Focused Feature: NPC epidemiology and genetics

The prevalence and prevention of nasopharyngeal carcinoma in China

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Abstract

Nasopharyngeal carcinoma (NPC) has remarkable epidemiological features, including regional, racial, and familial aggregations. The aim of this review is to describe the epidemiological characteristics of NPC and to propose possible causes for the high incidence patterns in southern China. Since the etiology of NPC is not completely understood, approaches to primary prevention of NPC remain under consideration. This situation highlights the need to conduct secondary prevention, including improving rates of early detection, early diagnosis, and early treatment in NPC patients. Since the 1970's, high-risk populations in southern China have been screened extensively for early detection of NPC using anti–Epstein-Barr virus (EBV) serum biomarkers. This review summarizes several large screening studies that have been conducted in the high-incidence areas of China. Screening markers, high-risk age range for screening, time intervals for blood re-examination, and the effectiveness of these screening studies will be discussed. Conduction of prospective randomized controlled screening trials in southern China can be expected to maximize the cost-effectiveness of early NPC detection screening.

Key words Nasopharyngeal carcinoma, epidemiology, screening

Descriptive Epidemiology

The epidemiology of nasopharyngeal carcinoma (NPC) is characterized by its unique geographic distribution. Southern China has one of the highest incidence rates of NPC in the world. Decades of epidemiological studies have shown that NPC has unique prevalence features, including regional, racial and familial aggregation.

According to the global registry of cancer incidence, NPC ranked 11th among all malignancies in China in 2008, with an incidence rate of 2.8/100 000 person-years in men and 1.9/100 000 person-years in women. This reflects the fact that the incidence and mortality rate of NPC vary greatly in different areas in China (Table 1)[1,2]. The trend is towards a lower incidence rate in North and West China and a higher rate in South and East China. Five provinces, including Guangdong, Hainan, Guangxi, Hunan, and Fujian, have higher incidence rates of NPC. Highest rates are noted among the Cantonese who inhabit the cities and counties in Pearl River Delta and West Pearl River Valley, of which Zhaoqing area, Zhongshan City, and Guangzhou City form a core high-incidence zone[3]. Sihui City in Zhaoqing area has the highest overall incidence, with a rate of 27.2/100 000 person-years in men and 11.3/100 000 person-years in women in the year 2003[4]. In Northern China, no county has an annual mortality rate higher than 3/100 000 persons. Since no complete NPC incidence data in China can be obtained, the authoritative mortality data in *Investigation of Cancer Mortality in China*[5], published in 1979, was used as a reference to describe the overall distribution of NPC (Figure 1).

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Table 1. Age-standard-incidence rate of nasopharyngeal carcinoma in some cancer registries in 1998-2002

Region	Age-standard-incidence rate	
	Male	Females
Sihui	27.2	11.3
Zhongshan	26.9	10.1
Guangzhou	22.2	9.8
Cangwu	19.7	7.3
Shanghai	4.1	1.5
Nangang District, Harbin City	1.1	0.5

Data are values per 100 000 person-years.
This table is adjusted from references [1,2] with permission.

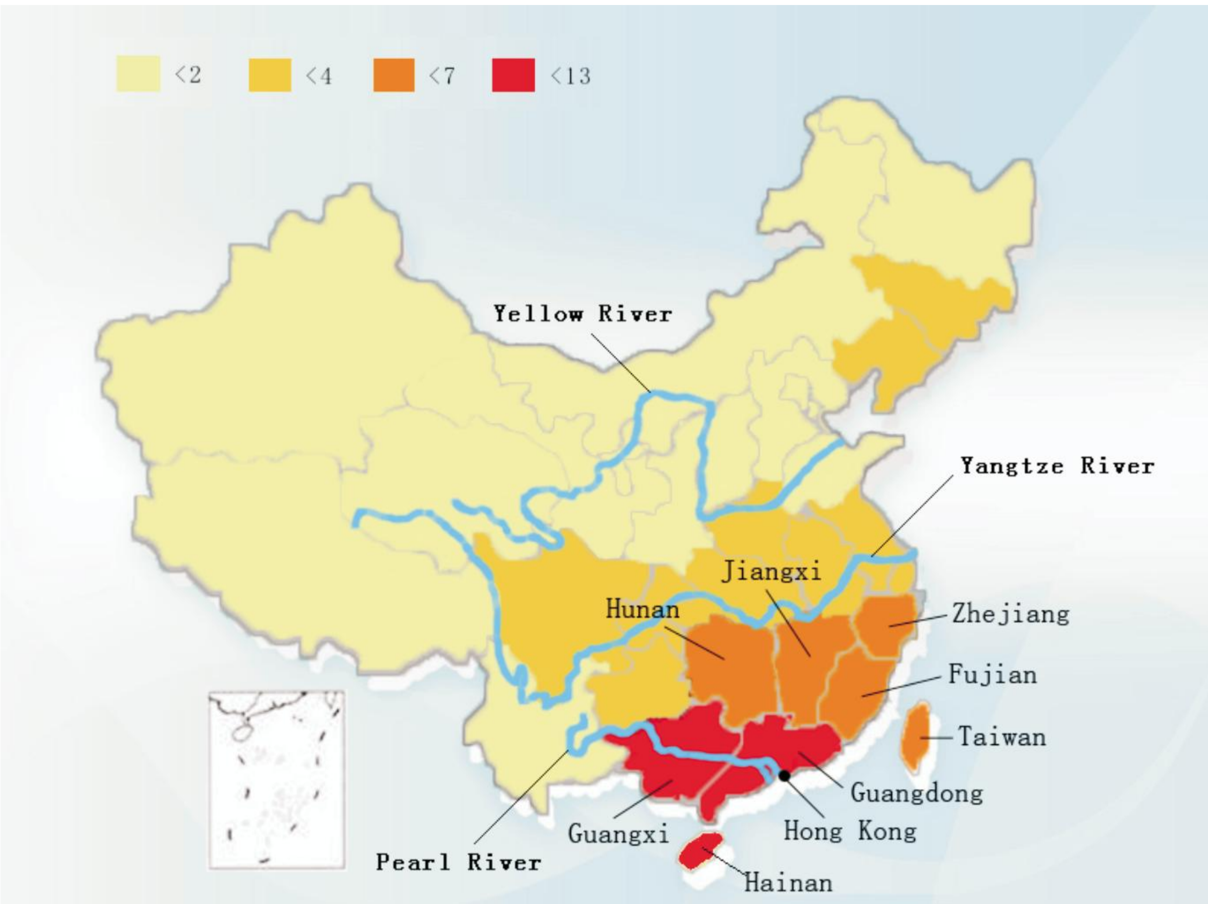

Figure. 1 The cancer mortality distribution map in China plotted by the Chinese death survey results in 1979. The numbers at the top of figure are values per 100 000 person-years. This figure was previously published and is cited from reference [5] with permission.

There is a common feature across populations demonstrating that the incidence rate of NPC in men is higher than in women, with a ratio of 2-3 to 1[1] independent of the area. On the other hand, NPC has different age-specific rate distributions in areas with high or low incidence rates. For most low-incidence areas, NPC incidence rises monotonically with age [6-8]. In contrast, NPC incidence among high-risk Cantonese of both sexes increases with age until it peaks between 40 and 59 years, after which it shows a significant decline[2,9]. This may be explained by early life exposure to carcinogenic agents.

In some high-incidence areas in the world, such as Hong Kong[10], Taiwan[11] and Singapore[12], the time trend incidence of NPC has declined significantly. A decreasing time trend was also observed in the Shanghai female population, with moderate risk during the 23 years from 1972–1974 to 1993–1994[13]. Among the Chinese Americans living in Los Angeles County and the San Francisco metropolitan area, the incidence also significantly decreased, and the overall decline in incidence was primarily due to a decline in the rate of type I tumors[14]. However, in traditional high-incidence areas in southern China, such as Sihui City in Guangdong province and Cangwu County in Guangxi province, the NPC incidence rate has remained stable for the last 20 years[2] (Table 2). Moreover, some areas, such as Zhongshan City, Guangdong province, show a trend towards increasing NPC incidence, with a world standardized incidence rate of 14.02/100 000 person-years in 1970 and 17.02/100 000 person-years in 1999, corresponding to an increase of 21.40% in the last 30 years[15].

The differences in time trends of NPC in these areas above mentioned may be related to changes in risk factor exposure in the corresponding populations. Although there is no strong supportive evidence, it may be attributable to the changing lifestyle among local residents from traditional Chinese to Western diets, followed by rapid economic growth and development in these corresponding areas. Changes in smoking habit, pickled food intake, and immigration may have great influences on incidence in the Hong Kong, Singapore, and Taiwan populations[2,10-12]. Other investigators found that in the United States, the decline in NPC incidence was mainly due to a decrease in keratinizing squamous cell carcinoma (WHO grade I), while the incidence of non-keratinizing carcinoma (WHO grades II and III) remained stable. Epidemiological studies found that smoking was the major factor causing keratinizing squamous cell carcinoma but had little to do with the incidence of non-keratinizing squamous cell carcinoma[16]. Thus, the decline of population smoking rate in these areas could at least partly, if not largely, explain the decline of NPC incidence.

In the past thirty years, in high-incidence areas in southern China such as Guangdong and Guangxi provinces, the economy has developed rapidly and people's diets and lifestyles as well as other aspects have greatly changed. Nevertheless, the NPC incidence rate has not decreased. More than 90% of NPC in these areas is non-keratinizing carcinoma, indicating that risk factors for non-keratinizing squamous cell carcinoma have remained stable among people in southern China. If the environmental etiological factors exist, their impact on NPC incidence may fall behind economic development and lifestyle change for several decades. The real economic development of China occurred in the early 1990's, so NPC incidence may have begun to decrease in southern China only in the subsequent 10–20 years.

NPC is a cancer with obvious familial aggregation. High-incidence families of NPC have been reported in both high-incidence[17-19] and low-incidence areas[20-22]. Moreover, the proportion of cancer patients with a family history is higher in high-incidence areas than in low-incidence areas. For example, the proportion of NPC patients with a family history is 7.2% and 5.9% in the high-incidence areas Hong Kong[23] and Guangzhou[24], respectively, whereas in middle-incidence areas such as Shanghai, it is 1.85%[25]. In cancer families, NPC occurs mainly in the first-degree relatives of the proband, and the incidence in first-degree relatives of NPC patients is 4–10 times that of the control group[23-26]. A complex segregation analysis in high-incidence families with NPC of preponderantly non-keratinizing type in southern China found no evidence for the role of a major gene, but rather that this histopathological type of NPC is a cancer with a multi-factorial mode of inheritance[27]. No matter where people in high-incidence areas of NPC in southern China migrate, including places like the United States, Australia, and Japan, the incidence of NPC is much higher in these people than in the local residents; however, the incidence of NPC in the second and third

Table 2. The average annual age standardized (world population) incidence rates of nasopharyngeal cancer in Cangwu, Guangxi and Sihui, Guangdong, China between 1983 and 2002

Period	Age-standard-incidence rate			
	Cangwu City		Sihui City	
	Males	Females	Males	Females
1983–1987	17.81	7.44	28.68	14.79
1988–1992	18.68	6.91	28.65	13.35
1993–1997	19.43	7.23	28.03	11.81
1998–2002	19.76	7.33	30.94	13.00

Data are values per 100 000 person-years.

generations is reduced by half compared to people in the original country[28,29]. On the other hand, the incidence of NPC in Caucasian males who were born and lived in China is significantly increased compared with those born in United States[30].

In different ethnic groups living in the same area, the incidences of NPC are distinct. For example, in Guangdong province, the incidence of NPC in people who speak the Guangzhou dialect is twice more than that of people who speak the Hakka, Hokkien, and Chiu Chau (Teochew) dialects[31]. When the people who speak the Guangzhou dialect migrate to Southeast Asia, their incidence of NPC is still higher than that in the Cantonese who speak other dialects[32]. Dialect is related to race as well as immigration. The people who speak the Hakka, Hokkien, and Chiu Chau dialects mainly descended from the ancestors in northern China, whereas those who speak the Guangzhou dialect mainly descended from local Bai-yue people in southern China. Thus, the role of genetic factors is likely to be most influential among speakers of the Guangzhou dialect. In Singapore, the Chinese called Cantonese are those who speak the Guangzhou dialect. As in mainland China, NPC incidence is higher in Guangzhou dialect speakers than in those who speak the Hokkien, Chiu Chau, Hakka, and Hainanese dialects[33]. A recent analysis of anthropological and sociological features of high-incidence populations led to the proposal of a common ancestor among Bai-yue (Daic or "proto-Austronesian" or "proto-Zhuang") peoples carrying NPC susceptibility, which was then transmitted to the Han Chinese in southern China through intermarriage[34].

Prevention and Screening of NPC

Although there have been many studies conducted on the etiology of NPC, currently an understanding of the interaction between Epstein-Barr virus (EBV) infection, genetic factors, and environment in the development of NPC has not been achieved. As a result, approaches to primary prevention of NPC remain under consideration. Thus, there is a need to conduct secondary prevention, such as improving rates of early detection, early diagnosis, and early treatment in NPC patients. Achievements in these areas might bring hope of providing a successful screening model in cancer.

Theoretically, NPC may be a malignancy suitable for screening in high-incidence areas. In southern China, especially in Guangdong and Guangxi provinces, NPC occurs with a high age-standardized incidence rate. More than 20/100 000 males (age-standardized) develop NPC annually, which is an indicative of a health threat for local population. Large-scale population screenings of NPC in China have been mainly concentrated in areas with a mortality more than 6/100 000 (standard rate by Chinese population) such as Guangdong and Guangxi provinces[35].

EBV-associated antibodies have a high sensitivity and specificity in NPC and can, therefore, be used for NPC diagnosis and as screening predictors. For example, IgA antibodies against EBV capsid antigen (VCA/IgA) provide a sensitivity and a specificity of up to 90% in the diagnosis of NPC, and multiple indicators have a better result[36]. Recent evaluation of anti-EBV biomarkers of VCA/IgA and IgA antibodies with ELISA-based EBV nuclear antigen 1 (EBNA1/IgA) confirmed the value of the combination diagnostic test employed in our previous retrospective performance studies, with a sensitivity of 95.29% and a specificity of 94.07% (unpublished data). NPC has a long pre-clinical phase, with an average time of 38 months from positive VCA/IgA antibody of EBV to the detection of NPC[37,38]. Furthermore, the examination of EBV-related antibodies is simple and cheap and can be conducted in many primary health care units. The patients with early stage (stages I and II) NPC have a satisfactory treatment result, with a 5-year survival rate of up to 94%, which is significantly different from that of patients diagnosed with late stage (stages III and IV) NPC, with a 5-year survival rate lower than 80%[39].

The incidence of NPC begins to significantly increase after 30 years old, reaches a peak between 50 and 59 years old, and then begins to decline after 60 years old. Thus, people ranging in age from 30 to 59 generally comprise a suitable population for screening in high-incidence areas[9,40]. The main NPC screening method is detection of EBV antibody and concurrent head and neck physical examination for the healthy residents ranging in age from 30 to 59 in high-risk areas. Commonly used EBV antibody indicators include VCA/IgA and EA/IgA examined by immune enzymatic methods. For subjects with a positive result of EBV antibody detection and head and neck abnormality, nasopharyngeal fiber endoscopy is performed and pathological biopsy is undertaken for confirmation of diagnosis where indicated. In recent years, the effects on the diagnosis of NPC by a variety of EBV-related indicators were comprehensively evaluated, and it has emerged that the combined detection of VCA/IgA and EBNA1/IgA by ELISA is superior to the traditional detection of VCA/IgA and EA/IgA by the immune enzymatic method. These new indicators have been used in a cluster randomized controlled population screening study in high-incidence areas of NPC in Guangdong province (http://clinicaltrials.gov/ct2/show/NCT00941538?term=nasopharyngeal+carcinoma&rank=5). An NPC screening trial was launched in 2008 in two high-risk areas in southern China, Sihui and Zhongshan. In the initial round of the trial, which was conducted

Table 3. The definitions of different risk group population for NPC screening and the corresponding screening intervals

Group	Definition	Screening interval
High-risk population	a) Subjects with an immunoenzymic assay titer of VCA/IgA ⩾1:80; b) Subjects in whom both titers of VCA/IgA and EA/IgA are ⩾1:5; and c) Subjects in whom either VCA/IgA and/or EA/IgA titer rises monotonically in the screening periods.	Every 6 months to 1 year.
The population with a positive result but that do not meet the high-risk criteria	Subjects with the titer of VCA/IgA ranging from 1:5 to 1:80	Every 2 to 3 years
Negative population	Subjects with negative result of EBV antibody detection	Every 5 years

between May 2008 and February 2010, about 60 000 subjects were recruited from randomly selected towns and communes by the cluster sampling method. Subjects who voluntarily attended the screening study were requested to donate a blood sample for serological test. All 37 NPC patients identified until now, 75.7% (28/37) of whom had early stage tumors, were included in the serologically-defined high-risk population.

Since EBV antibody levels are dynamic, the current frequency of NPC screening is usually adapted to the individual. As EBV antibody levels change, the cancer screening interval is periodically adjusted by reclassifying subjects according to their altered risk status in the follow-up period[40,35].

The definitions of risk for NPC screening and the corresponding screening intervals are shown in Table 3.

In China, Zeng *et al.*[41] first established the simple immune enzymatic method, which could examined the EBV antibody VCA/IgA in normal people, in the laboratory in 1976. In 1978, the first prospective prevention and treatment study site of NPC was founded in Wuzhou, Guangxi province, and 12 934 people were screened for NPC using EBV antibodies (VCA/IgA and EA/IgA) as the main screening indicators[42]. In this study, 13 patients with NPC were screened out, 9 in stage I and 4 in stage II[42]. Since then, several large-scale NPC screenings have been carried out in Guangxi, Guangdong and other places, and the screening results show that the early diagnosis rates of NPC in the screened population were all more than 80%[35,38,43-45].

Although NPC screening has been widely conducted in southern China, its exact effect is still difficult to determine. The main problems in the ongoing screening studies include the following: (1) A control group has not been included in some screening studies, or outpatients are being used as "controls" in some studies. These "controls" are unsuitable as comparison subjects for protocol evaluation; (2) Mortality needs to be included along with clinical stages and recent results of detected patients as indicators for evaluating the effect of screening; and (3) There is a lack of a cost-effective evaluation.

Thus, in order to accurately evaluate the effect of screening, randomized controlled screening studies should be carried out in high-incidence areas of NPC in southern China. Long-term follow-up should be performed to record mortality in both subject screening and control groups, and health economic evaluation should also be conducted.

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