Oral cancer is any cancerous tissue growth located in the mouth. It may arise as a primary lesion originating in any of the oral tissues, by metastasis from a distant site of origin, or by extension from a neighboring anatomic structure, such as the nasal cavity or the maxillary sinus. Oral cancers are an important part of head-and-neck cancer as oral, head, and neck cancer is an umbrella term for a number of cancers that start in the head and neck, including lip and oral cavity cancer; salivary gland cancer; paranasal sinus and nasal sinus cancer; nasopharyngeal cancer; oropharyngeal cancer; and hypopharyngeal cancer. Oral cancers may originate in any of the tissues of the mouth, and may be of varied histologic types: teratoma, adenocarcinoma derived from a major or minor salivary gland, lymphoma from tonsillar or other lymphoid tissue, or melanoma from the pigment producing cells of the oral mucosa. Far and away the most common oral cancer is squamous cell carcinoma, originating in the tissues that line the mouth and lips. Oral or mouth cancer most commonly involves the tissue of the lips or the tongue. It may also occur on the floor of the mouth, cheek lining, gingiva (gums), or palate (roof of the mouth). Most oral cancers look very similar under the microscope and are called squamous cell carcinoma. These are malignant and tend to spread rapidly.

Major Risk Factors

Low public awareness of the disease is a significant factor, but these cancers could be found at early highly survivable stages through a simple, painless, 5-min examination by a trained medical or dental professional. All cancers are genetic disease. Risk factors that predispose a person to oral cancer have been identified in epidemiological studies. Smoking and other tobacco use are associated with 70%-80% of oral cancer cases, caused by irritation of the mucous
membranes of the mouth from smoke and heat of cigarettes, cigars, and pipes [Figure 1]. Tobacco contains over 19 known carcinogens, and the combustion of it, and by products from this process, is the primary mode of involvement.\textsuperscript{10-12} Use of chewing tobacco or snuff causes irritation from direct contact with the mucous membranes. In many Asian cultures chewing betel, paan, and Areca is known to be a strong risk factor for developing oral cancer. Alcohol use is another high-risk activity associated with oral cancer. There is known to be a strong synergistic effect on oral cancer risk when a person is both a heavy smoker and a drinker. Their risk is greatly increased compared with a heavy smoker, or a heavy drinker alone.\textsuperscript{13}

Other risks include chronic irritation (such as that from rough teeth, dentures, or fillings). Some oral cancers begin as leukoplakia a white patch (lesion), red patches, (erythroplakia), or non-healing sores that have existed for more than 14 days. In the United States of America, oral cancer accounts for about 8\% of all malignant growths. Men are affected twice as often as women, particularly men older than 40/60. Human papillomavirus, (HPV), particularly type-16 and 18 (there are over 100 varieties), is a known risk factor for oral cancer.\textsuperscript{6,9} A fast-growing segment of those diagnosed does not present with the historic stereotypical demographics.\textsuperscript{14-18} Some of the potential symptoms include skin lesion, lump, or ulcer on the tongue, lip, or other mouth area, which are usually small and mostly pale-colored. Early sign may be a white patch (leukoplakia) or a red patch (erythroplakia) on the soft tissues of the mouth that may be a deep, hard-edged, painless crack in the tissue.

Oral examination confirms a visible and/or palpable (can be felt) lesion of the lip, tongue, or other mouth area. As the tumor enlarges, it may become an ulcer and bleed. Speech/talking difficulties, chewing problems, or swallowing difficulties may develop, particularly if the cancer is on the tongue.\textsuperscript{19-22} Although a dentist, physician, or other medical professional may suspect a particular lesion is malignant, the only definitive method for determining this is through biopsy and microscopic evaluation of the cells in the removed sample. A tissue biopsy, whether of the tongue or other oral tissues, and microscopic examination of the lesion confirm the diagnosis of oral cancer.

## HIGH-RISK HUMAN PAPILLOMAVIRUS AND EPSTEIN-BARR VIRUS

HPV and Epstein-Barr virus (EBV) are an important cause of oral cancer. Polymerase chain reaction and DNA sequencing analysis are the molecular techniques used in detecting HPV and EBV DNA in oral cancers. For HPV the most common types found in oral cancers are 16 and 18, whereas the others are 3, 8, and 1.\textsuperscript{23,24}

## DIET AND CANCER RISK

Diet is an important factor in cancer etiology and prevention in India. As a society, Indians have one of the most interesting diets, with many unique dietary constituents that have promise for cancer prevention. Very few well-designed, prospective epidemiological research studies exploring the relationships between diet and lifestyle and cancer have been carried out in India. Additional research is needed to assess the impact of diverse dietary habits, religious practices, and lifestyles on prevention of cancer.\textsuperscript{21,22} Cancer detection and prevention efforts can have enormous benefits for developing countries by reducing future disease burden while saving economic resources for needed improvements in societal infrastructure. As development and mechanization continue into the 21st century, India must grapple with a transition from the burden of communicable diseases to the burden of non-communicable diseases.

A large percentage of Indians, particularly Hindus, practice vegetarianism and avoid meat and fish products in their diet. Vegetarian diets have been associated with decreased risk for prostate cancer. Case-control studies that compared non-vegetarian and vegetarian diets and alcohol and tobacco use in India have reported that vegetarians have a reduced risk of oral, esophageal, and breast cancers.\textsuperscript{23} Vegetarian diets rely on pulses (e.g., beans, chickpeas, and lentils) as a source of protein and pulses have been significantly associated with reductions in cancer.

Diets high in saturated fats have been associated with increased risk for cancer. Fat intake, especially saturated fat, is increasing in the middle class in India, although some rural residents traditionally have had a high intake of ghee (clarified butter, high content of saturated fat) as well. Studies have given equivocal results regarding the link between fat intake and risk of cancer.\textsuperscript{27-28} Large epidemiological studies
have identified a possible association between increased dietary fiber and a decreased risk for cancers of the colon and breast. No large studies on dietary fiber have been conducted in India, and rates of colon and breast cancer are low compared with those in Western societies. The Indian diet, which generally includes adequate levels of vegetables, fruits, and fiber-rich grains, may provide some protection against increased risk for these cancers.[16,19,21]

Many of these foodstuffs have been studied for their disease prevention capabilities, including turmeric (curcumin), cumin, chilies, kalakhar, Amrita Bindu, and various plant seeds. Among the most studied in recent years is turmeric, an ingredient in the common Indian curry and a spice that has been shown to be a potent antioxidant and anti-inflammatory agent, with additional promise as a chemo-preventive agent. In a study in human blood cancer cell lines, turmeric suppressed and destroyed blood cancer cells. Turmeric has been shown to suppress tumor initiation, promotion, and metastasis in experimental studies.[12] To illustrate, turmeric may block the activity of nuclear factor kappa-B (NF-kB), which, in an activated state, appears to be associated with cancer cell growth in many cell types. Turmeric also has been found to inhibit the growth of 19 clinical strains of Helicobacter pylori, a carcinogenic bacterium linked to increased risk of adeno-carcinoma of the stomach and colorectal adenomas.

A dietary supplement that is a salt-spice-herbal mixture, was found to protect rats against cancer induced by N-methyl-N-nitrosoguanidine, a potent carcinogenic nitrosamine. Possible mechanisms that explain the chemo-preventive role of Amrita Bindu include prevention of depletion of vitamins A, C, and E, and of the anti-oxidant enzymes glutathione peroxidase and superoxide dismutase in the liver of rats. These actions in turn, prevent the rise of lipid peroxidation in the plasma and liver and enhance glutathionine action in both blood and liver.[2,5,7]

MICRONUTRIENTS

Micronutrients play a significant role in maintaining health and preventing disease, including cancer, through a wide range of mechanisms: anti-oxidation, anti-proliferation, and repair of DNA damage. Direct and indirect relationships between micronutrients and health have been described in experimental, epidemiological, and clinical trials. Vitamin deficiencies, specifically of vitamins A, C, and E, may contribute to the high prevalence of oral cancers in India. A study carried out in rural India found that the presence of lesions was associated in patients with oral pre-cancerous lesions with low plasma levels of vitamins E and b-carotene. A study of Kurchias (a tribal population in Kerala, India, who consume a diet high in micronutrients and have a low prevalence of CHD and other chronic diseases of aging, including cancer) found that levels of serum vitamins A and E were inversely related to levels of lipid peroxides and coronary heart disease (CHD) risk factors. Micronutrient deficiencies of iodine, iron, and vitamin A are highly prevalent in Indian children. Among 6- to 14-year-olds, goiter, caused by iodine deficiency and related to thyroid cancer, has a prevalence rate of 0.33%-2.4%.[19]

DIETARY GUIDELINES AND ASSOCIATED SAFETY MEASURES

For the past 70 years, Indian Council of Medical Research (ICMR) has produced information on nutritional requirements specific to the population of India. Approximately every 10 years, ICMR updates nutrition recommendations based on evolving information from surveys conducted by National Institute of Nutrition (NIN), Hyderabad, India. The latest survey, completed in 2000, found that the Indian diet and nutrient intakes have hardly changed in the last 20 years. For cancer prevention, the NIN recommends a diet that include high intake of fresh vegetables and fruits, with spices such as turmeric, in adequate amounts.

Doctors at Tata Memorial Hospital, Mumbai, India, are reporting a rise in pre-cancerous lesions in the mouth, which they are convinced are caused by chewing tobacco. Mouth cancer has a 10-year incubation period. It is very hard to treat and spreads very quickly. As health experts know that children started using Gutkha 6 or 7 years ago, they fear an epidemic of oral cancer will soon hit India. Dentists and trading standards officers in United Kingdom are now trying to highlight the health risks involved in chewing tobacco as Gutkha slowly makes its way to Europe. Surgical excision (removal) of the tumor is usually recommended if the tumor is small enough, and if surgery is likely to result in a functionally satisfactory result. Radiation therapy is often used in conjunction with surgery, or as the definitive radical treatment, especially if the tumor is inoperable. Chemotherapy is commonly used for more advanced tumors, often in combination with radiotherapy and surgery. Biological agents, such as cetuximab, have recently been shown to be effective in the treatment of squamous cell head-and-neck cancers, and are likely to have an increasing role in the future management of this condition. Survival rates for oral cancer depend on the precise site, and the stage of the cancer at diagnosis. Overall, survival is around 50% at 5 years when all stages of initial diagnosis are considered. Survival rates for stage-1 cancers are 90%, hence the emphasis on early detection to increase survival outcome for patients. Following treatment, rehabilitation may be necessary to improve movement,
chewing, swallowing, and speech. Speech therapists may be involved at this stage.

**CONCLUSION**

Oral cancers are an important component of head-and-neck cancer, with tobacco chewing and smoking as the major causes. Therefore, oral cancer occurrence can be controlled by having healthy lifestyle without ignoring the role of diet in our daily routine life. Areca nut (AN) extract may demonstrate mutagenic and genotoxic effects, in addition to inducing pre-neoplastic as well as neoplastic lesions in experimental animals. AN should, thus, be highly suspected as a human carcinogen.

Toxicity studies relating to AN-contained polyphenols and tannins are not conclusive, with both carcinogenic and anti-carcinogenic effects being reported. The mutagenicity and genotoxicity of areca alkaloids has been detected by many short-term assays. However, their genotoxicity to oral fibroblasts and keratinocytes, the target cells of betel quid (BQ), has not been identified. It would thus appear that AN toxicity is not completely due to its polyphenol, tannin, and alkaloid content. The single agent that is responsible for AN carcinogenicity awaits further clarification. Reactive oxygen species produced during auto-oxidation of AN polyphenols in the BQ-chewer’s saliva, are crucial in the initiation and promotion of oral cancer. Nitrosation of areca alkaloids also produces AN-specific nitrosamines that have been demonstrated to be mutagenic, genotoxic, and are capable of inducing tumors in experimental animals. Arecaidine and AN extract are further suggested to be tumor promoters. Antioxidants such as glutathione and N-acetyl-L-cysteine can potentially prevent such AN-elicted cytotoxicity. Further studies are needed to delineate the metabolism of AN ingredient and their roles in the multi-step chemical carcinogenesis, in order to enhance the success of the future chemoprevention of oral cancer.

MicroRNAs (miRNAs) are small non-coding RNAs that mediate gene expression at the post-transcriptional level by degrading or repressing target messenger RNAs (mRNA). They are about 22 nucleotides in length and regulate mRNA translation by base pairing to partially complementary sites, predominantly in the 3’ untranslated region (3’-UTR) of mRNA. In this review, we discussed miRNA biogenesis and function, together with its possible involvement in oral cancer. Despite its great importance in normal cell development and diseases, a small number of studies have attempted to investigate miRNA in oral cancer. Overexpression of oncogenic miRNA may reduce protein products of tumor-suppressor genes. On the other hand, loss of tumor-suppressor miRNA expression may cause elevated levels of oncogenic protein. One or both of these alterations could represent new targets for cancer diagnosis and treatment in the future. Many researchers have focused on genetic and epigenetic alterations in oral squamous cell carcinoma cells. The emergence of miRNA knowledge, and its potential interactive action with such alterations, therefore, creates a new understanding of cell transformation.

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