Review Article

Early detection and prevention of oral cancer: an appraisal

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ABSTRACT

Oral cancers (OC) represent the majority of head and neck cancers with more than half a million patients being affected each year worldwide. Oral squamous cell carcinoma is the sixth commonest cancer worldwide, accounting for approximately 4% of all cancers. Therefore, an improvement in the prevention and control of oral cancer is of critical importance. This may be achieved by reducing the risk through avoidance of tobacco and alcohol, recognizing and treating premalignant lesions and detecting developed OC at an early stage. Data search for the present review was done electronically. Electronic search was conducted using databases such as Pubmed and Medline, Cochrane library, articles published in peer-reviewed journals, text books, grey literature and from sites of World Health Organization, Centre For Diseases Control Report, Global Adult Tobacco Survey and Global Youth Tobacco Survey reports. This review ruled out web of causation and web of prevention including early detection and prevention to be an ideal strategy to reduce the prevalence of oral cancer and its impact on quality of life. Screening and early detection in population at risk have been proposed to decrease both morbidity and mortality associated with the oral cancer.

Keywords: Early detection, Prevention of oral cancer, Oral cancer

INTRODUCTION

Oral cancers (OC) represent the majority of head and neck cancers with more than half a million patients being affected each year worldwide.1 Oral squamous cell carcinoma (SCC) is the sixth commonest cancer worldwide, accounting for approximately 4% of all cancers. SCC of the oral cavity may comprise up to 50% of all cancers in developing and underdeveloped countries, and its prognosis is poor.2 Therefore, an improvement in the prevention and control of oral cancer is of critical importance. This may be achieved by reducing the risk through avoidance of tobacco and alcohol, recognizing and treating premalignant lesions and detecting developed OC at an early stage.3

Tobacco use, in any form, and alcohol use are the major risk factors for oral cancer. With dietary deficiencies, these factors cause more than 90 percent of OC. Preventing tobacco and alcohol use and increasing the consumption of fruits and vegetables can potentially prevent the vast majority of OC.4 When primary prevention fails, early detection through screening and relatively inexpensive treatment can avert most deaths. This review ruled out web of causation and web of prevention including early detection and prevention to be
an ideal strategy to reduce the prevalence of oral cancer and its impact on quality of life. However, oral cancer continues to be a major cancer in the Indian subcontinent.5

METHODS

Search methods

Data search for the present was done electronically. Electronic search was conducted using Databases such as Pubmed and Medline, Cochrane library, articles published in peer-reviewed journals, text books, grey literature and from sites of Government agencies such as World Health Organization, Centre For Diseases Control Report, Global Adult Tobacco Survey (GATS) and GYTS survey reports. The collected documents include original articles, reviews, short reports, letter to editor and editorials that focusses on prevalence of oral cancer, its early diagnosis and prevention.

Selection criteria

Studies on burden of oral cancer, screening for oral cancer or early diagnosis using visual examination, toluidine blue and preventive measures to curb it.

Data collection and analysis

All the articles collected were analysed according to the inclusion criteria which includes, prevalence, causes, early diagnosis and prevention of oral cancer. Studies not meeting the inclusion criteria are excluded (Figure 1).

200 articles identified through database searching

10 searches done using WHO, CDC sites

5 searches from the textbooks

215 records screened

40 records excluded

175 articles assessed for the eligibility

64 articles excluded with the reason

111 articles selected for the review

Figure 1: Methodology.

EPIDEMIOLOGY OF ORAL CANCER

Cancer is one of the major threats to public health in the developed world and increasingly in the developing world. In developed countries cancer is the second most common cause of death. According to the World Health Report 2004, cancer accounted for 7.1 million deaths in 2003 and it is estimated the overall number of new cases will rise by 50% in the next 20 years. In south-central Asia, cancer of the oral cavity ranks among the three most common types of cancer. In India, the age standardized incidence rate of oral cancer is 12.6 per 100,000 population.6

According to the statistics, in 2012 the incidence of oral cancer in India is 53842 in males and 23161 in females.7
Incidence of oral cancer increases by age. The commonest age is the fifth decade of life.8 Cancer in the tongue is the most common type of cancer and the common site is buccal mucosa and gingiva.9

Figure 2: Web of causation.

ETIOLOGY OF ORAL CANCER

Tobacco and tobacco products

Presently, it has been estimated that tobacco usage causes more than five million deaths worldwide, which is expected to rise up to more than eight million per year by 2030.10 As per the latest nationally representative GATS, India had 275 million current tobacco users in the year 2009-2010 (over 35 per cent of adults), majority of them used smokeless tobacco (164 million) and 42 million used both forms of tobacco.11 2-3% growth per annum of tobacco consumption in India and by 2020 it is predicted that it will account for 13% of all deaths in India two-forms. Tobacco is available in two-forms smoked and smokeless form.

Chemical constituents of tobacco

The most harmful compounds in smokeless tobacco are tobacco-specific nitrosamines and their levels are directly related to the risk of cancer. Smokeless tobacco has nicotine as an important constituent that causes addiction.12 Tobacco smoke contains many chemicals that are harmful to both smokers and nonsmokers.13 Of the more than 7,000 chemicals in tobacco smoke, at least 250 are known to be harmful, including hydrogen cyanide, carbon monoxide, and ammonia.14

Betel quid chewing

Habit of chewing areca nut is the major etiological factor of oral sub mllcous fibrosis (OSMF). Its extract acts as a
potent stimulator for collagen synthesis in human fibroblasts culture leading to excessive accumulation of collagen, leading to fibrosis. The high serum copper levels may also lead to generate high levels of free radicals by metal-catalysed Haber-Weiss reaction and this can be one of the reasons for the carcinogenesis in tobacco and areca nut users. \(^{15}\)

Alcohol

Moderate to heavy alcohol consumption is associated with higher risks of certain head and neck cancers. Alcohol may increase the risk of cancer, including: metabolizing ethanol in alcoholic drinks to acetaldehyde, acetaldehyde can damage both DNA and proteins generating reactive oxygen species, which can damage DNA, proteins, and lipids in the body through a process called oxidation. \(^{16}\)

Diet

According to World Health Organization reports, 35–55\% of human cancers and approximately 15\% of oropharyngeal cancers can be attributed to dietary deficiencies or imbalances. \(^{17}\)

The relationship between nutrition and cancer has to be approached from two different points of views. The direct effect of carcinogens presents in food and food additives. In vivo synthesis of carcinogens caused by changes in metabolism due to altered dietary habits. These add up to effects of diet on energy balance, risk of obesity, hormonal, and metabolic responses related to energy balance. \(^{18}\)

Genetic variations

Tumor cell chromosomes and alterations in these chromosomes resulted in conversion of normal to malignant proliferation. \(^{19}\) Chromosomal instability is a common feature of human tumors including oral cancer. \(^{20}\)

Approx. two-third of all head and neck cancer cells contain a deleted region located in chromosome 9p21-22. \(^{21}\)

Environmental factors

External environment

Involuntary exposure to many carcinogens in the environment, including microorganisms, radiations and many xeno chemicals, may account for the recent growing incidence of cancer and therefore that the risk attributable to environmental carcinogen may be far higher than it is usually agreed. \(^{22}\)

Internal environment

Poor oral hygiene with tobacco and alcohol consumption can destroy the integrity of the oral cavity. Improper toothbrushing and cleaning of adjacent soft tissues can leads to pre-malignant lesions. Use of chewing sticks or neem twigs leads to infrequent tooth cleaning is a prime cause of oral cancer. \(^{23}\)

Sunlight

Cancer of lip is the most common cancer. There is a strong association between exposure of sunlight and risk of lip cancer. \(^{24}\)

Viral infection

The majority of oral viral infections manifesting as oral diseases or cancers are caused by human herpesviruses and human papillomavirus. \(^{25}\)

Candidal infection

Candida and carcinogenesis is related to oral and oesophageal carcinoma. Candida might induce oral squamous cell carcinoma by directly producing carcinogenic compounds, for example, nitrosamines. \(^{26}\)

Point mutations thus induced may activate specific oncogenes and initiate the development of oral cancer. \(^{27}\)

CONFOUNDING FACTORS

Iron metabolism is important to maintain the health of oral mucosa, and many disease states, including cancers, are associated with Iron depletion. Serum Iron content can be a predictor for the progression of OSMF.

Vitamin C deficiency may reduce the availability of intracellular iron. Vitamin C is also necessary to convert folic acid to its active metabolite, folic acid. Deficiency of vitamin C can leads to oral cancer. Low socio-economic status may reflect exposure to harmful physical environments and agents which could increase the risk for oral cancer. Household income may have a direct impact on the housing and living environment which in turn affects health. It may also determine access to health services, social facilities and to the affordability of quality food.

These factors affect health and could potentially explain the association with increased oral cancer risk. \(^{28}\)

PREVENTION OF ORAL CANCER

Prevention can be defined as ‘the action of keeping from happening, or of rendering impossible, an anticipated event or act.’
Primordial prevention

Primordial prevention, a new concept, is receiving special attention in the prevention of chronic diseases. This is primary prevention in its purest sense, that is, prevention of emergence or development of risk factors in countries or population group in which they have not yet appeared.

In primordial prevention, efforts are directed towards discouraging children from adopting harmful lifestyles.

The main intervention in primordial prevention is through individual and mass education.

It aims to prevent the occurrence of the risk factors themselves by optimizing lifestyles that are associated with bad oral hygiene, improper diet, alcohol consumption, tobacco chewing and smoking. Such strategy requires tackling the roots of oral cancer risk factors by health promotion, healthy public policies, and improved physical environments conducive to healthy lifestyles throughout the whole course of life, from conception to older age. Very substantial health gains can be made for relatively modest expenditures on interventions.

Primary prevention

Primary prevention focuses on avoidance of known etiological factors and alterations in lifestyle to prevent cancer developing in the first place. This is particularly important because oral cancer is one of the few cancers with a high potential for prevention.

MODE OF INTERVENTION

Health promotion

It involves health education programs related to oral hygiene practices involving habit counselling and self-examination of oral mucosa.

Monthly self-examination routine

Supplies needed are flashlight, small mirror (optional), piece of gauze, wall mirror. It’s important to learn to recognize the normal healthy condition of your own mouth so that you can detect abnormal conditions and report anything unusual to a dental professional or a medical specialist.29
Antioxidants and fibre, with Diet assess The only cessation prevention additionally Intensive Behaviour counselling offered Because effective tobacco dependence treatments are available, every patient who uses tobacco should be offered at least one of these treatments are behaviour counselling and nicotine replacement therapy or pharmacological agents. Behaviour counselling Intensive counselling by a specialist increases quit rates additionally by 4-7% compared to normal. Relapse prevention strategies given individually suggest increased cessation rates by about 1.5-2%. Prochaska and Di Clemente have described a series of stages through which people pass in making changes in their behaviours. At each stage a person is thinking and feeling differently about the problem behaviour and finds that different processes and interventions help them move on to the next stage. The 5 A’s is a brief intervention method (or approach in counselling), used to guide the clinician in tobacco cessation counselling. This method can be effective and only takes 5-15 minutes. The 5 major steps in this intervention are ask, advise, assess, assist and arrange.30 Diet Among the dietary factors influencing cancer growth, with regard to the head and neck and especially oral SCC, fibre, antioxidants (β- carotene, tea, fresh fruits, and vegetables), animal fat, frying or broiling protein foods, and micronutrients (vitamin C, E, and K, zinc, folate) offer the best hopes for growth inhibition. Antioxidants Antioxidants can inhibit or decrease the production of components, which can induce cancer caused from frying or broiling protein and foods that generate heterocyclic amines. Consumption of six food items (i.e., milk, meat, cheese, carrots, green vegetables and fruits) was inversely and significantly correlated with development of oral cancer. Besides antioxidants, the beverage tea can act as an antioxidant and inhibit the carcinogenic effect of cigarette and tobacco, oesophagus or lung. Energy balance and fat food diet Essential fatty acids such as fish oil and vegetables rich in n-3 polysaturated fatty acids must be incorporated into diet and have a protective effect against cancer. Dietary factors associated with reduced risk of oral cancer include herbal tea, apple, margarine, milk, and citrus fruit or juice. Micronutrients Micronutrients like vitamin C, E, β-carotene, lycopene, folate, and zinc have important roles in carcinogenesis. Vitamin E and β-carotene can also cause regression of oral leukoplakia.31 Sunlight (actinic radiation) The incidence of lower lip cancer is higher in Caucasians in sunnier climates, and fair-skinned people are advised to wear sunscreen to prevent actinic damage.32 SECONDARY PREVENTION Secondary cancer prevention refers to early diagnostic and treatment of patients with oral premalignant lesions and screening the population at risk and asymptomatic.33 Mode of intervention is early diagnosis and prompt treatment. Early diagnosis Secondary prevention of cancer, or screening, involves the use of examinations and tests to detect a cancer as early as possible, before signs and symptoms would cause a patient to seek care. In some cases, the disease can be detected in a premalignant state (e.g., leukoplakia of the mouth.).34 Toluidine blue staining and cytology can be used for early diagnosis of lesions. These cellulo-morphological changes can be maintained and regularly updated on the annual basis in the process of detection of life threatening health hazards.35 Prompt treatment Chemoprevention Chemopreventive agents are directed toward secondary preventive stage where appropriate action can be directed toward early precursor lesions like leukoplakia. Intervention at this stage will reduce the morbidity and mortality associated with the oral cancer and also will not add financial burden to the patients.36 The use of specific natural and synthetic agents is directed toward secondary chemoprevention that has evolved as a promising strategy.
to inhibit, suppress or control the incidence of carcinogenesis.\textsuperscript{37}

Topical and systemic use of chemo preventive agents is an attractive alternative that reduces toxic effects.\textsuperscript{38}

\textbf{COMMONLY TRIED CHEMOPREVENTIVES IN ORAL CANCER}

Vitamin A and other retinoids, beta-carotene, vitamin E, dietary agents and newer agents.

\textbf{Retinoids}

Retinoids have been widely studied as chemo preventive agents. They have been shown to induce apoptosis, to suppress carcinogenesis, to decrease growth rate of epithelial cells, and to reduce free radicals.

\textbf{Vitamin A}

Vitamin A deficiency causes a change in the differentiation pathway, resulting in epithelial hyperplasia and squamous metaplasia. The mechanism underlying the chemo preventative effects of vitamin A and its derivatives is the restored expression of retinoic acid receptor-beta mRNA, which promotes normal tissue growth and differentiation.

\textbf{Beta carotene}

Beta carotene is a naturally occurring, nontoxic carotenoid with biologic properties that may be suitable against oral leukoplakia. Results of some trials indicate that beta carotene has substantial activity in oral pre-malignancy.

\textbf{Vitamin E}

Alpha-tocopherol is the only form of vitamin E that is actively maintained in human body. Vitamin E (alpha-tocopherol) is a potent antioxidant that neutralizes free oxygen radicals and inhibits 2 carcinogenic nitrosamine formation.

\textbf{Dietary agents}

A variety of grains, cereals, nuts, soya products, olives, beverages confer a protective effect against cancer. In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen containing as well as organosulfur compounds, which have been shown to suppress early and late stages of carcinogenesis.

Recently, the bioactive triterpene, lupeol, commonly found in fruits like fig, mango, etc., has attracted interest in the context of chemoprevention as its efficacy in inhibition of in vivo and in vitro cancer growth.

\textbf{Curcumin}

A spice widely used in Indian cuisine, has been identified to show considerable anti-tumor effects. It is a yellow pigment that is present in the rhizome of turmeric (\textit{Curcuma longa} L.) and related species and is one of the most extensively investigated phytochemicals, with regard to chemo preventive potential.

\textbf{Gingerol}

A phenolic substance that is responsible for the spicy taste of ginger (\textit{Zingiber officinale}) was reported to inhibit tumor promotion and PMA-induced ornithine decarboxylase activity and tumor necrosis factor production.

\textbf{Newer agents}

Potential new targets for chemoprevention, which are under consideration in oral cancer, include the following: H-ras gene, epidermal growth factor receptor inhibitors, p53 gene, COX-2 inhibitors, NF-KB.\textsuperscript{39}

\textbf{TERTIARY PREVENTION}

Tertiary prevention aims at the terminal stages. Mode of intervention is disability limitation and rehabilitation. Pain control and palliative care are major strategies of tertiary prevention.\textsuperscript{40}

Early-stage (I and II) oral SCC can be treated with surgery or radiation. In advanced- stage (III and IV) oral SCC, a combination of surgery and radiation therapy provides the best survival rate, although this increases the complications and morbidity.\textsuperscript{41}

\textbf{DISABILITY LIMITATION}

\textbf{Surgery}

Elective neck dissection to remove lymph nodes may be considered in selected cases, such as patients with stage I tongue cancer and stage II OC at other oral sites, who may be at high risk of microscopic but not clinically evident involvement of the neck nodes. Postoperative radiotherapy is indicated in patients with positive or involved resected margins who are not candidates for re-excision.\textsuperscript{3}

\textbf{Rehabilitation}

In the field of reconstruction, the development of microvascular surgery and the use of osseointegrated implants have allowed great improvements in function and esthetics. Microvascular free-tissue flaps allow the transfer of skin, fat, muscle, bone or any combination of these to primarily reconstruct the post ablative defect. The radial forearm flap has become the workhorse flap for soft-tissue defects, with the fibula or iliac
osseomyocutaneous flaps used for mandibular reconstruction.

The success of osseo-integrated implants, in both non-vascularized and vascularized bone grafts in patients with cancer, is well-substantiated. Implants have been placed successfully even in irradiated tissues. Certainly, however, the goal of providing patients who have oral cancer with teeth and the ability to manage a normal diet now is achievable.

**ORAL CANCER AND QUALITY OF LIFE**

The clinical manifestations of oral cancer and effects of treatment can lead to negative effects on the quality of life of the patient. Oral cancer has many physical, psychosocial and financial implications all of which can have large effects on the patients quality of life. Awareness of these impacts and their complexity can be used by health care providers to ensure to information and resources.

**Physical impact**

Treatment of oral cancer has adverse effects on the face, speech, voice and swallowing. Impairments can be attributed to the effects of the tumor itself or procedures before or during cancer treatment such as tracheostomy, pain from mucositis, xerostomia, amputation of oral structures or fibrosis due to radiation treatment. Self-esteem can be affected when normal facial appearance or communication ability is altered by oral cancer treatment.

**Esthetics impact**

Oral cancer treatment may include surgery that involves removing large areas of facial features. Altered facial appearance can cause social isolation and psychological distress. Reconstructive surgery may be necessary to help the patient recover facial features and functions.

**Speech impact**

Speech is usually affected by chemotherapy and radiation therapy. Typically, the severity is mild to moderate and is related primarily to treatment of the tongue, teeth, palate and lips. Patients with oral cancer may have trouble articulating speech rapidly when experiencing symptoms such as dry mouth or pain due to mucositis.

**Voice impact**

Voice quality in patients with oral cancer can be severely affected by different factors including impairment of vocal fold mobility, altered tongue anatomy and chronic laryngeal edema.

As a result, the patient’s voice can become strained, wheezy or harsh.

**Swallowing impact**

Dysphagia is a common result of oral cancer treatment. Patients with oral cancer have a higher risk of aspirating while eating due to the impact on efficiency and safety of swallowing.

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**Figure 4: Multiple psychosocial impacts on patients quality of life.**

- **Individual impact**
  - Poor coping mechanism
  - Withdrawal from social support

- **Family impact**
  - Abandonment of patient
  - Overwhelming patient

- **Healthcare provider impact**
  - Sense of omnipotence
  - Stress and burnout

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**Psychosocial impact**

Oral cancer represents a psychosocial challenge not only for patients but also for their family and diagnosing provider. Government institutions, nonprofit organization and internet forum are some of the available resources to assist patients with attaining balance in their lives at diagnosis, during treatment and through survivorship (Figure 4).

**CONCLUSION**

Cancer is a worldwide problem and oral cancer is one of the most prevalent cancers and one of the 10th familiar causes of death with a complex etiology. Despite advances in cancer treatment, the survival rates of patients suffering from head and neck cancer has not improved substantially. The data emphasize the necessity of early detection of the disease as survival is influenced by the extent of the disease at the time of diagnosis. Mortality and morbidity of oral cancer can be significantly reduced if detected in early stages. Screening and early detection in population at risk have been proposed to decrease both morbidity and mortality associated with the oral cancer. Findings suggest that the key to prevent oral cancer is to educate the mass in the primary level to quit the etiological factors. It can be concluded that tobacco cessation and nutritional intervention is one of the most valuable means of cancer prevention.

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