preserved foods

An astute radiation oncologist named John Ho in Hong Kong first proposed in 1971 that Cantonese-style salted fish, a common item in the local diet and a popular weaning food, may be an etiological factor for NPC.²⁴ A large number of case-control studies conducted in diverse (Cantonese, other Southern Chinese, Northern Chinese, and Thais) populations residing in different parts of Asia and North America have confirmed Ho's hypothesis.^{14,23,25–30} Age at first exposure was established as an important determinant of risk in exposed individuals; earlier age at exposure was associated with a higher risk of disease.^{23,25,27} Experimental data have further strengthened the evidence for Cantonese-style salted fish as a human nasopharyngeal carcinogen. Rats fed this human food developed nasal cavity carcinomas in a dose-dependent manner,^{31–33} and presence of carcinogenic nitrosamines/precursors^{34,35} and EBV-activating substances³⁶ were repeatedly found in samples of this food.

Cantonese-style salted fish is not a frequent food in many communities of Southern China. Studies conducted in these non-Cantonese populations revealed that intake of a variety of other preserved foods also is related to increased risk of NPC. Again, the epidemiological data suggest that higher disease risk is associated with an earlier age at exposure. These NPC-associated preserved foods include different types of salted and pickled leafy/stem vegetables and roots, fermented beans and bean pastes, salted and fermented eggs, and various seafood pastes.^{25,27–30} Presence of carcinogenic nitrosamines/precursors, and genotoxic and EBV-activating substances were detected in many of these preserved foods.^{36,37} Epidemiological data seem to suggest that the carcinogenic potential of these nonfish preserved foods are not as high as that of the Cantonese-style salted fish.

There is limited evidence that childhood consumption of salted fish, which is common among the indigenous peoples of Southeast Asia and natives of the Arctic region, is related to increased NPC risk in these populations with intermediate to

high rates of NPC.^{38,39} Samples of salted fish from Greenland have been found to contain carcinogenic nitrosamines/precursors, and genotoxic and EBV-activating substances.^{36,37}

Preserved foods also are relatively common among the Arabs of North Africa who display elevated incidence of NPC. A well-designed case-control study examining diet and NPC risk in Tunisia showed statistically significant associations between NPC risk and childhood exposure to three common preserved foods (harissa, qaddid, and toukليا) in the local diet.¹⁵ All three foods demonstrated presence of carcinogenic nitrosamines/precursors, and genotoxic and EBV-activating substances.^{36,37,40}

Farrow *et al.*⁴¹ recently reported on the first study examining the role of preserved foods on NPC in a low-risk population, the black and white residents in five areas of the United States. Increased risk was significantly associated with increasing intake for nonkeratinizing or undifferentiated NPC, the primary histological subtypes of NPC in high-risk Southern Chinese.⁴²

The cytochrome P450 2E1 (CYP2E1) enzyme catalyzes the metabolic activation of low-molecular weight nitrosamines such as those detected in NPC-associated foods. A variant form of the gene that is detectable by Rsa I digestion (the c2 allele) has been shown to exhibit higher enzymatic activity. If dietary nitrosamines from preserved foods are indeed playing a direct role in NPC development, then exposed individuals possessing varying CYP2E1 genotypes may experience differential levels of NPC risk. Hildesheim *et al.*⁴³ compared the CYP2E1 genotypes of 364 NPC cases and 320 population control subjects in Taiwan. Subjects possessing the c2/c2 genotype experienced a statistically significant 2.6-fold risk relative to those with one or two copies of the wild-type allele. This first study of metabolic genotype in relation to NPC risk further strengthens the notion that nitrosamine-containing preserved foods are important human nasopharyngeal carcinogens.

Fresh fruit and vegetables

Most case-control studies conducted among Southern Chinese noted a statistically significant deficit in intake of fresh fruit and vegetables among cases relative to control subjects. NPC cases were repeatedly shown to consume less citrus fruit, which are rich in Vitamin C, an inhibitor of *in vivo* formation of nitrosamines. Other NPC-protective foods include orange-colored vegetables (carrots and sweet potatoes), tomatoes, and

various dark green vegetables, all of which are rich in carotenoids.^{23,26–30} Given the close correlation between intake of fruit/vegetables and preserved foods (high consumers of the former tend to be low consumers of the latter), it is difficult to disentangle the effects of the two sets of foods in epidemiological data. Indeed, only some of the above studies demonstrated a statistically significant residual effect of fruit and vegetables after adjustment for intake of NPC-associated preserved foods. However, given its biological plausibility, a direct role of fresh fruit and vegetables in NPC risk reduction is quite likely.

Tobacco and alcohol

A number of epidemiological studies conducted in high- and low-risk populations during the past decade have strongly implicated the nasopharynx as a tobacco-susceptible cancer site. However, the magnitude of risk associated with a given level of smoking is much less pronounced than those for other upper respiratory sites. Ever smokers exhibit a roughly 30–100% excess risk relative to life-long nonsmokers. Risk of NPC is positively associated with number of cigarettes smoked on a regular basis and inversely associated with age at starting to smoke regularly. Risk is reduced among exsmokers relative to those who continue to smoke. Generally, risk is two- to four-fold among the heaviest smokers relative to life-long nonsmokers.^{44–51} In comparison, relative risk of 20 or higher are repeatedly observed for cancers of the lung and larynx among heavy smokers.⁵² It appears that either the nasopharyngeal epithelium is less sensitive to the carcinogenic effects of tobacco constituents, or the exposure level of the target cells to these compounds is lower for the nasopharynx than other upper respiratory sites.

Several studies in Chinese have examined the possible role of passive smoking, both during childhood and during adult years, on risk of NPC. Results are inconsistent.^{25,44,45,51} Given the moderate dose–risk relationship between active smoking and NPC, a passive-smoking/NPC association, even if it exists, may not be observable in epidemiological studies using traditional assessment of self-reported passive smoking with inherently large measurement errors.

The possible association between alcohol use and NPC has been investigated in a number of case-control studies among Chinese in and outside of China and among primarily whites in the United States. Virtually all studies conducted in Chinese yielded null results.^{44,51} On the other hand, the two United States

studies both noted substantial use of alcohol to be significantly related to NPC risk, after adjustment for cigarette smoking.^{46,50} Cigarette smoking and alcohol drinking are highly correlated lifestyle habits in the United States and other western societies. It is possible that the alcohol effect on NPC risk observed in the latter studies is the result of residual confounding from cigarette smoking.

Occupational exposures

Formaldehyde is a recognized nasal cavity carcinogen in rodents.⁵³ Thus, the report by Blair *et al.*⁵⁴ in 1986 that industrial workers exposed to formaldehyde experienced a statistically significant excess risk of NPC raised an alarm and led to a number of subsequent investigations. Meta-analysis of over 30 epidemiological studies yielded a statistically significant, dose-dependent association between formaldehyde exposure and risk of NPC.^{55,56} The International Agency for Research on Cancer⁵³ evaluated the carcinogenic risk of formaldehyde to humans in 1995 and concluded that ‘the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer’.

The nasopharynx traps primarily medium-size particles (5–10 µm) in inspired air, including dust particles from wood.⁵⁷ In conjunction with earlier studies, a pooled analysis involving close to 29 000 wood workers in Britain and the United States,⁵⁸ and two recent large-scale case-control studies in separate Chinese populations^{57,59} have yielded strong evidence that intense exposure to wood dust (as occurs under occupational settings) is associated with a duration-dependent, increased risk of NPC. There is some suggestion that exposure to chlorophenols, which serve as wood preservatives, independently contributes towards wood workers’ high risk for NPC.⁶⁰

Smoke particles from incomplete combustion of coal, wood, and other materials also are of the size and weight to be deposited mostly in the nasopharynx.⁵⁷ There is some evidence that intense exposure to smoke may be a risk factor for NPC; studies conducted in Chinese and in the United States have reported increasing risk of NPC with increasing duration of exposure to smoke on the job.^{45,57,61,62}

Herbal drugs

A number of Chinese herbs have been shown to contain EBV-inducing substances,⁶³ raising the

possibility that this might represent a cause of NPC in high-risk Chinese. Yu *et al.*^{23,25,26} conducted a series of case-control studies in Southern China to examine if frequency of use of one of the most popular herbal formulations, either during childhood or in adult years, was related to NPC risk. All of their results were null. Hildesheim *et al.*⁶⁴ in a case-control study conducted in the Philippines, asked subjects about ever use of any herbal medicines, and noted a statistically significant 2.5-fold risk among ever users. However, the latter study is difficult to interpret for the following reasons. Recall bias is a serious concern when a nonspecific question (such as general use of herbal medicines without naming specific formulations) was asked under a case-control setting. In addition, use of herbal medicines is part of the 'traditional' lifestyle, an established risk factor for NPC in Chinese as well as Southeast Asians. In other words, use of herbal medicine may simply be a marker of the NPC-related lifestyle.

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