

## RESEARCH ARTICLE

# Epidemiology of Nasopharyngeal Cancers in Iran: A 6-year Report

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### Abstract

**Background:** Nasopharyngeal cancer is a disease with distinct ethnic and geographical distribution. The aim of this review was to describe the epidemiological characteristics of nasopharyngeal cancer in Iran from 2004 to 2009 because no systematic study has been performed to evaluate the trends of its incidence yet. **Materials and Methods:** The data were derived from the databases of the National Cancer Data System Registry in the period of 2004-2009. Nasopharyngeal cancers were classified according to the International Classification of Diseases for Oncology. Incidence rates and trends were calculated and evaluated by gender, age decade, and histopathology types. **Results:** A total of 1,637 nasopharyngeal cancers were registered in Iran from 2004 to 2009 giving an incidence of 0.38 per 100,000. The male-to-female ratio was 2.08:1. The trend of incidence was found to have increased, with a significant increase observed in males. Undifferentiated carcinoma was the most common histopathology type in all the age decades. **Conclusions:** Because the incidence of nasopharyngeal cancers in Iran has increased, especially in males, further studies are recommended for understanding of the etiological factors involved in the rise of the disease.

**Keywords:** Nasopharyngeal cancer - incidence - trends - Iran

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### Introduction

Although nasopharyngeal cancer rarely occurs in most areas of the world, it is an important public health problem in some parts of Southeast Asia. Carcinomas account for 75-95% of nasopharyngeal cancers in low-risk populations and for almost all nasopharyngeal cancers in high-risk populations (Yu and Yuan, 2002). Geographical differences affect not only the incidence rates of nasopharyngeal cancer but also its histology and etiology. Pathology can have an important impact on the outcome of the disease. In 1978, the World Health Organization (WHO) offered a classification of nasopharyngeal carcinomas into three main histological types. Type 1 included keratinizing squamous cell carcinoma, type 2 referred to non-keratinizing carcinoma, and type 3 was assigned to undifferentiated carcinoma. The 1991 classification of WHO maintained the keratinizing squamous cell carcinoma as type 1 but combined the 1978 WHO types 2 and 3 into 'non-keratinizing carcinoma'. Then, nonkeratinizing carcinoma was classified further into 'differentiated' and 'undifferentiated'. The differentiated type made up the 1978 WHO type 2 while the undifferentiated type constituted the 1978 WHO type 3. The WHO classification in 2005 was the same as the one developed in 1991, except that 'basaloid squamous cell carcinoma' was added to the new classification (Wei et al., 2011; Wang et al., 2013).

The cancer is found in other histological forms including lymphoma, plasmocytoma, sarcoma and other non-epithelial tumors. In regions where the cancer is endemic, non-keratinizing carcinomas (WHO type 2) and undifferentiated carcinomas (WHO type 3) explain 95% of nasopharyngeal carcinoma (NPC) cases. In contrast, in non-endemic regions such as Western Europe and North America, the most frequently encountered carcinomas are keratinizing or squamous cell carcinomas (WHO type 1) (Dodge et al., 2005).

### Materials and Methods

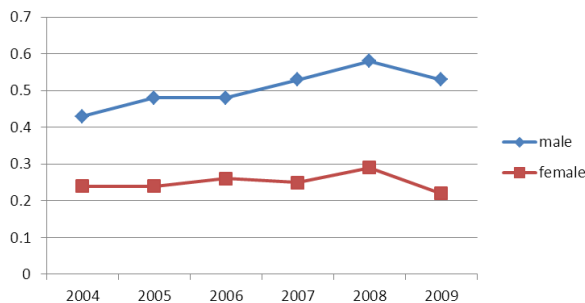
The data used in this study were taken from the database of the National Cancer Data System Registry. The cancer database was collected from all the hospitals, health centers and medical training centers, and laboratories by the Cancer Data System Registry of Iranian health ministry. According to the International Classification of Diseases for Oncology, the sites and histology were coded

Nasopharyngeal cancer, as investigated in this study, was viewed based on internationally accepted definitions (topography code 11), and the histological examinations were according to the pathology report of the patients.

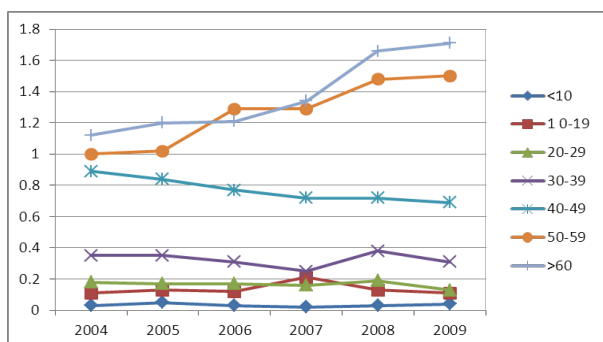
In this study, only malignant tumors were included, and International Classification of Disease for Oncology (ICD-O-3) codes for nasopharyngeal cancer was used for categorization. Since very few basaloid squamous

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cell carcinomas were reported, the available cases of nasopharyngeal carcinoma were classified according to the WHO classification as keratinizing squamous cell carcinoma [WHO 1](ICD-O codes 8070 and 8071), differentiated non-keratinizing squamous cell carcinoma [WHO 2] (ICD-O codes 8012, 8032, 8072 ,8073and 8074), anaplastic, lymphoepithelial and undifferentiated non-keratinizing squamous cell carcinoma [WHO 3] (ICD-O codes 8020, 8021and 8082), and carcinoma not otherwise specified [NOS](ICD-O code 8010)( Dodge et al., 2005). The remaining ICD-O codes were categorized as lymphomas and other nasopharyngeal cancers (i.e. melanoma, sarcoma, plasmocytoma, chordoma, malignant salivary gland tumor, PNET and other non-epithelial tumors). The information about the nasopharyngeal cancers diagnosed between 2004 and 2009 was collected and stratified by gender, age decade, and histopathology of cancer. The data regarding the population structure of Iran were received from the Statistics Centre of Iran. The incidence rates were calculated per 100,000 people. The data were analyzed using SPSS, version 16. The trend was analyzed by using chi-square test. The differences were considered significant at  $p < 0.05$ . Confidence intervals of 95% were calculated for standardized rates. For further comparisons, the cases were subdivided into two age



**Figure 1. Trend of Cancer Incidence in Males and Females**



**Figure 2. Trend of Nasopharyngeal Cancer Incidence in Age Decades**

groups (<30 and 30<years old). Logistic regression was used to compare the histopathology types in <30 year-old cases with those of 30<year-old ones.

**Results**

*The total number of the nasopharyngeal cancer patients and their mean age at diagnosis*

A total of 1637 cases of nasopharyngeal cancer were reported to the Cancer Data System Registry from 2004 to 2009. 40 patients were under 10 years of age, 128 patients between 10 and 19, 163 patients between 20 and 29, 194 patients between 30 and 39, 340 between 40 and 49, 334 between 50 and 59, and 455 patients over 60. The mean age was  $47.16 \pm 18.38$ . The males accounted for 67% of the cases ( $n = 1106$ ) and the females for 33% ( $n = 531$ ). The male-to-female ratio was 2.08:1.

*The incidence and trend of nasopharyngeal cancer*

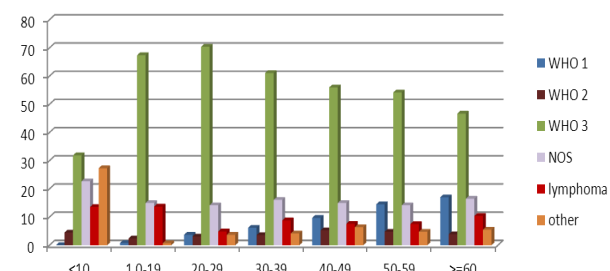
The age-adjusted incidence of nasopharyngeal cancer from 2004 to 2009 was 0.38 per 100,000 (CI 95%:  $0.384 \pm 0.019$ ). During the study period, the highest incidence rate was in 2008. From 2004 to 2009, the increase in the rate of cancer was 14%. The percentage difference between the highest and lowest incidence rates in these years was 30%. Using chi-square test for the trend of incidence, the incidence of cancer was significantly increasing ( $p = 0.017$ ).

*The incidence and trend of cancer by gender*

The incidence in the males (0.51 per 100,000) was higher than that in the females (0.25 per 100,000). For the males and the females, the p-value for the trend of incidence was 0.006 and 0.834 respectively; that is, the p-value was statistically significant for the males. (Figure 1).

*The trends of incidence in age decades*

The trend of cancer based on the decades of age is



**Figure 3. Percentage of Pathological Types in Age Decades**

**Table 1. The Percentage and Trends of Incidence in Different Pathological Types**

Pathological types	Total		Female		Male	
	Percentage	p-value	Percentage	p-value	Percentage	p-value
keratinizing squamous cell carcinomas (WHO 1)	10.60%	0.238	10.50%	0.969	10.70%	0.145
Differentiated non-keratinizing carcinomas (WHO 2)	4.10%	0.68	2.60%	0.922	4.80%	0.615
Undifferentiated carcinomas (WHO 3)	55.20%	0.208	50.60%	0.246	57.50%	0.023
carcinoma not otherwise specified [NOS]	15.30%	0.001	17.50%	0.271	14.20%	0.001
lymphomas	8.70%	0.685	7.90%	0.569	5.10%	0.955
other nasopharyngeal cancers	6.10%	0.693	10.90%	0.952	7.70%	0.569

shown in Figure 2. The p-value at ages over 50 was considered statistically significant. For 50-59 and  $\geq 60$  years, the p-value of the trend was 0.023 and 0.002 respectively.

#### *The patients classified histologically and the trends of histopathology*

Table 1 shows the histological types of nasopharyngeal cancer in the total population, males and females. The results showed that undifferentiated non-keratinizing carcinoma was the most frequent pathology during 2004 to 2009. Using the chi-square test of trend, the p-value for NOS (carcinoma not otherwise specified) was statistically significant. The incidence of undifferentiated non-keratinizing carcinoma (WHO 3) and NOS was significantly increased in the males; the p-value was 0.023 and 0.001 respectively. In addition, as Table 1 indicates, the p-value for the gender segregation of tumor types (except of undifferentiated non-keratinizing carcinoma and NOS in the males) was not statistically significant.

#### *The percentage of histopathologic types of nasopharyngeal cancer in the age groups*

Histopathologic types of nasopharyngeal cancer in age decades are shown in Figure -3. Undifferentiated carcinoma was the most common type in all the age decades. Keratinizing squamous cell carcinoma was 0% in patients under 10 years of age and 0.8% in patients between 10 and 19 years. As compared to patients under 30, those over 30 had significantly greater odds for keratinizing squamous cell carcinoma and other tumors than for undifferentiated non-keratinizing carcinoma. The p-values were 0.02 and  $<0.001$  for patients under and over 30 years respectively.

## **Discussion**

Since cancer can be life-threatening and treatment is costly and sometimes ineffective, prevention is very important. Gaining a better understanding of the epidemiology of cancers is the first step in cancer-preventive programs. The purpose of this review is to answer unresolved questions about epidemiology of nasopharyngeal cancer in Iran to clarify the underlying causes of this tumor. The geographical distribution of nasopharyngeal cancer is peculiar and reflects differences in terms of the tumor pathology and epidemiology. The incidence of nasopharyngeal cancer in the world is averagely less than one in 100,000 (Turkoz et al., 2011). Southern China is reported to have the highest age-adjusted rate of incidence for nasopharyngeal cancer, ranging from 25 to 50 per 100,000 people (Dodge et al., 2005). Intermediate rates have been found among certain populations in Southeast Asia as well as in natives of the Arctic region, North Africa, and the Middle East (Chang and Adami, 2006). In this study, the incidence of nasopharyngeal cancer in Iran was found to be 0.38 per 100,000, but it rose significantly from 2004 to 2009. Several studies conducted in China during past decades showed that the incidence of nasopharyngeal carcinoma had remained stable or slightly decreased in females living

in low-risk regions but slightly increased in males living in high-risk regions (Xu et al., 2013).

However, the incidence rate has decreased in Southern part of China (Guangzhou) in the recent years (Li et al., 2014). According to the literature, the incidence has declined in Taiwan and Singapore (Hsu et al., 2006; Luo et al., 2007). Between 1965 and 1999, the overall incidence rate in the United States remained unchanged at something about 0.7 per 100,000 persons (Lee and Ko, 2005). As observed, nasopharyngeal carcinoma risk is on a slow decline in many European countries (Arnold et al., 2013).

As our study revealed, the incidence rate of the disease in Iranians over 50 years of age and in males had increased. The fact that an increase occurred in the incidence in Iran within six years suggest that there might have been a change in the etiological factors. This sounds the alarms in that greater attention should be paid to the etiological factors in the country.

In our study, male-to-female ratio was 2.08:1. Most similar studies in other countries have revealed that nasopharyngeal cancer is more common in men than in women, and the ratio of males to females diagnosed with nasopharyngeal cancer is about 3 to 1 (Thompson, 2007). The majority of nasopharyngeal cancer cases in this study had undifferentiated carcinoma, which accounted for about 55.2% of the cases. Keratinizing carcinoma and nonkeratinizing subtype were present in 10.6% and 4.1% (the least common carcinoma) of the patients respectively. In similar studies previously did in other countries, undifferentiated carcinoma turned out as the most frequent tumor but with a different frequency in each study. Studies indicated that undifferentiated carcinoma in the new WHO classification accounted for 63% of all the cases of nasopharyngeal carcinoma in North America, but for 95% in southern China. However, differentiated non-keratinizing carcinoma comprised 12% of cases in North America, but it was less than 3% in southern China. As for differentiated keratinizing squamous cell carcinoma, it accounted for 25% of the cases in North America, but for less than 2% of those that occurred in southern China ((Tao and Chan, 2007)). A study in Sudan (i.e. an intermediate-risk country) showed that types 2 and 3 in WHO classification accounted for 15.58% and 65.97% of nasopharyngeal cancer specimens respectively. In contrast, type 1 was identified in only 1.18% (Abdullah et al., 2011). Keratinizing carcinoma was the predominant nasopharyngeal carcinoma type in 47% of the corresponding patients born in the Netherlands (Arnold et al., 2013).

In the present study, there was not any case of keratinizing squamous cell carcinoma in patients under 10 years of age, whereas undifferentiated carcinoma was the most common in this age group (31.9%) followed by other cancers (27.3%) especially sarcoma that was more common. It has been shown in the literature that undifferentiated carcinoma was the most common nasopharyngeal carcinoma in children (Sultan et al., 2010; Rouge et al., 2011; Liu et al., 2014). In our study, keratinizing squamous cell carcinoma and other tumors were of a significantly greater occurrence than undifferentiated non-keratinizing carcinoma in patients

over 30 as compared to patients under 30.

Comparing males and females, our study showed that lymphoma and other tumors were more common in females, and keratinizing carcinoma was of similar frequency in males and females. Moreover, the results also showed that there were ascending trends for NOS (carcinoma not otherwise specified) and undifferentiated non-keratinizing carcinoma (WHO 3) in males and NOS in all the patients in the studied 6-year period. In a study in Zhongshan, China, there was no obvious change in pathological proportions over 38 years (Wei et al., 2010). However, a decreasing incidence has been observed in WHO-1 tumors in the Netherlands and some high-incidence areas like southern China and Hong Kong in recent years. This is most probably due to the decline in smoking in those areas. In another study conducted in the Netherlands, the incidence of nonkeratinizing differentiated tumors was found to be increasing in males (Arnold et al., 2013).

Incidence of nasopharyngeal carcinoma is highly impacted by diet, environmental factors, genetic susceptibility and EBV infection. In areas with a high incidence, undifferentiated carcinoma is the most frequently observed histological subtype of nasopharyngeal carcinoma closely associated to infection with Epstein-Barr virus (EBV). Conversely, in low-incidence regions, differentiated carcinoma accounts for an up to 25 % of all nasopharyngeal carcinoma cases (Polesel et al., 2013). Tobacco, smoking, alcohol drinking, and the like, which are considered as well-established risk factors for head and neck carcinomas, appear to strongly affect differentiated nasopharyngeal carcinoma rather than undifferentiated ones (Polesel et al., 2011). Nasopharyngeal carcinoma risk was also found related to high consumption of preserved foods (Polesel et al., 2013). The results of a study in Thailand suggest that a history of ear or nose diseases as well as long exposure to wood dust may have a role to play in the development of nasopharyngeal carcinoma (Ekburanawat et al., 2010).

The increasing incidence of undifferentiated non-keratinizing tumors in Iranian men suggests a formidable role of EBV and other environmental risk factors. It is also to be borne in mind that the rise in the incidence may have been caused by the improvement in the registration of cancer cases over these six years. However, the significant increasing incidence from 2004 to 2009 requires further investigation. The trend of nasopharyngeal cancer incidence is expected to decline if data collection systems are improved, risk factors are identified, more attention is paid to environmental factors, and wrong habits are changed.

In conclusion, This study was the first research about the epidemiology of nasopharyngeal cancer in Iran during six years, but this period was not long enough to reflect certain changes. We hope to perform other studies in the future to evaluate risk factors and preventive measures..

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