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Prevention Of Oral Cancer: An Overview

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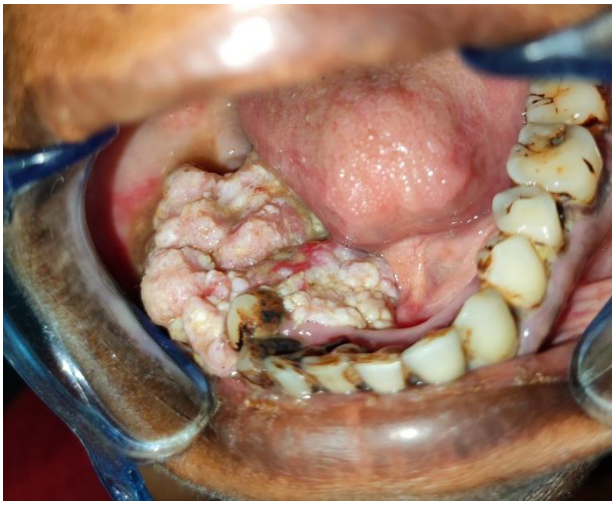
Abstract

Oral cancer is one of the most prevalent cancers worldwide and it is 11th most common cancer around the globe.[8] It is most frequent cause of mortality and morbidity in today's times. One can say that oral cancer is a preventable disease to a great extent, because risk factors of oral cancer includes smoked as well as smokeless tobacco, alcohol consumption, areca nut and betel quid chewing and unhealthy diet; all of which are avoidable risk factors.[7] Patients affected by oral cancer usually belong to low income economic group. Treatment of oral cancer is expensive and such patient cannot afford it. Hence, preventive measures are of utmost importance. Oral healthcare professionals can play a pivotal role in the prevention of oral cancers in two ways. First by thorough examination of oral mucosa to diagnose premalignant lesions and premalignant conditions. And second by educating and counselling patients to avoid the above mentioned risk factors and dietary recommendations. This article discusses the risk factors associated with oral cancer and various ways to prevent them.

Keywords: Oral cancer, prevention, tobacco, alcohol, risk factors, nutrition

Introduction

Head and neck cancer is the sixth most common human cancer and the oral cancer constitutes 48% of head and neck cancer cases. Ninety percent of oral cancer cases are histologically diagnosed as oral squamous cell carcinomas (OSCCs).[9] Squamous cell carcinoma, also called epidermoid carcinoma is defined as a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/ or the presence of intercellular bridge.[2] Oral squamous cell carcinomas may present as a non-healing ulcer and presence of mass in head or neck, which may lead to exophytic, proliferative and fungating growth in the oral cavity. Unfortunately, most of the patients are diagnosed after the development of symptoms at advanced stages of disease.



The occurrence of oral cancer is approximately 32% in buccal mucosa, 22% in tongue, 11% in lower lip, 11% in palate, 8% in vestibule, 5% in alveolus, 5% in floor of the mouth, and 3% in gingiva.[8] The prevalence as well as incidence of oral cancer are high in less developed countries like India, Taiwan, Sri Lanka, Pakistan and Bangladesh.[7] The male to female ratio is almost 2:1.[8] Regrettably, India alone accounts for one-fifth of all oral cancer cases and one-fourth of all oral cancer deaths.[8]

The major risk factors for oral cancer are tobacco use, in any form, and excessive alcohol use. These risk factors, supplemented by dietary deficiencies, are leading causes of oral cancer. Some other risk factors are inactive lifestyles along with obesity, betel nut chewing, poor oral hygiene, chronic trauma, air pollution and chronic infections.[7] Some chronic infections are risk factors for cancer; this is a particular issue in developing countries. Approximately 13% of cancers diagnosed in 2018 globally were attributed to carcinogenic infections, including Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus.[1]

Oral cancer is a multi-focal disease and its development is a multi-step disease.[6] Understanding mechanism of oral cancer is pertinent for its prevention. Cancer may begin as dysplastic changes clinically visible as premalignant lesions and conditions such as leukoplakia. Over the years accumulation of genetic and epigenetic alterations occurs and it progresses through well-defined pathologic stages to invasive epidermoid carcinoma.[6] Pathogenesis of cancer formation includes mutation of tumor-suppressor genes and activation of various oncogenes at various stages of carcinogenesis. Tobacco causes oral cancer by effects on p53 gene and mutations at the chromosomal region 3p. Another suggested hypothesis for development of oral cancer is oral inflammation due to involvement of several inflammation-related molecular pathways such as cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), p38a MAP kinase, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and STAT (signal transducer and activator of transcription).[9] The goal of this article is to discuss various risk factors associated with oral cancer and ways to prevent it.

Tobacco

Tobacco is consumed in two forms; smoked and smokeless tobacco. The association between tobacco and cancer is stated strongly in numerous epidemiological studies. Smokeless tobacco is available and consumed in the form of betel quid, oral snuff, and betel quid substitutes (known as guktha, nass, naswar, khaini, mawa, mishri, and gudakhu in vernacular languages) increases the risk of oral precancerous lesions and oral cancer between 2-fold and 15-fold.[8] Smoked and smokeless tobacco contains myriad cancer causing compounds; nicotine being most notorious of them all. The nicotine metabolites 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN) have carcinogenic properties.[8] NNK and NNN bind to the nicotinic acetylcholine receptor to promote cell proliferation and create a microenvironment for tumor growth. NNK, NNN, and their metabolites

Volume 5, Issue 4; July-August 2022; Page No 249-254

covalently bind with deoxyribonucleic acid (DNA) of keratinocyte stem cells forming DNA adducts.[4] These adducts are responsible for critical mutations involved in DNA replication. The metabolism of these carcinogens involves oxygenation by P450 enzymes in cytochromes and conjugation by glutathione-S-transferase (GST).[4]

Alcohol

Alcohol alone by itself has no role with cancer progression but synergistically functions with tobacco to develop cancer. Acetaldehyde, metabolism product of ethanol, is a known carcinogen. It is a tumor promoter, and hence the chronic consumption of alcohol promotes the development of oral cancer.[9] Carcinogenic impurities such as polycyclic aromatic and nitrosamines are present in alcohol. Alcohol increases the penetrability of oral mucosa due to which epithelial atrophy occurs. Alcohol may contribute in solubilizing of other carcinogenic compounds that may increase the permeability of oral epithelium to these compounds and enhance the penetration of carcinogens into target tissues.[4] Also, intake of alcohol alters intracellular metabolism at the target epithelial site and causes chronic irritation.[13] Chronic consumption of alcohol negatively affects overall nutritional status of person and causes hepatic damage which increases risk for cancer.[4]

Betel quid and Betel nut

Betel nut and tobacco along with slaked lime and other ingredients is wrapped in a betel quid is chewed in various parts of our country.[4] It is now regarded as type 1 carcinogen.[8] Betel quid, commonly known as paan, is easily available in market and consumed regularly by general population. In vitro studies have shown that betel nut and quid has contents like reactive oxygen species (ROS), methylating agents, and reactive metabolic intermediates which can cause DNA damage.[4]

Diet and Nutrition

In the past five decades, a lot many epidemiological studies have been conducted regarding diet and its relation to oral cancer. Several meta-analysis and systematic reviews have revealed that high intake of citrus fruits prevents oral cancer.[5] The working group of International Agency for Research on Cancer (IARC) has confirmed that low consumption of fruits and vegetables predisposes to increased risk of cancer development.[4] Few micronutrients like vitamins A (retinol), C (AA), and E (α-tocopherol); carotenoids (β-carotene); potassium; and selenium (38–43), β-carotene, retinol, retinoids, vitamin C (AA), and vitamin E (α-tocopherol) are antioxidants and act as scavenger of free radicals which are involved in pathogenesis of cancer development.[4] Also, researchers have proved that consumption of processed meat, salted meat and animal fat increases risk of oral cancer.[5]

Viral Infections

Viruses implicated in oral cancer are Herpes Simplex Virus (HSV), Human Papilloma Virus (HPV), Human Immunodeficiency Virus (HIV) and Epstein-Barr Virus (EBV). HSV acts as a mutagen and it gets transformed into malignant phenotype after isolation of an area of viral genome which increases the mutation frequency in the cultured cells.[3] EBV causes oral hairy leukoplakia and "lymphoproliferative disease" in immunocompromised patients. The causal relationship of EBV with oral squamous cell carcinoma (OSCC) is still uncertain.[4] HIV, a well-known virus causing Acquired Immunodeficiency Syndrome (AIDS), is notorious to cause Kaposi sarcoma, non-hodgkin lymohoma and oral squamous cell carcinoma.[2]

HPV may be an independent risk factor in development of oropharyngeal cancer and potentially malignant disorders.[8] HPV is a DNA virus and HPV 16 is the most common type associated with carcinoma development in head and neck area, followed by HPV 18.[9] It has been proposed that HPV infects basal cell layer of oral epithelium similarly like cervical epithelium. [9]

Genetic predisposition

It has been reported that almost 30% of immediate relatives of head and neck cancer patients and patients with cancer of respiratory tract and upper digestive tract are more likely to develop cancer. Such population has inability to metabolize carcinogens or pro-carcinogens and are not able to repair DNA damage; therefore, they are prone to develop an oral malignancy.[9] Genetic polymorphisms in the genes coding for the enzymes (P450 enzymes and XMEs) responsible for tobacco carcinogen metabolism are suspected to play key role

Volume 5, Issue 4; July-August 2022; Page No 249-254

in the genetic predisposition to tobacco-induced head and neck cancers.[4] Humans with the fast-metabolizing version (allele) of alcohol dehydrogenase (ADH3[1-1]) are more likely to develop oral cancer in the presence of alcoholic beverage consumption than those with the slow-metabolizing forms.[8]

Chronic irritation and inflammation

In presence of other local factors, chronic trauma can lead to neoplastic changes. [4] Chronic trauma may occur due to sharp teeth, restorations or ill-fitting dentures. [8] In pathological environments, the content of the extracellular matrix change with increase in various growth factors and enhance cell migration which is necessary for development of cancer. [9]

Preventive Measures For Oral Cancer

Public awareness

The aim of primary preventive action is to make the public aware of all the risk factors associated with oral cancer and bring a behavioral change. This also includes spreading the information about catastrophic effects of cancer, curability of it and various screening procedures available.[3] All categories of population including health care workers, consumers and law makers should be included in health promotion and education programs. Stringent laws and policies and various organisations enhances public education initiatives.[12] There can definitely be substantial decrease in number of cancer cases by reducing the exposure to tobacco and alcohol like carcinogens.[11] For this, national cancer programs have been set up according to WHO recommendations which implement worldwide as well as nationwide anti-tobacco cessation programs aiming to curb its advertisement and usage. The International Agency for Research on Cancer (IARC) organizes focused research on causes of cancer and its prevention providing evidence on global cancer prevalence and incidence, mechanisms of carcinogenesis, and the most efficacious strategies for screening, early diagnosis and prevention of cancer. [7]

Dietary counselling

Various studies have been conducted stating that high intake of fruits, vegetables and dietary fibre definitely decrease risk of oral and pharyngeal cancer. There is no need to state the fact that a healthy and balanced diet improves immune status of body. [5] Foods rich in anti-oxidants decrease free radical load which in turn decreases carcinogenesis. In-vitro and animal studies have showed that β-carotene and vitamin E modify biochemical and genetic changes occurring in the direction of carcinogenesis like increasing expression of a type of p53 tumor suppressor gene.[10] Oral health care professionals should educate patients about this.

Flavonoids

Flavonoids are natural compounds ubiquitously occurring in plants, and are derivatives of polyphenol phenyl benzopyran. According to their hydroxylation pattern and differences pertaining to the chromane ring, flavonoids can be further divided into subtypes: flavanones, flavones, flavonols, isoflavons, and flavan-3-ols. Recent findings have reinforced the part of flavonoids in the prevention of neurodegenerative and cardiovascular diseases and of cancer. Flavonoids have antioxidant, anti-inflammatory, antiproliferative, and apoptotic properties. Quercetin, a type of flavonoid, inhibits thymidylate synthase (TS), a key-S phase enzyme, thus inhibiting mitosis. Various other types of flavonoids like kaempferol, baicalein and apigenin also have such properties. The data reported in multiples studies states flavonoids as promising anticancer agents, with their safe toxicology profile and the possibility of being included in the diet makes them attractive candidates for cancer prevention and therapy.[18]

Role of oral physicians in prevention of oral cancer

The oral cavity is one of the few regions in the body that lends itself to routine screening of asymptomatic population for early cancer detection. The oral cavity is a site which is easily accessible for evaluation by dentists, physicians, nurses, and health care workers or even by self-examination. [6] Screening for oral cancer by visual examination is simple, economical and causes little distress. [11] Thorough examination of mucosal surfaces by dentist can reveal premalignant and malignant lesions, which leads to prompt treatment of such lesions, thereby improving reducing morbidity and mortality. The detection of malignant lesions early through screening techniques comes under umbrella of secondary preventive measures.[3] Routine biopsy in those clinically

Volume 5, Issue 4; July-August 2022; Page No 249-254

presenting with features of precancerous lesions may lead to timely diagnosis of underlying invasive oral cancer.[8] Proper history taking and asking for any adverse habits like smoked or smokeless tobacco; alcohol consumption and betel nut chewing gives hint of condition of oral mucosa of patient and if dysplastic changes are evident, timely treatment can be started.

Several other diagnostic methods are available as an adjunct to clinical examination. These include toluidine blue staining, light-based detection techniques, and salivary biomarkers, although biopsy and histopathological examination remains the gold standard.[16] Toluidine blue is a cationic metachromatic dye that stains areas of the dysplastic epithelium, making them royal blue. Autofluorescence imaging utilizes light of specific wavelengths, which when incident on tissues high in content like endogenous fluorophores, including collagen, elastin, keratin, adenine dinucleotide (FAD), and nicotinamide adenine dinucleotide (NADH), produce autofluorescence. The dysplastic tissue appears darker. Molecular studies have identified more than 100 biomarkers in human saliva that acts as indicators of pathological processes and carcinogenesis, such as viruses, cytokines (IL-1b, IL-8, TNF-α), protein receptors (CD44) and DNA and RNA markers that are overexpressed in a carcinogenic process. .[16]

In recent years, various advanced diagnostic techniques have been developed like microarrays, next generation sequencing, labon-chip, microfluidics based techniques, nano-diagnostics, liquid biopsy and synthetic biology. Oral cancer is a multifactorial and multistep disease which is associated with participation of altered genetics and epigenetics through complicated molecular network. This has paved the way for the emergence of sophisticated molecular techniques as diagnostic aids.[17]

Chemoprevention

The administration of an agent to stop a cancer from occurring is called as chemoprevention.[3] These agents can cause reversal of premalignant lesions and are aimed to interfere with the carcinogenetic process early in the pathway.[6] These include retinoids, curcumin, omega-3 fatty acids and selective COX-2 inhibitors. Anti-inflammatory actions of above agents down- regulates the mutation of genes associated with development of cancer.[9]

Nanotechnology

The American Chemical Society defined nanotechnology as the design (at the atomic, molecule, and supra molecular levels) characterization, production, and utilization of constitutions, equipment, and systems by controlling shape and size at a nanometer scale. Use of nanodetection systems is growing, and has emerged as probable non-invasive systems bringing the detection sensitivity of biomarkers to nanoscale. Nanoparticles can also be used for localised drug delivery for treatment of premalignant and malignant lesions.[15]

Conclusion

Oral cancer burden is snowballing, and the treatment expenses associated with it are high. Thus taking correct preventive measures are important and oral physicians play a pivotal role in prevention, screening and early diagnosis of oral cancer. Incorporating healthy diets and active lifestyle in our lives is need of the hour. Educating everyone about risk factors associated with oral cancer through public awareness programs should be mandatory. Such interventions are affordable and will definitely reduce morbidity and mortality associated with oral cancer.

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Volume 5, Issue 4; July-August 2022; Page No 249-254

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Volume 5, Issue 4; July-August 2022; Page No 249-254