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REVIEW ARTICLE **OPEN ACCESS**

Head and Neck Cancer: A Systematic Overview

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ABSTRACT
Cancer occurring in the internal surface of the head and neck region in a human body is referred to as head and neck cancer. It is one of the leading malignancies with high rates of incidence and deaths globally on an annual basis. The cause behind head and neck cancer can be mainly attributed to human lifestyle and sexual behavior. Being one of the most complicated diseases with low survival rates makes it one of the important topics of research. A large number of complex genes and pathways are involved in the disease, which makes the understanding of the disease mechanism and its treatment even more difficult. Tp53 being one of the most vital genes involved in head and neck cancer has been taken into account for the current review. The paper discusses the various aspects of etiopathogenesis in cancer of the head and neck region. It further highlights the current global scenario of the disease concerning other cancer types, intending to provide the readers with a better understanding of the severity of the disease. Genetics of the disease has also been discussed in brief and the need to strengthen further research in this field for a better prognosis of the disease has been concluded.
Keywords*: Tp53, Gene, Head and Neck Cancer, Tumour, Incidence, Carcinogenesis.*

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INTRODUCTION

Cancers occurring in the internal moist surface of the head and neck region in a human body are commonly known as head and neck cancer. The cancer of the head and neck region is the sixth most common malignancy worldwide with approximately 600,000 cases and 350,000 deaths occurring annually[1].Areas of high incidence include Mediterranean Europe and South America[2]. High-risk regions specifically for the cancer of the oral cavity include Melanesia, south-central Asia, western and southern Europe, and southern Africa. Similarly, high-risk regions for laryngeal cancer include southern and eastern Europe, South America, and western Asia[3].

The cancer of the head and neck mainly involves regions like the oral cavity, pharynx, larynx, nasal cavity, salivary glands, and skin[4].Cancer is mainly caused due to several risk factors (Fig.1). Some of the most important and common factors include tobacco and alcohol, responsible for approximately 70 – 75 % of the cases[5].Another common risk factor is the chewing of betel quid which is generally observed in various parts of Asia and most commonly in India[6].Cancer of the head and neck region is also caused due to infections by the human papillomavirus (HPV)[7].HPV-related malignancies of the head and neck region are not highly linked with the use of tobacco and alcohol but are instead more related to sexual behavior being mainly responsible for the transmission of HPV from one person to another[8,9].The majority of the head and neck cancer cases are caused by carcinogens or HPV, however, in a very small fraction of the cases, several members of the same family are affected as noticed in Fanconianemia[10].

ETIOPATHOGENESIS

Head and neck cancers are characterized by several symptoms like swelling of the jaws, unusual bleeding and pain in the mouth, a problem during breathing and speaking, pain during intake of food, bad odor of the mouth, nasal ulcers, and perforations in the nasal septum.

Head and neck cancer is a disease of major concern and is a potent threat to human health. Untreated the disease may lead to 50% mortality at a duration of 4 months[11,12].Patients suffering from head and

neck cancer need immediate treatment and proper care post-treatment. Commonly and most widely followed treatment strategies include surgery, radiotherapy, or both in combination with chemotherapy[4]. These particular treatment strategies enhance the chances of survivability up to 5 years in approximately 60% of the patients that have been freshly diagnosed with the disease[13].

Risk stratification of head and neck cancer is studied by anatomic site, stage, cellular, and tissue-specific characteristics of the tumor [14].Post risk stratification the treatment of cancerous lesions or tumors is very important, however, it is by far complicated too. It involves the collective expertise of several individuals which includes surgeons, oncologists, radiotherapists, plastic surgeons, and others. Head and neck cancer can be broadly divided into 4 categories or stages (Stage I, II, III, and IV) and more specifically into 2 stages - Early stage disease and locally advanced disease. Patients suffering from either stage I or stage II (early stage) of head and neck cancer are commonly treated with surgery or radiation therapy or both with the sole aim to cure the disease. Success rates of the treatment are as high as up to 90 % in the case of patients with stage I disease and up to 70% in the case of patients with stage II disease. Surgery is more preferred over radiation to avoid the toxic effects of the latter and to obtain the most accurate staging[15]. However, the preference of the mode of treatment is highly dependent on the location of the tumor, expertise, and availability of equipment at the treatment center, and more importantly the preference of the patient[16,17]. Radiotherapy is administered as the first option to patients suffering from early-stage oropharyngeal and hypopharyngeal cancer as it demonstrates similar cure rates to that of surgery and usually results in lower morbidity[18,19].

GLOBAL BURDEN OF HEAD AND NECK CANCER

The incidence of cancer as a life-threatening disease has been on an uprising trend all over the world. The occurrence of new cancer cases has been estimated in 6 regions of the world – Asia, Europe, North America, Latin America & the Caribbean, Africa, and Oceania (Fig.1).

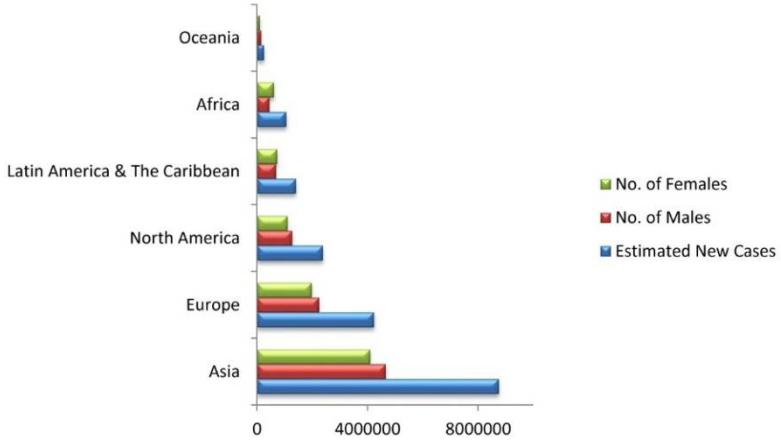

Fig.1. Distribution of new cases of cancer in 7 different regions of the world in 2018.

Asia leads the queue with 8750932 new cases and 5477064 numbers of deaths in the year 2018 with China contributing the maximum followed by India and Japan (Fig.2)

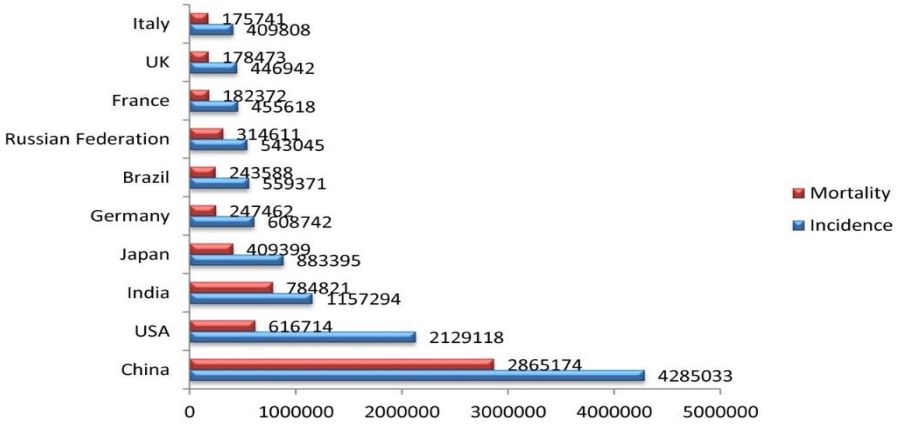

Fig.2. Top 10 countries with cancer incidence and mortality during the year 2018.

According to the 2018 GLOBOCAN statistics, there is an estimated 18078957 number of new cases of cancers globally among which approximately 887,659 cases (4.9%) account for the cancer of the head and neck region only. Table 1 shows a detailed distribution of the occurrence of new cases of various head and neck cancer types on a global scale.

Table.1: 2018 global statistics of new cases of head and neck cancer (Age: 0 - 85+) and sex-based occurrence

Cancer Types	**Estimated no. of new cases**	**No. of Males**	**No. of Females**
All Cancer Types	18078957	9456418	8622539
Types of Head and Neck Cancer			
Lip, Oral Cavity	354864	246420	108444
Larynx	177422	154977	22445
Nasopharynx	129079	93416	35663
Oropharynx	92887	74472	18415
Hypopharynx	80608	67490	13112
Salivary Glands	52799	29256	23543

The statistical data reveals that the cancer of the lip and oral cavity is the most predominant form of head and neck cancer (Fig. 3 and Fig. 4) and has a high occurrence in males (69.44%) as compared to females (30.56 %). This is quite evident based upon the lifestyle of the population. Males are more involved in habits like smoking and chewing tobacco and tobacco products as compared to females, thus leading to higher rates of cancer of the lip and oral cavity region.

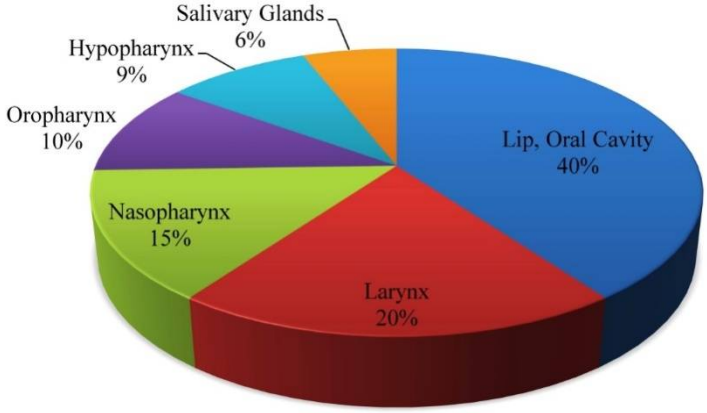

Fig.3. Percentage occurrence of various types of head and neck cancer in the year 2018. (Source: GLOBOCAN, 2018 [20])

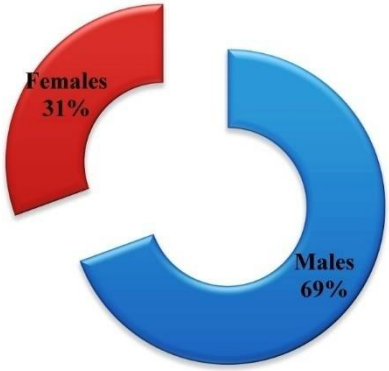

Fig.4. Sex-wise distribution of cancer of the lip and oral cavity region. (Source: GLOBOCAN, 2018[20])

As far as the number of deaths is concerned, the estimated number of mortalities in 2018 due to head and neck cancer lies approximately at 453307 (4.7%) from the cumulative figure of 9555027 deaths that occurred in the same year due to all cancer types. The mortality was also found to be higher in the case of cancer of the lip and oral cavity as compared to other regions. In a similar fashion to that of the occurrence, the males dominated the mortality figures as compared to their counterparts (Table.2).

Table.2. Estimated cases of sex-based mortality in head and neck cancers during 2018.

Cancer Types	Mortality	Male Mortality	Female Mortality
All Cancer Types	9555027	5385640	4169387
Types of Head and Neck Cancer			
Lip and Oral Cavity	177384	119693	57691
Larynx	94771	81806	18707
Nasopharynx	72987	54280	12965
Oropharynx	51005	42116	8889
Hypopharynx	34984	29415	5569
Salivary Glands	22176	13440	8736

GENETICS OF HEAD AND NECK CANCER

Current molecular events in head and neck cancer indicate alterations in Epidermal Growth Factor Receptor (EGFR), Phosphatidylinositol 3-kinase (PIK3CA), the NOTCH pathway, and TP53 genes. Large numbers of studies have been published analyzing the chain of events occurring in these genes in head and neck cancer patients[21].

In maximum cases of head and neck tumors, the EGFR is overexpressed. Keren et al.[22]conducted a meta-analysis study to find high levels of EGFR protein in 57.8% primary tumor samples from a total of 3346 samples. The mutations to EGFR in head and neck cancer patients have been inconsistent. Only 7.3% of Korean patients suffering from laryngeal cancer have been found to carry a mutation in the EGFR kinase domain[23]. 42.4% of head and neck cancer patients showed truncating EGFRvIII mutations and was found to provide resistance to targeted EGFR therapy[24]. In another such incidence, a cohort of Singaporean patients suffering from tongue cancer was found to have mutations in the EGFR pathway itself[14]. The varying mutational status of the EGFR thus makes it necessary to have a better understanding of the mechanisms responsible for the overexpression of the same in head and neck cancer.

The most frequently mutated pathway in head and neck cancer is the PI3K-AKT-PTEN pathway[14]and PIK3CA is the most frequently mutated gene in this pathway[25,26]. Mutation to PIK3CA leads to an increase in cell viability and growth, thereby supporting tumor growth in head and neck cancer patients. The aberrations are most commonly found in the advanced stage of the disease[27]and more frequent in the case of HPV +ve tumors [28,29,14]. Mutation to PIK3CA is less as compared to its amplification[30]. Low rates of PIK3CA amplification have been observed in a German head and neck cancer cohort (9%) and two Japanese groups accounting for 2.3% and 12% respectively[31,32,33].However studies from samples of 18 Vietnamese, 33 patients from Germany, and 86 from Greece, marked the complete absence of mutation to PIK3CA in the helical or kinase domain[30,32,34].The lack of sufficient sequencing studies masks the proper genetic mechanism of the PIK3CA. Additional studies are required in this area for a proper understanding of the PIK3CA mutation and the risk of head and neck cancer.

Sequence analysis of tumor samples led to the establishment of alterations to the NOTCH pathway as the third most common cause of head and neck cancer[25,35,14].Mutation to the NOTCH1 gene was found to be more common followed by mutations to NOTCH2 and NOTCH3 genes. In a study involving Chinese patients suffering from cancer of the oral cavity, 43.1% of tumor samples showed NOTCH1 mutations leading to the prediction of activation of the gene in half of the cases[36].The study carried out by Rettig et al.[37]found that mutations to the NOTCH1 gene were more common in the case of HPV-ve patients. Besides NOTCH1, alterations to other NOTCH pathway genes have also been reported. These genes include AR, EP300, NOTCH2, NOTCH3, PARP1, JAK2, JAK3, ARNT, and NCOA1[38].Further studies to correlate NOTCH mutations with head and neck cancers are required for a better prognosis of the disease.

Tumor suppressor protein (p53) or TP53 gene acts as a regulator of the cell cycle and brings about apoptosis under unfavorable conditions. This gene is mostly suppressed in cases of cancer of the head and neck[39]. In the case of HPV negative head and neck cancers, the TP53 activity is suppressed either by mutation or deletion Yadav *et al.*[40] while it is of wild type in HPV-positive cases. Large numbers of studies have revealedthe association of TP53 mutations with cancer of the buccal cavity[25,26,41]Higher rates of TP53 mutations is linked with risk factors like the use of tobacco and alcohol thereby linking to low survival rates[7]. The succeeding section provides the detailed role of p53 in head and neck carcinoma.

ROLE OF P53 IN HEAD AND NECK CANCER

TP53 has been recognized as one of the most frequently mutated genes in the case of head and neck cancers. An estimated 46 – 73 % of cases of head and cancer carry TP53 mutations[35,42].TP53 works as

a tumor suppressor gene whose primary function is to act as a transcription factor, thereby regulating the activity of various downstream target genes under various situations of cellular stresses[43]. The gene consists of 393 amino acids and 4 domains (which includes a highly conserved DNA binding domain). Tp53 gene encodes a protein p53 commonly referred to as "guardian of the genome" which can be attributed to its various activities that are mainly aimed at maintaining genomic stability[44]. P53 has a major role to play in several vital cell functions. This includes responding to critical situations like DNA damage and oncogenes-related stress conditions. DNA damage induces the activation of p53, which in turn arrests the cell cycle and attempts to repair the damage. If the DNA damage is not successfully repaired, p53 brings about cell apoptosis, thus preventing further replication of the damaged DNA (Fig.5). It also regulates various other cellular activities like cell cycle, redox homeostasis, metabolism, and various mitochondrial functions[45,46]

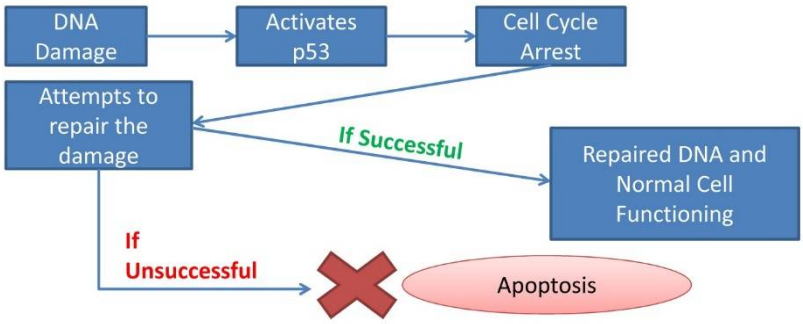

Fig.5. Mechanism of p53 in tumor suppression.

$_P$53 mediated apoptosis

P53 has been found to mediate cellular apoptosis by both transcriptional and post-translational mechanisms. During the process of apoptosis p53 proteins once induced by stress or oncogenesis, are localized to the mitochondria. On reaching the mitochondria, p53 induces the permeabilization of the outer mitochondrial membrane (POMM) and inhibits Bcl2, Bcl-xl, and Mcl-1 that act as antiapoptotic agents. It also induces the activation of proapoptoticBak and Bax proteins of the Bcl2 family of POMM regulators which triggers apoptosis[47]. P53 mediated POMM leads to the release of Cytochrome C, which in turn leads to the release of caspase 3, 6, and 7 (also known as executioner caspases) via apoptosome. Among all the executioner caspases, Caspase-3 is regarded as a vital mitochondrial p53 – interacting protein Frank et al.[48]which is localized both in the cytosol and also in the inner and outer mitochondrial membrane.

p53 mediated necrosis

Necrosis is an irreversible process of programmed cell death that occurs when the apoptotic process has failed and can also be induced by p53[49].The pathway of necrosis is independent of caspases and requires the involvement of receptor interaction protein kinases (RIP-1 and RIP-3). Sometimes, even p53 can directly induce necrosis instead of apoptosis in response to several cellular stresses or direct proportion to the severity of the stimulus arising because of the stress.

Mutations to the p53 gene have been observed early in the carcinogenesis of the head and neck. The mutations are found to be present in pre-malignant tumors or lesions, thus implying to play an important role in the early oncogenesis of the head and neck region[50]. Generally, 3 types of mutations are found to affect the functioning of the TP53 gene. This includes missense mutations that are mainly concentrated in the DNA binding domain (DBD), while the nonsense and frame-shift mutations occur uniformly throughout the gene. The missense mutations prevent p53 from forming a tetramer. The p53 can also get inactivated through other pathways. These include the overexpression of MDM2 which is a negative regulator of p53. Deletion of CDKN2A, a negative regulator of MDM2 also results in MDM2 amplification thereby leading to suppression of p53[51,52].

CONCLUSION

Head and neck cancer is one of the global life-threatening diseases that need to be given proper attention. Lack of sufficient molecular and genetic studies has led to low survival rates among patients. TP53 has a major role to play in our living system, regulating the cell cycle and preventing cellular damage. Suppression of the gene leads to tumor progression and cancer. Being one of the frequently mutated genes in head and neck cancer, its mechanism and interaction with other genes need to be studied in detail at the molecular level. In-depth research backed with sequence-analysis-based studies will provide a better understanding of the genetic determinants and help increase survivability to a greater extent.

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