

# Nasopharyngeal Carcinoma: Causes and Incidence

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Cancer is a condition characterized by problems in controlled cell division, resulting from the influence of external pathogens, parasites, chemicals, stress, and genetic factors on normally dividing cells. It is a general term, and all types of cancer share the common feature of having the ability to undergo unlimited division. Cancer types that exhibit irregular growth along with the property of spreading to other cells are referred to as malignant tumors.<sup>[1]</sup> In general, normal cells can divide approximately 50 to 60 times before reaching their replication limit. Cells exceeding this limit are directed toward apoptosis. However, cells with malignancy continue to divide beyond this threshold. These cells can transition to a spreading state by releasing cytokines and chemokines to the nearest blood vessels or lymphatic system. To increase their cumulative density, they block systems and adapt to serve their own purpose. They exhaust the organism's resources limitlessly, ultimately leading to an axiom that results in death.<sup>[2]</sup>

## NASOPHARYNGEAL CARCINOMA

The first breath inhaled through the nose is filtered through the nasal region or, alternatively termed, passing through the nasal cavity. Subsequently, the

### ABSTRACT

Global case analyses of nasopharyngeal carcinoma (NPC) were conducted, and survival and mortality rates were quantitatively determined. Generally, it was found that the factor causing this disease is the Epstein-Barr virus, and its 100% efficacy was proven in clinical trials. Other factors, such as inhaled chemicals, were questioned from a logical perspective, but studies mentioned them only in general terms due to weak provable characteristics. The virus is estimated to be transmitted through saliva, with approximately 90% of the world's population being infected individuals. The lethality is attributed to the proximity of the nasopharynx to the central nervous system and other vital tissues where essential functions are carried out. For instance, it is likely to be diagnosed as a neurological disease due to pressure on the nerves and may be detected late or remain undetected. Therefore, NPC should be evaluated as a parameter in all neurological diseases, jaw disorders, and circulatory diseases, among others. Considering inadequate diagnostic statistics in clinics, case incidences are generally observed in team islands in Asia, Micronesia, and South Asia. Although there may be solid foundations for evolutionary reasons, it is a debatable issue. Different variants of the virus exist, but they will not be explored in depth. The increased incidence of the disease due to rising tourist activities is a topic attempted to be linked as a fundamental reason. In this review, the incidence, treatment approaches, and mortality rates of NPC have been investigated.

**Keywords:** Cancer, case analysis, Epstein-Barr virus, nasopharyngeal carcinoma

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progressing air can be defined as the nasopharynx, extending from the initial curvature where the air encounters the trachea to the uvula (soft palate). Nasopharyngeal carcinoma specifically refers to the cancer that occurs in this region.<sup>[3]</sup>

### Epidemiology

Nasopharyngeal carcinoma is classified as a rare disease, particularly in Western countries, where its occurrence is scored at around 0.2% when compared to all types of cancer. In contrast, in Eastern countries, especially in China, the incidence of this cancer is

reported to be 20/100,000. Studies have calculated the incidence rate in Southeast Asia, North Africa, Greenland, and Mediterranean countries, including our country, to be 8-12/100,000.<sup>[4]</sup>

Another study recorded 86,691 cases of NPC worldwide in 2012, with 60,896 of them being male and 25,795 female. The incidence rate was found to be 1.7/100,000 in men and 0.7/100,000 in women globally. In the same year, 50,831 people lost their lives to NPC, with 35,756 recorded as male and 15,075 as female. Out of these cases, 57,190 were observed in Asia and South Asia alone. Specifically, China recorded 33,198 cases, Indonesia 13,084, Vietnam 4,931, India 3,947, and Malaysia 2,030 cases. Worldwide, incidence rates according to the Human Development Index (HDI) were measured as 0.6/100,000 in very high HDI countries, 0.7/100,000 in high HDI countries, 1.7/100,000 in medium HDI countries, and 1/100,000 in low HDI countries.<sup>[5]</sup>

### **Etiology**

The etiology of NPC is categorized into three main factors: viral, environmental, and genetic. Infections primarily caused by the Epstein-Barr virus (EBV) have been associated with a potential for cancer development even after many years. Moreover, in the majority of NPC cases, an antibody response developed in reaction to EBV has been detected.<sup>[6]</sup>

Biopsies taken from the nasopharynx have commonly revealed genetic materials of the EBV. The fact that the disease is observed more frequently in China and South Asian countries has led to the conclusion that it is related to both evolutionary and genetic factors. A study conducted in China in 1983, identifying antigens [Human leukocyte antigen (HLA)-Bw46 and HLA-A2], accelerated correlation studies related to the incident.<sup>[7]</sup>

Another research study found a decrease in the etiology and diagnosis of NPC in Chinese children born in America, suggesting various environmental factors. These include exposure to cigarette smoke, wood smoke, and fumes from fish smoked with dimethyl nitrosamine, which contains croton and has a proven carcinogenic effect.<sup>[8]</sup>

### **Clinical Features of Nasopharyngeal Cancer**

Unfortunately, worldwide, NPC is diagnosed in its metastatic form in 35% of cases.<sup>[9]</sup> The remaining 65% are identified based on symptoms depending on the compression in the nasopharyngeal region and the location of the spread.<sup>[10,11]</sup>

The most commonly encountered situation during the diagnostic process is the presence of a mass in the neck. Nasopharyngeal carcinoma is often considered to metastasize to the retro-parotid area or Rouvier lymph nodes, leading to pronounced symptoms in this area. Another finding is the formation of a mass in Rosenmüller's fossa, which can block the eustachian tube, causing ringing in the ears, hearing loss, and serous otitis. In the nasopharyngeal area, there are six channels: foramen ovale, foramen lacerum, foramen spinosum, foramen jugulare, carotid canal, and hypoglossal. Generally, extradural NPC observed through the foramen ovale and lacerum route is considered a common perception of metastasis to the head region. Another finding is the compression on the 6th cranial nerve, the abducens nerve, a common occurrence that results in outward gaze and double vision problems. Following this, compression on the 5th cranial nerve, trigeminal nerve, clinically results in pain in the upper parts of the neck and paresthesia in the facial area. Pressure on nerves due to compression in the retroparotid region and lymph nodes can lead to muscle paralysis, causing difficulty in swallowing and swallowing. Subsequently, disruption of nasal sound patterns decreases speech quality. Nerves, blood vessels, lymph nodes, or tissues passing through the nasal region are of critical importance. Depending on the site of spread, symptoms such as vomiting, loss of taste, compression on the optic nerves leading to vision loss or loss of corneal reflex, paralysis in the jaw muscles, loss of chewing and speaking, temporoparietal headaches, bloody nasal discharge, and restriction of head movements can occur. Studies have shown the possibility of metastases to the bone, lungs, and liver.<sup>[12]</sup>

Approximately 20% of commonly made errors in the initial examination are diagnostic mistakes, often occurring inadvertently due to cranial nerve compression and involvement of NPC, leading to conditions such as eye diseases and neurology.<sup>[13]</sup>

## **RISK FACTORS FOR NASOPHARYNGEAL CARCINOMA**

### **1. Epstein-Barr virus**

There are environmental factors associated with the development of nasopharyngeal cancer, and the first among them is the EBV. Scientifically classified as human herpesvirus-4, EBV is a double-stranded deoxyribonucleic acid (DNA) virus with an envelope.<sup>[14,15]</sup>

It is surrounded by an icosahedral capsid and tegument. While herpes viruses are found almost everywhere in nature, adapting to the human metabolism is a rare occurrence. Epstein-Barr virus induces proliferation in the cells it infects, and during latent infection, it actively carries out gene expression. This is a phenomenon rarely observed among other herpes viruses. Categorically, EBV is divided into two subgroups that can infect humans: EBV-1 and EBV-2. The virus enters through the airway and multiplies in the epithelial cells of the stratified squamous region in the oropharynx.<sup>[16]</sup>

Epstein-Barr virus has been identified as the first human virus implicated in carcinogenesis. It is known to infect 90% of the world's population. Despite humans carrying this virus for centuries, the overall cancerization rate is low when considering the total population. Generally, the virus is transmitted through saliva, but rare cases have shown transmission through blood and bone marrow. Salivary transmission typically occurs in childhood, where contaminated toys in communal settings like daycare or putting dirty hands to the mouth can facilitate it. In adults, transmission usually happens through kissing, leading to its colloquial designation as the 'kissing disease' in the literature.<sup>[16,17]</sup>

The general human population, constituting around 90%, may exhibit varying susceptibilities to EBV, primarily due to immunological variations. This plays a significant role in the pathogenesis of EBV. Diseases associated with the EBV virus include Burkitt's lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, NPC, and leiomyosarcoma in immunodeficient or immunosuppressed individuals.<sup>[17,18]</sup>

## 2. Smoking

Tobacco plays a significant role in NPC, as it does in various other cancer types. The nasopharynx and pharyngeal region are among the first areas exposed to cigarette smoke and toxic substances. The initial international studies identified the substantial role of cigarette smoke in lung cancer through statistical research. Other cancer types have been associated with tobacco tar. The established general ranking includes lung cancers, oral cavity, pharynx, larynx, esophagus, pancreas, bladder, and renal pelvis. Seventeen years later, another international research group expanded the scope of the study and obtained new findings.<sup>[19]</sup>

In light of the data from the study, toxic substances in cigarette smoke have been associated

with other cancer types. The cancer findings expressed in the research include various organs, sinuses, nasopharynx, liver, stomach, kidneys, and uterine cervix. The likelihood of NPC being caused by smoking was found to be 19% in the studied experimental group.<sup>[18-20]</sup>

## GENERAL TREATMENT APPROACHES

Globally, the standard treatment for NPC typically involves the administration of high-dose chemotherapy drugs along with radiotherapy.<sup>[19]</sup> Nasopharyngeal carcinoma is known to be a tumor type that is sensitive to radiation. External radiotherapy is generally sufficient, but depending on the patient's anatomy and age, additional doses of radiotherapy, such as interstitial implants, intracavitary brachytherapy, or stereotactic radiosurgery, may be recommended. Surgical procedures are not commonly encountered in the clinical setting unless there is an urgent situation, as accessibility to NPC is often challenging.<sup>[20,21]</sup>

### Radiotherapy

In the radiotherapy techniques, the patient must first be immobilized, and during the planned duration, they should receive radiation in this position. To achieve this, thermoplastic head masks, which are materials that soften rapidly with contact heat and quickly harden as they cool, are commonly used. In the second stage, the localization of the tumor is simulated.<sup>[22]</sup> If three-dimensional conformal radiotherapy is to be applied, the simulation is determined using computerized tomography and magnetic resonance imaging to ascertain the three-dimensional extent of the tumor. The pathways that could potentially show lymphatic spread should be well understood, as they may be within the radiation therapy field even if they are negative and  $N_0$ .<sup>[23,24]</sup>

Generally accepted standards set the total dose at 65 Gy for T1 and T2 lesions with fractionation (180-200 cGy/fraction/day), and for T3 and T4 lesions, it is adjusted to 70-75 Gy. For confirmed  $N_0$  cases, the prescribed radiation dose is 50 Gy, but an additional dose of 500-1500 cGy is given depending on the nodal spread. There is no specific scheme outlined for metastatic conditions.<sup>[24,25]</sup>

### Chemotherapy

Nasopharyngeal carcinoma is a tumor that can develop distant metastases in cases of head and neck cancers. It is both radiosensitive and chemosensitive.

Being a tumor group observed in a critical region, it has a high risk of metastasis; however, advanced NPC, accounting for 50% to 70%, reduces survival rates. A study conducted in 2006 reported that the use of chemotherapy led to a 6% increase in overall survival rates and a 10% increase in event-free survival rates. Due to its rarity, there is no optimized or standardized chemotherapy drug for NPC. Typically, efforts focus on shrinking the tumor region to ensure the effectiveness of radiotherapy, which is the primary goal.<sup>[24-26]</sup>

### Chemoradiotherapy

The effects of chemotherapy drugs and radiotherapy on normal cells and tumor cells are well-known. The literature also indicates that using these two components together has a supportive effect on each other. The advantage of using chemotherapy drugs with acceptable toxicity levels, whose doses are adjusted, in conjunction with radiotherapy, is that while radiotherapy provides local effects, chemotherapy can prevent micro-metastases. This facilitates overall survival and local control.<sup>[27]</sup>

On the other hand, to enhance the effectiveness of radiotherapy, chemical agents that affect mechanisms such as the inhibition of cellular repair mechanisms, cycle redistribution providing effectiveness in radiation-induced initial damage, elimination of hypoxic cells, and prevention of tumor cell repopulation are used. To explain the cytotoxic effects of radiation, double-strand breaks provided on DNA, which cannot be repaired, lead to cell destruction, but single-strand breaks in the DNA chain can be repaired within hours.<sup>[28]</sup> For this reason, an agent called cisplatin is used to increase effectiveness. The mechanism of action, in general terms, is that cisplatin, which interacts with DNA, crosslinks with the double helix of DNA, increasing the damage index with radiotherapy. The damaged cell membrane with the radiation effect generates free oxygen radicals, and the introduction of free oxygen radicals into the cytoplasm initiates the first steps of the process leading to apoptosis.<sup>[29-31]</sup>

Due to its ease of use and broad spectrum, cisplatin is generally used in various cancer types such as head and neck, ovarian, seminomatous testicular, bladder, prostate, cervical, and esophageal cancers. Cisplatin is administered only intravenously. The half-life of the drug in the circulatory system can be up to 60 hours, and it may still be present in the kidneys even four months after administration.<sup>[30-32]</sup>

Additionally, it is known to create a supra-additive effect when administered in combination with certain cancer drugs. These include the topoisomerase inhibitor etoposide, taxanes, and antimetabolites (cytarabine, gemcitabine, 5-fluorouracil, methotrexate, 6-mercaptopurine). Among the most common side effects of cisplatin treatment, is hearing loss at frequencies above 4000 Hz may occur.<sup>[30-34]</sup>

In conclusion, EBV is claimed to be present in 90% of the world's population. It is considered an acquired immunity condition, and it is concluded that this immunity is transferred to the next generations. The rare occurrence of this cancer type with smoking is more commonly associated with lung cancer, etc. The possibility of airborne chemicals causing this cancer is both logical and explanatorily correct within the possibilities. However, when the scientific literature is reviewed, matching or correlation analysis has not been adequately performed in studies. Saliva transmission is currently the most significant factor in this disease. Despite being a serious type of cancer, statistically, it is not a cancer type that can be taken seriously.

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