ORAL CANCER: RISK FACTORS, PREVENTION AND DIAGNOSTIC

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Although oral cancer is rare and attracts little attention, it ranks 12th among all cancers and constitutes the most life threatening of all dental conditions. The aetiology of oral cancer is multi-factorial and like other types of cancer, the key to decreasing the suffering of patients and increasing their survival rate is early detection. The global increase in frequency and mortality of oral cancer has intensified current research efforts in the field of prevention and early detection of this disease. Therefore, scientists have been searching for alternative approaches to biopsy. A number of molecular-based diagnostic markers have been used to detect the presence of oral cancer with varying degrees of sensitivity and specificity. In this paper, incidence, mortality, risk factors, prevention, and diagnostic of oral cancer have been reviewed.

Key Words: oral cancer, incidence and mortality, risk factors, prevention, diagnostic.

The term “oral cancer” (OC) includes a diverse group of tumors arising from the oral cavity. Usually included are cancers of the lip, tongue, pharynx, and oral cavity. The World Health Organization (WHO) reported oral cancer as having one of the highest mortality ratios amongst all malignancies [1]. Although OC is rare and attracts little attention, it is more common than Hodgkin’s disease or tumors of brain, liver, bone, thyroid gland, stomach, ovaries, or cancer of the cervix. It ranks 12th among all cancers [2]. The vast majority of malignant neoplasms in the mouth are squamous cell carcinomas (SCC). The aetiology of OC is multi-factorial. Genetic, environment, social and behavioral effects may all be implicated [3]. It is well known that alcohol and tobacco are two of the most important risk factors for development of OC. The consumption of alcohol and tobacco is closely associated not only with the development of OC, but also with the course of the disease and this consumption is associated with a poor prognosis [4]. Thus, environmental insults such as alcohol, ultraviolet light, and/or tobacco products presumably increase DNA damage, reduce murine double minute (MDM2), increase p53 expression, and thereby activate clusters of genes associated with cell growth, and/or cell death [5]. Many studies reported that, up to three-quarters of OC could be prevented by avoiding environmental factors, notably the consumption of tobacco and excess alcohol [6, 7]. The lack of public awareness of the signs, symptoms and risk factors associated with oral cancer has been reported [8]. Unfortunately, most oral cancers lack early signs [9], and despite improvements in diagnostic and therapeutic modalities, the prognosis of patients with oral malignancies has remained poor.

INCIDENCE AND MORTALITY

OC incidence and mortality rates vary widely across the world. Mortality rate is an important tool that provides implicit information about incidence, diagnosis stage, solving capacity of health services, available technology and health programs to be applied, among others. Although globally oral cancer represents an incidence of 3% (males) and 2% (females) of all malignant neoplasms, it has one of the lowest survival rates — 50 percent, within a five-year period [11]. There has been a nearly five-fold increase in incidence in oral cancer patients under age 40, many with no known risk factors [12, 13]. Study shows that one American dies from oral cancer every hour [14]. OC incidence in men is higher in the Bas Rhin in France, in the south of India, where is the most common cancer, in some areas in the center and east of Europe, and in some regions of Latin America [15, 16]. The highest incidence was registered in India in women with a moderate rise in mortality, in the Central and Eastern Europe in the 1980’s and 1990’s [17]. Cohort studies show that OC incidence has risen in all the age groups throughout the world in the last decades [16], especially in young men in Eastern European countries, such as, Estonia, Hungary, Ukraine, and Russia [17, 18]. In Australia, the incidence of OC in New South Wales increased by 27% in men and 3% in women the periods 1973–1977 and 1988–1992 [19], and most of the increase occurred in the early 1980’s in parallel with similar trends in Europe and the United States [20]. The risk of dying from OC in Australia is low and more than 75% occurred in people aged 60 years or older [19]. The prevalence of oral cancer in India is up to four times higher than in other countries [16]. Overall, comparisons are difficult
considering that OC mortality rate and incidence data are not published using the same format [16].

THE RISK FACTORS

**Tobacco.** All forms of tobacco — cigarettes, pipes, cigars, and smokeless tobacco have been implicated in the development of OC [21]. While tobacco confers the highest risk for OC of the floor of the mouth [22] also, it is associated with an increased risk for all sites of OC. Tobacco use is responsible for 90% of OC deaths in males [23].

**Alcohol.** Alcohol use is a second independent major risk factor for the development of OC [24, 25]. For non-smokers it is the most important risk factor. Above 30 grams of alcohol per day, risk increases linearly with amount of alcohol consumed [26].

**Chewing tobacco.** In addition to tobacco use, the use of chewing products such as betel nuts, paan, chauli, gutka, naswar, and areca increases the risk for OC; these products are socially acceptable in South Asia, the South Pacific Islands, and India [27].

**Shammah.** Shammah, a traditional smokeless tobacco habit in the Arabian Peninsula, has a significant association between the prevalence of leukoplakia and the daily duration of shammah application — in a dose-dependent manner [28].

**Marijuana.** The carcinogenic properties of marijuana smoke are similar to those of tobacco. Marijuana use may interact with mutagen sensitivity and other risk factors to increase the risk of head and neck cancer [29].

**Poor nutrition.** Dietary deficiencies, particularly of vitamin A, vitamin C, vitamin E, iron, selenium, folate and other trace elements have been linked to increased risk of OC [30, 31]. Intervention studies where diets have been supplemented have shown some beneficial effect on pre-malignant conditions and reducing the risk OC, but further work into diet and the role of chemoprevention in oral cancers is needed [32, 33].

**Ultraviolet light.** Solar irradiation is a major risk factor for cancer of the lip. The vast majority of lip cancer occur on the lower lip and many patients have outdoor occupations where sun exposure is increased. Lip cancer is three times more common in men than women which may be an effect of occupation, smoking and sun-exposure [34].

**Irritation.** Although it has been suggested that chronic irritation to the lining of the mouth from poorly fitting or defective complete dentures may be a risk factor for OC, the majority of studies have shown no correlation [35].

**Dental plaque.** Polymicrobial supragingival dental plaque is a possible independent risk factor, as it possesses a relevant mutagenic interaction with saliva, and thus oral health may be a co-factor in the development of OC [36].

**Mouth rinses.** Ethyl alcohol is added to mouth rinses as a solvent for other ingredients and as a preservative. Study shows that cancer was not statistically associated with mouthwash use in alcohol or tobacco users [37]. Currently, there is insufficient clinical evidence to suggest a relationship between ethyl alcohol found in mouth rinses and OC [38].

**Candidiasis.** Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is an autosomal recessive disease associated with a limited T lymphocyte defect, and exceptionally common in Finland, seems to favour the growth of Candida albicans and predispose to chronic mucositis and OC [39].

**Diabetes.** The molecular basis for the putative association of diabetes mellitus with oral squamous cell carcinomas (OSCC) from epidemiological studies, may involve insulin receptor substrate-1 and focal adhesion kinase [40].

**Free radicals.** Free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) can function both as initiators and promoters in carcinogenesis, while antioxidants provide protection against the cellular and molecular damage caused by reactive oxygen species and reactive nitrogen species [41]. The increase in ROS and RNS may have been the event that led to the consumption and reduction of salivary antioxidant systems, thus explaining the oxidative damage to the DNA and proteins, and possibly the promotion of OC [42].

**Viruses.** The role of viruses remains unclear. Evidence is perhaps strongest for infection with high-risk human papilloma viruses (HPV) [43–45]. Studies show an increased risk of OC in women with cervical cancer suggesting a common risk factor other than smoking, such as HPV infection: transmission of HPV via oral sex is one possibility. A recent multicentre case control study reported that infection with HPV-16 increased the risk of cancer of the oral cavity and particularly oropharynx [46, 47]. The role of infection with Epstein-Barr virus and herpes simplex viruses (HSV) remains uncertain [48]. The role of herpes simplex viruses, HSV-1 and HSV-2, as co-factors in association with tobacco, alcohol, or HPV-16 infection has also been examined [49]. Heavy use of tobacco, alcohol and HPV-16 infection was associated with an increased risk of OSCC but, after adjusting for age, tobacco, alcohol use, and number of sexual partners, the risk of cancer was not significantly increased in those with HSV-1 or HSV-2, though seropositivity to HSV-1 and HSV-2, may modify the risk associated with exposure to tobacco, alcohol, or HPV [49]. In a study using a fuzzy logic technique, HPV infection showed an association with OC [50].

**Family History.** Family history of OC is a risk factor.

**Head and neck cancer patients show an increased susceptibility to chromosome damage by mutagens [51]. Study used cDNA array and identified genes such as keratin 17 and 19, laminin-5, connexin-26 and vascular endothelial growth factor (VEGF) as being differentially expressed in head and neck SCC tissues, with respect to normal tissue [52].

PREVENTION OF ORAL CANCER

**Primary prevention.** Primary prevention has been estimated to be the most cost-effective method of preventing OC [53]. Previous study has shown poor public
Secondary prevention. Intervention and excision of leukoplakias and erythroplakias combined with elimination of risk factors associated with their development, reduces the incidence of OC [56]. Opportunistic screening for OC can be carried out during patients’ regular visits. Patient with positive finding should be referred to a specialist for a definitive diagnosis, biopsy and further management.

CURRENT EXPERIMENTAL MODELS

Several animal models have been used for investigation of carcinogenesis and development of diagnostic [57]. The most commonly used model is 7,12 dimethylbenz(a)anthracene (DMBA)-induced hamster cheek pouch carcinogenesis model [58]. Treatment by the administration of 4-nitroquinoline 1-oxide (4-NQO) in drinking water can induce tumors in oral cavities mice [59], and 4-NQO-induced rat tongue carcinogenesis [60]. Also, nitric oxide (NO) plays an important role in both carcinogenesis and tumor progression [61]. A significantly higher expression level of inducible nitric oxide synthase (iNOS) was found in rat tongue cancer induced by 4-NQO [62].

CURRENT ORAL CANCER DIAGNOSTIC

Clinical examination and histopathological studies of biopsied material are the classical and the most accepted diagnostic methods used for precancerous and cancerous oral lesions. While conventional oral examination may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant and/or malignant lesions. On the other hand, biopsy is a technique with surgical implications, technique limitations for some professionals, and psychological implications for some patients. Since most OCs arise as asymptomatic small lesions, formal diagnosis procedures begin only when the clinician or patient notices abnormal tissues [63]. Furthermore, microscopic investigation of the progressive cancer is often conducted too late for successful intervention [64]. Also, it is impractical to use imaging techniques for cancer screening, since they are time-consuming and expensive. These techniques are typically used for confirmation due to their insensitivity for small lesions [65]. With this in mind, scientists have been searching for alternative approaches. In this regard, cytokeratin expression profile provides useful information on cell differentiation status [66], but its potential for early diagnosis of OC is limited [67]. Furthermore, certain cytokeratins, such as K8 and K19 [68], are useful if not definitive indicators of malignancy, particularly if their presence is interpreted in conjunction with other information, such as DNA profile [69]. Mutation of the tumour suppressor gene p53 is another frequent genomic change in human cancers [70]. According to most studies, p53 is not present in normal oral mucosa [71, 72], but it is detectable by immunohistochemical methods in SCCs and potentially malignant lesions of the oral mucosa [73]. Likewise, p53 has been detected in cells of malignant tumours obtained by exfoliative cytology [74]. In addition, p53 mutations are present in only about 50% of squamous cell carcinomas of the oral cavity, and only seen at advanced stages of carcinogenesis [75]. Therefore, early diagnosis of OCs on the basis of p53 detection in oral mucosa smears is not a useful option, since exfoliative cytology does not obtain basal epithelial cells [76]. A dramatic switch from histopathological to molecular methods of disease diagnosis [77], and exfoliative cytology has gained importance as a rapid and simple method for obtaining DNA samples. Loss of heterogeneity (LOH) and other molecular changes indicative of oral carcinogenesis can be readily identified in exfoliated cells [78]. Polymerase chain reaction (PCR) techniques to amplify DNA from exfoliation samples from oral carcinomas, for analysis of restriction-fragment length polymorphisms (RFLPs) have been used [79]. They found that 66% of the tumours studied showed LOH at one position in the p53 sequence, while 55% showed LOH at some other location. Leukoplakia is a marker of an increased risk of OC, but there are no reliable clinical or histological features that can be used to predict whether the lesion will regress spontaneously or progress to cancer. Microsatellite analyses have been used to identify novel molecular targets (e.g., p16, p53, and cyclin D1) for chemopreventive drugs that could be useful in the treatment of oral leukoplakia [80]. NO could stimulate tumor growth and metastasis by promoting the migratory, invasive and angiogenic abilities of tumor cells, which may also be triggered by the activation of cyclooxygenase-2 (COX-2) [81]. Recently, much attention has been paid to the role of COX-2 in carcinogenesis. It’s also extensively expressed in OC and oral premalignant lesions and seems to be enhanced specifically in high-risk oral lesions [82]. A significantly higher expression level of iNOS was found in the human OSCC [83]. As a result, iNOS generating NO, and might be able to play an important role in OC progression. It is well known that saliva is a wonderful marker of early disease detection that leads to more effective treatment, risk assessment for future oral and systemic disease and a simple, non-invasive alternative to blood and urine tests. The study of salivary endothelin-1 (ET-1) levels in patients diagnosed with OSCC prior to treatment showed significantly raised salivary ET-1 levels in the OC, relative to controls, suggesting a potential utility of salivary analysis for ET-1 levels for monitoring patients at risk for OC [84]. In addition, detection of antioxidant enzymes may be a useful future marker in the molecular diagnosis of the OC [85].

CONCLUSIONS

OC constitutes the most life threatening of all dental condition. Unfortunately, most malignant oral tumors are not detected until they are in advanced stages. In essence, this poor outcome is related to the majority of patients presenting at an already advanced stage of disease at the time of diagnosis. Even though the biopsy study is fundamental, it is a diagnostic method
with limited sensitivity where one of the most important features is the subjectivity of the pathologist. In the last few years the interest in new diagnostic and prognostic methodology and also for monitoring patients in oral precancer and cancer has re-emerged. Furthermore, a number of molecular-based diagnostic markers have been used to detect the presence of OC with varying degrees of sensitivity and specificity. But, still lack of specific tumoral markers present in all malignant lesions of the oral cavity.

REFERENCES


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РАК РОТОВОЙ ПОЛОСТИ: ФАКТОРЫ РИСКА, ПРОФИЛАКТИКА И ДИАГНОСТИКА

Рак ротовой полости — редкое заболевание, не привлекавшее до недавнего времени особого интереса у исследователей. Указанная патология находится на 12-м месте среди других форм рака по частоте возникновения и относится к наиболее опасным заболеваниям ротовой полости. Этиология рака ротовой полости обусловлена многими факторами. Как при других злокачественных заболеваниях, ранняя диагностика способствует повышению уровня вызываемости и облегчению страданий больных. Повышение частоты заболеваемости и смертности от рака ротовой полости во всем мире привело к повышению интереса к исследованиям в области профилактики и ранней диагностики данной патологии. Таким образом, начался поиск новых подходов, которые могли бы стать альтернативой биопсии. Для выявления рака был использован ряд молекулярно-биологических маркеров с разной степенью чувствительности и специфичности. В данном обзоре рассмотрены современные представления о частоте возникновения, показателях смертности, поиске факторов риска, профилактике и диагностике рака ротовой полости.

Ключевые слова: рак ротовой полости, частота возникновения, смертность, факторы риска, профилактика, диагностика.