

## Incidence of nasopharyngeal carcinoma in Chinese immigrants, compared with Chinese in China and South East Asia: review

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### Abstract

**Objectives:** To evaluate the literature and to compare published data on age-standardised incidence rates of nasopharyngeal carcinoma in Chinese people living in and outside China.

**Design:** Systematic review of incidence rate studies and statistical incidence data concerning nasopharyngeal carcinoma in Chinese populations from 1960 to 2008.

**Data sources:** Sixteen papers were identified from the PubMed, Embase and Scopus electronic databases and from a hand search of the reference lists of the retrieved papers. Further searches for raw data on age-specific and age-standardised incidence rates of nasopharyngeal carcinoma were conducted. Textbooks on relevant subjects were referred to for background information. A total of 19 papers met the inclusion criteria.

**Results:** Seven studies included raw data on age-specific and age-standardised incidence rates of nasopharyngeal carcinoma in Chinese people. Twelve other studies reported on changes in the incidence of nasopharyngeal carcinoma in Chinese populations in selected countries or regions. Studies on age-specific and age-standardised rates obtained data from individual registries. Studies on incidence rates obtained data from hospital records, cancer notifications (from all sections of the medical profession), pathology records and death certificates. The results showed a decline in age-standardised incidence rates of nasopharyngeal carcinoma in Chinese immigrant populations, compared with Chinese people in China. There was also a trend towards decreasing incidence the further the population had immigrated. Thus, the incidence of nasopharyngeal carcinoma in Singaporean Chinese was higher than that in Hawaiian Chinese, and that in Hawaiian Chinese was higher than that in Californian Chinese.

**Conclusion:** This review found a decreasing trend in the incidence of nasopharyngeal carcinoma in Chinese migrants living in countries with a low risk of the disease.

**Key words:** Nasopharyngeal Neoplasms; Asian Continental Ancestry Group; China; Carcinogenesis; Emigration And Immigration

### Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignancy with an incidence of less than 1 per 100 000 person years in most parts of the world for both genders.<sup>1</sup> However, studies show that it is common in a particular race, the Chinese, and more specifically, the Cantonese.<sup>2–4</sup> Cantonese men and women from Guangdong show double the rates of this cancer compared with other dialect groups, including the Hakka, Hokkien and Chiu Chau peoples.<sup>3,4</sup> Moreover, Cantonese people who migrated to South East Asia continue to show double the risk of NPC, compared with other dialect groups of Southern China.<sup>5</sup> The highest incidences of NPC

are in Southern China (as high as 20 to 50 per 100 000 person years) and South East Asia.<sup>1,5,6</sup>

As the population dynamics of a country contribute to its levels of disease incidence, one important factor when assessing disease incidence in this review is migration of people from a high incidence country to a low incident country. It is now recognised that migration of populations may alter the immigrants' level of disease risk.<sup>3,5,7,8</sup> Chinese people make up one of the world's largest migrant populations, as shown in Figure 1, and provide a good resource for epidemiologic investigation of changes in the risk and incidence of NPC.<sup>9</sup>

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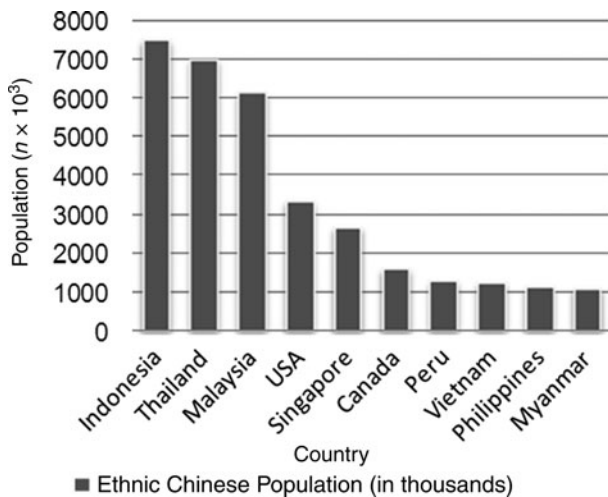


FIG. 1

Ten largest ethnic Chinese populations outside China.

The majority of residents in any migrant Chinese community are known to share a common geographical origin and/or dialect. It is important to assess whether changes in environment and living circumstances have a substantial impact on cancer risks in migrant populations. Studies have found decreased mortality rates for certain cancers in Chinese migrants living in the USA, compared with Chinese residents in Hong Kong;<sup>8</sup> however, the mortality rates of other cancers (i.e. colon, lung, leukaemia and female breast cancer) have increased. In particular, the incidence of NPC has been reported to have decreased in successive generations of Southern Chinese now living in countries with a low risk of this disease, such as the USA and Australia.<sup>3,5,6</sup>

An understanding that some Chinese immigrants may have originated from areas with a higher incidence of NPC (compared with other parts of China) will contribute to knowledge on NPC incidence in countries hosting migrant Chinese populations.<sup>1,5,10</sup>

#### Emigration from China

The Chinese diaspora is extensive. Chinese civilisation has existed for more than 4000 years, allowing its citizens millennia to migrate to most parts of the world. Dudley and Mei divide the history of Chinese emigration into four periods.<sup>11</sup>

The first is named the 'ancient period', and covers the Chinese dynasties of the previous 2000 to 3000 years up to the mid-Qing dynasty of the eighteenth century. During this period, most Chinese migration was to other Asian countries, mainly in South East Asia.

The second period of emigration spans from the nineteenth century to the late 1940s, and covers the decline of Imperial China and the Republican period. During this period, Chinese migrants travelled to most parts of the world rather than to a specific region, the so-called 'coolie trade' being an important influence.

The third period covers the first 30 years of the People's Republic of China (1949–1979). Chinese emigration during this period was severely restricted.

The fourth period of emigration is the contemporary period, which began with the opening of China to foreigners by the Chinese government.

It is instructive to study the Chinese immigration pattern in specific regions. Data are available for three defined destinations, as follows.

*Chinese in Hong Kong.* The first migration of Chinese to Hong Kong was reported during the Han dynasty (207BC to AD220). The continuous settlement of Chinese in Hong Kong began no later than the thirteenth century.<sup>12</sup> The origins of Hong Kong residents are indicated by their dialects, as follows: Cantonese 79 per cent, Hakka 4.9 per cent, Hoklo 6.3 per cent, Si Yi 4.4 per cent and all others 5.4 per cent. The descendants of an aboriginal tribe known as the Tankas make up 4 per cent of the total population.<sup>8</sup>

*Chinese in Singapore.* Most of the Chinese in Singapore originate from the south-eastern Chinese provinces of Fukien and Kwangtung. The major dialect groups (1990 census) are Hokkiens (42.2 per cent), Teochew (21.9 per cent), Cantonese (15.2 per cent), Hakka (7.3 per cent) and Hainanese (7.0 per cent); others make up 6.4 per cent.<sup>16</sup>

*Chinese in the USA.* The majority of Chinese people entering the USA originated from two community groups in Guangzhou province before 1900.<sup>12</sup> The first group comprised San Yi from the districts of Taishan, Kaiping and Enping. The second group consisted of Si Yi from Xihui, Shunde, Nanhai and Fanyu districts. In the early twentieth century, Chinese migrants from Zhongshan county emerged as a major contributor to the Chinese community in the US. The majority of Chinese Americans are concentrated in San Francisco, Los Angeles, New York City and Hawaii.<sup>8</sup>

#### Methods

We performed a systematic review, aiming to include all studies of nasopharyngeal carcinoma (NPC) incidence rates in Chinese populations between 1960 and 2008. An initial, broad search for all statistical and analytical reviews listed in the PubMed, Embase and Scopus electronic databases was performed, identifying all articles pertinent to the topic of 'incidence of nasopharyngeal carcinoma in the Chinese'. The following search terms were used: 'trends in incidence of nasopharyngeal carcinoma', 'nasopharyngeal cancer in Chinese migrants' and 'nasopharyngeal cancer incidence rates'.

Relevant articles focusing on the NPC incidence rates in Chinese populations were identified and reviewed. This was followed by a hand search of the reference lists of all retrieved papers, in order to identify any additional studies missed during the databases searches. Both unpublished studies and non-English publications were excluded in this review. We included studies covering countries with mainly Chinese populations and countries where the Chinese are in the minority, and studies assessing

NPC incidence and mortality rates (including age-standardised and age-specific rates) which covered at least three time periods. Studies of the latter type were targeted because trends are not evident when just two time periods are evaluated.

We did not differentiate NPC by histological type for the purpose of incidence studies, as this would have greatly limited the data retrieved.

A total of 19 papers met the inclusion criteria.

Our analysis used data from volumes II, III, IV, VII, VIII and IX of *Cancer Incidence in Five Continents*, in order to formulate incidence trends amongst Chinese populations in specific states and countries.<sup>1,13-16,18</sup> Data from other studies were also included.<sup>19,20</sup> We adjusted the age-standardised rates into world standardised incidence rates by direct standardisation in accordance with the World Standard Population.<sup>20</sup> (World Standard Population according to age group. Table I), as *Cancer Incidence in Five Continents* volumes II (1970) and III (1976) do not report incidence rates based on world standardised incidence rates.<sup>21</sup>

Age-standardised rate =

$$\sum_{\delta} = \frac{n_{\delta}w_{\delta}}{y_{\delta}}$$

Such that  $\delta$  = each age group,

$n_{\delta}$  = number of cases in the  $\delta$  age group,

$y_{\delta}$  = population size in the  $\delta$  age group, and

$w_{\delta}$  = proportion of the total world standard population in the  $\delta$  age group.

$n_{\delta}/y_{\delta}$  = age-specific rates for each  $\delta$  age category, and the sum of  $w_{\delta}$  is equal to 100 000, to express the age-standardised rate per 100 000 person years.

**Results**

The collected data were compared, in order to analyse changes in nasopharyngeal carcinoma (NPC) incidence in various Chinese populations.

TABLE I

WORLD STANDARD POPULATION BY AGE GROUP

Age group (years)	WSP (n)
0-4	12 000
5-9	10 000
10-14	9000
15-19	9000
20-24	8000
25-29	8000
30-34	6000
35-39	6000
40-44	6000
45-49	6000
50-54	5000
55-59	4000
60-64	4000
65-69	3000
70-74	2000
75-79	1000
80-84	500
85+	500
Total	100 000

WSP = world standard population

The selected areas of interest were Singapore, the San Francisco Bay area (USA), Los Angeles County (USA) and Hawaii (USA). China, Hong Kong and Taiwan were included for comparison. Countries in South East Asia (e.g. Malaysia and Indonesia) which have significant Chinese populations could not be compared, as data from these countries were insufficient to tabulate a trend.

Figure 2 and Table II show that age-standardised incidence rates for NPC in Singaporean Chinese, assessed from 1960 to 2002, have steadily decreased from the 1973-1977 time period onwards in both males and females.

The NPC incidence in the Hawaiian Chinese population, assessed over the same time period, showed a similar trend amongst females but no such decline amongst males. However, compared with Hawaiian data, the incidence amongst Singaporean Chinese was 3.2 (for males) and 4.7 (for females) times higher at the point of maximum difference.

A decreasing trend in age-standardised NPC incidence rates was also seen for both Chinese males and females living in San Francisco and in Los Angeles County, California, USA (Figure 3 and Table III).

To enable comparison, we selected regions with a predominantly Chinese population and for which NPC incidence data were available. Figure 4 shows the age-standardised NPC incidence rates in these regions, compared with those of the Chinese populations in Singapore, Hawaii, San Francisco and Los Angeles.

We also noted a trend towards decreasing NPC incidence the further the Chinese population had immigrated. The NPC incidence in Singaporean Chinese was higher than that in Hawaiian Chinese,

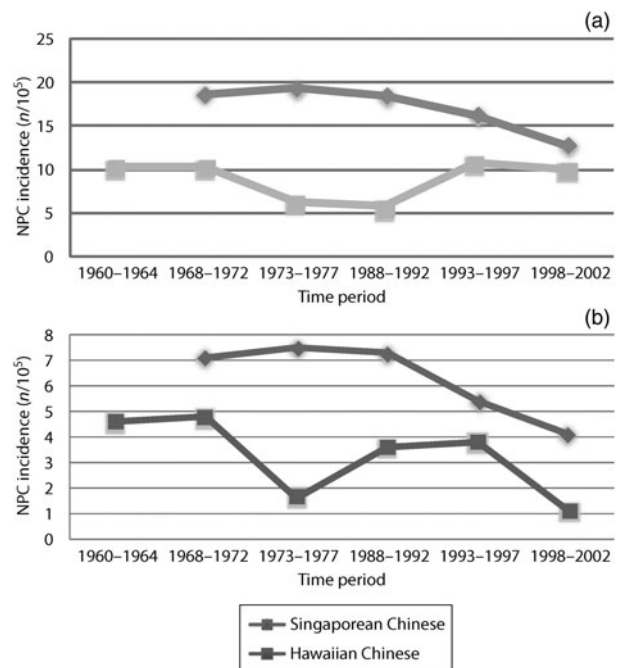


FIG. 2

World age-standardised nasopharyngeal carcinoma (NPC) incidence rates in Singaporean and Hawaiian Chinese populations over time. (a) Males; (b) females.

TABLE II  
NASOPHARYNGEAL CARCINOMA INCIDENCE IN CHINESE POPULATIONS OF SINGAPORE AND HAWAII, 1960–2002

Region	1960–1964	1968–1972	1973–1977	1988–1992	1993–1997	1998–2002
<i>Males</i>						
Singapore	–	18.7	19.4	18.5	16.3	12.8
Hawaii	10.3	10.3	6.2	5.7	10.7	9.9
<i>Females</i>						
Singapore	–	7.1	7.5	7.3	5.4	4.1
Hawaii	4.6	4.8	1.6	3.6	3.8	1.1

Data represent world age-standardised incidence per 100 000 population. – = Data not obtained

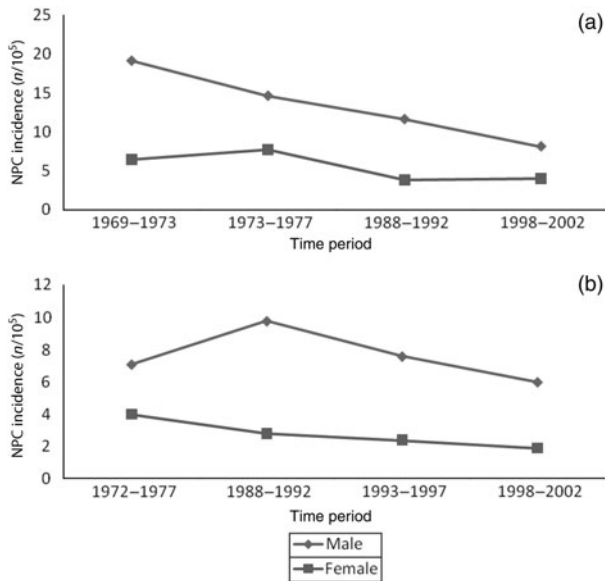


FIG. 3

World age-standardised nasopharyngeal carcinoma (NPC) incidence rates in Chinese males and females over time, in (a) San Francisco Bay Area and (b) Los Angeles County, California, USA.

and that in Hawaiian Chinese was higher than that in Californian Chinese.

**Discussion**

Chinese people living in different parts of the world show differing nasopharyngeal carcinoma (NPC) incidence rates. Historically, most Chinese migrants came from Southern China, where NPC is most prevalent. Chinese populations in Guangdong (especially the Cantonese subgroup), GuangXi,

Hunan and Fujian are at highest risk.<sup>5</sup> Huang *et al.* described NPC mortality in Guangzhou (1970–1976) to be lower among migrants from outside the Guangzhou province, compared with local residents, even though the former may have resided in Guangzhou for many years.<sup>22</sup>

The Singaporean Chinese population was chosen for comparison due to the accuracy of the data on this group (due to collection of NPC incidence data over recent decades).

The NPC incidence rate in Taiwan, the population of which is mainly Chinese, was not used, as data collection did not specify race and thus may have included races other than the Chinese.

However, we did use data on NPC incidence within the regions of China from which most Chinese migrants originate, to enable comparison with the NPC incidence of Chinese migrant populations.

*Incidence rate: downward transition*

Our results clearly demonstrate that the risk of NPC for Chinese migrants in the US (i.e. San Francisco Bay Area, Los Angeles and Hawaii) is lower than that for Singaporean Chinese. However, the age-standardised NPC incidence rate amongst Singaporean Chinese is lower than that in Guangzhou and Hong Kong.<sup>18</sup> Chinese people living in areas of southern China (including Hong Kong) have a higher NPC incidence compared with Chinese migrants living overseas.

These results indicate that Chinese migrants in lower NPC risk countries have a substantially decreased NPC incidence rate.

Interestingly, Sihui, Cangwu, Hong Kong and Hawaii share the same latitude (Sihui is 23.75° north, Cangwu 23.25° north; Hong Kong 22.15° north and Hawaii 18°–22° north) but have different age-standardised NPC incidence rates.<sup>23</sup>

TABLE III

NASOPHARYNGEAL CARCINOMA INCIDENCE IN CHINESE POPULATIONS OF SAN FRANCISCO BAY AREA AND LOS ANGELES COUNTY, CALIFORNIA, USA, 1969–2002

Group	1969–1973	1972/3*–1977	1988–1992	1993–1997	1998–2002
<i>San Fran Bay Area</i>					
Males	19.1	14.6	11.6	–	8.1
Females	6.4	7.7	3.8	–	4
<i>Los Angeles County</i>					
Males	–	7.1	9.8	7.6	6
Females	–	4	2.8	2.4	1.9

\*San Francisco Bay Area data for 1973–1997; Los Angeles County data for 1972–1977. Data represent world age-standardised incidence per 100 000 population. San Fran = San Francisco; – = data not obtained

All Chinese migrant populations contain a mixture of dialect groups, and this creates a lack of specificity in the data obtained. We can only state approximately that Chinese migrants are descendants of Southern Chinese populations. While a large segment of Chinese Americans are descendants from the high NPC risk Zhongshan prefecture, there is a noticeable admixture of other migrants originating from parts of China with lower NPC risk. This may lower NPC incidence rates among the US Chinese, compared with their counterparts in China and South East Asia.

When we focused on individual areas, we found that the age-standardised NPC incidence in both males and females has decreased in Singapore, the San Francisco Bay Area and Los Angeles County. Decreasing trends have also been reported in Hong Kong, Shanghai and Taiwan.<sup>1,5,20,25,26</sup>

The relationship between economic progress and NPC incidence is stark. Nasopharyngeal incidence rates in Hong Kong have been declining since the end of the Pacific War, due to the city's rapid economic development.<sup>27,28</sup> Singapore's economic boom

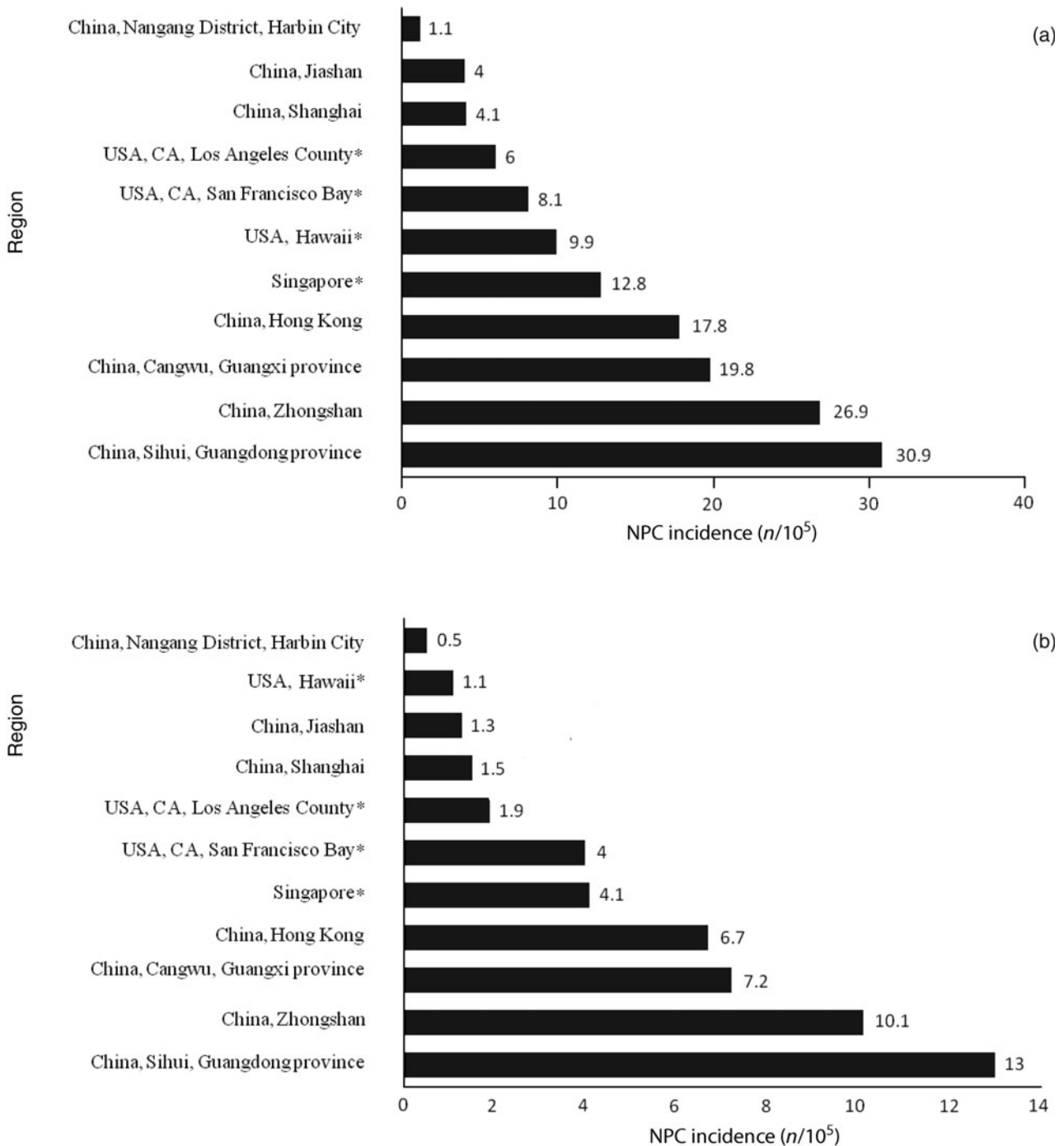


FIG. 4

Age-standardised nasopharyngeal carcinoma (NPC) incidence rates in selected countries with a dominant Chinese population (1998–2002): (a) males; (b) females. \* = Chinese population

followed 20 years behind Hong Kong's, following independence in 1965, and a declining NPC incidence trend is clearly seen (Figure 2).<sup>5</sup> Singapore, Hong Kong, Taiwan and the United States are included in the 2007 International Monetary Fund list of 'advanced economies'. China is included in the International Monetary Fund 'emerging market and developing countries' list.<sup>29</sup> The *Financial Times* and London Stock Exchange 'developed countries' list also includes Hong Kong, Singapore and the USA, among 21 other countries.<sup>30</sup> Taiwan is included in the *Financial Times* and London Stock Exchange 'advanced emerging countries' list, and China features in the 'secondary emerging markets' list. Shanghai is one of the more developed areas in China, and has shown a trend towards decreasing NPC incidence: during 1973–1977, the reported incidence was 5.6 per 100 000 person years in men and 2.5 per 100 000 person years in women, but by 1988–1992 it had declined to 4.5 and 2.5 per 100 000 person years, respectively.<sup>1</sup>

#### *Causes of nasopharyngeal carcinoma*

Ho proposed that NPC resulted from a combination of genetic susceptibility, Epstein–Barr virus (EBV) infection and consumption of salted fish since childhood.<sup>31</sup> Evidence for a disease susceptibility gene for NPC was first reported by Lu *et al.*<sup>32</sup> Over the years, studies of genetic polymorphisms of some metabolic enzyme genes (*CYP2E1* and *GSTM1*) and some DNA repair genes (*hOGG1* and *XRCC1*) have found an association with increased risk of NPC.<sup>33–36</sup> Other gene linkage studies have mapped major susceptibility loci to chromosomes 3, 4 and 14.<sup>37,38</sup> In Asian Chinese, human leukocyte antigen alleles A2 and B46 are also associated with a high risk of developing NPC.<sup>39,40</sup>

The factor discovered to have the strongest positive association with NPC is salted foods.<sup>3,28,41–45</sup> Consumption of salt-preserved foods (e.g. fish, leafy vegetables, eggs and root vegetables), fresh pork and beef organ meats, beer, and liquor are all positively associated with NPC.<sup>42</sup> The presence of carcinogenic nitrosamines or nitrosamine precursors and EBV-activating substances have been found in salted foods.<sup>46–48</sup>

Occupational hazards are related to a high risk of NPC, such as exposure to wood dust and industrial heat.<sup>49</sup> Smoke, dust and chemical fumes have also been reported as causative agents.<sup>28,45</sup>

Yu suggested a possible link between burning incense sticks and NPC.<sup>50</sup> Incense sticks are found to contain polycyclic aromatic hydrocarbon, a known carcinogenic.<sup>51</sup> Studies have shown that burning incense sticks, used in religious worship by the Chinese, is a highly possible risk factor for NPC.<sup>52,53</sup>

#### **Epstein–Barr virus infection in nasopharyngeal carcinoma**

Epstein–Barr virus infects B lymphocytes and epithelial cells, inducing growth transformation. This virus is commonly found in the saliva of healthy individuals. The source of the virus may originate from lymphocytes patrolling the oral mucosa, or from

EBV replication in epithelial cells after reactivation from latently infected lymphocytes. The virus can be shed from the lymphocytes into the nasopharynx, or may stay to replicate in mucosal epithelial cells. This then induces an immunoglobulin A response. Increased viral shedding in combination with possible genetic changes (e.g. absence of p16 expression) causes a focus of latent infection in basal epithelial cells. This focus may rapidly become malignant and invade the basement membrane.<sup>54</sup>

Certain EBV strains have been found in the Chinese population, using restriction enzyme polymorphism methods. A strain prevalent in the southern Chinese has lost the *Bam*HI restriction site, and the loss of an *Xho*I restriction enzyme polymorphism has also been found within the latent membrane protein 1 gene of the virus.<sup>54</sup> Latent membrane protein 1 has profound growth-stimulating effects *in vitro*. Further studies on prevalent Chinese EBV strains have found distinct sequence variation in the amino terminus of latent membrane protein 1.<sup>54</sup> These factors influence the viral replication process, leading to expression of latent transformed genes and causing infected cells to proliferate.

The EBV strain detected with higher frequency among Chinese NPC patients (i.e. the Cf strain) has been distinguished from that found in the majority of Caucasian NPC patients (i.e. the DF strain) in the USA, using polymorphisms in the *Bam*HI F and I regions. Differences in EBV strains have been detected among US Chinese migrants. First and second generation Chinese migrants show retention of the Cf EBV genotype.<sup>55</sup>

Environmental factors such as phorbol ester contamination in water supplies lead to increased reactivation and replication of EBV.<sup>54</sup> Consumption of salted foods may cause the same results. Further studies are needed to investigate these links.

#### **Conclusion**

Migration to another country affects every aspect of the migrant's life. This review has shown that there is a decreasing trend in the incidence of nasopharyngeal carcinoma (NPC) in Chinese migrants who live in countries with a low NPC risk. The reasons for this are multifactorial. We recognise that Chinese culture itself may play a role in NPC development (incense sticks, salted food and organ meats have been implicated), and that the migration of Chinese people to another country may alter such practices. Further studies and lifestyle investigations of Chinese migrants are needed in order to investigate further their risk of developing NPC.

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