

Etiology and Pathogenesis of Nasopharyngeal Carcinoma

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Ou Baoxiang

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1. Epidemiology of Nasopharyngeal Carcinoma

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- A. Introduction
- B. Geographical Distribution
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 - I. Sex and Age
 - II. Occupation
 - III. Distribution of Different Ethnic Groups
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A. Introduction

Nasopharyngeal carcinoma (NPC) is unique in its epidemiologic features. The occurrence of NPC is very rare in the vast majority of countries. However, the incidence is relatively high in Southeast Asia and Southern provinces of China, predominantly high in Guangdong, so this disease has got the name of "Guangdong (Canton) tumor".

There is no conclusive evidence to demonstrate that NPC as a disease has existed since antiquity. While Wells et al. (1963, 1964)^{(1), (2)} studied several Romano-Egyptian cases from the period 3500-3000 B. C. and suspected that some of them with destruction of the skull might be due to NPC, Ho (1972)⁽³⁾ did not ascertain the lesions that were actually caused by NPC by reexamining the x-ray films. In China, the description of symptoms from "Shuliu", "Luoli", "Xiashiju", etc. in the antique medical literature were quite similar to the metastasis of lymph node of NPC, but also no evidence could be made to conclude those were real cases of metastatic nasopharyngeal carcinoma.

In Western countries, Durand-Fardel (1837) is generally credited as the first one giving the clinical description of a case of NPC, while, Michaux reported the first histologically proven case, In China,

103 cases of neck gland enlargement which might be the metastatic type of NPC were reported by Todd⁽⁴⁾ in 1921 in Canton. Ch'eng⁽⁵⁾ reported the first case of lymphoepithelioma of the nasopharynx in 1935. Thereafter, clinical and pathological reports appeared everywhere in this country.

Before 1962 there was no real attempt to study the epidemiology of NPC both outside or inside China. The literature was mainly concerned with clinical case analysis or relative frequency to the total number of cancer patients or to all biopsies or autopsies. While these are not good indices in epidemiologic studies, they did reveal the high frequency of occurrence of NPC in China, especially in the population of Guangdong Province. Since 1958, a large scale mass screening was carried out in Guangdong, Guangxi Zhuang Autonomous Region, etc. and the prevalences of NPC in some local areas were obtained. A cancer mortality survey was conducted in Guangdong and Guangxi in 1973 and in other provinces (except Taiwan) in 1975~1978. The geographical distribution of NPC in this country was delineated which provides the basic data for further epidemiologic study on nasopharyngeal carcinoma.

B. Geographical Distribution

Cases of nasopharyngeal carcinoma have been reported in many countries and regions all over the world, yet it is uncommon in Europe, North-America, Latin-America and Oceania. According to the data collected from 32 countries and 60 cancer registries in the "Cancer Incidence in Five Continents"⁽⁶⁾, the incidence of NPC for most of them was less than 1 per 100,000 population (Age-standardized according to UICC 'World' population). The incidence of NPC in selected countries and regions is presented in Table 1. It can be seen that few countries or regions have an NPC incidence of above 1 per 100,000, and it occurs chiefly among the Chinese or in places thickly inhabited by the Chinese. The frequency is relatively higher in countries in Africa, such as Tunisia, Algeria, Morocco, Sudan and some parts of Uganda and Kenya, but no available data of incidence or mortality rate could be obtained. In Asia, besides Singapore, the incidence rate of NPC is also higher in Thailand and Vietnam. While in Japan, although the people there originated from Mongolia as was the case with the Chinese, the incidence of NPC is lower than 1 per 100,000.

Table 1 Incidence rates* of nasopharyngeal carcinoma in selected countries and regions

Countries or regions	Year	Males	Females
Cuba	1968~72	0.9**	0.3
Brazil, Recife	1968~72	0.6	0.4
Canada, Brit. Col.	1969~72	1.1	0.5
Quebec	1969~72	0.6	0.2
Newfoundland	1969~72	1.2	0.3
U. S. A. Chinese	1969~73	19.1	6.4
White	1969~73	0.7	0.3
Black	1969~73	1.1	0.3
Hawaii, Hawaiian	1968~72	4.4	1.6
Chinese	1968~72	10.3	5.1
Caucasian	1968~72	1.0	0.9
Finland	1966~70	0.4	0.2
Norway, Urban	1968~72	0.4	0.2
Rural	1968~72	0.4	0.1
Poland, Warsaw City	1968~72	0.6	0.2
Warsaw Suburbs	1968~72	0.1	0.2
Switzerland, Geneva	1970~72	0.4	0.2
UK, Liverpool	1968~72	0.4	0.3
Birmingham	1968~72	0.4	0.2
Japan, Okayama	1968~71	0.1	0.0
Osaka	1968~71	0.4	0.1
India, Bombay	1968~72	0.4	0.3
Israel, born Afr. and Asia	1967~71	1.7	0.7
born Israel	1967~71	1.5	0.5
Singapore, Chinese	1968~72	18.7	7.1
Malay	1968~72	4.8	0.6
Indian	1968~72	0.9	0.0
N. Zealand, Maori	1968~71	0.0	1.0

* Age-standardized according to UICC 'World' Population

** All rates expressed in this paper are per 100,000 per annum

In China, the distribution of nasopharyngeal carcinoma revealed significant geographical variations. The mortality rate of NPC is much higher in the Southern provinces, predominantly high in Guangdong, which is possibly the highest risk area in the world. According to the data provided by the investigation of causes of death in 29 provinces, municipalities and autonomous regions (not

including Taiwan)^{7,8)}, the average crude death rate of NPC was 2.00, 2.56 for males and 1.41 for females. The age-standardized rate to the UICC 'World' population was 3.40 for males and 1.77 for females. The proportion of NPC death to all tumor deaths as a whole was 2.81%, ranking eighth. It was 3.11% for males and 2.34 for females, ranking seventh and ninth for males and females respectively. The provinces such as Guangdong, Guangxi Zhuang Autonomous Region, Fujian, Hunan and Jiangxi showed marked higher mortality than the average level of the whole nation. The proportion of NPC death to the total tumor death in the above mentioned provinces was 13.74%; 11.56%; 3.63%; 6.58% and 4.35% respectively. It is of interest to note that the total death rates of all tumors in the provinces such as Guangdong, Guangxi, Fujian, Hunan and Jiangxi were lower in level, ranking behind 23rd of the death list of 29 provinces, municipalities and autonomous regions. Nevertheless, the death rates of NPC ranked from the first to the fifth place in sequence. (Table 2).

A comparison of relative frequency of NPC death to cancer deaths of other sites among the whole nation, Guangdong Province and Sihui County is shown in Fig. 1-1.

When the age-standardized mortality rates of NPC calculated by city or county are compared with the level of the whole nation, the significant high rates in males were found in 56 counties or cities such as Sihui, Zhuhai, Foshan, Panyu, etc. in Guangdong Province, accounting for 52%; 29 units in Guangxi such as Cangwu, He County, Wuzhou, Ziyuan, etc. (28%); 10 counties (10%) in Hunan such as Xintian, Lingling, Yizhang, etc.; Dayu and Gaoan in Jiangxi; Zhaoan and Dongshan in Fujian and Baoxing County in Sichuan Province. For females, the mortality rates of NPC were higher in 48 counties (45%) in Guangdong such as Nanao, Zhuhai, Sihui, etc.; 19 counties (22%) in Guangxi such as Wuzhou, Zhongshan, Cangwu, etc.; 19 counties (18%) in Hunan Province such as Luxi, Changning, Fenghuang, etc.; 6 counties in Fujian such as Zhaoan, Dongshan, Minhou, etc.; Xunniao and Ganzhou of Jiangxi; Wan County of Sichuan; Songtao Miao Autonomous Region of Guizhou; Yingshan County of Hubei and Xining of Qinghai Province.

Furthermore, in the high risk province of NPC, Guangdong, the mortality of NPC also revealed marked variations. Most of the high death frequency areas are mainly located in the central part of Guangdong, i. e. Zhaoqing, Foshan, and Guangzhou area. For males,

**Table 2 The percentages of death rates from NPC
accounted for in all cancer deaths and their ranks by
provinces, municipalities and autonomous regions of China**

Province, Municipality Autonomous region	Males			Females		
	Age-std	%	Rank	Age-std	%	Rank
	rate*			rate*		
Whole nation	3.40	3.11	7	1.77	2.34	9
Guangdong	12.46	15.29	3	5.00	11.05	4
Guangxi	8.54	12.70	3	3.54	16.34	4
Fujian	6.05	3.85	6	2.87	3.15	9
Hunan	5.55	8.23	4	3.02	4.72	7
Jiangxi	4.21	5.25	6	1.97	3.16	9
Zhejiang	4.13	2.77	7	1.90	2.11	9
Sichuan	3.25	3.77	6	1.71	2.65	9
Hubei	2.97	2.93	7	1.72	2.24	9
Guizhou	2.87	6.25	6	1.33	3.74	9
Jiangsu	2.87	1.52	7	1.42	1.20	9
Jilin	2.59	2.15	7	1.24	1.55	9
Anhui	2.38	1.90	7	1.31	1.51	9
Shanghai	2.59	1.34	7	1.03	1.05	9
Liaoning	2.17	1.85	7	1.33	1.67	9
Heilongjiang	1.96	2.10	7	1.26	2.04	9
Shanxi	1.97	1.38	7	1.32	1.09	9
Henan	2.08	1.44	7	1.19	1.19	9
Shaanxi	1.74	1.44	7	1.25	1.33	9
Ningxia	1.86	1.18	7	1.18	1.17	9
Nei Mongol	1.65	1.68	7	1.14	1.25	9
Hebei	1.72	1.29	7	1.18	1.33	9
Tianjin	1.67	1.65	7	1.06	1.28	9
Yunnan	1.64	3.73	7	0.94	2.50	9
Shandong	1.63	1.55	7	1.09	1.51	9
Xinjiang	1.30	1.51	7	0.59	0.76	9
Beijing	1.42	1.30	7	0.65	0.82	9
Qinghai	1.16	0.97	7	0.66	0.78	9
Xizang	0.89	0.95	7	0.71	0.86	9
Gansu	0.56	0.63	7	0.53	0.68	5

* Age-standardized according to UICC 'World' Population

Zhaoqing prefecture had the highest NPC mortality rate of 20.63, and in this prefecture, Sihui County was the highest one with a mortality of 34.01. It was 10 times as high as that of the national level. It is

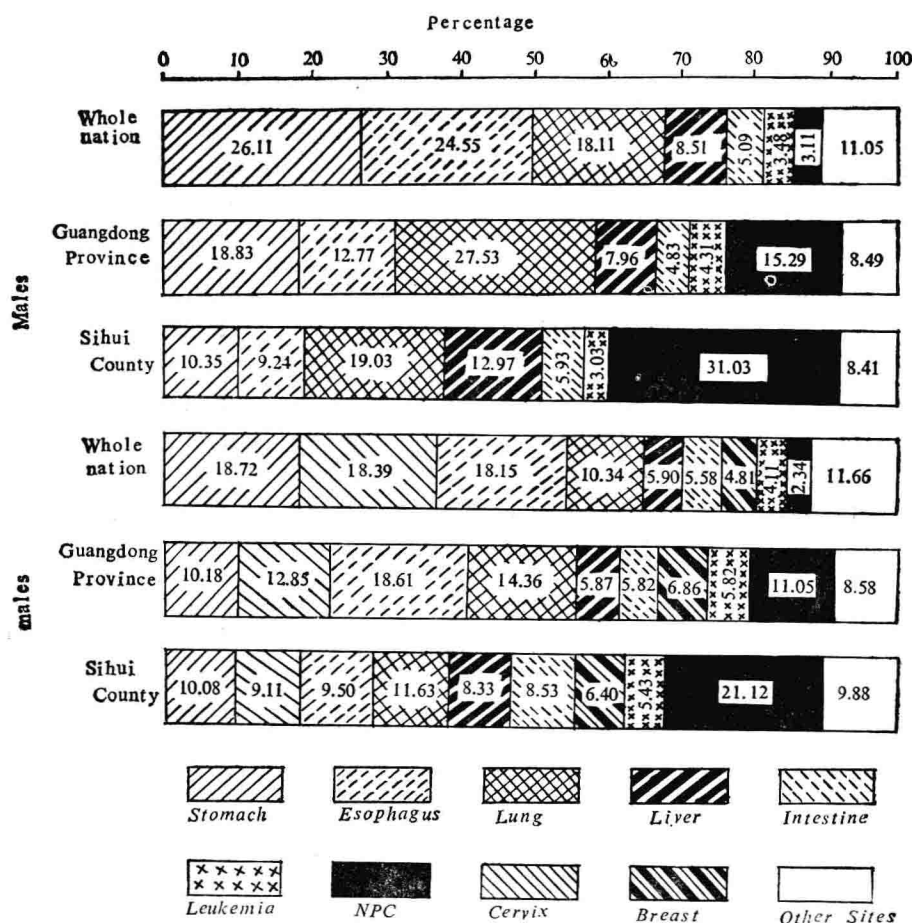


Fig. 1-1 Death rates comparison of NPC and other cancers

shown in Fig. 1 that the relative frequency of NPC death to all sites of Cancers was 31.03%, ranking first. In Foshan and Guangzhou, the age-standardized mortality rates of NPC respectively were 18.12 and 16.76. The rates in the other 6 prefectures were all less than the average level of Guangdong. For females, the highest mortality rate was in Foshan prefecture with an age-standardized rate of 7.69, then followed by Zhaoqing (7.27) and Guangzhou (7.09). In Sihui County, the NPC death rate was 11.15, next only to Nanao (11.49), and it also ranked first (21.12%). The death rate of Guangzhou was 7.09. In the other 6 prefectures, the death rates were again lower than the average figure of this province. This characteristic geographical distribution as shown in Fig 1-2 provides information for further epidemiological study.

No significant difference in NPC death rate was found between

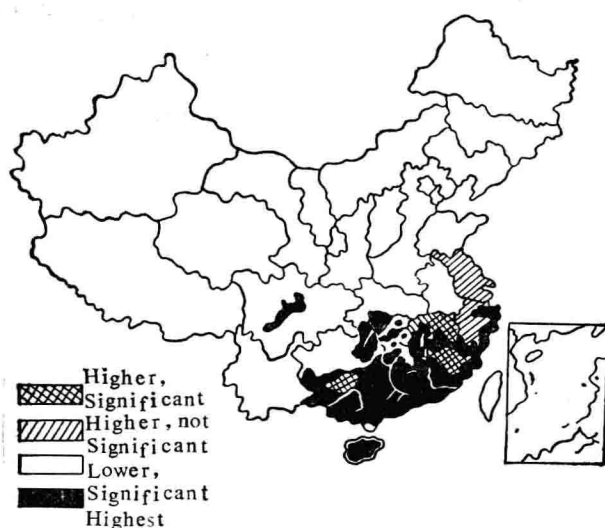


Fig. 1-2 Geographical distribution of mortality from nasopharyngeal cancer in males, China

(From "Survey on Death from Malignant Tumors in China" P. 248 Fig. 10-7)

the urban and rural areas. Nevertheless, among the municipalities, Guangzhou was the highest one with age-standardized rate of 12.34 for males and 5.24 for females, that is 6.8 and 5.7 fold as high as the average level of all municipalities for males and females respectively. As to the rural areas, the age-standardized mortality in Sihui County was 24.88 for males and 8.65 for females (all rates here were standardized to the 1964 Census Population of China), that is respectively 12.4 and 8.1 times as high as the average of all rural areas as a whole. (See Table 3)

Table 3 Age-standardized mortality rate* of nasopharyngeal cancer for urban and rural areas

	Total	Males	Females
Municipality: Large	1.44	1.88	0.93
Median	1.48	1.97	0.96
Small	1.73	2.28	1.11
Rural county	1.54	2.01	1.67
Guangzhou City		12.73	5.55
Sihui County		24.88	8.65

* Age-standardized according to 1964 Census Population of China

A comparison made on the death rates of nasopharyngeal carcinoma among selected metropolises is shown in Table 4.

Table 4 Mortality rate of nasopharyngeal carcinoma of selected metropolis

Metropolis	Males			Females		
	Crude rate	Age-std. rate*	Age-std. rate**	Crude rate	Age-std. rate*	Age-std. rate**
Guangzhou	13.75	12.34	16.76	6.36	5.24	7.09
Chengdu	4.00	3.16	4.27	1.93	1.48	2.27
Wuhan	2.63	2.47	3.64	1.66	1.29	1.92
Shenyang	2.11	1.89	2.86	1.20	1.13	1.72
Nanjing	2.28	1.96	2.78	1.61	1.16	1.78
Shanghai	2.27	1.79	2.59	1.04	0.74	1.03
Tianjin	1.42	1.18	1.67	0.88	0.72	1.06
Beijing	1.11	0.95	1.42	0.54	0.44	0.65
Xian	0.97	0.93	1.47	0.67	0.57	0.67

* Age-standardized according to 1964 Census Population of China

** Age-standardized according to UICC 'World' Population

If a comparison is made among the 2,000 and more counties, 13 of them showing a high NPC mortality of over 20 per 100,000 in males are located in Guangdong Province. Moreover, 10 of the 13 counties are located inside Guangzhou, Zhaoqing and Foshan Prefecture. For the other 3 counties, except Liannan and Ruyuan two Yao Auto. Rgn. belong to Shaoguan Prefecture, Dongguan County belongs to Huiyang Prefecture but is near to Guangzhou. The mortality rates of the 13 counties are shown in Table 5.

Table 5 Age-standardized mortality rate of over 20/100,000 in males by county

County	Males	Females	County	Males	Females
Sihui	34.01	11.15	Xinxing	21.08	6.27
Zhuhai	28.51	10.91	Liannan	20.94	5.32
Deqing	24.33	8.17	Gaoyao	20.79	5.95
Panyu	23.46	9.90	Zhongshan	20.21	10.16
Hua County	23.00	10.72	Dongguan	20.24	6.09
Doumen	22.69	10.96	Ruyuan	20.00	2.72
Guangning	21.77	8.02			

C. Time Trends

Observations based on the data provided by Zhongshan County, Sihui, Guangzhou and Shanghai all revealed little fluctuation in the incidence or mortality rates of NPC in a decade (Table 6 and Fig 1-3). The NPC death rate in Yuexiu district of Guangzhou was 7.13 in 1964~65; 7.91 in 1972~74 and 7.83 in 1978^[9,10]. There was not much change in the last 10 odd years. In Shanghai, the standardized mortality of NPC in 1963~1965 was 2.7 for males, 1.5 for females and in 1976~1979 2.9 and 1.2 for males and females respectively, again no remarkable variation. While during the same period, the standardized mortality of lung cancer increased from 28.5 to 52.0 in males and 11.1 to 18.3 in females, indicating that the incidence or mortality rate of NPC is quite stable.

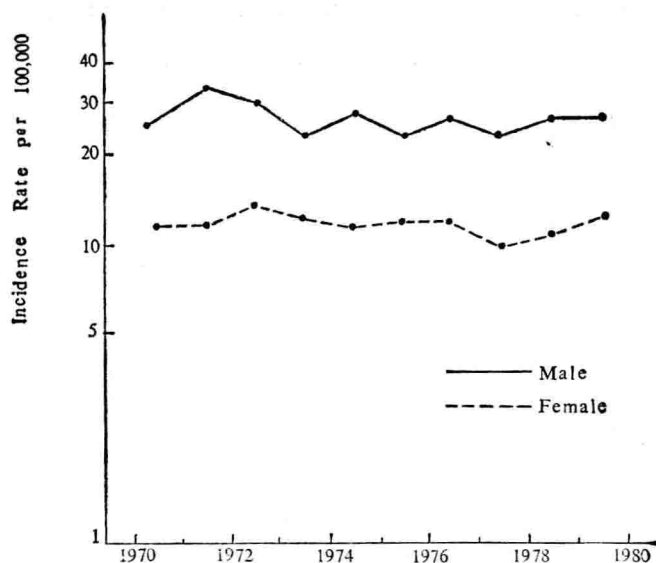


Fig. 1-3 incidence rate from nasopharyngeal cancer in Zhongshan, Guangdong province, 1970~1979

According to the analysis on data of Cancer Registry in Singapore in 1968~77 by Day^[13], the results showed that there was not much change in incidence of NPC either adjusted for age only or adjusted both for age and ethnic group. While in the same period the incidence of cancer of the esophagus decreased and that of the colon increased ($p < 0.01$).

**Table 6 Age-standardized incidence rate* of
nasopharyngeal carcinoma in Zhongshan, Guangdong, 1970-1979**

Year	Males	Females	Total
1970	25.70	11.08	17.80
1971**	33.81	11.82	22.40
1972	29.87	13.55	21.19
1973	22.99	12.18	17.17
1974	27.10	11.03	18.93
1975	23.21	11.95	17.57
1976	26.05	11.59	19.68
1977	22.55	9.83	16.21
1978	25.08	10.73	17.67
1979	25.65	12.27	17.44

* Age-standardized according to UICC 'World' Population

** A screening was carried out for NPC this year and more NPC cases were found

D. Characteristics of persons

I. Sex and Age:

The sex ratios of NPC in most of the countries were very similar to each other. There were more male NPC patients than females. According to a nation-wide survey of causes of death, the ratio of NPC for male to female was 1.96:1, varying between 1.22 to 2.48. No significant difference in sex ratio was found between high and low risk areas. This result showed a discrepancy from that registered in California reported by Zippen et al (1962)^[14], where sex ratio for Chinese NPC patient was 5.8, perhaps the number of Chinese patients in the registration was too small (totally 41 cases including 35 male cases and 6 females).

Nasopharyngeal cancer may occur in any age. In China, it was reported that the youngest patient was 3 years old, and the oldest 86 years in age. The shape of the age-specific incidence and mortality curves was quite different from those of other epithelial cancers. It showed a very steep rise after 20 years of age, reaching a plateau from 40 to 60 years of age, when the rise started to decline. This suggests that there may be exposure to certain carcinogenic agents or virus infection during the early life or something related to genetic susceptibility.

It is worthy to note that despite the high incidence of NPC in Guangdong, children cases of NPC were relatively rare. For example,

Table 7 A comparison between incidences of nasopharyngeal cancer by sex and age-group in Sihui county

Age-group (yr.)	Males	Females	Total
0-	0.00	0.00	0.00
10-	0.75	0.82	0.79
20-	7.07	6.24	6.64
30-	46.77	29.73	37.99
40-	94.35	25.58	54.99
50-	92.49	31.05	56.20
60-	74.33	19.63	41.04
70+	36.74	15.06	21.68
Total	24.30	11.90	17.93

in the high risk county Sihui, Out of a total of 595 new cases of NPC from 1971 to 1981, merely 6 of them (1.01%) were under 20 years of age, and none under 10 years; while in the data obtained from a nationwide survey of cancer deaths, the ratio of cases of NPC deaths under 10 years of age was 0.42%, and that of cases under 20 was 2.12%. According to the data recorded in the Zhongshan Medical College, of the 35,830 cases of NPC in Guangdong diagnosed with pathological confirmation for 15 years from 1964 to 1978, 46 cases were under the age of 14, accounting for 0.12%; while in Liaoning Province of North-east China, the Shenyang Medical College diagnosed, 839 cases of NPC from 1957 to 1973, and 41 (4.8%) were under 10 years of age. Commoun reported 485 cases of NPC in Tunisia from 1969 to 1974, among whom 82 cases were children and teen-agers (17%). In other countries such as Uganda, Sudan, India and American blacks, the proportions of NPC patients under 20 years of age were also relatively higher than that in Guangdong. This special phenomenon which appeared in NPC high risk area with smaller proportion of children and young adults needs further study to elucidate whether there is any difference in etiologic factors or host susceptibilities.

II. Occupation,

There are few reports concerning the association between occupation and occurrence of NPC. The results of matched case-control study in U.S.A. conducted by Anderson (1978)^[15] showed excess relative risks for person exposed to smoke and fume as well as chemical agents. Lin's (1971)^[16] analysis on NPC mortality rates in

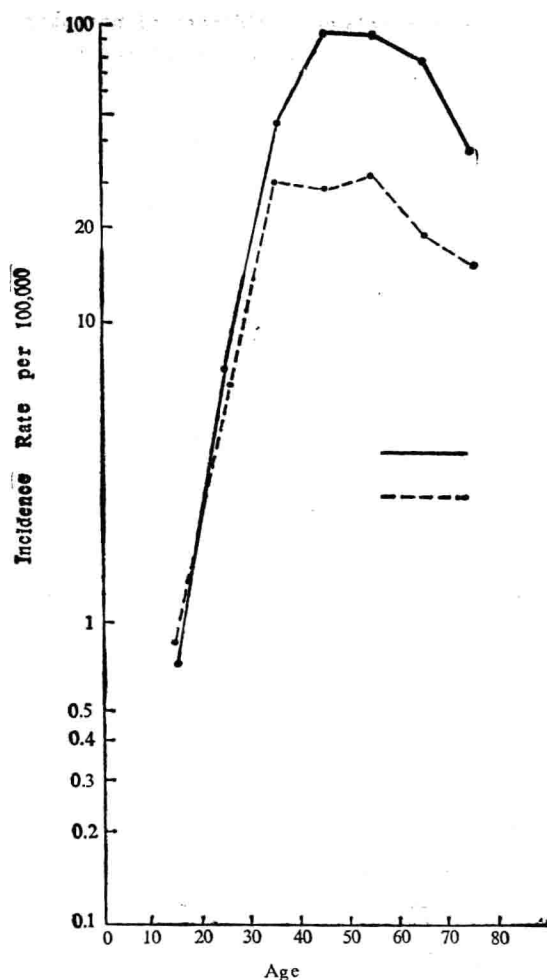


Fig. 1-4 Age-specific incidence rate of nasopharyngeal cancer by sex in Sihui county, Guangdong, 1971~1981

males with occupation in Taiwan showed higher risks in those engaged in salt production, national defense, public service and mining; their rates were 8.26; 5.88; 4.49 and 3.18 per 100,000 population respectively.

A historical prospective study on the cancer deaths of workers engaged in porcelain and pottery production continuously for at least 5 years in Foshan City of Guangdong was conducted by the Public Health Department of Zhongshan Medical College^[17]. The results revealed that the NPC mortality of the workers was 16.5 and of the local inhabitants in Foshan as the controls was 14.7. Indirect method of standardization was used for age adjustment. The standardized mortality ratio (SMR) was 72% ($p > 0.05$). No significant difference