



# NASOPHARYNGEAL CANCER IN THE WORLD: EPIDEMIOLOGY, INCIDENCE, MORTALITY AND RISK FACTORS

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**Abstract – Objective:** *Nasopharyngeal cancer is one of the most common cancers in the head and neck areas. Men are two to three times more likely to develop it than women. The peak age of incidence is between 50 and 60 years. Informing about the occurrence, death and risk factors in prevention programs is very important. The aim of this study was to investigate the incidence, mortality, and risk factors for nasopharyngeal cancer in the world.*

**Materials and Methods:** *This review study was conducted on published English studies by January 2017 by searching in the databases of PubMed, Scopus and web of science. The search strategy included the key words "nasopharyngeal cancer", "epidemiology", "incidence", "mortality", "risk factor", "world". Studies related to incidence, mortality and risk factors for nasopharyngeal cancer were entered into the review.*

**Results:** *Nasopharyngeal cancer is generally more common in Southeast Asia. The five countries with the highest incidence of nasopharyngeal cancer in the world were China, Indonesia, Vietnam, India and Malaysia, respectively. The standard incidence of nasopharyngeal cancer in the world was 1.2 per 100,000 (in men 1.7 per 100,000; in women, 0.7 per 100,000). The five countries with the highest number of deaths were China, Indonesia, Vietnam, India and Malaysia, respectively. The standardized mortality rate for nasopharyngeal cancer in the world was 0.7 per 100,000 (in men 1.0 per 100,000; in women 0.4 per 100,000). The most important risk factors for nasopharyngeal cancer were Epstein-Barr virus (EBV), heredity, human leukocyte antigen (HLA) genes, salt-preserved fish consumption, and history of respiratory diseases.*

**Conclusions:** *The incidence of nasopharyngeal cancer is related to the geographic region. Training programs, early screening, good life promotion policies, timely treatment and diagnosis are good for reducing the burden of this cancer.*

**KEYWORDS:** *Nasopharyngeal Cancer, Incidence, Mortality, Risk Factor, World.*

## INTRODUCTION

One of the most common cancers in the head and neck is nasopharyngeal cancer<sup>1,2</sup>. It is a malignant disease and its incidence is dependent on geographical and racial variations. Nasopharyngeal carcinoma has been reported in most parts of the world with age standardi-

zed incidence rate, regardless of gender, less than one per 100,000 per year<sup>3-5</sup>. This cancer has an unbalanced geographical distribution. 81% of the new cases occurred in Asia and 9% in Africa; the rest were reported elsewhere in the world. Southeast Asian countries account for 67% of the global burden of cancer<sup>6</sup>. In addition to geographic variation, some ethnic groups



may be at risk of nasopharyngeal cancer. For example: Bidayuh on the island of Borneo, Nagas in Northern India and Inuits in the Arctic, with an age-old standard of more than 16 per 100,000 per year in men<sup>7</sup>.

Men are two to three times more likely to develop it than women. The peak age of incidence is between 50 and 60 years<sup>8</sup>. Elderly people are at higher risk for relapse and also have a lower survival rate<sup>9</sup>. On the other hand, the highest mortality rate has been observed in people over the age of 85 years<sup>10</sup>. Diagnosis of nasopharyngeal cancer occurs at advanced stages. The prognosis for advanced nasopharyngeal cancer is very weak. However, nasopharyngeal cancers are potentially curable in the early stages. Identification in the early stages of screening may lead to improved results. Informing about the occurrence, death, and risk factors in prevention programs is very important. The aim of this study was to investigate the incidence, mortality, and risk factors for nasopharyngeal cancer in the world.

## MATERIALS AND METHODS

This review study was conducted on published English studies by January 2017 by searching in the databases of PubMed, Scopus and web of science. The search strategy included the key words “nasopharyngeal cancer”, “epidemiology”, “incidence”, “mortality”, “risk factor”, “world”. Studies related to incidence, mortality and risk factors for nasopharyngeal cancer were entered into the review.

## RESULTS

### NUMBER AND INCIDENCE

In 2012, there were 86,691 cases of nasopharyngeal cancer worldwide (60,896 cases in men and 25,795 cases in women, Sex Ratio = 2.36). The standard incidence of nasopharyngeal cancer in the world was 1.2 per 100,000 (1.7 per 100,000 in men and 0.7 per 100,000 in women)<sup>11</sup>. The five countries with the highest number of nasopharyngeal cancer cases inclu-

ded China with 42,100 cases<sup>12</sup>, Indonesia with 13,084 cases, Vietnam with 4,931 cases, India with 3,947 and Malaysia with 2,030 cases, respectively<sup>13</sup>. In Singapore, nasopharyngeal cancer is the 8<sup>th</sup> common cancer in men, with the age-standardized rate of 9.5 per 100,000 per year<sup>14</sup>. In Indonesia, a relatively high incidence, at least 5.7 per 100,000 in males and 1.9 in women per 100,000 compared to the global incidence rate of 1.9 per 100,000 in men and 0.8 per 100,000 in women, has been reported<sup>15</sup>. It should be noted that the correct incidence of nasopharyngeal cancer in Indonesia is not clear due to incomplete cancer recording<sup>16</sup>. The lowest incidence of nasopharyngeal cancer has been reported significantly from the United States, America and Europe. Nasopharyngeal cancers in Europe and North America include less than 1% of all cases of cancer (17). This geographic distribution indicates the difference in the pathology of the nasopharyngeal cancer and its epidemiology in these areas<sup>17,18</sup>. The high prevalence of nasopharyngeal cancer in these countries is due to exposure to all types of risk factors associated with this cancer and to lowering health budgets. Diagnosis in the advanced stage and the lack of access to treatment, metastatic state of the cancer is more observed in these areas<sup>19,20</sup>.

### NUMBER AND MORTALITY RATE

In the world in 2012, 50,831 deaths from nasopharynx occurred (35,756 deaths in men and 15075 deaths in women, Sex Ratio = 2.37). The standardized mortality rate for nasopharyngeal cancer in the world was 0.7 per 100,000 (1.0 per 100,000 in men and 0.4 per 100,000 in women)<sup>11</sup>. The five countries that had the highest number of deaths from nasopharyngeal cancer included China with 21,300 deaths<sup>12</sup>, Indonesia with 7,391 deaths, Vietnam with 2,885 deaths, India with 2,836 deaths, and Thailand with 1114 cases, respectively<sup>13</sup>. One of the main causes of death in Indonesia is nasopharyngeal cancer and at the time of initial diagnosis, 80% of the patients are at an advanced stage of the disease<sup>16</sup>. In Singapore, older patients with a diagnosis at stage 2 or stage 3 are at higher risk of recurrence and lower overall survival<sup>9</sup>. Nasopharyngeal cancers

**TABLE 1.** Factors related to the nasopharyngeal cancer.

<b>Modifiable and environmental risk factors</b>	<b>Genetic or unmodifiable risk factors</b>
Epstein-Barr virus (EBV)	Family history of NPC
HLA class I genotypes	Age
Salt-preserved fish	Sex
Lack of fresh fruits and vegetables	Socioeconomic status
Chronic respiratory tract conditions	
Tobacco smoke	
Herbal medicines	
Occupational dusts	
Formaldehyde	

are treated by radiation, but the result of treatment varies widely throughout the world. 8% of new cases have occurred in countries with poor treatment outcome. Global inequality in access to and the need for optimal services planning shows a meaningful relationship between survival and access to radiation therapy<sup>6</sup>. Over the past two decades, the treatment of nasopharyngeal cancer has improved significantly with the simultaneous introduction of chemotherapy and radiotherapy. The overall incidence of patients with metastases has remained about 25-34% and the survival of these patients is low<sup>21,22</sup>. Lack of knowledge of general practitioners working in Asian medical centers may lead to a delay in diagnosis of nasopharyngeal cancer<sup>16</sup>.

## RISK FACTORS FOR NASOPHARYNGEAL CANCER

Table 1 shows factors related to the nasopharyngeal cancer (based on modifiable or unmodifiable risk factors). The most important risk factors for nasopharyngeal cancer are presented in Table 2. Then, based on studies, the risk factors have been discussed.

### SUMMARY OF POSSIBLE RISK FACTORS FOR NASOPHARYNGEAL CANCER

#### EPSTEIN-BARR VIRUS (EBV)

In many studies, a very strong association has been shown between nasopharyngeal carcinoma and EBV infection<sup>23-26</sup>. Approximately about 30 versions of the EBV gene are in the nucleus of malignant cells. Most versions are “mini circular

chromosomes”, called episomes. These episomes are in some cases adjacent to viral DNA versions<sup>27</sup>. This association leads to the use of new methods using viral serological tests to make diagnosis and screening in the population at risk<sup>28</sup>. High levels of IgA antibodies with the capsid antigen of EBV and early antigen (EA) in areas with high incidence of nasopharynx are a valuable screening tool<sup>24</sup>.

#### INHERITANCE AND ETHNICITY

People with a family history of cancer, in particular a family history of nasopharyngeal cancer, are at risk more than 4 to 10 times for nasopharyngeal cancer<sup>4,29,30</sup>. Studies<sup>4</sup> conducted in Southern China revealed the role of a genetic combination with environmental effects in the development of nasopharyngeal cancer. In Southern China, there are three main ethnic groups: Cantonese, Hokkien-Teochiu (Minan-Chaoshan) and Hakka. The highest incidence of nasopharyngeal cancer was seen among Cantonese and the lowest among Hokkien-Teochiu and Hakka<sup>31</sup>. The remarkable feature of ethnic distribution in the Cantonese population is the genetic factor, but the combined role of genetic with the particular lifestyle and environmental factors should not be ignored<sup>32</sup>.

#### SALT-PRESERVED FISH AND OTHER FOODS

Many studies<sup>32-34</sup> have documented the consumption of salt-preserved fish as one of the risk factors for the cancer. In Chinese populations, the relative risk of nasopharyngeal carcinoma in weekly consumers is lower than those who use salt-preserved fish very little or at all. Overall, it was about 1.4 to 3.2. Relative risk varied from 1.8 to 7.5 for those who consu-

**TABLE 2.** Summary of possible risk factors for NPC.

<b>Factor</b>	<b>Strength of association</b>	<b>Consistency of association</b>	<b>Subgroup-specific associations</b>
EBV	Strong	Consistent	More consistent association with types II and III NPC
Family history of NPC	Strong	Consistent	
HLA class I genotypes	Moderate to strong	Consistent	Inconsistent associations with HLA class II genotypes
Salt-preserved fish	Moderate to strong	Consistent	Stronger association with consumption at weaning
Lack of fresh fruits and vegetables	Moderate	Fairly consistent	
Chronic respiratory tract conditions	Moderate	Fairly consistent	
Tobacco smoke	Weak to moderate	Fairly consistent	Stronger association with type I NPC
Herbal medicines	Weak to moderate	Inconsistent	
Occupational dusts	Weak to moderate	Inconsistent	More consistent association with wood dust exposure
Formaldehyde	Weak to moderate	Inconsistent	



med daily<sup>35-40</sup>. The risk of nasopharyngeal cancer in relation to other preservative foods, including meat, eggs, fruits and vegetables, increases in Southern China, Southeast Asia, North Africa/Middle East, and Arctic natives<sup>37,41-43</sup>. These preservative foods are also involved in people in areas with a low incidence in Northern China and the United States<sup>44,45</sup>.

## **HUMAN LEUKOCYTE ANTIGEN GENES**

Gene-related research on nasopharyngeal cancer focuses on human leukocyte antigen genes<sup>46</sup>. In people with a weak HLA allele in the presence of EBV, the antigens likely increase the risk of nasopharyngeal cancer. In people with a strong HLA allele in the presence of EBV, the risk for this cancer is lower<sup>47,48</sup>. In the meta-analysis on the Southern population of China, there was the evidence of a positive association of nasopharyngeal cancer with increased risk in HLA-A2, B14, B46 and a reverse association with HLA-A11, B13 and B22<sup>49</sup>.

## **FRESH VEGETABLES AND FRUITS**

Sufficient and adequate consumption of fresh fruits and vegetables is associated with a 30-50% reduction in the risk of nasopharyngeal cancer<sup>32</sup>. In contrast, lack of enough vegetables and fruits increases the risk of developing nasopharyngeal cancer<sup>50</sup>. The results of a meta-analysis study showed that high consumption of vegetables is associated with a 36% reduction in the risk of nasopharyngeal cancer<sup>43</sup>.

## **HISTORY OF RESPIRATORY DISEASES**

Most studies<sup>37,40,51-58</sup> showed that the risk of developing nasopharyngeal cancer in people with chronic rhinitis, sinusitis, nasal polyps, or ear infection, is almost twice. These findings indicate that benign inflammation and respiratory infection may make nasopharynx mucus susceptible to this cancer. In addition, some bacteria can reduce the conversion of nitrate to nitrite, which can then form N-nitroso carcinogenic compounds<sup>59</sup>.

## **ALCOHOL CONSUMPTION**

Alcohol consumption is associated with nasopharyngeal cancer in a complicated way. Many studies<sup>32</sup> have shown that there is no strong evidence for the association between alcohol consumption and the risk of nasopharyngeal cancer. The results of a meta-analysis recently showed that high alcohol consumption is associated with a significant increase in the risk of nasopharyngeal cancer<sup>60</sup>.

## **CIGARETTE SMOKING**

Many studies<sup>30,42,51,61-67</sup> have highlighted that cigarette smoking is associated with nasopharyngeal cancers. The pattern of the relationship between smoking and the risk of nasopharyngeal cancer is

dose-dependent<sup>51,63</sup>. The results of a meta-analysis showed that the risk of the cancer in smokers was 60% higher than non-smokers<sup>68</sup>.

## **OCCUPATIONAL EXPOSURE**

Exposure to wood dust is known to be a risk factor for nasopharyngeal cancer<sup>64,69-72</sup>. The results of a study on 29,000 wood workers in the UK and the United States showed the association between the exposure to wood dust and the increased risk of nasopharyngeal carcinoma<sup>73</sup>. Several studies<sup>74</sup> have shown that exposure to formaldehyde increases the risk of nasopharyngeal cancer. In addition, IARC investigations in 2005<sup>75</sup> and two meta-analyses<sup>76,77</sup> refer to the dose-response relationship between formaldehyde and the risk of developing nasopharyngeal cancer. Exposure to other chemicals or stimulants, such as steam, smoke and chemicals, flammable products, cotton dust<sup>52</sup> or solvents such as phenoxy acid and chlorophenol, causes an increased risk of nasopharyngeal cancer<sup>51,78</sup>.

## **HERBAL REMEDIES**

Several studies have reported the association between the use of herbal medicines and the increased risk of nasopharyngeal cancer. Hildesheim et al<sup>79</sup> in a case-control study conducted in the Philippines, asked to subjects about ever use of any herbal medicines, and noted a statistically significant 2.5-fold risk among ever users. However, the latter study is difficult to interpret for the following reasons: recall bias is a serious concern when a nonspecific question (such as general use of herbal medicines without naming specific formulations) was asked under a case-control setting. In addition, the use of herbal medicines is part of the 'traditional' lifestyle, an established risk factor for NPC in Chinese as well as Southeast Asians. In other words, the use of herbal medicine may simply be a marker of the NPC-related lifestyle<sup>79-83</sup>. The consumption of slow-cooked (several hours) and canton style herbal teas are associated with reduced risk of nasopharyngeal cancer<sup>84</sup>.

## **AGE AND SEX**

The incidence of nasopharyngeal cancer in men is 2 to 3 times higher than women<sup>66,85</sup>. Differences between men and women may be due to different lifestyle habits (e.g., tobacco consumption) or biological differences<sup>32</sup>. In most low-risk groups, the incidence of nasopharyngeal cancer is consistent with increasing age<sup>86-88</sup>. In contrast, in high-risk groups, the incidence increases in age group of 50 to 59 years, and then decreases<sup>89</sup>. This is due to the fact that these groups are exposed to carcinogenic agents in the early stages of life<sup>90</sup>. Nasopharyngeal cancer may take several decades to develop malignant cells, and then signs appear. Therefore, exposure to carcinogens in early life may have significant effects on the incidence of this cancer<sup>32</sup>.



## SOCIOECONOMIC STATUS

Among the populations at risk for nasopharyngeal disease, including South China, natives of Southeast Asia and the Arabs of North Africa, the lower social class is associated with a higher risk of nasopharyngeal cancer<sup>41,91,92</sup>. The consumption of stored food is known to be one of the most important risk factors for nasopharyngeal cancer. Given that these foods are cheap, consumption of these foods is higher for people with low socioeconomic status. Relationship between the social class and the risk factors for nasopharyngeal cancer, such as exposure to dust and smoking in the United States, have been reported<sup>(66)</sup>.

## CONCLUSIONS

We aimed at determining the incidence and mortality rate of nasopharyngeal cancer in the world and the relationship between environmental risk factors and the incidence of nasopharyngeal cancer. The findings of this study showed that the standardized incidence of nasopharyngeal cancer in the world was 1.2 per 100,000, and the standardized mortality rate for nasopharyngeal carcinoma was 0.7 per 100,000. The disease is more common in Southeast Asia. The most important risk factors for nasopharyngeal cancer include: EBV, heredity, human leukocyte antigen (HLA), salt-preserved fish, and history of respiratory diseases. Fruit and vegetable consumption is known as a protective agent for this cancer. Training programs, early screening, good life promotion policies, timely treatment and diagnosis are good for reducing the burden of this cancer.

## CONFLICT OF INTEREST:

The authors declared no competing interests.

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