

## RESEARCH ARTICLE

## Declining Incidence of Nasopharyngeal Carcinoma in Brunei Darussalam: a Three Decade Study (1986-2014)

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### Abstract

**Background:** Nasopharyngeal carcinoma (NPC) is linked to Epstein Barr virus infection and is particularly common in the Far East, particularly among some Chinese groups. Certain ethnicities have been reported to have low incidence of NPC. This study looked at NPC in Brunei Darussalam over a three decade period. **Materials and Methods:** The cancer registry from 1986 to 2014 maintained by the State Laboratory was retrospectively reviewed. The age standardized rates (ASR) and the age specific incidence rates (ASIR) were calculated. Non NPC tumors were excluded from the study. **Results:** Altogether, there were a total of 450 NPC cases diagnosed accounting for 4.4% of all total cancer cases over the study period, declining from 10.3% in 1986-1990 to 2.3% in 2011-2014. The most common tumor type was the undifferentiated carcinoma (96.4%). The case characteristics were mean age  $50.4 \pm 14.4$  years old, male 69%, and predominately Malays 74.4%, followed by Chinese 16.7%. The mean age of diagnosis increased over the study period from  $45.6 \pm 17.1$  years (1986-1989) to  $54.1 \pm 12.5$  years (ANOVA,  $p < 0.01$  for trend). There were no differences in the mean age of diagnosis between the ethnic groups or genders. The ASR showed a declining trend from 11.1 per 100,000 in 1986-1990 to 5.95 per 100,000 in 2011-2014, similar trends been observed for both genders. Among the age groups, declining trends were seen in all the other age groups apart from the >70 years group. The overall ASRs for the Malays and Chinese were 7.92/100,000 and 8.83/100,000 respectively, both showing declining trends. **Conclusions:** The incidence of NPC in Brunei Darussalam is comparable to rates reported from Singapore and Malaysia, but higher than rates reported from the other Southeast Asian nations. Unlike higher rates reported for Chinese compared to the Malays in other countries, the rates between the Malays and Chinese in our study was comparable. Importantly, the ASR is declining overall and for both genders and ethnic groups.

**Keywords:** Nasopharyngeal neoplasm - incidence - trend - epidemiology - Brunei Darussalam

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### Introduction

Nasopharyngeal carcinoma (NPC) is a tumor that arises from the epithelium of the posterior nasopharynx and is the most common tumor of the upper aerodigestive tract. The underlying pathogenesis is influenced by a combination of factors; genetic (i.e. certain HLA types), environmental (i.e. nitrosamine containing food such as salted food, rancid butter, tobacco, wood and formaldehyde) and viral infection (Epstein Barr virus-EBV) resulting in sequence of changes from dysplasia to carcinoma. (Chan et al., 2002; Wei and Sham, 2005; Tsao et al., 2014; Petersson, 2015) In 1978, the World Health Organization has classified NPC into three histological subtypes; squamous cell carcinoma (SCC) as WHO type 1, non-keratinizing carcinoma (WHO type 2), and undifferentiated carcinoma (WHO type 3). In 1991, the use of numerical designation was eliminated and the tumor classified as keratinizing SCC and non-keratinizing

carcinoma, the latter being subdivided into differentiated and undifferentiated. (Shanmugaratnam and Sobin., 1993) The current classification included an additional category; basaloid SCC (Chan et al., 2005).

NPC exhibit peculiar geographic and ethnic distributions. It is particularly common in the East. In 2012, the Western Pacific (WPRO) and South-East Asia (SEARO) region accounted for 53.3% and 24.4% respectively, of the estimated global NPC burden. (IARC 2012) The other WHO Member States regions, Africa 7.0%, Europe 5.8%, the Americas 4.7% and East Mediterranean 4.7% accounted for the rest (IARC 2012). Globally, it is estimated that there are annually 80,000 new cases of NPC with 50,000 deaths (Bray et al., 2005). Apart from South-East Asia, Southern China (Guangdong province) has reported some of the highest rates with annual incidence of >20/100,000. (Zhang et al., 2015) NPC is particularly common in certain ethnic races; especially Chinese and this correspond to the high

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rates reported in the South-East Asia and Southern China. Differences are also seen in the tumor types (Petersson F., 2015) and also the stage of disease (Ianovski et al., 2010) at presentations.

As the incidence of cancers is increasing worldwide, it is very important to be aware of the characteristics and incidence, including diseases trends at the individual country, regional and international levels. These will allow for effective prevention programs to be formulated that suite the individual country, at the same time in line with regional and international policies in diseases prevention. In our setting, there has only been one study that looked at NPC. (Yeo et al., 2012) This study which looked at EBV and NPC reported that the incidence in Chinese was lower than the Malay (Yeo et al., 2009). However, this study only looked at one time point and did not assess the trend. This present study assessed the trend in the incidence of NPC over a three decade periods (1986-2014) and also assessed the trends among the genders and the two major ethnic groups (Malays and Chinese) in Brunei Darussalam.

## Materials and Methods

### Setting

Brunei Darussalam is a small developing nation with a total area of 5,765 km<sup>2</sup> and estimated population of 415,717 (July 2013; Department of Economic Planning, Ministry of Finance). The population breakdown consists of ethnic group (Malays 66.3%, ethnic Chinese 11% and indigenous 2.7%) and the expatriate group (20%).

### Data Source

The cancer registry maintained by the Department of Pathology were retrospectively review from 1986-2014. In this registry, only histology proven cancers are registered. All biopsies specimen are sent to the State pathology Laboratory (located in the only government tertiary hospital, RIPAS, Bandar Seri Begawan) for analyses. Being the only state histopathology laboratory, the registry capture all the tissue diagnoses NPC cases for the whole country and is therefore representative.

For this study only NPC (WHO Classification) were studied. (Chan et al., 2005) Based on this classification; NPC is classified into Nasopharyngeal tumors not within this classification were excluded. In total, 15 cases were excluded which included lymphoma (n=13) and adenoid cystic tumor (n=2).

### Statistic

The data were entered into the Excel (Microsoft) and later transferred into the Statistical Package for Social Sciences (SPSS, Version 16.0, Chicago, IL USA) program for analysis. Data for 1990 were missing and this was excluded from analysis; calculation of the Age Standardized Rates (ASR) and Age Specific Incidence Rates (ASIR). Chi-squared test was used to compare the categorical variables and the ANOVA and Mann-Whitney non-parametric test were used to compare the continuous variables. A p value of less than 0.05 was taken as significant.

## Results

Altogether, there were a total of 450 NPC cases diagnosed over the study period, accounting for 4.4% of all total cancer cases. The incidence rates among all cancers declined from 10.3% in 1986-1990 to 2.3% in 2011-2014 (Figure 1).

The most common tumor type was the undifferentiated carcinoma, accounting for over 96.4% and the remainders were keratinizing squamous cell carcinoma (3.6%)

There were more men (69%) compared to women and the mean age of diagnosis was 50.4 ± 14.4 years old with a

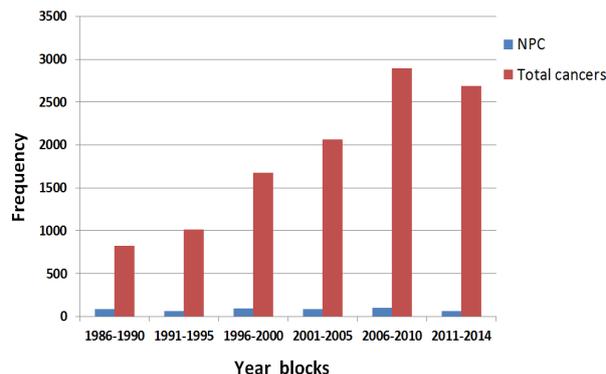


Figure 1. Proportion of Nasopharyngeal Carcinoma among All Cancer Cases Encountered

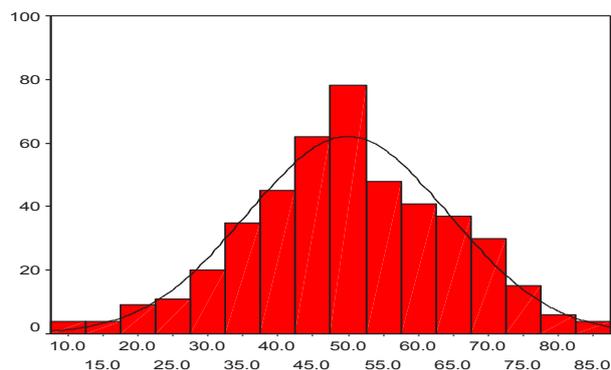
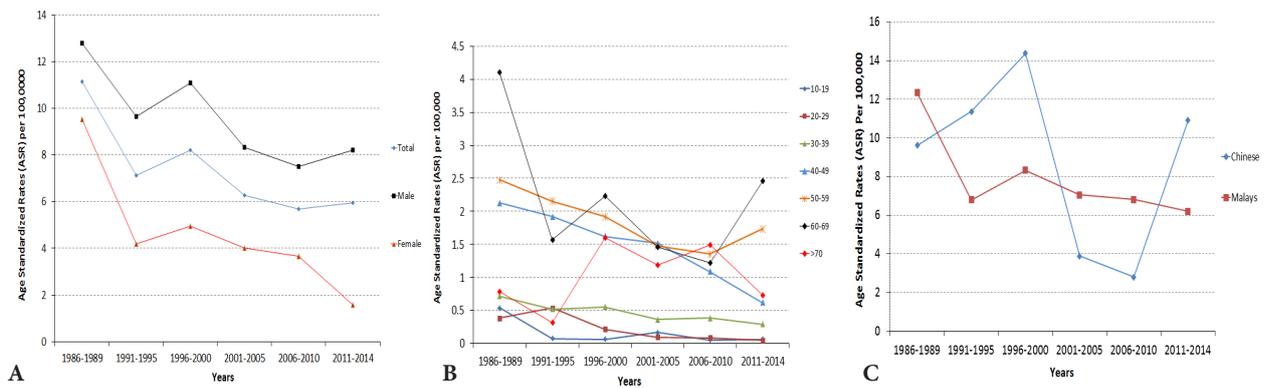


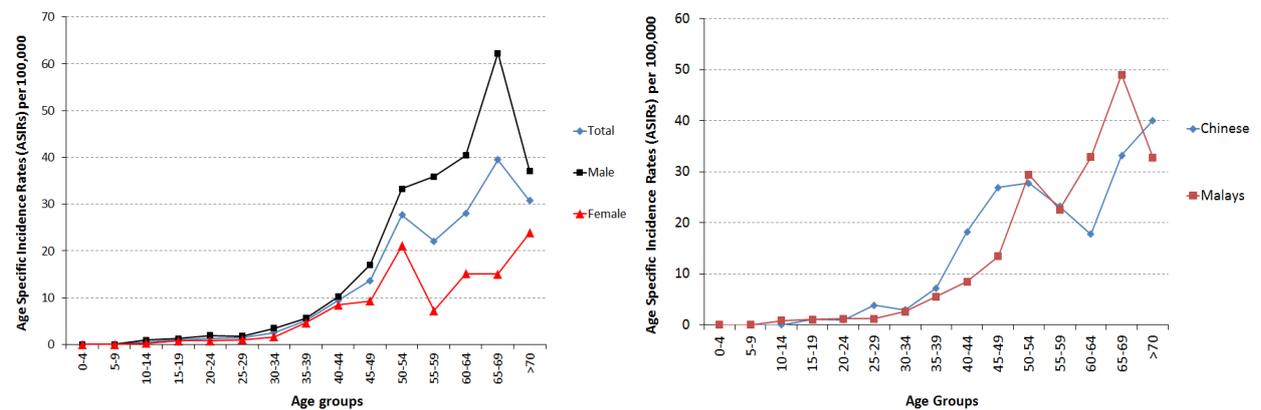
Figure 2. Age Distribution Showing Unimodal Distribution

Table 1. Mean Age of Diagnosis

Variables	Mean age (Standard deviation) years	p values
<b>Genders</b>		
Men	50.4 ± 14.3	p>0.05
Women	49.1 ± 14.6	
<b>Ethnicity</b>		
Malays	50.7 ± 14.6	0.274 for trend
Chinese	47.9 ± 13.3	
Indigenous	49.7 ± 16.5	
Others	44.7 ± 8.1	
<b>Years</b>		
1986-1989	45.6 ± 17.1	p<0.001 for trend
1991-1995	45.5 ± 12.8	
1996-2000	50.7 ± 13.4	
2001-2005	49.8 ± 14.2	
2006-2010	52.9 ± 14.6	
2011-2014	54.1 ± 12.5	



**Figure 3. A) The Age Standardized Rates (ASR) for NPC Over the Study Period for Overall, Male and Female, B) the ASRs for the Different Age Groups, and C) the ASRs for the two Major Ethnic Groups (Malays and Chinese)**



**Figure 4. a) The Overall Age Specific Incidence Rates (ASIRs) for NPC; Overall, Male and Female, B) the ASIRs for the two Major Ethnic Groups (Malays and Chinese)**

significant increasing trend seen over the period (ANOVA  $p < 0.001$ ). There was only one peak in the age distribution (Figure 2). Among the genders and the ethnic groups, there were no differences ( $p > 0.05$ ) (Table 1).

The ASR showed declining trend from 11.13 in 1986-1989 to 5.95 per 100,000 in the latest time block (2011-2014) (Figure 3a). Declining trends were also among the genders; Male ASR 12.78/100,000 (1986-1990) to 8.2/100,000 (2010-2014) and Female ASR 9.52/100,000 (1986-1990) to 1.59/100,000 (2010-2014). Apart from the >70 years age group, declining trends were seen in all the other age groups (Figure 3b).

The overall ASRs for the Malays and Chinese were 7.92/100,000 and 8.83/100,000 respectively. There was a wide fluctuation for the Chinese and this likely due to the overall small population. For the Malays, the trend was declining with no fluctuation (Figure 3c).

The ASIRs showed continued increase with fluctuation, peaking in the 65-69 age group. Similar trend was observed in the male but for the female group, the peak was in the >70 years group (Figure 4a). The ASIRs for the two major ethnic groups were comparable (Figure 4b). The ASIRs for the Chinese were higher until the 50-54 years age groups, when the Malays were higher, until the >70 years age group.

## Discussion

In our study, we showed that NPC accounted for 4.4%

of all cancers encountered in our population over the three decade with a declining trend from 10.3% in 1986-1990 to 2.3% in 2011-2014. Of importance is that the decline occurred in the background of increasing number of cancer cases seen each year. The total number of NPC cases had initially leveled off and in the later part of the study, actually declined. In Brunei, the continued increase of total cancers cases mainly due to increase in several cancers; colorectal cancer, breast and ovarian cancer.

The mean age of diagnosis of our population is comparable to what have been reported, most common in the 50-60 age groups. There was only one mode. There were no difference in the mean age of diagnosis between the genders and the ethnic groups. Importantly, between the time periods, the mean age of diagnosis increased significantly. This is likely due to effect of ageing population.

Similar to what have been reported in the literature, our study showed that NPC is more common among men, two to three times more common (Our study ASR male; female ratio was by a factor of 1.87, Hawaiian (Caucasians 0.78, Chinese 2.4), Singapore (overall 2.81, Chinese 2.79, Malays 2.71) and Malaysia (overall 2.66, Chinese 2.45, Malays 2.83 and Indians 3.0). High incidence among men is probably related to exposure to higher risk factor such as smoking. Genetic differences (human leucocyte antigen, enzymes polymorphisms including DNA repair enzymes and susceptibility loci in chromosomes) have been shown to play a role in ethnic differences, but it is unknown if it

play a role in gender differences. Other risk factors such as exposure to burning woods (i.e. cooking), consumption of salted food and exposure to EBV would be equally shared risk factors. Alcohol consumption (Chan et al., 2002; Wei and Sham, 2005; Chen et al., 2009) and occupational exposure to formaldehyde and wood or wood dust are also reported to be important factors (Hildesheim et al., 2001). However, in our setting, such exposures are not or now less common. Environmental factors are important as migrant studies have shown that the rates decline to intermediate rates between the countries of origin and countries of residence. (Yu and Hussain 2009; Mousavi et al., 2010). Low economic social status, an indirect indicator to exposures of the risk factors has also been reported to be associated with NPC. (Turkoz et al., 2011)

The predominant tumor type among our population is the undifferentiated carcinoma (previously known as WHO type 3 tumor), accounting for over 95% of all tumor. These findings are consistent with have been reported in other countries. (Wided et al., 2015) In Singapore, undifferentiated NPC accounts for 85.1% of all nasopharyngeal cancers. (Singapore Cancer Registry 2007) Of the three tumor types, undifferentiated NPC has been strongly linked to EBV infection (Raab-Traub, 2002) which serves as a driver for pathogenesis of this particular tumor type. (Chan et al., 2002)

NPC is known to vary between countries. In South-East Asia, the incidence of NPC vary between countries with higher rates in Malaysia (8th common cancer, ASR 7.2/100,000), Singapore (11th, 6.4/100,000), Indonesia (9th, 5.6/100,000) and Viet Nam (7th, 5.4/100,000) to lower rates in Myanmar (15th, 2.4/100,000), Philippines (15th, 2.2/100,000), Thailand (16th, 2.1/100,000), Cambodia (19th, 1.9/100,000), and the LAO republic (17th, 1.7/100,000). Based on the IARC data, Brunei registered an ASR of 5.0/100,000 for NPC which placed it as the 12th most common cancers for that year. (IARC, 2012) The rate reported for 2011-2014 was 6.0/100,000 placing Brunei third in the South-East Asia region. Compared to the other parts of the world, the incidence are low with ASR of <1.0/100,000. (Jemal et al., 2011; IARC 2012) Outside of South-East Asia, the highest reported have come from Southern China (Guangdong province) with rates of 21.73/100,000 (male 30.29/100,000 and female 13.09/100,000). (Zhang et al., 2015)

Of important note is that the rates have been decreasing trend. The ASR declined from a high of just over 11/100,000 in 1986-1990 period to just under 6/100,000 in the latest period 2011-2014. The drop was rapid from 1986-1990 to 1991-1995 and then slowly leveled off after that. Interestingly, our overall ASRs for the two major ethnic groups were comparable; Malays (7.92/100,000) and Chinese (8.83/100,000). This is in contrast to the findings from neighboring countries, Singapore and Malaysia which have almost similar population ethnicities, apart from very few ethnic local Indians in Brunei Darussalam. The NPC rates are much higher among the Chinese in both Singapore (Male ASR 12.5/100,000) and Malaysia (Male 10.9/100,000, Female 3.9/100,000) compared to the Malays; Singapore (Male ASR 6.8/100,000) and Malaysia (Male 4.9/100,000). In

both countries, the Indian had the lowest rates. (Singapore Cancer Registry 2007; Malaysia Cancer Registry 2007)

In the last three decades, the incidence rates of NPC have been declining among Chinese. These have been reported among Chinese residing in the South-East Asia, Hong Kong, Taiwan, and Singapore (Luo et al., 2007). Data from the Singapore cancer registry reported declining trends of NPC with an estimated annual decline of 0.96% for male and 1.89% for female in the period between 1968 and 2007. (Singapore Cancer Registry 2007) Declining trend has been reported from Guangzhou (Li et al., 2014), but not in Zhongshan. (Wei et al., 2010) Declining trends were also observed in our study for both Chinese and Malays. The decline was smooth among the Malays whereas there was wide fluctuation for the Chinese. This is likely accounted for by the overall small Chinese population in the country as even small fluctuations in the incident cases can lead to wide fluctuation in the calculated rates. Declining rate has also been reported in the northern Africa, Tunisia seen more in adult with annual average change of -3.3% for men and -2.7% for women. In the younger age group, the rates were stable. (Wided et al., 2015) Importantly, along with the declining incidence of NPC, the mortality rate has also declined. (Huang et al., 2012)

The declining rates observed in our studies, consistent with what have been generally reported elsewhere are accounted for by several important factors. In Brunei, the most important factor is perhaps the improvement in the standards of living; decline in reliance on firewood resulting in less exposure to smoke, consumption of less salted preserved meats and also consumption of more fresh produces (vegetables and fruits). The prevalence of tobacco use and exposure to EBV remain the same, but may still play a role in the decline in the incidence of NPC. Exposures to the latter two factors are now probably occurring at later age and hence may affect the NPC pathogenesis.

Declining in the incidence of NPC has implications in policy planning. Generally, we have observed that cancers linked to infections such as *Helicobacter pylori* and gastric cancer, Human papilloma virus (HPV) and cervix cancer and EBV and NPC are declining not just in Brunei but also other parts of the world. On the other hand cancers linked to non-communicable diseases especially obesity continues to increase. Cancers such as colorectal and breast cancers are increasing and these cancers are largely preventable. (IARC 2012) Screening programs such as colorectal cancer screening or screening mammography have been shown to be effective. Therefore, available resources that may be scarce in some countries should be targeted to the more common and increasing cancers. However, some resources should also be allocated cancers that are declining, including NPC for early detection, effective intervention and also prevention.

In conclusion, our study showed that the incidence of NPC was comparable to what have been reported in neighboring countries with almost similar population demographics. However, the rates between the two major ethnic groups (Malays and Chinese) were comparable, unlike rates reported in Singapore and Malays. Importantly,

the incidence rates are declining, overall, for the genders and the Malays and Chinese.

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