

ORIGINAL ARTICLE

Nasopharyngeal Cancer : Geographic Variation and Risk FactorsKaren Michell Othaya Kumar^{1,2}, Rabiatul Basria S.M.N. Mydin^{1,3}¹ School of Distant Education, Universiti Sains Malaysia, 11800 Gelugor, Pulau Pinang, Malaysia.² Klinik Genetik, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia.³ Oncological and Radiological Science Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, 13200 Bertam, Kepala Batas, Pulau Pinang, Malaysia**ABSTRACT**

Introduction: Nasopharyngeal cancer is known to be a rare malignancy that effects the head and neck region involving the nasopharynx. It has a 0.8% occurrence rate among all types of cancer and has many risk factors ranging from viral infections to dietary intake habits. This study aims in determining the geographical variations across the world and its associated risk factors with nasopharyngeal cancer. **Methods:** The study was initiated by extracting relevant literature articles from electronic databases such as PubMed, Science Direct and SEER from 2008-2018. Search strategy also included key terms; nasopharyngeal cancer, nasopharyngeal carcinoma, prevalence, risk factors, geographic variation, distribution, incidences, epidemiology and mortality. **Results:** Nasopharyngeal cancer is most common in Asia and China had the most number of new cases diagnosed in 2018. The standard incidence rate of nasopharyngeal cancer globally in 2018 was 1.5 per 100,000. The standardized mortality rate for nasopharyngeal cancer globally in 2018 was 0.84 per 100,000. The 5 identified countries with the highest mortality rates were China, Indonesia, Vietnam, India and Philippines accordingly. Among the risk factors attributing to the incidences of nasopharyngeal cancer are Epstein Barr Virus (EBV) infection, salted and preserved food consumption and tobacco smoking. **Conclusion:** Nasopharyngeal cancer is strongly associated with the variation of geographical regions therefore adequate knowledge, early detection, immediate administration of treatment and rapid detection is vital in reducing the global incidence burden.

Keywords: Nasopharyngeal cancer, Nasopharyngeal carcinoma, Prevalence, Risk factors, Geographic variation

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INTRODUCTION

NPC is a highly prevalent malignant disease and is the primary cause explaining the increased mortality rate in regions around southern China(1). According to the global cancer statistics by World Health Organization (WHO) (2) NPC accounts for 0.8% of all the cancers reported worldwide. This disease and its occurrence throughout the world are reliant on geographical and ethnical diversity evidently based on its distribution globally. The reported incidence is under 1 in every 100,000 persons occurring both men and women with a sex ratio of 2.62. It is also common in Southeast Asia and some parts of northern Africa, with an uneven geographical dispersion with 85 % of the newly diagnosed cases reported in Asia and 7% in the African continent, the remaining 8% were reported in different continents around the world. Apart from geographical variations between continents, ethnicity is also said to be a risk factor to develop nasopharyngeal cancer. This is evident among the Bidayuh tribe from Borneo, Nagas from the northern part of India and Inuits at the Arctic where the

age standardized ratio is higher than 16 per 100,000 a year in men. Men are more prevalent at developing NPC about 2-3 times more at risk compared to women. The common age group to develop nasopharyngeal cancer are those between 50-60 years of age (3). The purpose of this study is to examine the geographical variation and the risk factors that are associated with the emergence of nasopharyngeal cancer as it facilitates further studies to further explore the possible contributing factors which are associated with nasopharyngeal cancer.

METHODS**Search Strategy**

Our study was initiated by extracting relevant literature articles from several electronic databases which were reviewed for the purpose of this study. All studies that were published within year 2008-2018 that were available in PubMed, Science Direct, SEER (Surveillance, Epidemiology and End Results Program). In addition a common search engine Google Scholar was also used to supplement in retrieving relevant journal articles. All journal articles that used as reference were of English Language. The key words used are; nasopharyngeal cancer, nasopharyngeal carcinoma, prevalence, risk factors, geographic variation, distribution, incidences, epidemiology. All related studies with correspondence

to epidemiology, incidence, risk factors and mortality in nasopharyngeal cancer were compiled in this study.

Data collection

The primary source of data on nasopharyngeal cancer used in facilitating this study were taken from GLOBOCAN 2018, a product of an International Agency for Research on Cancer (IARC) which tabulates the incidence, mortality and prevalence of cancer for the year 2018. All the data recorded were new cases of nasopharyngeal cancer reported in 2018.

RESULTS

The number of cases reported for nasopharyngeal cancer globally were 129,079 cases (93,416 incidences in men and 35,663 cases in women, with a sex ratio = 2.62). Nasopharyngeal cancer is the 24th most common cancer globally with a standard incidence rate of 1.5 per 100,000 (2.2 per 100,000 in men and 0.8 per 100,000 in women). The highest incidence of nasopharyngeal carcinoma is reported in the Asian continent with 109,221 cases followed by Africa 9502 cases, Europe 5019 cases, Latin America and the Caribbean 2682 cases, North America 2410 cases and Oceania had the least cases of 245 (Fig.1). The five countries with the highest number of incidences of NPC consists of China 60,558 cases which makes up (59%) of the world's cases, followed by Indonesia 17,992 cases (18%), Vietnam 6,212 cases or (6%), India with 5086 cases (5%) and Philippines 2913 cases at (3%) (2).

Estimated age-standardized incidence rates (World) in 2018, nasopharynx, both sexes, all ages

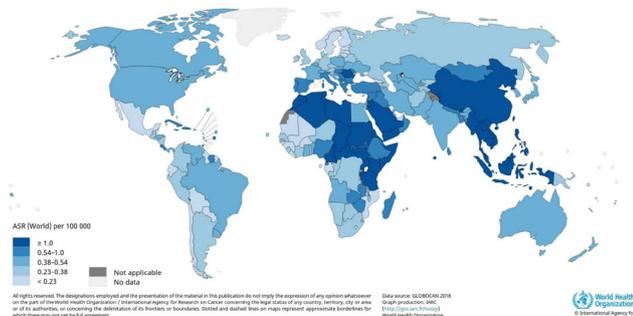


Figure 1: Map view on the geographical incidence of nasopharyngeal cancer across the globe in 2018. Geographical variation for nasopharyngeal cancer across the globe for the year 2018.

Asia has the highest age standardized ratio (Fig.2) with the rate of 2.1 with Brunei being the highest. In Brunei, nasopharyngeal cancer is the 7th most common cancer with the ASR rate of 9.9 per 100,000 in a year (Fig.3). Indonesia has a relatively high incidence rate with 10.5 per 100,000 in males and 2.9 per 100,000 in women in contrast with the global incidence rate of 2.2 per 100,000 in men and 0.8 per 100,000 in women that was reported. It is however must be highlighted that the accuracy in the given numbers are debateable as the records are deemed incomplete (4).

Globally in 2018, 72987 deaths were reported from nasopharynx cancer (54,280 mortalities in males and

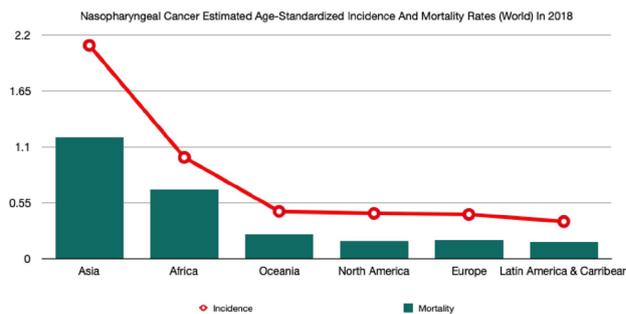


Figure 2: Nasopharyngeal cancer age standardized incidence and mortality rate in different continents, 2018. The bar chart shows the age standardized incidence and mortality rate among five continents globally.

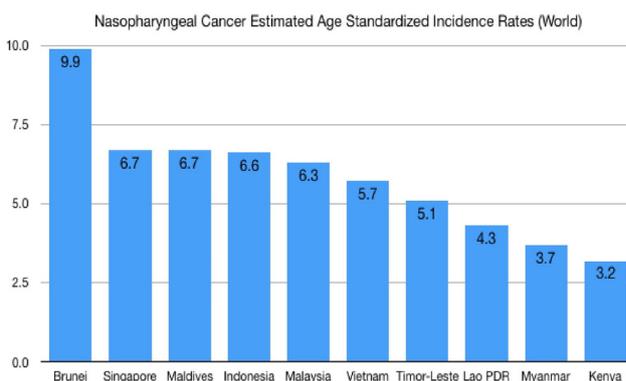


Figure 3: Age standardised rate variations among the countries around the world, 2018. The bar charts illustrates the age-standardized rate difference across the global.

18,707 in women, with the Sex Ratio of 2.90). The standardized mortality rate for NPC globally was 0.84 per 100,000 (1.3 per 100,000 in males and 0.4 per 100,000 in women) (2). Fig.4 illustrates the five countries with the highest number of incidences and mortalities. China with 31,413 deaths, Indonesia 11,204 deaths, Vietnam with 4232 deaths, India with 3715 deaths and Philippines with 1899 deaths, accordingly. Fig.5 concludes that males were more prevalent in developing nasopharyngeal cancer as compared to females with a ratio of 3:1. Nasopharyngeal cancer was more prevalent among the males and females of Eastern Asia with reported cases of 46783 and a mortality rate of 24893 in males and 17521cases and 8245 mortalities in females.

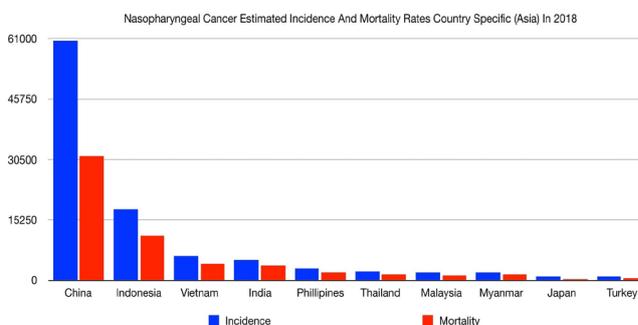


Figure 4: Nasopharyngeal cancer number of incidence and mortality rate country specific in Asia, 2018. Histogram shows the comparison between the incidence and mortality rates among countries in Asia.

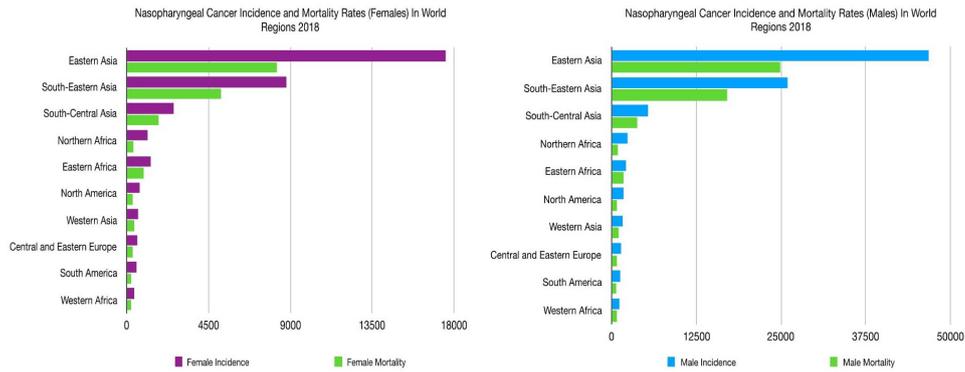


Figure 5: Nasopharyngeal cancer incidence and mortality rate among males and females in world regions, 2018. The bar charts shows the comparison between the incidence and mortality rates among males and females in different regions of the world.

Asia records the highest number of both new cases and mortality rates among males and females collectively.

Though China has the highest number of new cases, however in terms of ASR rates the top 5 countries in (Fig.6) Brunei has the highest ASR and mortality rate at 9.9 per 100,000 cases and 5.8 per 100,000 cases respectively. Followed by Singapore 6.7 per 100,000 new cases and 3.5 per 100,000 mortalities. Maldives comes third with 6.7 per 100,000 incidence with 3.9 per 100,000 mortalities. Indonesia with 6.6 per 100,000 incidence rate and 4.3 per 100,000 mortality rate and finally Malaysia with 6.3 per 100,000 new cases and 3.7 per 100,000 death rate (5).

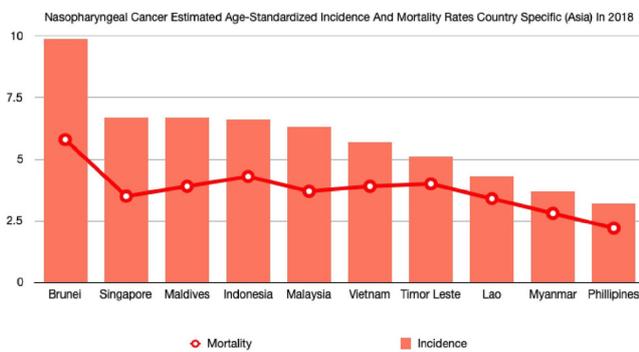


Figure 6: Nasopharyngeal cancer number of incidence and mortality rate country specific in Asia, 2018. The bar charts shows the comparison between the incidence and mortality rates in top 10 Asian countries.

The risk factors that contributes to the emergence of nasopharyngeal carcinoma can be divided in to three main components which are viral, environmental and genetic components (6). Table I summarizes the associated risk factors with the incidences of nasopharyngeal cancer.

Epstein Barr virus (EBV) is said to be the main cause of nasopharyngeal cancer due to the increase of infected migrants to low risk countries and this combined with genetic and environmental factors precipitates the incidence of NPC. Ironically, though an infection with

Table I: Risk factors associated with nasopharyngeal cancer

VIRAL AND ENVIRONMENTAL FACTORS	GENETIC AND DEMOGRAPHIC FACTORS
Epstein-Barr virus EBV	Familial history of nasopharyngeal cancer
Salted or preserved food consumption	Blood group
Less intake of fruits and vegetables	Gender
Tobacco smoking or consumption	Late detection rate
Herbal products usage	Socioeconomic status
Occupation and domestic hazard exposure	
Oral hygiene	
Sexually transmitted human papillomavirus (HPV) as risk factor associated with NPC	

EBV is said to further progress nasopharyngeal cancer, there are only a handful of the infected individual that develops this malignancy (6) EBV is a form of γ -herpesvirus which acts upon the immune system which penetrates it through the lymphocytes and epithelial cells and have a latency in almost 90% of adults around the world. This infection is transmitted primarily through the oral route mainly via saliva and highly contagious and presents in early stages of life. EBV infects B lymphocytes however the route of penetrance remains unknown. EBV can replicate in epithelial cells of the oropharyngeal region and in B lymphocytes irrespective of normal and malignant nasopharyngeal tissues (7) In the nasopharyngeal cancer group were noted to have the highest serum level containing EBV IgA and IgG antibodies as compared to the control group, 0.352 ± 0.045 and 0.453 ± 0.08 accordingly ($p < 0.01$) which proves to point that there is a strong link between EBV and NPC which are indicated by the high levels in serum with IgA and IgG antibodies. In addition this goes on to further support that EBV is a remarkably vital risk factor in the development of NPC (8) The relationship between NPC and EBV was discovered in 1966 when there were reports of nasopharyngeal cancer patients whom have

higher antibody response to an antigen which was later found out to be EBV as such, many studies were conducted to prove the evidence that nasopharyngeal cancer was caused by EBV mainly type III (9).

28 studies on the habits of smoking and NPC incidence were carried out which includes various case-controlled studies done in China, Southeast Asia regions and some cohort studies in Singapore, United States and Taiwan. These studies concluded that there is an association between smoking and heightened risk of NPC however it is rather conflicting due to differences in sample size, study methodology methods and accuracy of the studies. In an analytical study involving 32 studies reported, there was an evidence of increased risk of nasopharyngeal cancer in smokers compared to non-smokers. A meta-analysis reports that the risk of cancer incidence among smokers were 60% higher compared to non-smokers (10) Smokers who has a cumulative exposure of ≥ 30 pack/year are two times more risk compared to those with exposure of ≤ 30 pack/year. Both low and high dose dependent smoker have higher risk of developing NPC and it increases the risk by 1-2% with every pack/year of smoking (11) The risk of nasopharyngeal cancer is increased with the duration of smoking and the frequency of smoking. Ironically, these reports does not conclude the increase in risk of developing NPC among non-smokers (12).

Poor oral hygiene especially among the elderly has been greatly linked to the cancers which involves various organs like stomach, pancreas, esophagus and head and neck (13). Periodontitis is characterized by damaged connective tissues and dental bones resulting in a secondary response immunity towards bacterial infection with involvement of the periodontal region (14) is said to heighten the risk possibility as the response towards inflammation maybe the route of carcinogenic promotion (15). Furthermore, tooth loss counts increases bacterial load which is known to have implications by producing nitrosamines determined to be carcinogens which facilitates nasopharyngeal cancer development (16). Oral hygiene is closely linked to nasopharyngeal cancer as those who paid less attention to brushing their teeth had more decayed teeth and have a higher risk of developing the disease (17) However the neglect on oral hygiene as a risk factor is debatable as positive results maybe the subsequent effects of other lifestyle habits like smoking, decumbent socioeconomic status, compromised health status and unhealthy dietary habits. Therefore, a need for a more comprehensive information on the associated risk factors.

The blood types A and AB were found to be higher in reported nasopharyngeal carcinoma cases in contrast with those in the control group (30.6% vs 27.1%). There is a significant increase in risk in patients with blood group A or AB, as opposed to those with blood type O. It also goes on to show that the advanced type of

nasopharyngeal cancer is more common in males with blood group A. ABO antigens are mediators of microbial infections, hence it is hypothesized that ABO grouping type may interfere with EBV that could possibly initiate nasopharyngeal carcinogenesis process Therefore, there is a need for further studies to elucidate the association of ABO group and EBV infection status (18). Blood type A was identified as a risk factor and type O as protective factor, however further studies are needed to affirm the findings (17).

Occupational hazard may serve to be the subsequent leading risk factor in contributing to the massive numbers of nasopharyngeal cancer. A cohort study conducted in Shanghai, China where 400 female workers were selected among 526 factories showed that there was a compelling relationship between the risk of NPC incidences in line with the prolonged period of work particularly those involved with the usage of dye where they are exposed to hazards like inks used in printing (19) Wood dust exposure is identified as one of the risk factors of nasopharyngeal cancer. In addition, radiation (ionizing), heavy metals, fume inhalation and volatile chemical exposure increases risk of nasopharyngeal cancer (20) Individuals with altars at home for religious purposes also have a higher risk developing NPC however most research studies done in Singapore and Hong Kong (21) have not found direct association (7) There is a distinct increase in risk among fire wood users with family history of nasopharyngeal cancer (21).

The intake of preserved vegetables is a risk factor in nasopharyngeal cancer due to the high concentration of nitrates and nitrosamines known to cause mutations which promotes the forming of deoxyribonucleic acid (DNA) adduct gives rise to point mutations and increases the risk of cancer. As such the intake of fresh vegetables and fruits proves to be of protective factor against cancer and higher consumption of vegetables among adults is linked to an approximately 40% decrease being of risk in developing nasopharyngeal cancer as they contain components that are beneficial towards eliminating cancer (22).

Dietary habits are among the main contributing factors in nasopharyngeal cancer, especially the consumption of salted fish or preserved foods which contains nitrosamine and other chemical compounds known to be a precursor to EBV activation (23). Studies done among the Chinese population showed that there is relative risk associated with nasopharyngeal cancer and the consumption of salted fish. The Arab population showed an increased risk of nasopharyngeal cancer with the intake of preserved food (24). Those who consume food products of salted meat at least once every month were at 2 times more risk of developing nasopharyngeal cancer. The consumption of salted vegetables with a frequency of at least once weekly was found to have significant increased risk in developing nasopharyngeal

cancer. However no evidence was reported to prove that fermented food products like bean, shrimp or fish pastes increases risk of nasopharyngeal cancer (24).

Previous studies showed is that the consumption of herbal tea and slow cooked soups are said to be of protective factor against NPC incidence. The aboriginal people of Guangdong routinely drink herbal tea with the belief that the tea is able to prevent and cure illness like the common flu and throat infections.. Slow cooked stews or broths are herbal soup which is made by cooking meat for prolonged time following the traditional medicine principles with herbs like Fragrant Solomonseal Rhizome (*Rhizoma polygonati odorati*), Chinese date (*Fructus jujubae*) and lotus seeds (*Semen nelumbinis*). However a previous study done on the Filipino community denies this finding. The study proposed that the consumption of herbal medications actually interfere with EBV via a directive proliferation effect on EBV modified cells. But there are studies done in Taiwan that counter defies this and shows no direct association with herbal tea or soup consumption to increase nasopharyngeal risk (24).

Human papillomavirus (HPV) is one of the most common form of sexually transmitted disease (STD) and is the leading cause of cervical cancer in women. Findings through molecular evidence indicates the role of HPV in causing nasopharyngeal cancer. Studies have shown that being exposed to HPV is able to amplify the risk of nasopharyngeal cancer and HPV-16 had been identified as the common type linked to the disease. 2 cases of nasopharyngeal cancer associated with HPV has been reported in husbands of women who were diagnosed with cervical cancer which upon further investigation reveals a history of prolonged oral-genital sex. However, is the route of transmission has not been established as it not well depicted and has no solid ground evidence but contributes to the fact that oral-genital sex is a credible source of transmitting HPV infection. HPV affiliated nasopharyngeal cancer is bound to increase when the knowledge on the route of HPV transmission is discovered in future (25).

Genetic factor imparts an important role in the pathophysiology of cancer involving nasopharynx. In South China, the incidence of nasopharyngeal cancer is about 20-50 folds higher when compared to Western regions of the world. Migrant Chinese people in the United States which has a low incidence number compared to Asia notably at a higher risk of nasopharyngeal cancer though there has been assimilation of culture with the local population.

Native people of the South China region are one of the most at high risk of developing NPC as such the lower class of society is said to have higher risk of NPC. This is due to the fact that people of the lower class consume stored food which is known to be a risk factor in NPC. Since the stored food is more affordable and consumed

more by people of lower socioeconomic status. It is also observed that the most of the lower class of people at the social status level have a soaring risk of NPC occurrence in both sexes with males higher than females in trend (26) The relationship between risk factors of NPC and socioeconomic status for example the exposure to cigarette smoke and dust in the United States has been studied and reported in previous study (10).

Approximately 80% of patients of nasopharyngeal cancer were at the advanced stage of illness and deemed too late to administer treatment. The primary healthcare in Indonesia are in general operated by health care centres known as Puskesmas. Therefore it is noted that the inadequate knowledge among the physicians serving at these health centres on the nature and physiology of nasopharyngeal cancer could be the leading cause in which diagnosis is delayed (4) where there were 14% of the patients developed metastasis at the point of diagnosis and about 29% of them who have no metastasis responded to therapy (27).

CONCLUSION

The aim of the study was to explore the geographical variation and the risk factors associated with the incidence of nasopharyngeal cancer. From the results obtained the standardized incidence rate of nasopharyngeal cancer globally was 1.5 per 100,000 and the mortality rate for cancer of the nasopharynx was 0.84 per 100,000. The incidence of NPC was most commonly prevalent in the Asian continent mainly Southeast Asia region. The associated risk factors linked to nasopharyngeal cancer comprises of viral infections, dietary and lifestyle habits and environmental factors. Adequate knowledge, early detection, immediate administration of treatment and rapid detection is vital in reducing the number of incidence globally.

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