Non-Habit Induced Oral Cancer: A Review

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Abstract

The purpose of this article is to review non-habit induced oral cancers in India and study its interrelationships and risk factors on the health of an individual. Oral Cancer is a major issue related to the health of an individual inevery country around the world and has a wide variation in the global burden of the disease. It is a noteworthy issue regarding public health in India and accounts for 30% of the total cumulative cancers reported across the country. Consumption of tobacco and alcohol leads the etiological factors responsible for causing Oral Cancers, but, at times non-habit induced oral cancers have also been recorded. This article focuses on the various etiological factors responsible for causing oral malignancies in individuals having no history of alcohol and tobacco-related habits and highlights their interrelationship and pathophysiology responsible for causing malignancies.

Keywords: *Oral Cancer, Carcinogens, Pathogenesis, Carcinogenic, Metastasis, Tumerogenesis, Exposure.*

Introduction

Oral Cancer is a major issue related to public health inevery individual country around the world and has a wide variation in the global burden of the disease. Incidences in India and South-east Asia ranks highest in the world with Oral Cancer ranking amongst the top three cancers in the Indian sub-continent.[1] In the head and neck region, the Oral cavity is the predominant site of primary malignant tumors, and oral cancer is the prime cause of morbidity and mortality amongst all cancers in India. Oral Cancer is a noteworthy issue regarding public health in India and accounts for 30% of total cumulative cancers reported across the country, with a prevalence rate as high as 20 out of 1,00,000 people having carcinoma of the oral cavity.[2]

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In western countries, the tongue and floor of the mouth are the predominant regions of oral cancers due to smoking tobacco and alcohol consumption habits. On the contrary, cancers of buccal mucosa, alveolus and retromolar region are the predominant sites in the Indian subcontinent due to the habit of chewing tobacco and areca nut.[3]

Consumption of tobacco and alcohol leads the etiological factors responsible for causing Oral Cancers, but, at times non-habit induced oral cancers have also been recorded. Poor oral hygiene, ill-fitting dentures, sharp cusps, sharp crowns and bridges, hereditary predisposition, racial and demographic factors, chemical carcinogens, radiation, viruses like Human Papilloma Virus (HPV) infections, etc have now been found responsible playing a role in the pathogenesis of Squamous Cell Carcinoma of head and neck region. The most common reason behind younger generations acquiring non-habit induced Oral Squamous Cell Carcinoma is a genetic predisposition, viral factors such as Human Papilloma Virus (HPV) and Epstein–Barr virus (EBV), immune-suppressive conditions, Fanconi's anemia, and occupational exposures.[4-6]

Etiology: Hereditary and Demographic Factors: The risk of developing cancers in genetically linked

relatives of cancer patients is three times higher than non-genetically linked control groups. Incidences of occurrence of nasopharyngeal cancers in the southeast asian population are higher as compared to other regions of the world.[7] Similarly occurrence of carcinomas can also be influenced by geographical and environmental factors like mineral content in water, diet, climate changes, etc.

Chemical Carcinogens: Directly or indirectly the human body comes in contact with various chemicals that can be carcinogenic and can induce carcinogenesis or tumorigenesis in an individual. Polycyclic aromatic hydrocarbons like benzanthracene, methylcholanthrene, etcpresent in tobacco, smoke, air pollutants or industrial oils can cause skin cancer, oral cancer and lung cancer in an individual exposed to these carcinogenic agents. Aromatic amines like beta-naphthylamine, benzidine and azo dyes used as food coloring agents can be a potential causative agent of oncogenesis. Carcinogenicity of chemical agents is dose-dependent and multiple-dose exposure can have the same oncogenes as compared to single-dose exposure. The mutagens bind to DNA, RNA, or cytoplasmic proteins within the cell and initiate miscoding errors during cell replication. These mutagens interact with the genetic substances of the cell and cause mutagenesis, ultimately affecting clonal proliferation.[7]

Physical Carcinogens: Radiation like UV radiation from sunlight, UV lamps, and ionizing radiation like X-rays, alpha-radiation, beta-radiation, gamma-radiation, or radioactive isotopes have the potential for inducing mutagenesis and even killing a cell. The radiation-induced mutation is generally irreversible and depends upon various factors like a dose of exposure, a period of exposure, type of radiation, number of cells exposed to the radiation, etc.[7]

Biological Carcinogens: In certain cases of reported non-habit induced Oral Squamous Cell Carcinoma, not only chemical or physical carcinogens, but the presence of variousbiological carcinogens like Human Papilloma Virus (HPV), Epstein - Barr virus (EBV), and Herpes Simplex Virus are also seen playing a prime role in promoting cancers.[8-10]

HPVis one of the major etiological factors in non-habit induced Oral Squamous Cell Carcinoma cases reported worldwide. Cases of Human Papilloma Virus infections have also turned up at several areas in the human body like the anus and genital tract, urethra, skin, larynx, mucosa lining the trachea and the bronchus, nasal passage, maxillary sinus, frontal sinus, sphenoid sinus, ethmoid sinus and oral cavity.[11,12] High-risk prototypes of the Human Papilloma Virus, HPV-16, and HPV-18 have been recognized as being capable of transforming epithelial cells in the upper respiratory tract into cancer cells.[13] HPV infection plays a major role in the causation of cancer of the pharynx, but it has also been recognized as an etiological factor behind cancers of the Oral Cavity. Oral HPV infection may be associated with different precancerous lesions of oral cavities like leukoplakia, erythroplakia, oral lichen planus (OLP), nicotine stomatitis, oral submucous fibrosis (OSMF), and tobacco pouch keratosis.[14-16]

HPVbelongs to an age-old known family of pathogens that were known to cause infection of the epithelial tissues in organisms belonging to the family of amphibians, reptiles, birds, and mammals. This cluster of DNA viruses forms a discrete Papovaviridae family, which encompasses Papillomaviridae and Polyomaviruses. HPV can be phylogenetically put into genera like alpha, beta, gamma, mu, and nu, different species, and 150 types out of which 120 types are fully sequenced. About 80% to 90% of viruses in the same species split similar biological properties like tissue morphology, disease illustration, and pathogenicity. The life cycle of the virus is initiated through micro lesions in the epithelium of the human body and is recognized byspecialized distinguishable programs of squamous epithelial keratinocytesthat have been infected, where virusessynthesis DNA and their expressions occur through capsid proteins. Basal cells are directly infected from the Virions released from the stratum corneum and stratum granulosum throughthe synthesis of capsid proteins as well as activation of late and early promoters.[14,17, 18]

If clinical features are observed, HPV-associated tumors can be distinguished as a shape somewhat resembling a strawberry-like exophytic lesion, most commonly seen at the base of the tongue or can also be seen in the tonsilar region and poorly distinguishable histopathological findings, as well as cystic changes, are seen in metastatic lymph nodes of head and neck region present near the tumor.[15-21]

Epstein-Barr virus is a double-stranded DNA containing oncogenic human herpes virus, also known to be the first human tumor-causing virus.[19,22,23] It can appear in individual showing no visible symptoms and

persist for a lifetime as a latent infection.[22] Presence of EBV have been reported in various epithelial cell malignancies, like, nasopharyngeal Carcinomas, so it can also be a potential etiological factor behind various malignancies of the oral cavity.[24] Studies have also shown that Epstein-Barr Virus is also engaged in various B-lymphocyte induced cell malignancies, like Burkitt's lymphoma and Hodgkin lymphoma.[22,23] Epstein Barr Virus malignancy is linked with various proteins in the viruses that controlthe proliferation of the cell, immune response as well as apoptosis of the cell. Latent Membrane protein help in activating the signaling pathway, whereas the nuclear antigens of EBV help in gene expression.[20] However, Epstein-Barr Virus affecting Carcinogenesis of Oral mucosal remains uncertain, because various techniques like PCR, nested PCR, RT-qPCR, IHC, and ISH, are used for detecting the virus, and sensitivity and specificity of the tests varies according to the techniques which have been used, leading to different interrelations between Epstein-Barr Virus infection and Oral Squamous Cell Carcinoma.[21,]

Non-Habit Oral Cancer in Females: Studies suggest the occurrence of non-habit induced oral Carcinoma has a higher incidence rate in female gender as compared to males.[23] The cancer cells derived from head and neck carcinomas show estrogen metabolism genes, especially estradiol in tongue carcinomas. Several studies have also indicated an alteration in the level of various hormones like Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), prolactin, and testosterone in the bodies of female patients reporting with non-habit induced Oral Squamous Cell Carcinoma. The exact role of estrogen behind Oral Carcinoma occurrence is still under research scrutiny and should be studied further to shed light and extract the etiology behind the presence of estrogen receptors in non-habit induced head and neck cancers in the female body.[24]

The Oral Cavity is exposed to various forms of trauma either through ill-fitting dentures, sharp cusps, impinging dental restorations, and root pieces. Chronic irritation to the soft tissues due to the above-mentioned causes can progress towards the emergence of reactive oxygen species (ROS) and reactive nitrogen species (RNS) from various inflammatory cells like lymphocytes, macrophages, etc. When the body's defense mechanism falls behind and concentration of free radicalslike Superoxide Radical (O_2), Hydroperoxyl Radical (HO_2), Hydroxyl Radical (OH), Nitric Oxide (NO), Nitrogen dioxide (NO_2) exceeds the body's antioxidant levels, a mutation occurs in the parent cells leading to carcinogenesis. Ill-fitting dentures serve as a source of chronic irritation and trauma to the buccal mucosa and can be an etiology behind the occurrence of Oral Carcinomas in older generations due to possible synergistic effects of long-standing trauma and delayed DNA repair mechanism.[17]

Conclusion

From various studies, it has been seen that non-habit induced Oral Squamous Cell Carcinoma tends to have a negative nodal status and a tumor size which seldom exceeds T2 (STNMP staging). STNMP is a newly introduced system for giving the notation of intra-oral carcinomas and it is completely different from all previous TNM staging in that along with the conventional notation including tumor (T), node (N), and metastasis (M) which is in generalused in cancer staging, but, an additional notation of site (S) and the pathology (P) have also been considered. The two new additional features have been conceded as a prime factor in estimating the prognosis of the patient. The phenotype of non-habit associated Oral Squamous Cell Carcinoma is generally a well to moderately differentiated carcinoma. When compared the expression of p53 in non-habit associated Oral Squamous Cell Carcinoma shows a significant decrease in its expression than habit induced carcinomas. This suggests a good response to radiotherapy and cancer management procedures and thus an improved overall prognosis. However, a low prognosis rate is seen in non-habit induced Oral Squamous Cell Carcinoma patients due to delayed treatment and medical management as well as lack of awareness amongst the population over the issue.

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