Review Article

Oral cancer as a leading annoyance of the South Asian territory: An epidemiologic and clinical review

Vineet Gupta, Puneet Kumar[1], Prince Kumar[2], Suresh Yadav[3], Ashish Khattar[4], Shallu Tyagi[5]

Department of Oral and Maxillofacial Pathology, DJ Dental College and Hospital, Modinagar, Ghaziabad, Departments of [1]Public Health Dentistry and [2]Prosthodontics, Shree Bankey Bihari Dental College and Research Centre, Ghaziabad, Departments of [3]Oral and Maxillofacial Surgery, and [5]Pedodontics, Kalka Dental College, Meerut, Uttar Pradesh, [4]Private Practitioner, Pitampura, New Delhi, India

ABSTRACT

Oral cancer is one of the most fatal health problems faced by the mankind today. In India, because of cultural, ethnic, geographic factors, and the popularity of addictive habits, the frequency of oral cancer is high. It ranks number one in terms of incidence among men and third among women. Several factors such as tobacco and tobacco-related products, alcohol, genetic predisposition, and hormonal factors are suspected as possible causative factors. The exciting opportunity provided by the well-established oral precancerous lesions for intervention and early detection programs is also discussed. The poor survival revealed by existing studies is mainly due to the overwhelming proportion of advanced cases. The excellent opportunity for more research and efforts in prevention and control of oral cancer in India is highlighted in this review. Here authors sought to epidemiologically review oral cancer in South Asian province with special focus on major risk factors and future perspectives.

Key words: Oncogenes, oral cancer, squamous cell carcinoma, tobacco

INTRODUCTION

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.[1,2] Oral cancers are 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 hypo-pharyngeal cancer.[3,4] 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.[2,5,6] 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.[5-9] These are malignant and tend to spread rapidly.

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.106252

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

Address for correspondence: Dr. Prince Kumar, Department of Prosthodontics, Shree Bankey Bihari Dental College and Research Centre, Masuri, Ghaziabad, India. E-mail: princekumar@its.edu.in

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.[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.[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.[6,9] A fast-growing segment of those diagnosed does not present with the historic stereotypical demographics.[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.[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.

Figure 1: Smoke-related major risk factors

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.[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.[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.[22] 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.[17,20] 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.[22] 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%.[9]

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-elicited 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.

ACKNOWLEDGEMENT

The authors would like to express gratitude to their colleagues in India, especially Dr. Prince Kumar, for help regarding designing, preparation and editing of the manuscript.

REFERENCES

1. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, and the prevention of cancer: A global perspective/World Cancer Research Fund, in association with American Institute for Cancer Research. Washington, DC: American Institute for Cancer Research; 1997.
2. Schaefer EJ. Lipoproteins, nutrition, and heart disease. Am J Clin Nutr 2002;75:191-212.
3. Jeng JH, Chang MC, Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: Current awareness and future perspectives. Oral Oncol 2001;37:477-92.
4. Gomes CC, Gomez RS. Micro RNA and oral cancer: Future perspectives. Oral Oncol 2008;44:910-4.
5. Popkin BM, Horton S, Kim S, Mahal A, Shuigao J. Trends in diet, nutritional status, and diet-related noncommunicable diseases in China and India: The economic costs of the nutrition transition. Nutr Rev 2001;59:379-90.
6. Gopalan C. Rising incidence of obesity, coronary heart disease and diabetes in the Indian urban middle class. Possible role of genetic and environmental factors. World Rev Nutr Diet 2001;90:127-43.
7. Fenley J, Bray F, Pisani DM. World Health Organization. GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide. Lyon, France: IARC Press; 2001.
8. Seow A, Chia KS, Lee HP. Cervical cancer: Trends in incidence and mortality in Singapore 1968 to 1987. Ann Acad Med Singapore 1992;21:328-33.
9. Chambers JC, Wander GS, Kooner JS. Homocysteine and coronary heart disease amongst Indian Asians. Indian Heart J 2000;52:S5-8.
10. Chan CK, Singh J, Rasid BK, Devaraj T. Penang cancer cases reported to the National Cancer Registry of Malaysia, 1987-1990: An epidemiological analysis. Med J Malaysia 1994;49:122-31.
11. Sankaranarayanan R. Oral cancer in India: An epidemiologic and clinical review. Oral Surg Oral Med Oral Pathol 1990;69:325-30.
12. Gupta PC. Mouth cancer in India: A new epidemic? J Indian Med Assoc 1999;97:370-3.
13. Sinha R, Anderson DE, McDonald SS, Greenwald P. Cancer risk and diet in India. J Postgrad Med 2003;49:222-8.
14. Gajalakshmi V, Swaminathan R, Shanta V. An independent survey to assess completeness of registration: Population based cancer registry, Chennai, India. Asian Pac J Cancer Prev 2001;2:179-83.
15. Rao DN, Ganesh B, Rao RS, Desai PB. Risk assessment of tobacco, alcohol and diet in oral cancer-a case-control study. Int J Cancer 1994;58:469-73.
16. Patel PS, Raval GN, Patel DD, Sainger RN, Shah MH, Shah JS, *et al*. A Study of Various sociodemographic factors and plasma vitamin levels in oral and pharyngeal cancer in Gujarat, India. Asian Pac J Cancer Prev 2001;2:215-24.
17. Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M,

et al. Dietary exposures and oral precancerous lesions in Srikakulam district, Andhra Pradesh, India. Public Health Nutr 2002;5:303-12.
18. Ray A. Cancer preventive role of selected dietary factors. Indian J Cancer 2005;42:15-24.
19. Michels KB. The role of nutrition in cancer development and prevention. Int J Cancer 2004;114:163-5.
20. Krishnaswamy K, Polasa K. Diet, nutrition and cancer-the Indian scenario. Indian J Med Res 1995;102:200-9.
21. Oral, head and neck cancer basics. Available form: http://www.everydayhealth.com. [Last Accessed on 2012 Oct 1].
22. Head and neck cancer. Available from: http://en.wikipedia.org. [Last Accessed on 2012 Oct 1].
23. Benjamin P, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP. Human papillomavirus (HPV) in head and neck cancer. Cancer 1997;79:595-604.
24. Tyan YS, Liu ST, Ong WR, Chen ML, Shu CH, Chang YS. Detection of Epstein-Barr virus and human papillomavirus in head and neck tumors. J Clin Microbiol 1993;31:53-6.

Cite this article as: Gupta V, Kumar P, Kumar P, Yadav S, Khattar A, Tyagi S. Oral cancer as a leading annoyance of the South Asian territory: An epidemiologic and clinical review. Clin Cancer Investig J 2012;1:196-200.

Source of Support Nil, **Conflict of Interest:** No.