RESEARCH ARTICLE

Time Trends of Nasopharyngeal Carcinoma in Urban Guangzhou over a 12-Year Period (2000-2011): Declines in Both Incidence and Mortality

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Abstract

Nasopharyngeal carcinoma (NPC) is an uncommon disease in most countries but occurs with much greater frequency in southern China. This study aimed to examine the secular trends of NPC in urban Guangzhou over the time period of 2000–2011 using data from the Guangzhou Cancer Registry. Age-adjusted annual incidence rates of NPC were calculated by the direct method using the WHO World Standard Population (1960) as the reference. The average annual percentage change (AAPC) was used as an estimate of the trend. A total of 7,532 new cases of NPC and 3,449 related deaths were registered. In both genders, the peak incidence occurred in the 50- to 59-year age group, and this age distribution pattern remained similar throughout. The AAPC in NPC incidence rates was -3.26% (95% CI: -5.4%--1.1) for males and -5.74% (95% CI: -8.9%--2.5) for females, resulting in a total decrease of 39.3% (from 22.14 to 13.44 per 100,000 population) for males and 48.6% (from 10.1 to 5.18 per 100,000 population) for females over this 12-year period. The AAPCs in NPC mortality rates were -4.62% (95%CI: -3.5%--5.7) for males and -6.75% (95% CI: -5.2%--8.3) for females, resulting in a total decrease of -46.1% (from 12.1 to 6.54 per 100,000 population) for males and 51.7% (from 4.14 to 2.00 per 100,000 population) for females. The age-adjusted incidence and mortality rates of NPC declined during 2000–2011 in urban Guangzhou but remained high. Future efforts to improve prevention, early detection and treatment strategies are needed.

Keywords: Nasopharyngeal carcinoma - epidemiology - incidence - mortality

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Introduction

Nasopharyngeal cancer (NPC), which is a non-lymphomatous, squamous cell carcinoma occurring in the epithelial lining of the nasopharynx, is an uncommon disease in most countries, and its age-adjusted incidence for both sexes is less than 1 per 100,000 population. However, the disease occurs with much higher frequency in southern China, northern Africa and Alaska. The ethnic Chinese living in the province of Guangdong are especially prone to the disease; the age-adjusted incidence rate there is more than 20 per 100,000 population (Wei and Sham, 2005; M. P. Curado, 2007). The highest risk has been observed among Cantonese of the Guangdong province, thus giving NPC a special name: "Canton tumour".

In these high incidence regions, the trends of NPC in recent years have been controversial. Steady downward trends for NPC incidence and mortality have been observed in Hong Kong (Lee et al., 2003; Xie et al., 2012b), Taiwan (Hsu et al., 2006) , and the Netherlands (Arnold et al., 2013) and among Singapore Chinese (Luo et al., 2007). A study conducted in Chinese-Americans living in Los Angeles County and the San Francisco metropolitan area also showed a decreased rate among men from 1992 to 2002, with the overall decline limited primarily to type I tumours, which are moderately differentiated squamous cell carcinomas (Sun et al., 2005). From 1973 to 2005, there was also a general trend of decrease in NPC mortality in both men and women in China (Huang et al., 2012). However, a similar study conducted over a 20-year period (1978-2002) in Sihui and Cangwu (Sihui county is located in the middle east part of Guangdong province, and Cangwu county is located in Guangxi province at the border between Guangxi and Guangdong) found stable incidence rates (Jia et al., 2006). Stable rates were also found in Zhongshan during 1970-2007 (Wei et al., 2010). The difference between the mortality rates of NPC in three periods during 1973-2005 was not as significant seen in men in Guangxi (Deng et al., 2014).

Guangzhou, the capital of Guangdong province, has the highest NPC incidence in the world. With rapid economic development and continuous improvement in living standards, the effects of lifestyle factors on the occurrence of cancers have changed. In the late 1990s, a cancer registry was established in Guangzhou to report the incidence and mortality of cancers, including NPC. This gave us an opportunity to investigate the changes in NPC in rapidly developing cities. To understand the

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Table 1. Proportion (%) of Diagnoses Type for NPC Incident Cases, Mortality *vs.* Incidence (M: I) Ratios for Males and Females in Guangzhou, 2000-2011

Period	Diagnosis with histological verification		Report by death certificate only		M:I	
	male	female	male	female	male	female
2000--02	87.16	90.92	-	-	0.5	0.4
2003--05	86.31	88.28	2.54	2.09	0.51	0.39
2006--08	88.76	89.84	1.11	1.37	0.48	0.4
2009--11	90.38	91.17	0.72	0.96	0.46	0.38

changing patterns of NPC in Guangzhou, we calculated the incidence and mortality rates of NPC and employed joinpoint regression models to explore secular trends in urban Guangzhou over the 2000-2011 time period.

Materials and Methods

Cancer registry

Guangzhou is the largest city in the southern part of China, with a population of approximately 8 million and an area of 7, 434.4 km2. It is the capital of Guangdong province and is situated at latitude 22°N and longitude 112°E. The Guangzhou Cancer Registry was established in 1998. Because of a lack of mortality data for the suburban area in 2000-2008, only data from urban areas were analysed in this study. This analysis included the population from six districts (Yuexiu, Liwan, Haizhu, Baiyun, Huangpu and Luogan) within Guangzhou city, with an area of 1, 335.3 km2. The population was 4 million in 2010, with the Han race making up more than 99%. The data for 2000-2002 were accepted by Cancer Incidence in Five Continents, Volume IX. The process of cancer registration has changed from manual to a network direct report system. Cancer incidence data were obtained from 170 hospitals capable of diagnosing cancers in Guangzhou. For each incident cancer case, information including registered identification number (ID), medical ID, China Identity Card Number (unique for each resident), ICD 10th edition code, name, sex, birth date, occupation, ethnicity, resident address, phone number, cancer site, basis for diagnosis, treatment, prognosis and pathological report if available (date of diagnosis, hospital and doctor name for diagnosis) were all registered. All cases were distributed to Community Health Service Centres for follow up. The doctors in the Community Health Service Centres supplemented the incidence data during the death investigation process. Table 1 shows the proportion of diagnoses with histological confirmation. Up to 86.31-91.17% of NPC patients were diagnosed by pathology. Death data were obtained from the Health Information Centre in Guangzhou and population data from the Guangzhou city bureau of statistics (NBS).

Statistical analysis

The raw data were coded and verified for eligibility using a series of comprehensive cross-checking programs before registration. First, they were checked punctiliously to eliminate duplications, using the China Identity Card Number, together with each patient's name, address and date of birth. Data were checked using IARCcrgTools. Original records were checked in case of doubt. The

Table 2. Incidence Rates Per 100,000 During Different Periods

Period	Age-specific incidence rate for different age groups					
	0-30	30-39	40-49	50-59	60-69	70+
Male population						
2000-2002	2.15	20.97	58.39	50.77	58.43	76.6
2003-2005	1.47	16.21	39.31	46.56	57.37	54.46
2006-2008	1.23	13.89	38.82	60.24	59.99	43.27
2009-2011	1.91	18.47	36.91	47.63	48.94	38.12
AAPC (%)	-0.43	-1.43	-5.56*	-0.07	-1.53	-9.89*
Female population						
2000-2002	1.75	12.86	28.79	20.87	20.25	20.37
2003-2005	1.89	9.83	23.5	25.61	23.54	15.54
2006-2008	0.8	7.2	15.72	18.24	22.21	14.55
2009-2011	1.19	6.66	13.53	18.9	18.03	10.91
AAPC (%)	-6.23	-7.61*	-8.94*	-2.7	-1.25	-6.73*

AAPC: average annual percentage change.**p*<0.05

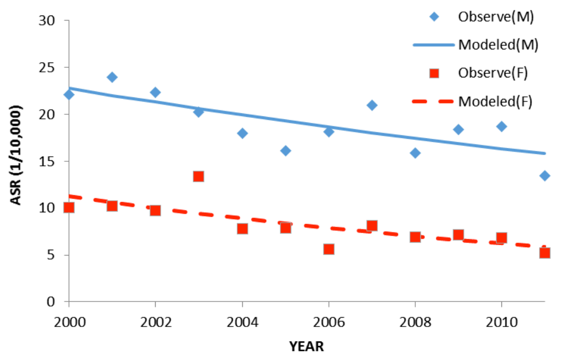

Figure 1. Incidence Trend of NPC in Urban of Guangzhou During 2000-2011. M:mael F:Female.The AAPC for NPC in male was -3.26%(95%CI:-5.4%—-1.1%), in female was -5.74%(95%CI:-8.9%—-2.5%)

incidence rates calculated were then compared with those in reports from previous years, with further verification sought if obvious anomalies or inconsistencies were detected.

Excel 2010 was used to establish the database and perform the data analysis of crude incidence/mortality rates, age-specific rates, age-standardized rates, standard error and 95% CI. Age-adjusted annual incidence and mortality rates were calculated by the direct method using the WHO World Standard Population (1960) (M. P. Curado, 2007) . Differences between the genders were evaluated by comparing the adjusted rates in the male population with the corresponding rates in the female population using the χ^2 test. The trend test was adopted using the Joinpoint Regression Program, Version 4.0.4 (Kim et al., 2000).

Results

Incidence

From 2000 to 2011, a total of 7, 532 NPC cases, including 5, 261 males and 2, 271 females, in urban areas of Guangzhou were registered.

Table 2 summarizes the incidence rates for different gender and age groups during various periods. The age-specific incidence ranged widely from 0.8 for females aged 0-30 years during 2006-2008 to 76.60 for males aged ≥70 years during 2000-2002. The age-specific incidence rates declined in all male and female age groups, but only significantly so in the groups aged 40-49/70+ years in

Table 3. Mortality Rates Per 100,000 During Different Periods

Period	Age-specific incidence rate for different age groups 0-30	30-39	40-49	50-59	60-69	70+
Male population						
2000-2002	0.22	5.8	25.37	33.6	37.87	49.45
2003-2005	0.58	3.28	19.54	24.76	36.19	39
2006-2008	0.12	4.25	15.36	27.8	35.41	35.3
2009-2011	0.17	2.84	11.1	23.76	32.18	34.77
AAPC (%)	-	-6.36*	-8.71*	-3.13*	-1.92	-4.48*
Female population						
2000-2002	0.21	1.91	8.35	9.5	14.02	19.4
2003-2005	0.13	1.97	7.28	11.12	14.34	11.93
2006-2008	0	0.78	3.79	7.72	11.24	14.78
2009-2011	0.05	1.21	4.04	6.34	7.3	11.69
AAPC (%)	-	-8.19*	-9.26*	-5.43*	-6.01*	-5.13*

AAPC: average annual percentage change.*p<0.05. -:Because of containing 0, Joinpoint regression cannot process

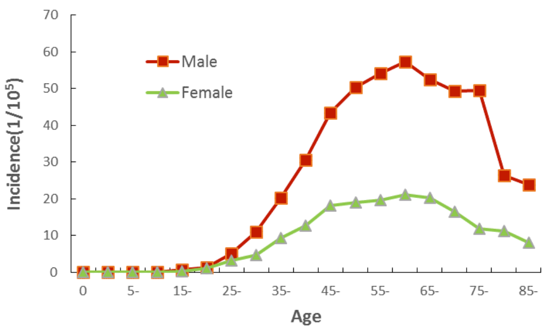

Figure 2. NPC incidence in Guangzhou by age, 2000-2011

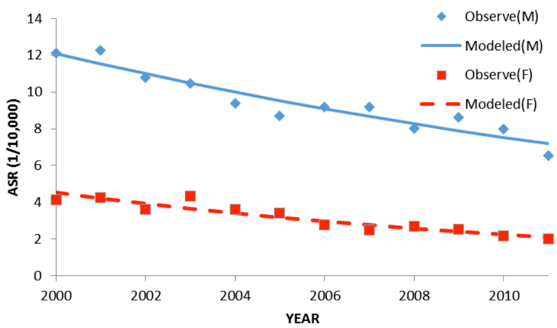

Figure 3. Mortality Trend of NPC in Urban of Guangzhou during 2000-2011. M:mael F:Female.The AAPC for NPC in male was -4.62%(95%CI:-3.5%—-5.7%), in female was -6.75%(95%CI:-5.2%—-8.3%)

males and 30-49/70+ years in females.

Joinpoint analysis identified only one trend in the age-adjusted incidence rate of NPC in both males and females over the 12-year period (Figure 1): an average decrease of 3.26% in males and 5.74% in females. The age-adjusted male incidence rate fell by 39.29% (from 22.14 to 13.44), while the age-adjusted female incidence rate fell 48.63% (from 10.07 to 5.18).

NPC was very rare among individuals younger than 30 years, but the rate rose sharply with older ages, reaching a peak at age 60-65 years in Guangzhou (Figure 2).

Mortality

During 2000-2011, a total of 3, 449 NPC cases died in urban Guangzhou, including 2, 558 males and 891 females.

Table 4. Male/Female Ratio in Incidence and Mortality Rates During Different Periods

year	Age-adjusted incidence rate M/F ratio	95%CI	p-value	Age-adjusted mortality rate M/F ratio	95%CI	p-value
2000--02	2.25	2.04-2.48	<0.001	2.9	2.51-3.36	<0.001
2003--05	1.88	1.71-2.07	<0.001	2.54	2.19-2.95	<0.001
2006--08	2.66	2.40-2.94	<0.001	3.32	2.84-3.88	<0.001
2009--11	2.63	2.38-2.91	<0.001	3.41	2.91-4.00	<0.001

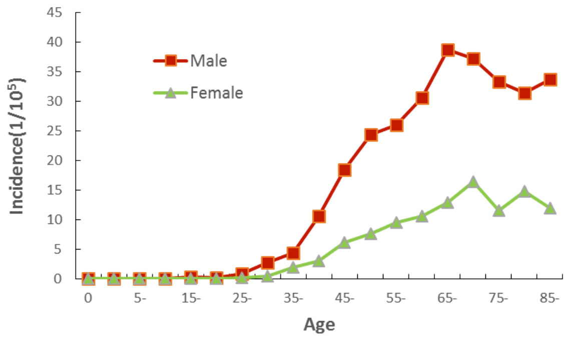

Figure 4. NPC Mortality in Guangzhou by age, 2000-2011

Table 3 summarizes the mortality rates for different gender and age groups during different periods. The age-specific mortality ranged widely from 0.00 for females aged 0-30 years during 2006-2008 to 49.45 for males aged ≥70 years during 2000-2002. The age-specific mortality rates declined in all male and female age groups. The greatest AAPC was -8.71% for males and -9.26% for females aged 40-49 years.

Joinpoint analysis identified only one trend in the age-adjusted mortality rate of NPC in both males and females over the 12-year period (Figure 3): an average decline of 4.62% in males and 6.75% in females. The age-adjusted mortality rate fell by 46.08% (from 12.13 to 6.54) in males and by 51.69% (from 4.14 to 2.00) in females. Age-specific mortality rates are shown in Figure 4.

Differences by gender

Throughout the entire period, the age-adjusted incidence rate in males was significantly higher than that in females. The age-adjusted male/female ratio for incidence varied from 1.88 to 2.66 (Table 4). Similarly, the age-adjusted mortality rate in males was significantly higher than that in females. The age-adjusted male/female ratio for mortality varied from 2.54 to 3.41 (Table 4).

Discussion

Our study shows that the world standardized incidence rate of NPC in urban Guangzhou decreased steadily since 2000 by an average of 3.26% per year in males and 5.74% per year in females, resulting in an overall decline of more than 35% in both males and females. This trend differs from those of other regions in mainland China; the incidence rates of NPC in Shanghai (Yang et al., 2009), Wuhan (Xie et al., 2012a), Zhongshan (Wei et al., 2010), Sihui and Cangwu (Jia et al., 2006) were stable over a long period. However, the encouraging reduction seen in this study was similar to those observed in other developed regions with high NPC occurrence rates (Lee et al., 2003; Hsu et al., 2006; Luo et al., 2007; Arnold et al., 2013). In Hong Kong, a consistent decreasing trend in the world standardized incidence rate resulted in a total decrease of 29% in males and 30% in females during 1980-1999 (Lee et al., 2003). The reduction was attributed mainly to changes in environmental risk factors (the lifestyle for most citizens changed progressively from a traditional Southern Chinese to a more Western lifestyle, and preserved salted fish was no longer a common food in most households). This decline continued, and the age-standardized incidence rates decreased steadily from 35.6 per 100,000 in 1983 to 14.9 per 100,000 population in 2008 for males, and from 12.7 per 100,000 in 1983 to 4.8 per 100,000 population in 2008 for females (Xie et al., 2013) .

Commonly suspected risk factors for NPC include Epstein-Barr virus (EBV) infection, environmental factors, and genetic susceptibility. Associations between NPC risk and certain genetic variations, such as polymorphisms in the CYP2E1 (Hildesheim et al., 1995; Jia et al., 2009) and HLA genes (Tse et al., 2009; Bei et al., 2010), have been suggested by previous studies. EBV has been identified consistently as an important risk factor and in patients with nasopharyngeal carcinoma from regions of high and low incidence, with a dose-response relationship between the EBV antibody level and NPC risk (Chen et al., 1985; Wei and Sham, 2005; Chang and Adami, 2006; Han et al., 2012; Tsao et al., 2014). Intake of Cantonese-style salted fish and preserved food, which contain high levels of nitrosamines, has long been the non-environmental factor most consistently and strongly related to NPC risk (Yu et al., 1988; Chang and Adami, 2006; Lau et al., 2013). Cigarette smoking, other smoking, herbal medicines, and occupational exposures to fumes, smokes, dusts or chemicals have also been associated with increased NPC risk (Chang and Adami, 2006; Ekburanawat et al., 2010). Frequent consumption of fresh fruits and/or vegetables, especially during childhood, has been associated with a lower risk of NPC (Polesel et al., 2013). Tea, especially green tea, has been shown to decrease the risk of several cancers. Green tea contains several components, including catechins, a category of polyphenols with chemo-preventive properties (Cabrera et al., 2006).

The declining time trend in NPC incidence observed in urban Guangzhou may be related to changes in the population and/or environmental factors. Since 1978, China has followed a policy of reform and openness to the outside world. Guangzhou was the city at the forefront of this movement. The population has increased by 3 million in the last three decades. Many people from northern China, where the incidence rate of NPC is low, moved to Guangzhou, and some people from Guangzhou, who are native Cantonese, moved to other regions. Therefore, the genetic background may have changed. The age-specific incidence rates for different age groups show that the AAPC varied widely, from -0.03% to -9.89% in males and from -1.25% to -8.94% in females. The greatest declines occurred in the 70+ age group in males and the 40-49 age group in females. These imbalances among different age groups imply that population changes may have had an effect. At the same time, with rapid economic development and the continuous improvement of living standards, the influences of lifestyle on cancer occurrence have changed. The lifestyle for many citizens changed progressively from a traditional Southern Chinese lifestyle to an integrated lifestyle, particularly in terms of diet. Preserved salted fish is no longer a common food in most households. Despite the remarkable decrease over the years, the incidence rates remained high: the age-standardized rate in 2011 was 13.44 for males and 5.18 for females. In addition to environmental factors, it is highly likely that inherited genetic predisposition also plays an important role in oncogenesis.

The male/female ratio of age-adjusted rates in urban Guangzhou in 2009-11 was 2.63 (95% CI 2.38-2.91, p<0.01) for incidence and 3.41 (95% CI 2.90-4.00, p<0.01) for mortality. This higher proportion of males was observed in all age groups throughout the entire period (Table 4). The same pattern is seen in many endemic and non-endemic registries. The incidence of NPC is 2- to 3-fold higher in males than in females (Chang and Adami, 2006). Such a male predominance in NPC incidence and mortality may be explained in part by gender differences in the prevalence of certain environmental risk factors, such as smoking and hazardous occupational exposures. It is also possible that some intrinsic exposures, such as sex hormones, could account for the observed male predominance, for example via a protective effect of endogenous oestrogen (Xie et al., 2013).

It is also encouraging to note that both genders showed a progressive decrease in mortality rate (Fig. 2), resulting in a total decrease in the age-standardized rate of 46.08% for males and 51.69% for females during the study period. The decrease in mortality is mainly caused by that in the incidence rate. This trend is the same as in China, 1973-2005 (Huang et al., 2012).

In this study, we analysed the age-standardized mortality/incidence ratios (M:I ratio) in males and females (Table 1). The M:I ratio is a comparison between the number of deaths, obtained from a source independent of the registry (usually, the vital statistics system), and the number of new cases of a specific cancer registered during the same period of time. When the quality of the mortality data is good (especially with regard to accurate recording of the cause of death) and there is a steady state of constant incidence and survival, the M:I ratio is approximated by 1-year survival probability (5 years) (Parkin and Bray, 2009). The ratios in males have decreased marginally since 2010 but have remained stable in females. However, the M:I ratio in females was lower than that in males for the entire period (Table 1), which implied that females had a higher survival rate after treatment than did male patients. The M:I ratio is far lower than that in Hong Kong in 1995-1999, suggesting the lack of earlier presentation; many patients with NPC were diagnosed at a late stage.

A major limitation of the present study was that we could not examine the time trend of NPC incidence rates among different histological subtypes, since many cases in 2000-2003 lacked histological classification and were only reported as squamous cell carcinoma. Given the known limitations in interpretation of changing epidemiology over an extended period, the current data are indeed encouraging. Further improvements (identifying the key etiological factors, public education to promote primary/secondary prevention and early presentation, management provisions to minimize delay, and clinical research to enhance treatment efficacy) are obviously still needed.

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