

Review

The Enigmatic Epidemiology of Nasopharyngeal Carcinoma

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Abstract

Nasopharyngeal carcinoma (NPC) has a unique and complex etiology that is not completely understood. Although NPC is rare in most populations, it is a leading form of cancer in a few well-defined populations, including natives of southern China, Southeast Asia, the Arctic, and the Middle East/North Africa. The distinctive racial/ethnic and geographic distribution of NPC worldwide suggests that both environmental factors and genetic traits contribute to its development. This review aims to summarize the current knowledge regarding the epidemiology of NPC and to propose new avenues of research that could help illuminate the causes and ultimately the prevention of this remarkable disease. 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, whereas 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, no concrete preventive measures for NPC exist. Given the unresolved gaps 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. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1765–77)

Purpose

Intriguing hallmarks of nasopharyngeal carcinoma (NPC) include its striking racial/ethnic and geographic variation, as well as its multifactorial etiology involving the interplay of environmental, viral, and genetic risk factors. The precise roles of these factors in the development of NPC, however, remain unknown. The purpose of this review is to highlight what is understood about the epidemiology of NPC, as well as to present unresolved research questions that call for large-scale molecular epidemiologic studies of NPC to illuminate the underlying causes of this fascinating disease.

Review Methods

A thorough review of the literature related to the etiology of NPC was undertaken, starting with a Medline search from 1966 onward. Additional papers, book sections, and monographs were identified through examination of reference lists. Because this review aims to present the epidemiologic evidence in a range of topic areas, rather than to calculate overall estimates of effect, formal quantitative methods were not used. All relevant papers have been cited to provide a comprehensive summary of the evidence. Inclusion or exclusion criteria were not applied to individual reports, but the strength, consistency, and relevance of the findings were considered in weighing the evidence.

Descriptive Epidemiology

Overview. Although NPC is a rare malignancy throughout most of the world (1), it is endemic in a few well-defined populations (Table 1). In 2002, ~80,000 incident cases of nasopharyngeal cancer were diagnosed worldwide and the estimated number of deaths exceeded 50,000, making it the 23rd most common new cancer in the world (2); in contrast, NPC was the fourth most common new malignancy in Hong Kong (1). Arising in the epithelial lining of the nasopharynx, NPC comprises the vast majority of nasopharyngeal cancers in both high- and low-incidence populations (3–6). The WHO classifies NPC into three histologic types: keratinizing squamous cell carcinoma (type I); and nonkeratinizing carcinoma, characterized as differentiated (type II) or undifferentiated (type III; ref. 7). Type III NPC comprises over 95% of NPC in high-incidence areas, and most of the remaining 5% is type II NPC (5, 8); in contrast, type I NPC is predominant in low-incidence regions, and may have an etiology distinct from that of the other two histologic types (9).

Geographic Variation. Because NPC represents virtually all nasopharyngeal cancers, population-wide incidence data on cancer of the nasopharynx are a close approximation of NPC incidence data. In most regions, the age-standardized incidence rate of NPC for both males and females is <1 per 100,000 person-years. However, dramatically elevated rates are observed in the Cantonese population of southern China (including Hong Kong), and intermediate rates are observed in several indigenous populations in Southeast Asia, and in natives of the Arctic region, North Africa, and the Middle East (Table 1; ref. 1). Even within China, there is at least 50-fold variation in NPC incidence across regions, with rates generally increasing from northern China (e.g., Beijing and Tianjin) to southern China (e.g., Hong Kong; Table 1; ref. 1).

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Table 1. Age-standardized (world) incidence rates of nasopharyngeal cancer in selected populations

Region and population (if applicable)	Years	Incidence rate (per 100,000 person-years)*	
		Males	Females
China and East Asia			
China, Hong Kong	1993-1997	21.4	8.3
China, Taiwan	1997	8.9	3.4
China, Shanghai	1993-1997	4.2	1.5
China, Tianjin	1993-1997	1.7	0.5
China, Beijing	1993-1997	1.0	0.6
Japan, Osaka Prefecture	1993-1997	0.5	0.1
Korea, Seoul	1993-1997	1.0	0.3
Southeast Asia			
Singapore, Chinese [†]	1998-2002	12.5	4.2
Singapore, Malay [†]	1998-2002	5.7	2.0
Singapore, Indian [†]	1998-2002	1.5	0.1
Malaysia, Sarawak Bidayuh (native) [‡]	1996-1998	31.5	11.8
Malaysia, Sarawak Chinese [‡]	1996-1998	12.0	4.1
Malaysia, Sarawak Malay [‡]	1996-1998	7.8	1.9
Viet Nam, Hanoi	1993-1997	10.4	4.6
Viet Nam, Ho Chi Minh City	1995-1998	4.8	1.7
Thailand, Bangkok	1995-1997	4.5	1.6
Philippines, Manila	1993-1997	7.2	2.5
Arctic			
Canada, Northwest Territories	1983-1997	9.2	6.0
Greenland, native [§]	1992-2002	12.7	9.2
United States, Alaska native	1992-2002	7.8	2.4
Middle East/North Africa			
Algeria, Algiers	1993-1997	2.7	1.3
Israel, Jews born in Africa or Asia	1993-1997	1.4	1.9
Israel, non-Jews	1993-1997	1.0	0.5
Kuwait, Kuwaitis	1994-1997	2.6	0.9
Kuwait, non-Kuwaitis	1994-1997	0.5	0.4
North America			
Canada	1993-1997	0.8	0.3
United States, White	1998-2002	0.4	0.2
United States, Black	1998-2002	0.8	0.3
United States, Hawaii Chinese	1993-1997	10.7	3.8
United States, Hawaii Filipino	1993-1997	3.5	1.5
United States, Hawaii native	1993-1997	3.6	0.9
United States, Los Angeles Chinese	1993-1997	7.6	2.4
United States, Los Angeles Filipino	1993-1997	3.7	1.6

*Ref. (1), unless otherwise stated.

[†] Ref. (49).[‡] Ref. (334).[§] Ref. (335).^{||} Ref. (336).

Sex and Age Distributions. In almost all populations surveyed, the incidence of NPC is 2- to 3-fold higher in males than in females (1). In most low-risk populations, NPC incidence increases monotonically with increasing age (Fig. 1A; refs. 10-12). In contrast, in high-risk groups, the incidence peaks around ages 50 to 59 years and declines thereafter (Fig. 1B; refs. 5, 13), suggesting the involvement of exposure to carcinogenic agents early in life (14). Likewise, the minor incidence peak observed among adolescents and young adults in Southeast Asia, the Middle East/North Africa, and the United States (10, 15-22) is consistent with exposure to a common agent in early life (23).

Racial/Ethnic Patterns. Although geographic regions have generally been classified as high- or low-incidence areas, the racial/ethnic distribution of NPC within regions is far from uniform. In the southeastern Chinese province of Guangdong, where the overall NPC incidence rate is >20 per 100,000 person-years among males, rates in Cantonese speakers are double those in other dialect groups such as the Hakka, Hokkien, and Chiu Chau (24). Likewise, in the Malaysian state of Selangor, rates in Chinese residents have historically been highest among Cantonese, intermediate among Khek, and lowest among Hokkien and Teochiu (25). In the United States, rates are highest among Chinese Americans, followed distantly by Filipino Ameri-

cans, then Japanese Americans, Blacks, Hispanics, and finally Whites (11).

In Southeast Asia, NPC risk seems to vary with degree of racial and social admixture with southern Chinese. Incidence is low among Singapore Indians who have had practically no intermingling with Chinese, but much higher in the Thai, Macaonese, and Malay indigenous populations, which have a history of intermarriage with Chinese ancestors (26). Similarly, rates in Ho Chi Minh City are roughly half those in Hanoi, where a higher proportion of the population is of ethnic Chinese descent (22). Close ties have existed between Japan and China for thousands of years, but mainly with northern China (26), and the incidence of NPC in Japan is low (1, 27).

Migrant Studies. Even when high- or intermediate-risk persons migrate to lower-risk countries, their incidence of NPC remains much higher than those of other races. Indeed, among southern Chinese living in Singapore, Malaysia, and Japan, NPC rates are comparable with those in natives of southern China (1, 25, 27). Likewise, NPC incidence is higher in North African migrants to Israel and their offspring than in native Israelis (28). However, although the incidence of NPC among Chinese in the United States remains 10 to 20 times higher than that among U.S. Whites and Blacks, only about half it is as high as that observed in southern China (Table 1; ref. 1). Similar incidence patterns have been described among Chinese

migrants to the United Kingdom (29) and Australia (30). Moreover, risk seems to decrease with longer duration of residence (30) and with succeeding generations in the West (31). In contrast, risk of NPC increases among White males born in China or the Philippines, compared with those born in the United States (32), and among males of French origin born in North Africa, compared with those born in southern France (33).

However, the apparent decline in NPC incidence among Chinese after migration to the West may be overestimated, because reported rates do not account for the mixture of high- and low-risk migrants in the source population. Because cancer registries generally do not record data on ethnic subgroup, rates in Chinese ethnic subgroups cannot be accurately estimated. Furthermore, migrants are self-selected (34), and because lower socioeconomic status (35-41) and certain aspects of a traditional Asian lifestyle are associated with elevated risk of NPC, individuals who migrate overseas may be an inherently lower-risk group. Thus, NPC incidence rates among migrants generally are not directly comparable with those among natives of their country of origin.

Secular Trends. Historical evidence from ancient China (26), Egypt (42), and Iran (43) suggests that NPC is not a disease of modern environmental hazards; rather, genetic and/or stable environmental risk factors may have persisted for centuries. According to modern cancer registry data, NPC incidence has remained high in Southeast Asia for several decades (44, 45). However, incidence has declined steadily in Hong Kong since the 1970s (1, 13, 44-47), in Taiwan since the 1980s (48), and in Singapore Chinese since the late 1990s (1, 44-47, 49). The lag in

trends may be attributable to the onset of rapid economic development, which occurred in the mid-1940s in Hong Kong, the 1950s in Taiwan, and the 1960s in Singapore (41). On the other hand, the incidence rate of NPC increased among Singapore Malays between 1968 and 1997 (50), and remained steady or increased slightly (among males in Cangwu county) in Southeastern China between 1978/1983 and 2002 (52).

Between 1965 and 1999, the incidence rate of NPC in the United States was fairly stable, around 0.7 per 100,000 person-years overall (10-12). However, in Chinese residents of California in particular, the incidence among men but not women decreased significantly between 1992 and 2002 (51), a decline restricted to type I NPC. The incidence of types II and III NPC may have remained unchanged because risk among immigrants does not diminish with increasing time spent in the United States. Alternatively, a decrease in risk among long-term residents in the United States may be offset by the ongoing influx of new Chinese immigrants. No increasing trend in NPC incidence has been noted in parallel with the onset of the HIV epidemic, with no apparent elevation in NPC risk among AIDS patients (53).

Risk Factors

Epstein-Barr virus. The ubiquitous EBV infects and persists latently in over 90% of the world population (54). In Hong Kong, 80% of children have been infected by 6 years of age; almost 100% have seroconverted by age 10 years (55). Although primary EBV infection is typically subclinical, the virus is associated with later development of several malignancies, including NPC (56). Transmission, mainly through saliva, occurs earlier in life in developing countries, where living conditions are crowded and less hygienic (57). 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 oropharyngeal epithelial cells (58), as well as in B lymphocytes in both normal and malignant nasopharyngeal tissue (59).

The involvement of EBV in NPC has been postulated since 1966, when NPC patients were found to express antibodies against an antigen later identified as that of EBV (60). This finding was confirmed in 1970, when anti-EBV antibodies were observed to be higher in NPC patients than in controls (61). Subsequent studies showed that NPC patients have elevated IgG and IgA antibody titers to the EBV viral capsid antigen IgA and early antigen, as well as increased IgG against the latent viral nuclear antigens 1 and 2 (EBNA-1, EBNA-2) and neutralizing antibodies against EBV-specific DNase (62-74). Moreover, these antibody titers, especially of IgA, precede tumor development by several years (75) and are correlated with tumor burden, remission, and recurrence (76-84). Based on these patterns, antibody against viral capsid antigen is now established as the basis of a screening test for NPC in high-risk populations (85-90), particularly in combination with anti-EBV DNase antibodies (73, 91). More recently, circulating cell-free EBV DNA has been detected in a higher proportion of NPC patients than controls (92-95), and levels are positively correlated with disease stage and prognosis (92-97), although prospective studies of predisease levels have yet to be done.

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 (67, 98-107), although EBV detection in type I NPC has not always been consistent (108, 109). Because the EBV episome is identical in every tumor cell—as assessed by the number of terminal repeats in the latent, circularized form of the virus in NPC tumors (106, 107, 110-112)—NPC may originate from a single progenitor cell infected with EBV before clonal

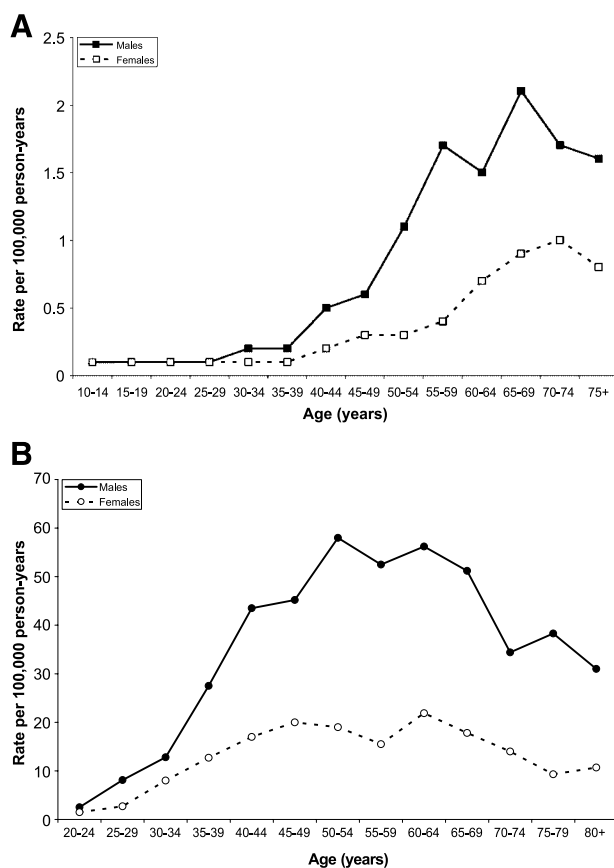


Figure 1. A. Age-specific incidence rates of NPC among White males and females in the United States, 1992 to 2003 (334). B. Age-specific incidence rates of NPC among males and females in Hong Kong, 1980 to 1999 (13).

expansion. Clonal EBV has also been detected in severe dysplasia or carcinoma *in situ* of the nasopharynx (113, 114), indicating a role for the virus in the early stages of tumor progression.

Considerable research has been directed toward determining whether at least part of the international pattern of NPC incidence can be explained by the distribution of different EBV strains. Compared with the prototype B95.8 EBV strain, consistent nucleotide variation in the amino terminus of the oncogenic viral latent membrane protein 1 (LMP1), including the loss of a *Xho*I restriction site, has been detected in EBV in NPC tumors from southern and northern Chinese, Malays, Alaska natives, and some U.S. Caucasians, but not North Africans (115-122). Other types of sequence variation in the LMP1 carboxyl terminus—including the number of copies of a 33-bp repeat element, a 15-bp insertion in the third repeat element, and a 30-bp deletion in the carboxyl terminus—have repeatedly been detected in Chinese NPC tumors (119-121, 123, 124). The 30-bp deletion, detected also in a proportion of Alaska native, Caucasian (125, 126), Malaysian (122), and North African NPC (127, 128), seems to enhance the transforming potential of LMP1 *in vitro*, and may be present in more aggressive disease forms (117, 129-131). However, there is no strong evidence that the deleted variant is associated with increased risk of NPC (120, 123, 132, 133), and there is a lack of large, well-designed epidemiologic studies of risk associations with EBV variants. Furthermore, the detection of specific LMP1 mutations in NPC tumors from diverse regions suggests that EBV strain variation is not geographically correlated with NPC incidence. Alternatively, the predominance of specific LMP1 variants in NPC could be influenced by immune selection, as certain key LMP1 mutations may produce a reduced CTL response (134).

The collective evidence strongly indicates a causal role of EBV in the development of NPC (56); early-life infection, which is typical of high-incidence areas (55, 135), may be critical. However, EBV alone is not a sufficient cause of NPC, because virtually all adults worldwide are infected with the virus, yet only a small proportion of individuals develop NPC. Therefore, it is apparent that environmental and/or genetic cofactors also contribute to NPC risk.

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 (136-141). 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 (38, 39, 138-147), as well as in low-incidence northern Chinese (148) and the U.S. population (excluding type I NPC; ref. 149). Salt-preserved foods are a dietary staple in all NPC-endemic populations (150-152); hence, this dietary pattern may explain part of the international distribution of NPC incidence.

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 (3, 26). Furthermore, salted fish is a traditional weaning food, resulting in early and frequent feeding of infants (26)—especially in the Cantonese population (138) and in families of lower socioeconomic status (137, 153). Childhood exposure, especially at weaning, seems more strongly related to NPC risk than adulthood exposure (35, 137, 138, 146, 148, 154-157). Further, increasing duration and frequency of consumption are independently associated with elevated risk of NPC (137, 138, 146, 148, 154, 155). Comparing

persons who were weaned on salt-preserved fish to those who were not, the relative risk of NPC ranged from 1.7 to 7.5.

The carcinogenic potential of salt-preserved fish is supported by experiments in rats, which develop malignant nasal and nasopharyngeal tumors after salted fish consumption (158-160). The process of salt preservation is inefficient, allowing fish and other foods to become partially putrefied (161). As a result, these foods accumulate significant levels of nitrosamines, which are known carcinogens in animals (150, 152, 162, 163). Salt-preserved fish also contains bacterial mutagens, direct genotoxins, and EBV-reactivating substances (164-166), any or all of which could also contribute to the observed association. However, there have been no prospective studies of NPC risk associations with salt-preserved fish consumption, or virtually any other environmental exposure, in endemic areas.

Fresh Fruits and Vegetables. In contrast to preserved foods, frequent consumption of fresh fruits and/or vegetables, especially during childhood (138), has been associated with a lower risk of NPC (138-140, 147, 149, 157, 167). Some studies found inverse associations with intake of specific fruits or vegetables—including carrots (139, 148), Chinese flowering cabbage (139), green leafy vegetables (156), fresh soybean products (157); and citrus fruit, oranges, or tangerines (139, 140, 149)—or with dietary intake of vitamin E (144) or C (149), or serum levels of carotene (168), but there have been few detailed evaluations of dietary associations with NPC risk. The apparent protective effect of fruits and vegetables may be attributed to antioxidant effects (169), prevention of nitrosamine formation (170), and other anticarcinogenic properties (171).

Tobacco, Other Smoke, and Alcohol. The majority of case-control studies examining cigarette smoking and risk of NPC in a variety of populations reported an increased risk of 2- to 6-fold (9, 39, 40, 73, 142, 172-181), establishing tobacco smoke as a consensus risk factor for NPC (182), although some studies found no association (24, 38, 74, 137, 141, 148, 154, 183-186). Reports of a positive association between domestic exposure to secondhand smoke and risk of NPC (40, 146, 180) are likewise countered by studies with null findings (39, 174). The discrepancy in findings may be due in part to differences in study design and/or exposure assessment, as well as study population; several of the studies reporting a positive association were conducted in low- or intermediate-incidence populations (9, 142, 173, 175-178, 180). In one U.S. study, an estimated two thirds of type I NPC was attributable to smoking, but risk of type II or III NPC was not associated with smoking (9). Thus, the declining prevalence of smoking (187) may explain the recent decreasing trend in the incidence of type I NPC in the United States (52). Nevertheless, any excess risk of NPC attributable to smoking is an order of magnitude lower than the excess risk of lung cancer and other respiratory tract malignancies (188).

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 (151, 168, 189). However, chimneyless homes are also found in regions with a low incidence of NPC (190, 191). In two studies in China (156, 192), NPC cases were up to five times more likely to be exposed to domestic wood fire than controls, but others found no such association (35, 137, 146, 174, 183). 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 (177, 185), and one finding a higher risk among individuals with religious altars at home (35), but most studies finding no association (73, 137, 146, 174).

Alcohol consumption also seems not to be associated with NPC risk, because most (35, 38, 39, 73, 74, 141, 148, 154, 172, 173, 180, 183-185), but not all (9, 139, 175), case-control studies were

negative. Again, inconsistent findings may be due to differences in study characteristics, as well as chance or confounding.

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 (156, 172, 177, 185, 193), although three studies in southern China found no association (137, 138, 146). 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* (194-197). 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 (198). Although use of certain EBV-inducing herbs of the Euphorbiaceae family was not associated with risk in southern China (137, 146, 174), 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 (193), suggesting a direct proliferative effect of herbal medicines on EBV-transformed cells.

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 (73, 154, 174, 177, 184). A few studies reported no association between solvents overall and risk of NPC (177, 179, 199, 200), and other studies observed no associations with any occupational exposures examined (74, 148, 185).

An increased risk of NPC following workplace exposure to formaldehyde is supported by experimental observations in rodents (201, 202), but epidemiologic evidence in humans is limited, especially for endemic types II and III. Although three case-control studies observed a 2- to 4-fold excess risk of NPC (177, 199, 203), and a U.S. study found an increased risk of type I but not type II or III NPC (204), most case-control studies in high- and low-incidence areas (40, 179, 199, 200, 205, 206), as well as occupational cohort studies in nonendemic areas (207-213), found no significant association of formaldehyde exposure with overall NPC risk. Cohorts of formaldehyde workers in Denmark (214) and fiberboard manufacturers in Sweden (215) experienced a significant excess of nasal cavity cancers or NPC, respectively, but U.S. cohorts of male embalmers and funeral directors, who also have occupational formaldehyde exposure, had no excess risk (216, 217). A meta-analysis of 47 available studies a decade ago did not support a causal association between formaldehyde and NPC risk (218), but a more recent evaluation by the IARC did find sufficient evidence of carcinogenicity (219). The study population most extensively examined for a relationship between formaldehyde exposure and NPC is a historical cohort of >25,000 workers employed before 1966 in 10 U.S. facilities that produced or used formaldehyde (220-228). Compared with the general U.S. population, these workers experienced a significant excess of NPC mortality (220, 223), with significant dose-response trends according to estimated peak exposure and cumulative exposure to formaldehyde, but not average intensity or duration of exposure (223). However, the positive association was driven by the findings in a single plant in Connecticut where five of the nine observed NPC deaths occurred (224-228), whereas there was no excess NPC mortality among workers in the other nine facilities (227, 228). Because most of the NPC cases had a short duration and low average intensity of exposure to formaldehyde (225, 226), occupational or nonoccupational exposures other than formaldehyde may

have been responsible for excess of NPC mortality among the workers in Connecticut.

Specific types of dust have also been examined in association with NPC risk. Several studies, with some exceptions (180, 205, 229), 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 (38, 40, 186, 199, 230-235). 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 (229); exposure to wood solvents and preservatives, such as chlorophenols, may also be involved (179, 181, 231). In three studies from China, textile workers, who typically have heavy exposure to cotton dust, were at significantly increased NPC risk (186, 200, 236), which could be attributable to irritation and inflammation of the nasopharynx, either directly or via bacterial endotoxins in cotton dust (237). 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 (174).

Occupational exposure to industrial heat (40) or combustion products (174) 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 (232, 236), furnacemen, boiler firemen, smiths and forging-press operators, bakers, metal workers (236), and restaurant waitstaff (238) 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 (200, 203, 239), 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 (38, 186, 232), studies assessing overall use of pesticides found no association with NPC risk (141, 177, 181, 200).

Other Exposures. Most studies investigating prior chronic ear, nose, throat, and lower respiratory tract conditions found that they approximately doubled the risk of NPC (35, 141, 146, 168, 172, 174, 179-181, 184, 185). 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 (240).

Infectious mononucleosis, a manifestation of late childhood or young adulthood infection with EBV (241, 242), has not been well studied in relation to NPC, perhaps because late infection with EBV is rare in areas with high NPC incidence. In one U.S. study, a history of infectious mononucleosis decreased the risk of NPC by 60%, although the association was not statistically significant (9). Another study of U.S. males also reported a nonsignificant 60% decrease in NPC risk ≥ 5 years following infectious mononucleosis, but a nonsignificant increase in NPC risk during the first 5 years (243).

In Taiwan, habitual chewing of betel nut (*Areca catechu*) for ≥ 20 years was associated with 70% higher risk of NPC in families with ≥ 2 affected members (244), whereas a study in the Philippines found no such association with overall NPC (177). Although betel nut chewing is consistently associated with increased risk of oral cancer (245), its role in NPC, if any, is unclear.

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 (246). Furthermore, nickel levels were higher in NPC cases

than controls in the high-incidence county. 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 (247). 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 (248), as well as high soil levels of radioactive thorium and uranium (249). All of these findings regarding a possible role of trace elements in NPC incidence or mortality remain to be confirmed in analytic epidemiologic studies.

Familial Clustering. Familial aggregation of NPC has been widely documented in high-incidence (190, 250-253), intermediate-incidence (254-257), and low-incidence populations (258-267). 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. Indeed, in a complex segregation analysis of familial NPC in southern China (268), multiple genetic and environmental factors, rather than a single major susceptibility gene, seemed most likely to explain the observed pattern of inheritance. In epidemiologic studies, the excess risk was generally 4- to 10-fold among individuals with a first-degree relative with NPC, compared with those without a family history (73, 137, 141, 174, 180, 269-274). Risk of cancers of the salivary gland and uterine cervix may also be elevated in family members of NPC cases (257, 274).

Environmental risk factors, such as salted fish, smoking, and exposure to wood products (73, 244), as well as elevated anti-EBV antibody levels and some genetic polymorphisms (270), seem to increase risk of both familial and nonfamilial NPC. In Whites, familial cases tend to have type II or III NPC, as opposed to the predominantly type I tumors in nonfamilial cases (267). In other populations, familial NPC patients are clinically and histologically similar to nonfamilial NPC patients (73, 253, 256, 270). Although some studies found that familial NPC cases tend to be younger than nonfamilial cases (73, 275), others did not (253, 256, 270).

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 (276, 277).

Some *HLA* alleles have been consistently associated with NPC risk. In southern Chinese and other Asian populations, *HLA-A2-B46* (252, 277-284) and *B17* (281, 282, 285-287) were generally associated with a 2- to 3-fold increase in NPC risk. In contrast, 30% to 50% lower risk of NPC was found in association with *HLA-A11* in both Chinese and Whites (277,

281-283, 287, 288), *B13* in Chinese (279, 282), and *A2* in Whites (288, 289). In a meta-analysis of studies in southern Chinese populations, the combined evidence suggested a positive association of NPC risk with *HLA-A2, B14, and B46*, and an inverse association with *HLA-A11, B13, and B22* (290). In a linkage study, a gene closely linked to the *HLA* locus conferred a 21-fold excess risk of NPC (291); a separate study mapped an NPC susceptibility locus to a region near *HLA-A* (292). Reported associations between NPC risk and other *HLA* genes, including class II alleles, must be interpreted with caution due to the probability of chance findings based on multiple comparisons.

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. Polymorphisms in *cytochrome P450 2E1 (CYP2E1)*; refs. 293-295) and *CYP2A6* (296) and the absence of *glutathione S-transferase M1 (GSTM1)*; refs. 297-299) and/or *GSTT1* (298) were associated with 2- to 5-fold increased risk of NPC. In Taiwan, a variant of *CYP2E1* was evenly distributed between familial and nonfamilial NPC cases (270), with no association between NPC risk and genetic polymorphisms in *CYP1A1, GSTM1, GSTT1, GSTP1, or N-acetyltransferase 2 (NAT2)*; ref. 300). Among Cantonese subjects, no association was found with genetic variation in *CYP2A13* (301). In Thailand (302) and China (303), polymorphisms in the *polymeric immunoglobulin receptor (PIGR)*, a cell surface receptor proposed to mediate EBV entry into the nasal epithelium, were associated with increased risk of NPC. Otherwise, reported genetic associations have yet to be replicated. 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 (304).

Genetic changes other than gene polymorphisms may also be related to NPC development. For example, studies of loss of heterozygosity in NPC tumors detected a high frequency of allelic loss, especially on chromosomes 3p, 9p, 11q, 13q, and 14q (305-315); such findings suggest that tumor-suppressor genes at these loci may be involved in NPC development. A recent meta-analysis of comparative genomic hybridization results revealed several "hotspots" where chromosomal losses and gains have consistently been detected in NPC tumors (316). In addition, tumor-suppressor genes, such as *Ras association domain family 1A (RASSF1A)*; refs. 317-321), *cyclin-dependent kinase inhibitor 2A (CDKN2A, p16/INK4A)*; refs. 318-320, 322), and *immunoglobulin superfamily member 4 (IGSF4, TSLC1)*; refs. 321, 323, 324) may frequently be inactivated in NPC tumors by promoter methylation. Gene and protein expression profiling (325-331) and genome-wide scans in families with multiple NPC cases—approaches that identified putative susceptibility loci on chromosomes 4p15.1-q12 (332) and 3p21.31-21.2 (333)—offer further means of identifying susceptibility genes or loci. Potential causal pathways discovered by these investigations remain to be confirmed in large epidemiologic studies.

Discussion

In most areas where NPC is endemic, EBV infection is presumed to occur at an early age. During the latency period between EBV infection and NPC onset, usually lasting several decades, other factors must contribute to NPC development. Because the incidence of NPC in southern China has remained high for many decades and perhaps centuries, it is unlikely that modern environmental exposures play an important causal role. We propose that the major risk factors for NPC are ubiquitous environmental agents that interact with a

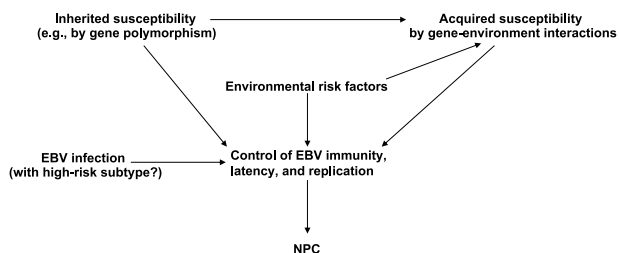


Figure 2. Proposed causal model of endemic (types II and III) NPC.

Table 2. Summary of 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

genetic background of susceptibility to result in adverse immune control of EBV infection; an impaired host response to EBV may permit the virus to infect the nasopharyngeal epithelium, leading ultimately to NPC (Fig. 2). The strength of the evidence supporting an etiologic role for various factors in NPC is summarized in Table 2.

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. Smoking cessation may also moderately reduce risk of NPC, especially type I. Because most epidemiologic studies of NPC have been based in high-incidence populations, additional studies in low-incidence populations are needed for better understanding of how risk factors and potential preventive measures for NPC differ between endemic and nonendemic NPC. In addition, prospective studies of environmental exposures in endemic populations are needed to lend clarity to inconsistent findings regarding weak to moderate risk factors.

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. Documentation of secular trends in age at EBV infection, and in weaning and dietary practices and socioeconomic factors, could be informative if linked with NPC incidence data in endemic areas; such data might help explain the recent declines in NPC incidence in Hong Kong, Taiwan, and Singapore (1, 13, 44-49). Specific herbal medicines and their constituents should be more closely studied for evidence of causality, and larger occupational studies with more detailed, prospective exposure assessment are needed to determine which, if any, occupational exposures increase NPC risk. Detailed characterization of NPC risk factors in young adults can help reveal the origins of the adolescent incidence peak in some populations. In addition, precise information on the ethnic background and risk factor profiles of Chinese migrants can clarify whether the incidence of NPC decreases among migrants who move out of Asia, or whether migrants are at fundamentally lower risk. Any changes in risk after migration are likely explained by altered exposure to environmental risk factors, such as diet, that follow from cultural assimilation; intermarriage between ethnic groups may also play a role. Factors that reduce the risk of NPC after migration may serve as the basis for effective preventive measures.

Another salient research priority is to improve understanding of the mechanism of EBV involvement in NPC, providing new opportunities for EBV-targeted therapeutic and preventive approaches, such as adoptive immunotherapy and an EBV vaccine. At present, however, four decades of laboratory studies have made little progress in elucidating the role of EBV in NPC. As genetic information grows increasingly plentiful

and accurate, it will become possible to identify NPC susceptibility genes and determine the relative contributions of genetic and environmental risk factors to NPC risk. To achieve these goals and advance the scientific understanding of NPC, it will be necessary to conduct large-scale, population-based epidemiologic studies of NPC with detailed risk factor information and extensive genetic and molecular testing. Because cohort studies with prospective exposure assessment would require decades to accrue the number of NPC cases necessary for robust analyses of gene-environment interactions, case-control studies based in high-incidence regions represent a more feasible and efficient method of investigation; yet, to date, such studies in southern China have lacked genetic and molecular data and strictly population-based controls. Comprehending how viral, genetic, and environmental factors interact to cause NPC will illuminate the pathways by which this malignancy—a model for a chronic disease caused by genes, environment, and an infectious agent—develops, as well as how it may be prevented.

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