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Review

Preventive measures in oral cancer: An overview

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ABSTRACT

Worldwide oral cancer is creating an alarming situation and it's a matter of global concern as it is the 11th most common carcinoma around the globe. After cardiovascular ailments, cancer is the next biggest killer. Approximately 90% of the total oral malignancies are squamous cell carcinomas. The etiological base of oral cancer is tobacco intake, smoking, smokeless tobacco (snuff or chewing tobacco), alcohol and areca nut intake, excessive sunlight exposure, reverse end smoking and Human Papilloma Virus (HPV). The treatment measures for oral cancer are very costly and affordability is low. So, taking preventive measures at the first place itself is of immense importance. Preventive measure is a multidisciplinary approach involving co-ordinated efforts from all the sectors of the society. The preventive measures are categorised into primary, secondary and tertiary measures. Along with the various screening tests employed to detect oral cancer the review focuses on biomarkers, melatonin, tea constituents, polyphenols, chemoprevention, Chios mastic gum extract, Poly (ADP-ribose) Polymerase 1 (PARP1) targeted optical imaging agent, and their role in oral cancer prevention and control. The review gives a brief outline on the preventive measures to be adopted to help prevent oral cancer and improve the quality of life.

1. Introduction

Oral cancer is rising day by day. Squamous cell carcinomas account for 90% [1]. Invasive squamous cell carcinoma means that the cancer cells have spread to deeper parts of the oral cavity [2]. 75% of oral cancers are related to lifestyle choices. The distribution of oral cancer is approximately 32% in buccal mucosa, 22% in tongue, 11% in lower lip, 11% in palate, 8% in vestibule, 5% in alveolus, 5% in floor of the mouth, and 3% in gingiva [3]. The occurrence of oral cancer are high in countries like India, Taiwan, Sri Lanka, Pakistan and Bangladesh [4]. Approximately 25% of all upcoming cases are oral cancer in these countries and it is seen majorly in men [4]. The International Agency for Research on Cancer has recently stated that smokeless tobacco can be considered as a cause of oral cancer [5]. The risk factors are many including smoking, betel nut, tobacco chewing, drinking, poor nutrition, HPV virus, mouth washes with a high alcohol content, poor oral hygiene, immune system suppression, age, gender, *etc.* Other risk factors include genetic factors, mate drinking and chronic trauma [6,7]. But there are strong synergistic effects if the person is both a smoker and a drinker [8]. Tobacco smoke includes more than 4000 chemicals and 60 of them are found to be carcinogens which include nicotine, methoxy methyl furfural, arsenic, and methanol [9]. Alcohol increases the activation of procarcinogens & behaves like a solvent for entry of harmful carcinogens into the body cells. Once the tumor attains a finite size, pain in the area develops and medical assistance comes into action [10]. As they are asymptomatic at the earlier stages, detection of oral cancer becomes difficult. Diagnosis at the earliest stage is therefore very important for increasing the rates of patient survival. The survival rates are approximately 80–90% when detected at the earliest [10].

The delay in detection leads to higher chances of mortality. This poor survival rate has not improved despite several treatment options available. Hence the major goal is to focus on preventive measures at the first place so that mortality due to oral cancer is reduced and is in control.

Screening methods employed is for early detection and prediction of oral cancer which includes OralCDx, Vizilite, VizilitePlus, Micolux/DL, Orascoptic DK, and VELscope [11]. These help to locate the oral cancer and help in diagnosis. Salivary biomarkers like L-phenylalanine, angiogenetic marker *i.e.* Cluster of differentiation factor 34 (CD34), Genomic biomarkers such as integrin α3 and integrin β4, Cloning of an acidic laccase gene 2 which is a proteomic biomarker aid in early diagnosis, monitoring and differentiation of oral cancer [12]. Favourable agents for chemoprevention of oral cancer include β-carotene, retinoids, N-acetyl cysteine, NSAID's, vitamin-E, retinoids, and curcumin [13,14]. Melatonin which is secreted by the pineal gland also plays an important role as it has protective action against oral cancer, has anti-

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oxidant activity and produces oncostatic effects (Fig. 2) [15].

Tea (*camellia sinensis*) constituents inhibit carcinogenesis of oral cavity, lung, oesophagus, *etc* by inducing apoptosis and reducing cell proliferation. Epigallocatechin-3 is a key polyphenol present in tea which inhibits many potential targets [16,17]. Chios mastic gum extract which is a resin procured from trunk and leaves of *Pistacia lentiscus* has proven to show apoptosis, inhibit cell proliferation and have antioxidant properties [18].

1.1. Risk factors in oral cancer

Oral squamous cell carcinomas arise because of a wide range of risk factors. Some common risk factors associated with oral cancer include tobacco and alcohol intake, smoking, reverse end smoking, smokeless tobacco in the form of snuff and tobacco chewing, betel quid, areca nut, use of mouth washes with greater alcohol content, excessive sunlight exposure, HPV virus, Herpes simplex virus, Hepatitis-C virus, Epstein-Barr Virus, poor oral hygiene and poor nutrition [6,7].

By limiting consumption of tobacco in any form and controlling alcohol intake the risk of oral cancer over the globe can be controlled and reduced to a desired level (approximately three-fourth) [19].

1.1.1. Correlation of oral cancer with herpes virus

Viruses like Herpes Simplex Virus (HSV) is a risk factor in the formation of oral squamous cell carcinomas and they interfere with the cell cycle by encoding viral oncoproteins [20].

HSV 1 causes ocular and oral infections whereas HSV 2 leads to genital infection. Although knowing HSV *in vitro* can alter some animal cells to a malignant phenotype, the association between oral cancer and HSV is still a topic of dispute. The transformation to a malignant phenotype is due to the virus behaving as a mutagen, and an area of the viral genome gets isolated, which increases the mutation frequency in cultured cells. This marks the initiation and characteristics of malignancy appear. Also, co-carcinogenic activity *in vivo* is shown by HSV [21].

1.2. Microscopic features observed during oral epithelial dysplasia

Oral epithelial dysplasia since ancient times has been categorised into the 3 major sections: minimum, moderate and critical. Minimum dysplasia (grade I) wherein the atypical or immature basal cells proliferate above the parabasal region, but they do not proliferate beyond the epithelia's lower third region. In Moderate dysplasia (grade II) similar multiplication of atypical cells occurs which extends into the central one-third of the epithelial region. Also, severe dysplasia (grade III) is associated with uncharacteristic multiplication of cells from the basal layer into the upper third of the epithelial tissue [22].

Cellular changes in epithelium: Nucleus size shows uncharacteristic difference (anisonucleosis), cell size shows unusual discrepancy (anisocytosis), augmented nuclear/cytoplasmic ratio, distended cells and nuclei, nuclei that are hyperchromatic, greater mitotic figures, unusual mitotic figures (atypical in form or position), cellular and nuclear pleomorphism and enhanced amount and dimensions of nucleoli is observed [22].

Architectural changes in tissue: Polarity loss, basal to squamous cell disorganized maturation, includes top-to-bottom transformation of carcinoma *in situ*, improved density of cells, hyperplasia of the basal cells, dyskeratosis (premature keratinisation and deep in the epithelium keratin pearls are observed), drop-like bulbous rete pegs, secondary nodules in the form of extensions on rete tips [22].

1.3. Pathophysiology of oral cavity cancer

The normal physiology of the oral cavity is affected drastically by oral cavity cancer. The disruption is the normal physiology is associated with the development of potentially malignant disorders such as oral lichen planus, leukoplakia, erythroplakia, submucous fibrosis [11], palatal lesions observed in reverse smokers and actinic keratosis among others [19]. Lichen planus includes several variants such as erosive (deep ulcers), reticular (white lines that are very fine), bullous (vesicles incorporated with fluid). Leukoplakia is associated with a white patchy plaque that won't rub off easily and the risk associated with it is questionable. One of the problems associated with leukoplakia is that it is asymptomatic and the patient carrying the disease remains unaware of the conditions. The major difference between leukoplakia and erythoplakia is that the latter develops a red fiery patch that carries a higher risk of dysplasia and is symptomatic to an extent. The connective tissues of the cheek undergo fibrosis which develops progressive trismus and is well known as submucous fibrosis [11]. Actinic keratosis occurs mainly on the labial mucosa and are known to develop crust forming lesions [19]. All these lesions must be encouraged for excision or biopsy [11]. The transformations to malignant forms described above have a frequency range of 0.13%–2.2% [19].

1.4. In vitro studies on oral cancer

Different oral cancer *in vitro* studies have been conducted till date and the outcomes of the *in vitro* studies aid in preventing oral cancer. *In vitro* studies on (−)-gossypol suggest that it plays a potent anticancer role in squamous cell carcinoma *in vitro* and the agent can be developed as a new therapeutic agent for squamous cell carcinoma either alone or in amalgamation with some different therapeutic agents [23].

1.5. Role of Agrin, Perlecan and Neuroendocrine factors in oral cancer

It is found that in oral squamous cell carcinoma tissues, the expression of agrin and perlecan are high in comparison to control tissues and it may be dependent on the various sites of origin. For *e.g.*, Expression of agrin was found to be higher in the cell lines that aroused from the primary site (SCC-9), whereas the expression of perlecan was higher in cell lines that aroused from the metastatic region (SCC-9 LN-1). Moreover, it was found that glycans play a vital role at various pathophysiological steps of tumor development, particularly by behaving as a co-receptor to stabilize growth-factor receptor signalling complexes and increasing motility, intracellular signalling and integrin-mediated cell adhesion. The interruption of glycosaminoglycans (GAGs) alteration by heparanase (a endoglycoside known to cleave heparan sulfate side chains of proteoglycans) was shown to smooth the progress of tumor cell invasion, angiogenesis and metastasis [24].

By direct and indirect mechanisms, neuroendocrine factor Somatostatin (SST) plays a key role in human tumor inhibition, for example, behaving as a cancer gene suppressor with anticancer effects. In a variety of cancers, SST has the capacity to suppress cancer growth [25].

1.6. Association of oral cancer with microbiota

The microbiome is well characterized in esophageal adenocarcinoma than in esophageal squamous cell carcinoma. Esophageal squamous dysplasia is found to develop in individuals with less esophageal microbial complexity. Alteration in the bacterial microbiota of the saliva has greater chance of esophageal squamous cell carcinoma. *Fusobacterium nucleatum* plays a key role in esophageal carcinoma. The composition of intestinal microbiota can be altered by microbiota transplants, prebiotics, antibiotics, and probiotics. Prebiotics or probiotics might target the microbiome for cancer prevention [26].

The microbiota's capacity to adjust the toxicity and efficacy of chemotherapy has gained attention. Production of reactive oxygen species (ROS) is stimulated by gut microbiota by immune cells. ROS increase the DNA degradation triggered by oxaliplatin, blocking DNA replication and transcription which results in apoptosis. A biomarker of esophageal squamous cell carcinoma is *Porphyromonas gingivalis*.

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