



**EPIDEMIOLOGY OF NASOPHARYNGEAL
CARCINOMA (NPC) IN PAHANG, MALAYSIA**

BY

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is among the most frequently reported cancer in Malaysia. The Malaysian National Cancer Registry Report 2007-2011 stated that NPC was the fifth most common cancer among Malaysian and the third most common cancer among Malaysian men. While there have been several studies on NPC previously carried out in a few states in Malaysia, a comprehensive study in Pahang had never been reported. This study was designed to feature the number of cases and distribution of newly diagnosed NPC in Pahang, as well as to investigate the risk factors of the disease. This study involved two main referral hospitals in Pahang, namely Hospital Tengku Ampuan Afzan (HTAA) in Kuantan and Hospital Sultan Haji Ahmad Shah (HOSHAS) in Temerloh. NPC cases diagnosed within the year 2012-2017 in those hospitals were included in this study. The crude rate (CR) and age-standardized rate (ASR) were computed to investigate the NPC incidence. Furthermore, the patients that met the inclusion and exclusion criteria were invited to participate in a case-control study. A face-to-face interview was conducted using adapted questionnaires which included demographic data, family history of cancers and lifestyles (smoking status, alcohol drinking status and dietary intake of preserved foods). Then, the NPC cases were matched with similar gender, ethnic and age (within five years) of control group consisting cancer free individual. Logistic Regression analysis was performed to identify the factor associated with NPC. A total of 143 new cases of NPC were reported from both hospitals. The age at diagnosis of the patients ranged from 14 to 82 years old with mean age of 52.0 ± 13.7 years old. Majority of cases were male gender (74.1%) with the ratio of male to female was 2.9:1. Ethnically, Chinese males were found to have the highest incidence with the mean ASR of 4.7 per 100,000 populations. Overall, the mean ASR for Pahang were 2.4 per 100,000 population in males and 0.9 per 100,000 population in females. The incidence of NPC in Pahang within the studied time frame were intermediate in males and low in female. In the case-control study, family history of NPC ($p=0.002$) and smoking status ($p=0.006$) were significantly associated with the risk for NPC. An individual who had family history of NPC had a risk more than seven times to develop the disease (AOR= 7.90, 95% CI= 2.12, 29.38) compared with those who did not have the history of the disease. Furthermore, the current smoker was found to have three folds increase odds in the risk for NPC (AOR=3.01, 95% CI=1.38, 6.59) compared to never smoker. The finding in the case-control study suggested that the family history of NPC and smoking status has been linked to NPC risk in Pahang population.

خلاصة البحث

يعتبر سرطان البلعوم الأنفي (NPC) من أكثر أنواع السرطان انتشارًا في ماليزيا. ذكر تقرير السجل الوطني للسرطان الماليزي من 2007-2011 أن NPC كان خامس أكثر أنواع السرطانات شيوعًا بين الماليزيين وثالث أكثر أنواع السرطانات شيوعًا بين الرجال الماليزيين. بينما كانت هناك العديد من الدراسات حول NPC التي أجريت سابقًا في بضع ولايات في ماليزيا، لم يتم الإبلاغ عن دراسة شاملة في باهانج. صُممت هذه الدراسة لتضمين عدد الحالات وتوزيع NPC المشخص حديثًا في باهانج، وكذلك لاستقصاء عوامل الخطر للمرض. شملت هذه الدراسة مستشفى رئيسيين في باهانج، وهما مستشفى تينغكو أمبوان أفزان (HTAA) في كوانتان ومستشفى السلطان حاجي أحمد شاه (HOSHAS) في تيميرلوه. تم تضمين حالات NPC التي تم تشخيصها خلال عوام 2012-2017 في تلك المستشفيات في هذه الدراسة. تم حساب المعدل الخام (CR) ومعدل العمر الموحد (ASR) للتحقيق في حدوث NPC وعلاوة على ذلك، تمت دعوة المرضى الذين حققوا معايير الشمول والإبعاد من المشاركة في دراسة الحالات والشواهد. وأجريت مقابلة وجهًا لوجه باستخدام استبيانات معدلة تضمنت البيانات الديموغرافية، والتاريخ العائلي للسرطانات وأنماط الحياة (حالة التدخين، وحالة شرب الكحول، والمدخول الغذائي للأطعمة المحفوظة). ثم تم مطابقة حالات NPC مع الجنس، والعرق والعمر (في غضون خمس سنوات) من المجموعة الضابطة التي تتكون من فرد خال من السرطان. تم إجراء تحليل الانحدار اللوجستي لتحديد العامل المرتبط بـ NPC وتم الإبلاغ عن ما مجموعه 143 حالة جديدة من NPC من كلا المستشفيات. تراوحت أعمار المرضى بين 14 و 82 عامًا عند تشخيص متوسط العمر 52.0 ± 13.7 عامًا. كانت غالبية الحالات بين الجنسين للذكور (74.1%) وكانت نسبة الذكور إلى الإناث 2.9:1. عرقيًا، تم العثور على الذكور الصينية لديها أعلى نسبة مع معدل ASR يعني 4.7 لكل 100,000 من السكان. بشكل عام، كان متوسط معدل ASR في باهانج هو 2.4 لكل 100,000 نسمة من الذكور و 0.9 لكل 100,000 من الإناث. كانت نسبة حدوث NPC في باهانج ضمن الإطار الزمني المدروس متوسطة عند الذكور ومنخفضة عند الإناث. في دراسة الحالات والشواهد، ارتبط تاريخ عائلة NPC (ع = 0.002) وحالة التدخين (ع = 0.006) بشكل كبير مع خطر NPC. كان لدى الفرد الذي كان له تاريخ عائلي في NPC خطر أكثر من سبع مرات للإصابة بالمرض (AOR = 7.90, 95% CI = 2.12, 29.38) مقارنة مع أولئك الذين ليس لديهم تاريخ للمرض. علاوة على ذلك، تم العثور على أن المدخن الحالي لديه ثلاثة أضعاف زيادة لاحتمالية الإصابة بـ NPC (AOR = 3.01, 95% CI = 1.38, 6.59) مقارنة مع الذي لم يدخن أبدًا. تشير النتيجة التي توصلت إليها دراسة الحالات والشواهد إلى أن تاريخ عائلة NPC وحالة التدخين قد تم ربطه بمخاطر NPC لدى سكان باهانج.

APPROVAL PAGE

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LIST OF ABBREVIATIONS

AOR	Adjusted Odd Ratio
AR	Age-specific Rate
ASR	Age-standardized Rate
CI	Confidence Interval
CR	Crude Rate
EBV	Epstein-Barr virus
et al.	(et alia); and others
HLA	Human Leukocyte antigen
HOSHAS	Hospital Sultan Haji Ahmad Shah
HTAA	Hospital Tengku Ampuan Afzan
IARC	International Agency for Research on Cancer
MLR	Multiple Logistic Regression
NA	Not Available
NPC	Nasopharyngeal Carcinoma
OR	Odd Ratio
ROC	Receiver Operating Characteristics
SLR	Simple Logistic Regression
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Nasopharyngeal carcinoma (NPC) is a type of cancer that is relatively more prevalent in certain countries in Asia such as Southern China and Southeast Asia compared to other regions in the world. In Malaysia, NPC has been one of the significant health problems as it is among the five most commonly diagnosed cancer in the country's population and third most common cancer among Malaysian men. The Malaysian National Cancer Registry Report (2007-2011) revealed that there were in total 5090 cases of NPC diagnosed in the country within those five years, comprising of 3785 males and 1305 females. The disease is particularly prevalent in the Chinese, followed by Malays and Indians. In addition, high incidence and prevalence of NPC has also been observed among indigenous groups in East Malaysia, particularly among the ethnic *Bidayuh* in Sarawak.

While there have been several studies on NPC previously carried out in several states in Malaysia, a comprehensive study in Pahang has never been reported. Most of the studies in Peninsular Malaysia were conducted in the West-coastal region especially in Penang, Selangor and Kuala Lumpur. Basic information on NPC epidemiology for research in Pahang is crucially needed before further research on the disease in the region is carried out. Thus, this epidemiological study is designed to feature the number of cases and distribution of NPC, as well as to identify the risk factors of the disease.

NPC is a multifactorial disease. Possible interaction between Epstein-Barr virus (EBV) infection, genetic and environment factors in the disease development has been speculated. To date, the well-established risk factors for NPC include EBV infection,

high consumption of salt-preserved fish, a family history of NPC, and certain human leukocyte antigen (HLA) class I genotypes (Chang & Adami, 2006). Further potential risk factors include consumption of other preserved foods, tobacco smoking and alcohol drinking. However, the exact roles of these factors in the development of NPC remains enigmatic.

This study aimed to provide the first ever six-year comprehensive data on the epidemiology of NPC in Malaysia, and more specifically in the state of Pahang. As the causes of NPC are complex, there is need for researcher to discover the role of family history of NPC and/or other cancers as well as certain lifestyles that can contribute to the development of the disease.

1.2 RESEARCH PROBLEM

In the recent years, cancer becomes one of the leading causes of morbidity and mortality globally. The World Health Organization reported that cancer was the second leading cause death of non-communicable diseases worldwide after cardiovascular diseases (WHO, 2014). The specialized cancer agency of the World Health Organization, The International Agency for Research on Cancer (IARC) has reported that in 2012 alone, there were approximately 14.1 million new cases and 8.2 million cancer-related deaths occurred where more than half occurred in less developed regions. This figure is expected to increase to 22 million in the next two decade (Ferlay et al., 2015). In addition, cancer was responsible for 8.8 million deaths in 2015. That accounts for nearly one in six of all global deaths. In this regard, cancer represents a threat for many of countries and causes a tremendous burden on patients, families and the society they live in. Furthermore, the economic impact of cancer is significant and increasing. For

example, Stewart and Wild (2014) reported that the total annual economic cost of cancer in 2010 was established at approximately US\$ 1.16 trillion.

Besides financial cost, cancer brings a psychosocial effect on patients and their families. The impact of cancer and the treatment may affect the patients' quality of life and emotions directly. The symptoms of this disease such as fatigue, pain and nausea would lead to emotional distress and anxiety. People with cancer and their families can experience a range of feelings during their cancer journey such as anger, sadness, fear and hopeless. Furthermore, the cancer treatment such as chemotherapy, radiotherapy and hormonal therapy can give direct physical effects on the patient which can cause psychological problems.

According to Ferlay and colleagues (2015), the most commonly diagnosed cancer type worldwide was lung (1.82 million) with 1.6 million deaths. The other five frequent cancers were breast (1.67 million), colorectal (1.36 million), prostate (1.1 million), stomach (951,000) and liver (782,000). These six cancers represent 55% of the global incidence burden in 2012. Meanwhile, the most common causes of cancer death were lung cancer followed by liver cancer (745,000 deaths) and stomach cancer (723,000 deaths).

Globally, nasopharyngeal carcinoma (NPC) is considered as a rare malignancy with an incidence rate below 1 per 100,000 persons per year for both genders. In 2012, NPC ranked the 24th most common new cancer in the world with 86,691 cases and 50,831 deaths (Ferlay et al., 2015). Notably, NPC is a disease with remarkable geographic and racial distribution worldwide in which it is prevalent in certain regions such as southern China, Southeast Asia, North Africa and the Arctic.

In Malaysia, cancer has been identified as the fourth leading cause of death in government and private hospitals (MOH, 2014). The five most common cancer sites

that are frequently reported in Malaysia are breast, colorectal, lung, lymphoma and nasopharynx (Manan, Tamin, Abdullah, Abidin, & Wahab, 2016). Nasopharyngeal carcinoma (NPC) is among the most frequently reported cancer in Malaysian male. The Malaysian National Cancer Registry Report 2007-2011 revealed that NPC is leading cancer among adult males and the ethnic Chinese were found to have the highest prevalence. In addition, the native ethnic groups from Sarawak were discovered to have high incidence of NPC. Devi, Pisani, Tang and Parkin (2004) discovered a surprisingly high prevalence of NPC among *Bidayuh* native group in Sarawak where the prevalence was the highest rate recorded by any population-based registry between years of 1996 until 1998.

The major etiological factors of NPC still remains uncertain. It presents as a complex disease with distinctive distribution. The remarkable racial and geographic distribution of NPC suggests possible associations of three interacting etiological factors, namely Epstein-Barr virus (EBV) infection, genetic and environmental factors (Jia & Qin, 2012). There are evidences that strongly indicate the role of EBV in the pathogenesis of NPC. However, EBV alone is not a sufficient cause for this malignancy as majority of humans worldwide has been infected with the virus but only a small proportion of individuals develop NPC. Therefore, it is likely that genetic factor and environmental exposure also contribute to the risk. Family history of the disease and lifestyle trends such as smoking, alcohol drinking as well as consumption of salted fish or preserved foods have been suggested as the important risk factors of NPC.

Updated statistics of NPC in Malaysia is currently lacking. In addition, data on the risk factors for the development of this disease in the country is considered as largely insufficient. Hence, this study was conducted to investigate the incidence of NPC in

Pahang as well as its association with family history of NPC and/or other cancers and lifestyle risk factors.

1.3 RESEARCH OBJECTIVES

1.3.1 General Objective

To investigate the distribution and incidence of NPC case in Pahang for year 2012-2017 as well as risk factors associated with the disease.

1.3.2 Specific Objectives

1. To calculate the crude rate (CR) and age-standardized rate (ASR) of NPC by gender and ethnicity.
2. To assess the association between NPC with family history of NPC and/or other cancers.
3. To evaluate the association between NPC with lifestyle risk factors (smoking status, alcohol drinking status and dietary intake of preserved foods).

1.4 RESEARCH QUESTIONS

1. What is the incidence and distribution of NPC in Pahang?
2. Does family history of NPC and/or other cancers associated with NPC cases?
3. What are the lifestyle risk factors that associate with NPC cases in Pahang?

1.5 RESEARCH HYPOTHESES

1. The incidence of NPC in Pahang is increasing each year.
2. There is an association between family history of NPC and/or other cancers with NPC cases.
3. The incidence of NPC in Pahang is associated with lifestyle factors such as smoking status, alcohol drinking status and dietary intake of preserved foods.

1.6 SIGNIFICANCE OF THE STUDY

The relevance of conducting this study is based on two main reasons. Firstly, this study explored the incidence and distribution of NPC in one of state in Malaysia that is Pahang. As NPC is rare cancer worldwide but it is common in certain region including in Malaysia, it is necessary to discover the incidence and identify the affected group. The existing data is limited as there was only certain states conducted the research regarding the disease. Therefore, it is believed that this study will provide the first ever data on NPC available in Pahang.

Secondly, the association of lifestyle factors such as smoking status, alcohol drinking status and dietary intake of preserved foods with NPC were identified. The recognition of the lifestyle risk factors is important as preventive measures so that the incidence could be reduced. The risk can be modified by practicing the healthy lifestyles. Moreover, as the genetic trait plays a role as one of the causes of NPC, the risk of this factor to the disease development needs to be recognized. This study investigated the association between the family history of NPC and/or other cancers with the disease. An understanding of the association will provide insight prevention option.

1.7 DEFINITIONS OF TERMS

Age-specific rate (AR)

Incidence rate in a specified age group. It is calculated by dividing the number of new NPC cases in a five year age group and sex structure with Pahang population in the particular age group and multiply by 100,000.

Age-standardized incidence (ASR)

Summary of the individual age-specific rate (AR) using an external population called a standard population.

Crude rate (CR)

The number of new NPC cases observed in Pahang population during the defined period, divided by the number of Pahang population at risk at the same period and multiply by 100,000

Incidence

Proportion of newly diagnosed cases of NPC in Pahang population within year 2012-2017.

Prevalence

Proportion of existing cases (old and new) of NPC in a population at a single point in time.

CHAPTER TWO

LITERATURE REVIEW

2.1 NASOPHARYNGEAL CARCINOMA (NPC)

Nasopharynx is the uppermost part of pharynx (Figure 2.1). It is located behind the nasal cavity and lies just above the soft palate (Singh, 2014, p. 199). It plays a role as a passageway for air from the nose to the pharynx and eventually to the lung.

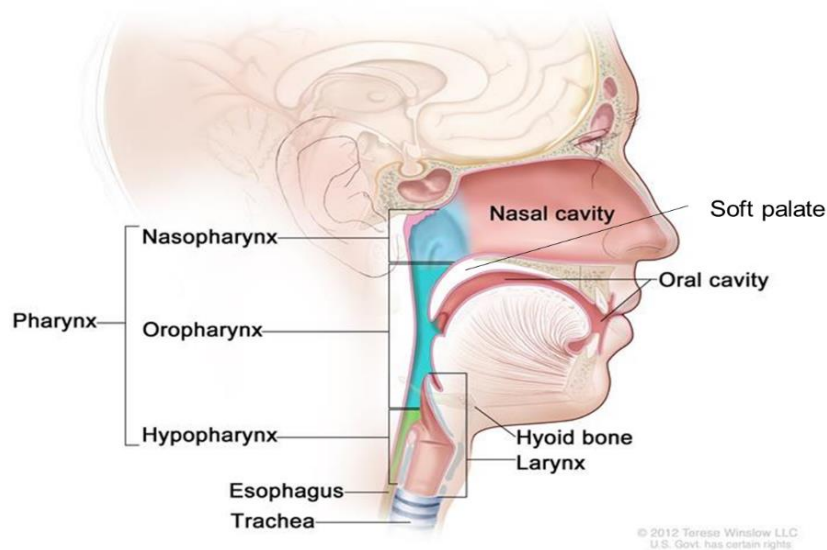


Figure 2.1 Anatomy of the pharynx
Source: (<http://www.cancer.gov/types/head-and-neck>)

According to American Cancer Society (2015), several type of tumors can develop in the nasopharynx. Some of these tumors are benign and others are malignant. Benign tumors in nasopharynx are relatively rare and tend to develop in children and young adults. This kind of tumors do not spread to other parts of the body and usually not life threatening. The examples are *angiofibromas* and *hemangiomas*. On the other

hand, malignant tumors can invade surrounding tissues and spread to other parts of the body. This process is called metastasis. These tumors include *lymphomas*, *adenocarcinoma* and *adenoid cystic carcinoma*.

A carcinoma is a cancer that originates an abnormal clonal expansion of epithelial cells. NPC is the most common type of malignant tumor of the nasopharynx, which arises from the mucosal epithelium. The lateral nasopharyngeal recess known as Fossa of Rosenmüller (FOR) was recognized as the most common site of origin of NPC (Gibb, 1999). This tumor can metastasize to other parts of the body such as bone, lung and liver. Usually, the first presenting symptom of NPC is painless neck lumps. This is due to the tumor spreading to lymph nodes in the neck which cause the area become bigger than normal.

Khoo and Pua (2013) divided the symptoms presented by NPC patients into three others categories. Firstly, nasal symptoms such as blood stained nasal discharge, blood stained saliva or nasal blockage. Secondly, aural symptoms. For instances unilateral blocked ear, pressure sensation in the ears, mild hearing loss or tinnitus. Lastly, ophthalmo-neurologic symptoms namely unilateral facial numbness, diplopia or unilateral headache. The Malaysian Nasopharyngeal Carcinoma Study Group reported that there were 40% of newly diagnosed NPC in 2007 to 2010 presented with neck lumps, followed by nasal symptoms (26%), aural symptoms (14%) and ophthalmo-neurologic symptoms (10%).

The diagnosis of NPC is usually determined by histopathological examination of biopsy specimens. The World Health Organization (WHO) classification in 1978 recognized three histological subtypes of NPC; keratinizing squamous cell carcinoma, KSCC (WHO type I), non-keratinizing carcinoma (WHO type II), and undifferentiated carcinoma (WHO type III). However, this classification was modified in 1991 and

divided into two groups, keratinizing (K) and non-keratinizing (NK). This new classification exhibited the WHO type I was retained whereas the WHO type II and type III were combined into a single category known as NK carcinoma. The reason for combination of NK group was due to the exhibition of similar epidemiology and biologic characteristics including EBV relationship (Feng, 2013). In 2005, WHO classified NPC into KSCC, NK carcinoma which including differentiated and undifferentiated variants, and basaloid squamous cell carcinoma, BSCC (Chan, Pilch, Kuo, Wenig & Lee, 2005). BSCC is a new type introduced and relatively uncommon in both endemic and non-endemic areas.

To verify the tumor stage for NPC, it requires several procedures including clinical examination followed by imaging test such as computerized tomography (CT), magnetic resonance imaging (MRI), chest X-ray, ultrasound, and positron emission tomography (PET) scans. On the other hand, the most common system used to describe the spread of NPC is the “tumor node metastasis” (TNM) staging system which was jointly developed by The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). This staging system is based on the anatomical criteria, in which T refers to the local extent of the primary tumor, N refers to the extent of regional nodes involvement and M refers to the distant spread (metastasis) of the tumor. Then, the TNM scores are combined to determine the overall stage (Table 2.1). In the past, the staging system undergoes periodic revisions in order to improve the classification of the extent of the tumor. The staging system that released lately was the seventh version of the AJCC system (Edges, Byrd & Compton, 2010).

Table 2.1 TNM clinical classification for tumors of the nasopharynx
Source: Khoo & Pua (2013)

Primary Tumor (T)	
T1	Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension (posterolateral infiltration of tumor)
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
Regional lymph node (N)	
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s), 6cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6cm or less, in greatest dimension
N2	Bilateral metastasis in cervical lymph node(s), 6cm or less in greatest dimension, above the supraclavicular fossa
N3	Metastasis in lymph node(s) greater than 6cm in dimension and/or to supraclavicular fossa
N3a	Greater than 6cm in dimension
N3b	Extension to the supraclavicular fossa
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Clinical Stage Groups (Anatomic Stage/Prognostic Groups)	
Stage I	T1,N0,M0
Stage II	T1,N1,M0; T2,N0,M0; T2,N1,M0
Stage III	T1,N2,M0; T2,N2,M0; T3,N0,M0; T3,N2,M0
Stage IVA	T4,N0,M0; T4,N1,M0; T4,N2,M0
Stage IVB	Any T,N3,M0
Stage IVC	Any T, any N, M1

2.2 DISTRIBUTION OF NPC WORLDWIDE

NPC is a relatively rare cancer in most parts of the world. In 2012, there were approximately 87,000 new cases reported per year and constituting 0.6% of all cancer (Ferlay et al., 2015). This makes NPC as the 24th most common of all new cancers worldwide with the age-standardized rate (ASR) for both sexes in many countries at 1.2 per 100,000 persons per year. There were an estimated 51,000 deaths per year from NPC, accounting for 0.6% of total number of cancer death all over the world. Notably, NPC exhibits a distinct geographic and racial distribution across the world (Figure 2.2).

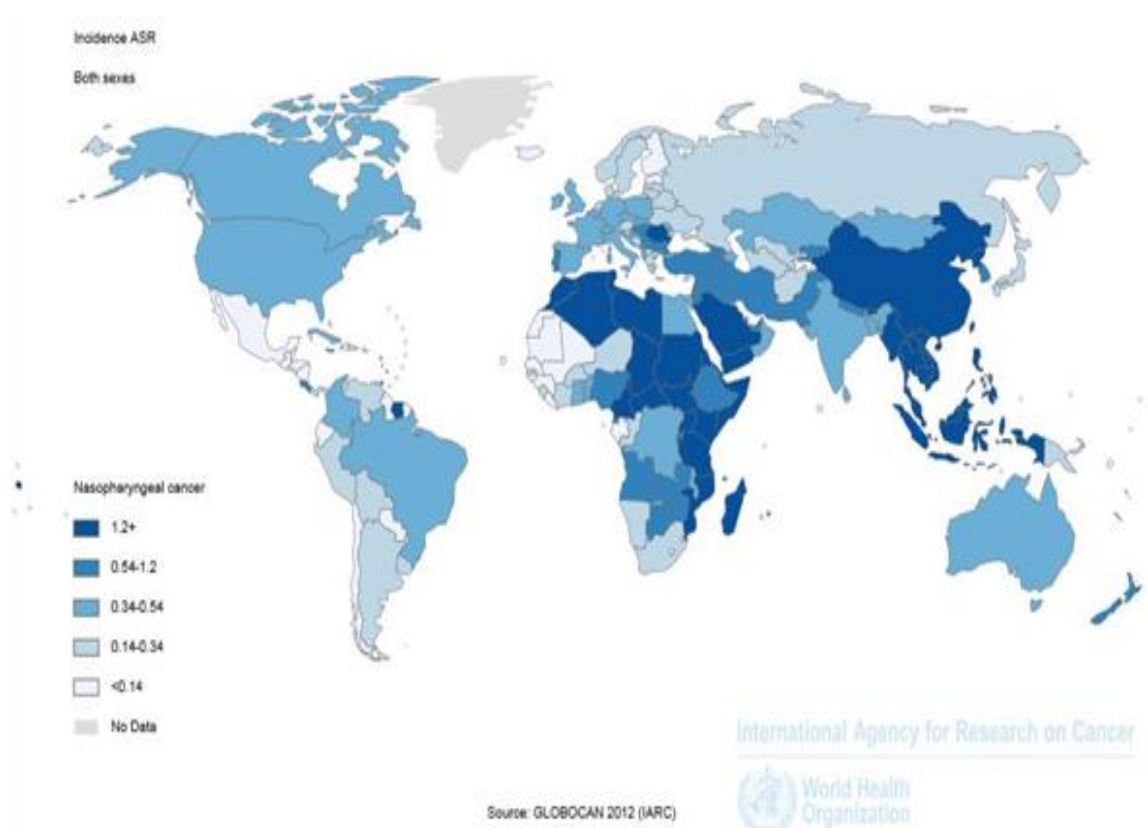


Figure 2.2 Global nasopharyngeal carcinoma incidence: estimated age-standardized incidence rate per 100 000, both sexes, all ages.

Source: GLOBOCAN 2012 (IARC)