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Oral Carcinogenesis

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Oral cancer

Oral cancer is the sub group of head and neck malignancies that develop at the lips, tongue, and salivary gland, gingival, floor of the mouth, oropharnyx, buccal surfaces and other intra oral locations. It is estimated by WHO to be the fifth most common cancer worldwide. There are several types of oral cancer, but over 90% are squamous cell carcinoma worldwide (Shah *et al.*, 2003).

Epidemiology

An estimated 263, 900 new cases and 128,000 deaths from oral cavity cancers (including lip cancer) occurred in 2010 worldwide. Generally, the highest oral cavity cancer rates are found in Melanesia, South-Central Asia, and Central and Eastern Europe and the lowest in Africa, Central America, and Eastern Asia for both males and females. Oral cavity cancer mortality rates among males decreased significantly in most countries, including those of Europe and Asia, over the past decades (Mayne *et al.,* 2006). But rates continued to increase in several Eastern European countries, including Hungary and Slovakia. The increase in females in most European countries largely reflects the ongoing tobacco epidemic. This contrasts with the decreasing trends at all ages in both males and females in the United States and United Kingdom. The highest incidence rates of oral cancer occur in developing countries like Pakistan, Brazil, India, and France. India has always been cited as the country with the highest incidence worldwide. Sri Lanka and Pakistan are ranked at the top. In India alone over 100,000 cases are registered every year (Makita *et al.*, 2007).

Age and sex distribution

In most countries around the world, oral cancer is more common in men than in women. Thus oral/pharyngeal ratio is lower in men than in women, suggesting that some cancer. The risk of developing oral cancer increases with age and the majority of cases occur in people aged 50 or over. About 6% of oral cancers occur in young people under the age of 45 years (Llewellyn *et al.,* 2001). The rising incidence in oral and oropharyngeal cancer and mortality rates in young adults is reported from many countries in the European Union and parts of United States. In Scotland, where this trend was first reported, the incidence rate between 1990 and 1999 in males under 45 has more than doubled from 0.6 to 1.3 per 100,000. Fortunately, the disease is not more aggressive than that occurring in older adults either in the USA or in Southern England. (Warnakulasuriya *et al.*, 2007).

Risk factors

OSCC is a multi-causal disease with close interrelationships among etiologic factors includes lifestyle habits (tobacco exposure and alcohol consumption), dietary factors, occupational activity, socioeconomic status, exposure to external agents, and genetic susceptibility (Franceschi *et al.*, 2000).

Tobacco

Smoking and tobacco use are considered the strongest risk factors for oral cancer. Cigarettes, cigars, or pipes, tobacco chewing, and dipping snuff are all linked to oral cancer. The uses of other tobacco products also increase the risk of oral cancer. The major carcinogen in tobacco belongs to the family of nicotine derived nitrosoamines collectively called "tobacco specific nitrosamines". Polynuclear aromatic hydrocarbons such as Benzo[a]pyrene and aromatic amines are the other carcinogens found in tobacco. (Manjari *et al.*, 1999).

Betel quid and Areca nut

Betel chewing is reported to be the most important etiological factor in oral sub mucous fibrosis. The use of betel quid, containing both areca nut and tobacco, is associated with a much higher relative risk of oral cancer (Kwan, 1976)

Alcohol

Alcohol exerts an independent effect on risk for oral cancer and acts synergistically with tobacco use to increase risks dramatically. The effect of alcohol may be direct e.g N-nitroso compounds, mycotoxins, tannins, aldehydes, among others, as well as systemic. Intermediate metabolites of alcohol, such as acetaldehyde, may be more toxic than the direct action of alcohol on the mucosa. Additionally, the effects of alcohol may be mediated through the production of prostaglandin, lipid peroxidation and the generation of free radicals mediated reactive oxygen species, both may induce specific DNA

mutations and cancer. Several studies were reported that alcohol is the major risk factor for oral cancer (Mufti et *al.*, 1993).

Diet and Nutrition

There is a strong epidemiological evidence for a protective effect of fruits and vegetables against most of the important human cancers. Diet high in vegetables, fruits, tea, and fiber decreases the risk of oral and pharyngeal cancers because these nutrients can prevent the activation of carcinogens and increase their detoxification. Micronutrients like vitamin C, E, β-carotene, folate and Zinc have an important role in prevention of oral cancer. These factors can cause polymorphism in detoxifying enzyme GST and other metabolic genes which modulate the risk of cancer and decrease the genotoxic damage. According to world health organization (WHO) reports 35-55% of human cancers and approximately 15% of oropharyngeal cancers can be attributed to dietary deficiencies or imbalance. Several studies were reported that imbalance of fruits and vegetables may caused by oral cancer (Stewart and Kleihues, 2003).

Radiation

Ultraviolet radiation (e.g. from excessive exposure to sunlight) can damage the cells in lips is a risk factor in the development of lip cancer. Several studies were reported that UV radiation caused by lip cancer (Gallagher *et al.,* 2010).

Viral infection

Human papilloma virus (HPV) could also be considered to be related to life style and it is strongly associated with the development of oropharyngeal cancers. The role of HPV in the development of OSCC is less well established and probably involves only a small minority of cases, generally estimated around 5%. (Gillison *et al.*, 2000).

Epstein-Barr virus

The Epstein-Barr virus (EBV) is a member of the herpes virus family. Even though its contribution to malignant transformation of B lymphocytes has been well established, the influence of EBV in the pathogenesis of oral squamous cell carcinoma remains elusive. It has been reported the EBV is more frequently detected in oral lesions such as oral lichen planus and oral squamous cell carcinoma in comparison with healthy oral epithelium (Sand *et al.*, 2002).

Hepatities C virus

Squamous cell carcinomas have been reported in HPV-infected patients, while HCV infection has been found to be more prevalent in patients with oral lichen planus. However, 1-2% of the patients with oral lichen planus develop squamous cell carcinoma of the oral cavity, which implies the existence of common pathogenic mechanism among them finally HCV-RNA strands were detected in OLP tissues and

there is evidence to indicate that HCV may occasionally replicate in oral lichen tissue and contribute to mucosal damage (Nagao *et al.*, 1995).

Socio economic status (SES)

A review of oral cancer incidence and mortality in different socioeconomic levels around the world concluded that most studies did not show a clear trend in terms of incidence but excess mortality was observed for lower SES in various populations. SES may affect a variety of lifestyle factors that alter the risk of oral cancer as well as oral premalignant lesions, including tobacco chewing, smoking and alcohol drinking. Subjects with low SES may additionally have less fruit and vegetable and vitamin intake. Studying the association of SES and oral premalignant lesions may help to clarify its possible association with oral cancers (Faggiano *et al.*, 1997).

Symptoms

- Red, white or red and white patches in the mouth (white patches are most common)
- Changes in the soft tissues of the mouth, including lumps, swelling, crusting and eroded tissue
- Mouth sores that do not heal within two weeks
- Bleeding from the mouth
- Pain or tenderness in the face, mouth or neck
- Persistent ear pain
- Facial numbness
- Difficulty chewing, swallowing or speaking
- Chronic sore throat
- Hoarseness
- Loose or shifting teeth or a change in the dentures fit
- Unexplained weight loss (Wein *et al.,* 2010).

Early warning

If any of these signs or symptoms persists for more than three weeks, see your dentist or physician for an evaluation. Any suspicious area in the mouth usually requires a biopsy to confirm the presence of cancer.

Premalignant lesions

Many oral SCCs develop from premalignant conditions of the oral cavity. A wide array of conditions have been implicated in the development of oral cancer, including leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, oral submucous fibrosis, discoid lupus erythematosus, and hereditary disorders such as dyskeratosis, congenital and epidermolysis bullosa. (Elwood *et al.*, 1984)

Despite the general accessibility of the oral cavity during physical examination, many

malignancies are not diagnosed until later stages of disease. In order to prevent malignant transformation of these precursor lesions, multiple screening and detection techniques have been developed to address this problem. The early detection of cancer is of critical importance because survival rates markedly improve when the oral lesion is identified at an early stage.

Diagnosis

Early diagnosis of oral cancer is a priority public health objective, in which oral health professionals should play a leading role. Early detection of cancer should lead to less damage from cancer treatments and to a better prognosis. Early detection of cancer distinguishes ‘‘screening” (application of a test to evaluate presence of the disease in asymptomatic individuals who apparently do not suffer from it) from ‘‘detection of cases” (application of a particular procedure to patients with an identified lesion). Conventional oral exploration (visual and palpation examination) constitutes the gold standard screening study for oral precancer and cancer; the relevant study for the detection of cases is the biopsy and histopathological diagnosis. There are also a number of techniques that may variously contribute to the diagnosis of oral cancer. (Kaczmarczyk *et al.*, 2011)

Biopsy

To establish with certainty the diagnosis of the oral cancer, a pathologist will take tissue sample from mouth, specifically from the area where the tumor is suspected, in order to perform a microscopic examination. If cancer cells are found, your doctor will determine how fast they multiply to recommend the most appropriate and effective treatment. (Seoane *et al.*, 2002).

Toluidine blue *(TB)*

The use of toluidine blue (tolonium chloride) as a diagnostic aid for the detection of oral cancer has been evaluated in a large number of studies over many decades. It has also been suggested that TB may provide information on lesion margins, accelerate the decision to biopsy, and guide biopsy site selection and the treatment of oral potentially malignant and malignant lesions (Epstein *et al.*, 2007).

CT and MRI scan

Dental panoramic tomography (DPT), computed tomography (CT), and magnetic resonance imaging (MRI) are frequently used to supplement the clinical evaluation and staging of the primary tumor and regional lymph nodes. CT is the technique of choice to evaluate bone invasion by the tumor. The introduction of cone beam computed tomography (CBCT) provides and alternative for the preoperative study of

patients with oral cancer to determine the degree of invasion and extension of the lesion towards the jaw bones. MRI is more informative when evaluating the extent of soft tissue invasion, neurovascular bundle infiltration, and cervical lymph node involvement (Closman *et al.*, 2007).

Prevention

The decreased prevalence of oral cancer, the following must be considered, avoiding tobacco, limiting alcohol intake, choosing a predominantly plant-base diet, reducing fat intake (Monosaturated type), red or processed meat, avoiding exposure of meat to open flames, usage of aluminum foil to wrap meat before roasting and using microwave ovens in order to reduce formation of heterocyclic amines. Intake of optimal levels micronutrients such as vitamin C, E, β-carotene, folate and antioxidant are recommended (McLaughlin *et al.,* 1988).

Genetic alterations in oral squamous cell carcinoma

OSCC arises from an accumulation of molecular lesions in two major classes of genes: Tumor suppressor genes (TSG), which promote tumor development when inactivated and oncogenes, which promote tumor development when activated. Most activated oncogenes initiates' cellular growth, but inactivated TSGs lose control over the cell cycle. The uncontrolled growth signal for proliferation may be induced by different members of the signal transduction pathway, such as growth factor and/or their receptor, cytoplasmic protein kinases and nuclear transcription factors (Califano *et al.*, 1996).

They found that the most common genetic alteration in SCCHN is loss of chromosomal region 9p21, which occurs in 70-80% of dysplastic lesions of the oral mucosa, suggesting that this loss is an early event in oral carcinogenesis. This region of chromosome 9p21, known as the CDKN2A locus, encodes the tumor suppressors p16 and p14ARF, which frequently are inactivated by promoter hypermethylation (Reed *et al.*, 1996).

Loss of the chromosome 3p region is another common early genetic alteration in oral carcinogenesis. The chromosome 3p region includes *FHIT* (fragile histidine triad gene) and RSSFIA, tumor suppressor genes inactivated by exonic deletion and hypermethylation. Loss of heterozygosity (LOH) of chromosome region 17p and mutation of the p53 gene are genetic alterations that occur in the later stage of progression from dysplasia to invasive squamous carcinoma (Dong *et al.*, 2003).

Alterations of p53, including mutation or deletion, are associated with increased genomic instability in oral dysplasia and may accelerate the rate of genetic alterations in oral carcinogenesis. Amplification of 11q13 and overexpression of cyclin D1 have been described

in 40% of cases of oral squamous dysplasia. In general, loss of chromosomal material at 9p, 3p, and 17p is observed in relatively high proportions of dysplastic lesions, indicating that those events are early markers of oral carcinogenesis, whereas losses at 13q and 8p are observed more frequently in carcinomas than in dysplasia and are associated with later stages of carcinogenesis (Califano *et al.*, 1996).

Treatment

Treatment of oral cancer depends on the type of cancer and the stage of the cancer. Early stage (I and II) oral cancer may be curable by surgery or radiation therapy alone but advanced cancer (stage III and IV) are generally treated by surgery followed by radiation therapy. Chemotherapy may also be used, particularly in patients with confirmed metastases to other tissues and organs (Harris *et al.*, 1998).

Chemotherapy

With chemotherapy, drugs are used to destroy cancer cells. Take these drugs either through veins (intravenously) or orally. The type of drugs and the length of treatment depend on the size, type, and location of the tumor. Chemotherapy may also be used before surgery in order to shrink a tumor. Or, in the case of a large and invasive tumor, chemotherapy may be used in combination with radiation therapy and in place of surgery (Al-Saleh *et al.*, 2011).

Surgery

The type of surgery needs depends on the size and location of the tumor. For tumors that have invaded nearby tissues, surgery is more extensive. Sometimes surgeons need to remove bone from the jaw or roof of the mouth. To treat a cancer of our tongue or the upper part of our throat, our surgeon may need to remove tissues from the oral region (larynx). If the cancer has spread beyond the mouth, surgeon also may need to remove lymph nodes in the neck (Ozkan *et al.*, 2005).

Radiation therapy

Radiation therapy uses X-rays to kill cancer cells. This approach also may be used along with surgery to destroy small amounts of cancer cells that couldn't be removed during surgery. These treatments also affect the normal tissues near the tumor and may result in dry mouth, loss of teeth, skin changes and loss of hair follicles. The side effects of radiation and other cancer treatments must be discussed in detail with the physician and with the dentist who will care for you after the treatment is done (Perri *et al.*, 2011).

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