Tobacco Addiction: Effect on Human Health

Chapter 2

Premalignant and Malignant Lesions of the Oral Cavity: Tobacco as an Etiological Factor

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Abbreviations

WHO: World Health Organization; OSMF: Oral Submucous Fibrosis; HPV: Human Papilloma Virus; OSCC: Oral Squamous Cell Carcinoma; NFHS: National Family Health Survey; GATS: Global Adult Tobacco Survey; GYTS: Global Youth Tobacco Survey; PVL: Proliferative Verrucous Leukoplakia; TSG: Tumour Suppressor Gene; UV: Ultra Violet; DNA: Deoxyribonucleic Acid; HTLV: Human T-Cell Lymphoma Virus; HIV: Human Immunodeficiency Virus; CD: Cluster Of Differentiation; EBV: Epstein-Barr Virus; HHV8: Human Herpes Virus 8; HBV: Hepatitis B Virus; P53: Tumor Protein 53; Rb: Retinoblastoma Protein; ICAM: Intercellular Adhesion Molecule; TGFR: Transforming Growth Factor Beta Receptor; MMP: Matrix Metalloproteinase; TIMP: Tissue Inhibitor Of Metalloproteinase

1. Introduction

The precancerous lesion was defined by World Health Organization (WHO), in 1978 as a morphologically altered tissue associated with a significantly increased risk of cancer. Precancerous lesions of oral cavity include oral submucous fibrosis (OSMF), Plummer Vinson syndrome, erosive lichen planus, dyskeratosis congenita, chronic hyperplastic candidiasis, Cowden's syndrome, discoid lupus erythromatosus, dystrophic epidermolysis bullosa, and xeroderma pigmentosa [1]. In 2005, WHO decided to use the term 'Potentially Malignant Disorders (PMD)' as it describes that the pathological condition may transform into cancer.

Precancerous lesions that are identified PMD are leukoplakia, erythroplakia, palatal changes associated with reverse smoking, oral lichen planus, OSMF, and discoid lupus erythromatosus [2]. Causative factors for PMDs include human papilloma virus (HPV), candida, tobacco, 'gutkha', areca nut, vitamins (such as, A, B, C, D, and E) deficiency and minerals (such as, iron, calcium, copper, zinc and magnesium etc) deficiency [3].

The majority of oral cancers are squamous cell carcinomas. The tongue, buccal mucosa, oropharyngeal region and floor of the mouth are the commonest sites for occurrence of the disease. Lesser affected regions of the oral cavity are the lips, gingiva, dorsal tongue and palate sites. Approximately ninety-five percent of oral squamous cell carcinoma (OSCC) occurs in people older than 40 years, with an average age at diagnosis of approximately 60 years [1]. Lip carcinoma accounts for approximately 12% of all non-cutaneous head and neck cancer. While most of the lip cancer involves lower lip, upper lip cancer involves only 2-7% of lip cancers, followed by commissural areas (<1%) which are less susceptible to OSCC [4]. Most common lip carcinomas are basal cell carcinoma and squamous cell carcinoma. Less common carcinomas are keratoacanthoma, minor salivary gland tumours, melanoma and mesenchymal tumours. Other head and neck cancers include tumours of the salivary glands, thyroid glands, lymph nodes, bone and soft tissue. The incidence of oral cancer is age-related, which may reflect time for the accumulation of genetic changes and duration of exposure to endogenous and exogenous factors (including chemical and physical irritants, viruses, hormonal effects, cellular aging and decreased immunological responses etc). Evidence from long term follow-up from immuno-suppressed patients after solid organ and hematopoietic stem cell transplantation elucidates that immunosuppression increases the risk of development of OSCC [5].

Tobacco consumption in smokeless and smoking form is considered as the major risk factors for premalignant and malignant lesions in oral cavity. Dried tobacco leaves are mainly smoked in cigarettes, cigars, pipe tobacco and flavored shisha tobacco. They are also consumed as snuff, chewing tobacco and dipping tobacco. Tobacco contains the alkaloid nicotine, a potent para-sympathomimetic stimulant. It also contains several potent carcinogens that include nitrosamines, polycyclic aromatic hydrocarbons, nitrosodicthanolamine, nitrosoproline, polonium etc [6]. Prevention and control of tobacco-induced oral mucosal lesions is the prime requisite currently and mainly involves measures undertaken at primary, secondary and tertiary levels. Primary prevention plays a pivotal role in controlling tobacco induced lesions and measures can be taken at policy level, community as well as individual level.

2. Global scenario for Oral Cancers and Tobacco Addiction

Worldwide, oral carcinoma is one of the most prevalent cancers and is one of the 10 most common causes of death. In 2012, approximately 145,400 deaths and 300,400 new cases were reported worldwide from oral cavity cancer (including lip cancer). The highest rates are

found in Melanesia, South-Central Asia, and Central and Eastern Europe (Figure 1), while the lowest is in Western Africa and Eastern Asia [7]. In USA alone, a total of 48,330 incidences of new oral cancers were reported in 2016, among which 34,780 were male and 13,550 were female. The estimated deaths in USA due to oral cancers were 9,750, among which 6,910 were male and 2,660 were female in 2016 [8]. In high-income countries, smoking causes approximately 71% of deaths due to oral cavity cancer (including pharynx) while the burden is 37% of deaths for low-to-middle-income countries. Alcohol is accountable for about 33% and 14% of deaths in high and low income countries, respectively [9]. However, for last few decades oral cavity cancer incidence rates have decreased significantly in Asia, Northern America, and Australia for both males and females, and in Southern and Western Europe for males only. Although, due to tobacco epidemic, the rates of oral cavity cancer incidences have increased in several countries of Eastern and Northern Europe for both sexes and in Southern and Western Europe for females only [10].

Oral use of smokeless tobacco is widely prevalent in the South-East Asia Region; the different forms include chewing, sucking and applying tobacco preparations to the teeth and gums. Smokeless tobacco products and betel quid with or without tobacco are the major risk factors for oral cavity cancer in Taiwan, India, and other South Asian countries [11]. Greater than 250 million people use smokeless tobacco products in the South-East Asian subcontinent; approximately 17% of total population in South-East Asia uses oral tobacco out of which 95% belong to India and Bangladesh [12]. Increasing use has been reported not only among men, but also among such vulnerable groups as children, teenagers, women of reproductive age and by immigrants of South Asian origin wherever they have settled. A global epidemiological study held among the cohort of young individual revealed high (10-20%) prevalence of use of smokeless form of tobacco in adolescents (13-15 year) in South-East Asia. Among the downtrodden youths (45%-71%) prevalence of tobacco use has been studied in South-East Asia [13]. High incidence rates have been reported in developing nations like India, Pakistan, Bangladesh, Taiwan and Sri Lanka. While an increasing trend has been observed in Pakistan, Taiwan and Thailand, a decreasing trend is seen in Philippines and Sri Lanka. The mean age of occurrence of cancer in different parts of oral cavity is usually between 51-55 years in most countries [14-16].

Considering all age groups men are more affected than women. It is true when we observe the male versus female incidences for oral cavity cancers in different parts of Asia. The age-standardized rate for 2012 study for incidences per 100,000 people showed highest rates for male and females in Melanesia, which are 22.9 and 16 respectively. The incidences oral cancer for male and females are 9.9 and 4.7 in South Central Asia, 4 and 2.5 for South-Eastern Asia; 2.7 and 1.6 for Western Asia and 2.4 and 2.2 for Eastern Asia respectively [7]. Among African continents the oral cancer incidences for male and females are 6.3 and 2.3 for Southern

Africa, 4.5 and 2.8 for Eastern Africa; and 1.7 and 1.4 for Western Africa respectively. Among European continents, the oral cancer incidences for male and females are 9.1 and 2 for Central & East Europe, 7.9 and 3.2 for Western Europe, 5.9 and 3.2 for Northern Europe and 5.8 and 2.1 for Southern Europe respectively. Among Americans, Northern America has highest incidences of oral cavity cancers, 7.2 and 3.2 for male and female respectively. South America has 5.3 and 2.4, and Central America has 2.6 and 1.7 incidences of oral cavity cancers for males and females respectively per 100,000 people [7]. Australia has incidences of 8.3 and 3.7 for males and females respectively out of 100,000 people. Aetiological factors for oral carcinoma in these countries include high rate of smoking tobacco, increased alcohol consumption, diet low in fruits and vegetables. Overall incidence of oral cancer in Australia is decreasing. There is a high prevalence of oropharyngeal carcinoma due to HPV infection in these countries, which has a better prognosis than that induced by smoking [17,18].

3. Tobacco consumption in India

Tobacco addictions, in the forms of both smoking and smokeless, are the main reasons for the increasing incidence of oral cancers in India. The social awareness for the hazards of tobacco use is very minimal in India. Moreover, the low socio-economic status and low nutritional value-diet, lacking vegetables and fruits, contribute towards higher risks for cancer development. In addition, viral infections, such as HPV and poor oral hygiene, are other important risk factors. Poor oral hygiene has been advocated as a risk factor for oral cancer. This has been assessed by measuring tooth loss or status of the dentition and periodontal disease. Poor general oral condition associated with increased risk of development of OSCC in both genders [19,20]. However, from current trend of tobacco smoking among young people aged 15 years and over in India, WHO predicts that the tobacco usage will be reduced by 30% in 2025 with respect to the statistics for 2010 (Table 1) [16].

In some parts of India, such as the states of Bihar and Maharashtra, smokeless tobacco use is more common than smoking. Apart from regional preferences due to different socio-cultural norms, the preference for smokeless tobacco is inversely related to education and income. In countries of South Asia, particularly India, traditional values do not favour smoking by the young or by women, but there is no such taboo against using smokeless tobacco. Most women, who use tobacco in India, use it in smokeless forms. In India it has been estimated that roughly one-third of women and two-thirds of men use tobacco in one form or another. In an epidemiological study conducted in eight rural areas of India, smokeless tobacco use was 3–53% among men and 3–49% among women. Moreover, 2-26% of men and 0–4% of women of these areas were indulged in consuming both smoking and smokeless forms of tobacco [21]. A study conducted by National Family Health Survey (NFHS) during 2005–06, found that tobacco use is more prevalent among men, illiterates, poor, and vulnerable section of the society [22]. Another study conducted among individuals of 15 years of age or older in 2009–10

by Global Adult Tobacco Survey (GATS) indicates that 47.9% adult males and 20.3% adult females are tobacco users. About 24.3% males and 2.9% females of the adults use smoke, while 32.9% males and 18.4% females use smokeless tobacco. Global Youth Tobacco Survey (GYTS) conducted a study among 24,000 students (aged 13-15 years) in 2009, and found that 14.6% students were tobacco users in India [23].

Smokeless tobacco use showed a variation of usage from 7.2% to 59.4% in different states of India. In a survey from Mumbai, the smokeless tobacco use was 57.1% among women and 45.7% among men [12]. In Trivandrum and Kerala chewing habits were observed by 26.8% men and 26.4% women of the studied population [24]. In Jammu & Kashmir, Goa, Himachal Pradesh, Haryana, Punjab, Kerala, Andhra Pradesh, Tamil Nadu, Delhi, Karnataka, Meghalaya, Rajasthan and West Bengal individuals mainly consumed smoking forms of tobacco whereas in Maharashtra, Uttar Pradesh, Sikkim, Madhya Pradesh, Assam, Orissa, Bihar, and Arunachal Pradesh smokeless tobacco use predominated. In Gujarat, Manipur and Mizoram areas, equal frequency of usage of smokeless and smoking tobacco was observed among men while among female the ratio was 5:1 respectively. In North Eastern states of India females are reported to be the extensive user tobacco Gul than men and a significant population of Assam, Meghalaya, Nagaland, Sikkim, and Mizoram are affected with the tobacco epidemic. Tobacco water is used extensively in North East Indian states, especially Mizoram and Manipur. Frequency of use of tobacco water use was almost similar among male and females [12,25].

Who surveyed a study on tobacco addiction for more than 10 years of span with 35,288 respondents of Karnataka and 29,931 respondents of Utter Pradesh. According to the study, tobacco use in smokeless form was predominant among women and among men less than 30 years in both urban and rural areas; however, smoking was the predominant form of tobacco use among men more than 30 years age. The overall prevalence for use of smokeless tobacco was observed to be 13.9% in Karnataka (13.4% among men and 14.4% among women) and 17.5% in Uttar Pradesh (24.3% among men and 6.6% among women). Use of smokeless tobacco was higher among females as compared to males in the age-groups above 40 years in Karnataka [25]. In Uttar Pradesh, the proportion of men using smokeless tobacco was higher than women, in all age-groups and prevalence of smokeless tobacco use increased with age in both sexes. Betel-tobacco quid was found to be extensively consumed in Karnataka, but had limited practice in Uttar Pradesh. The prevalence rate of use of this tobacco modality was 14.2% (26.9% among males and 0.6% among females) in Karnataka and 2.0% (2.3% among males and 1.4% among females) in Uttar Pradesh. Overall, a higher prevalence among rural areas was observed in all age-groups of Karnataka as compared to urban areas, but the trends were variable in different age-groups in Uttar Pradesh. An inverse correlation of decrease in prevalence rates of betel-tobacco quid/smokeless tobacco use with increasing educational

levels was observed in different age-groups in Karnataka, and similar pattern was noticed only among females in Uttar Pradesh. An inverse association of betel-tobacco quid use with increasing family income levels was observed in Karnataka but not in Uttar Pradesh[12,25].

4. Premalignant disorders of the Oral Cavity

The mechanisms for transformation of the oral premalignant disorders into malignancies are not well understood; among many hypotheses the 'field cancerization theory' is the most accepted. Field cancerization involves the formation of multiple areas of premalignant disease with a higher-than-expected rate of multiple local second primary tumors. Many theories have been proposed to explain the occurrence of carcinomas in specific sites. One theory states that multiple squamous cell lesions occur irrespective of each other. This is due to the exposure of the oral cavity to carcinogens at the same time leading to multiple genetic aberrations in the entire area. Another theory states that multiple lesions arise due to the migration of dysplastic and altered cells with two different patterns, (a) migration of malignant cells through the saliva (micro metastasis); (b) intra-epithelial migration of the progenitor cells of initially transformed malignant cells. The mechanism is different from the metastasis, since metastatic cells are usually transported through lymphatic and vascular system from primary cancer sites [26,27].

Potentially malignant oral lesions reflect underlying cellular changes, which are either red or white or mixed red and white appearance. Along with the clinical manifestations, the associated cellular changes are termed as dysplasia, which is defined as loss of uniformity of individual cells and their architectural orientation. The WHO 2005 classification recognizes five histopathological stages in the epithelial precursor lesions: (i) Squamous hyperplasia: It can be acanthosis and basilar hyperplasia. The histopathology shows regular stratification without cellular atypia. (ii) Mild dysplasia: The architectural disturbance is restricted to the lower third of the epithelium accompanied by mild cytological atypia. (iii) Moderate dysplasia: The dysplastic change extends to the middle third of the epithelium with moderate cytological atypia. (iv) Severe dysplasia: The dysplastic changes involve more than two-thirds of the epithelium with severe cytological atypia. (v) Carcinoma-in-situ: Full thickness architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia [2,28].

Oral leukoplakia is defined as a predominantly white lesion of the oral mucosa. The disorder can further be divided into a homogenous and a non-homogenous type. The homogenous form is clinically characterized as a white, well-demarcated plaque with an identical clinical appearance all throughout the entire lesion (Figure 2). The surface texture may vary from a smooth thin surface to a leathery appearance referred to as "cracked mud". Another characteristic feature is the lack of a peripheral erythematous zone in homogenous leukoplakia. If the surface texture is homogenous but contains papillary (nodular) or exophytic components, the leukoplakia is also regarded as nonhomogenous. The nonhomogenous type of oral leukopla-

kia may show white patches or plaque amidst red tissue. Due to the concomitant occurrence of white and red areas, the nonhomogenous leukoplakia is also called erythroleukoplakia or speckled leukoplakia. The clinical manifestation of the white areas may vary from large white verrucous areas to small nodular structures. Both homogenous and nonhomogenous leukoplakia may be observed in all sites of oral mucosa [28]. Oral leukoplakia includes white component dominated by papillary or finger-like projections, which are referred to as verrucous or verruciform leukoplakia. Oral leukoplakia with this clinical manifestation but with a more angry-looking growth pattern and recurrence rate is designated as proliferative verrucous leukoplakia (PVL) having high malignant potential. As the common surface pattern is similar to oral papillomas, the PVL is suspected to have a viral etiology. Oral erythroplakia has not been so well studied as leukoplakia. It is defined as a red, velvety, plaque-like lesion of the oral mucosa that cannot be characterized as any other definable lesion (Figure 3) [28,29].

5. Signs & symptoms of oral malignant lesions

The classical complaint of patients suffering from OSCC is discomfort which compels them to immediate treatment. Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses and weight loss may occur with advancement of the disease. The high risk sites for oral carcinoma include the lower lip, the anterior floor of the mouth and the lateral borders of the tongue. The patient may develop tissue changes, which include a red, white or mixed red and white lesion and a change in the surface texture producing a smooth, granular, rough or crusted lesion or ulceration (Figure 4). The lesion may be flat or elevated and ulcerated or nonulcerated and may be minimally palpable or indurated. Loss of function of tongue can affect speech, swallowing and food intake [28,29].

Lymphatic spread of oral carcinoma usually involves the submandibular and digastric nodes, the upper cervical nodes, and finally the remaining nodes of the cervical chain. The nodes most commonly involved are those that are on the same side as the primary node, although the closer the tumour is to the midline and the more posterior in the oral cavity or oropharynx, the more common are the involvement of the bilateral or contralateral nodes. The nodes are not tender until and unless they are associated with secondary infection or an inflammatory response is present, which may occur after biopsy [28]. Oral malignant melanomas are relatively rare cancers and occur commonly in the maxillary gingival, more frequently on the palate with fewer incidences in the mandibular gingival [30]. Though, these lesions are biologically aggressive, they are clinically asymptomatic in the early stages and usually present merely as a hyperpigmented patch on the gingival surface (Figure 5).

Verrucous carcinoma is described clinically as papillary, verrucoid, fungating or cauliflower-like and may develop from progression of proliferative verrucous leukoplakia that progress to carcinoma (Figure 4). Verrucous carcinoma rarely spreads through lymphatic route

and generally remains locally destructive. There are a few other variants of SCC other than verrucous carcinoma. Basaloid carcinoma is composed of solid growth of basaloid cells with small cystic spaces. It has been suggested that HPV-associated cancers of oral cavity are more likely to have basaloid features. Spindle cell carcinomas are rare variants of SCC, where epithelial changes ranging from prominent dysplasia to frank SCC in conjunction with a dysplastic spindle cell element [28].

6. Etiopathogenesis for Oral Cancer

Carcinogenesis is a genetic process that leads to a change in tissue morphology and cellular behavior. The development of oral malignancy is attributed to a powerful alliance of two factors: nicotine and carcinogens. Nicotine is addictive and toxic, but it is not a carcinogen. This addiction, however, causes people to use tobacco products continually, and these products contain many carcinogens. Carcinogens alter the gene responses for proto-oncogenes and tumour suppressor genes (TSGs) that ignite the pathogenesis of oral carcinoma. Other genetic factors which play a major role in oral cancer include chromosomal aberrations in the telomere region of chromosome, genetic mutations of proto-oncogenes and TSGs, or epigenetic changes like DNA methylation or histone modification [6]. In addition, angiogenesis, immune function and hemostatic regulation of surrounding normal cells also play important roles in disease pathogenesis (Figure 6).

Tobacco and alcohol are great risk factors for oral and oropharyngeal cancers. Nitrosamines, polycyclic aromatic hydrocarbons, nitrosodicthanolamine, nitrosoproline, and polonium are the potent carcinogens in tobacco. Carbon monoxide, thiocyanate, hydrogen cyanide, nicotine and its metabolites are major constituents in tobacco smoke. Epidemiological studies have found that up to eighty percent of oral cancer patients are associated with smoking. In addition to the risk of primary cancers, the risk of secondary and recurrent primary oral cancers is related to continuation of smoking after cancer treatment. A follow up study for 1 year of primary oral cancer patients (after surgery) found that 18% of these patients develop a recurrent oral cancer, and those who continued to smoke had a 30% risk of secondary oral cancer development [31]. It has been suggested that the deleterious effect of smoking on the development of cancer decreases 5 to 10 years post stoppage. The incidence of OSCC varies worldwide and may be explained partly by differences in the use of tobacco products. Benign hyperkeratosis and epithelial dysplasia have been reported following short-term use of smokeless tobacco and chronic use is associated with an increasing incidence of malignant lesions [32].

Genetic damage is the step towards the process of carcinogenesis. Three classes of carcinogenic agents have been identified: 1) chemical, 2) radiant energy and 3) microbial agents. Another cause of oral carcinogenesis is mechanical trauma; for example, sharp cuspal edges of teeth causing trauma to the buccal mucosa or lateral border of the tongue. Chemicals and radi-

ant energy are the primary causes of cancer in humans whereas oncogenic viruses are involved in the pathogenesis of cancer in mainly animals and some human tumours.

Chemical carcinogens have highly reactive electrophile groups that directly damage the DNA. There are two types of chemical carcinogens: direct and indirect acting. Direct acting agents (for e.g. alkylating agents used for chemotherapy) are carcinogenic from the initial states, whereas indirect acting agents (for eg. benzopyrene, azo dyes, aflatoxins) are not carcinogen during initial states and are converted into carcinogens by endogenous metabolic pathways. Hence, polymorphisms of endogenous enzymes that are critical for metabolic conversion of chemicals compounds (such as, cytochrome P-450), may promote carcinogenesis.

Radiations, such as UV rays of sun, X-rays, radio-nucleotides etc, can also induce DNA breakage and considered as carcinogen. Ionizing radiations cause chromosomal aberrations, translocations and less frequently point mutations, leading to genetic damage and carcinogenesis. UV induces the formation of pyrimidine dimers within DNA, and may lead to carcinoma and melanoma of the skin [28].

The study of oncogenic retroviruses in animals has provided spectacular insights into the genetic basis of cancer. The human T-cell lymphoma virus-1 (HTLV-1) has been demonstrated to cause cancer in humans. HTLV-1 has been reported to be associated with a variant of T cell leukemia/lymphoma in humans. Similar to the HIV, HTLV-1 has affinity for CD4+T cells, and these T cells are the major victims of neoplastic transformations. The role of viruses, such as HTLV-1 and HPV are a new parameter for the pathogenesis of human cancers. The HTLV-1 genome, in addition to the usual retroviral genome, contains a unique region called the pX which encodes a major TAX protein, which turns on genes for cytokines and their receptors in infected T cells. Although this proliferation is initially polyclonal, the proliferating T cells are at increased risk for secondary mutations that lead to the outgrowth of a monoclonal leukemia. By interfering with several transcription factors, such as NF-κB, the TAX protein can transactivate the expression of genes that encode cytokines, cytokine receptors and co-stimulatory molecules. This inappropriate gene expression leads to autocrine signaling loops and increased activation of promitogenic signaling cascades. Furthermore, TAX can drive progression through the cell cycle by directly binding to and activating cyclins. In addition, TAX can repress the function of several tumour suppressor genes that control the cell cycle, including P16 and P53 [33,34].

Recently, several DNA and RNA viruses, have been identified and correlated to the developement of OSCC. Four DNA viruses HPV, Epstein-Barr virus (EBV), human herpes virus 8 (HHV8), and Hepatitis B virus (HBV) are gaining immense attention in cancer biology because they are strongly associated with human cancer. Very recently, the association of HPV, specifically HPV-16 and -18, with oral squamous cell carcinoma is also gaining importance.

Certain EBV gene products contribute to oncogenesis by stimulating a normal B cell proliferation pathway [34,35].

7. Conclusion

Oral mucosa, salivary gland and jaws are the sites of oral cavity that are affected during pathogenesis. Neoplastic lesions of oral cavity include fibromas, leukoplakia, erythroplakia and OSCC. The risk for erythroplakia to undergo malignant transformation is higher than leukoplakia. OSCC covers 90% of cancer of oral cavity and is highly associated to tobacco and alcohol consumption. In recent times a trend in oral cancer is observed in young adults and the risk of OSCC is being increased. Among young adults with any habit of tobacco consuming, tongue and buccal mucosa are the sites for occurrence of oral cancer. Immune factors, dietary factors, genetic factors and oral sex are the major etiology of OSCC in young patients. Furthermore, according to the Oral Cancer Foundation, oral cancer now affects one woman for every two men, as compared to the earlier trend of six men for every woman. The incidence of HPV associated oral lesions is also increasing in recent years. HPV oncoproteins, mainly E6 and E7 bind to Rb (retinoblastoma) and p53 thus regulate their functions. More than 30 different types of tumors may arise in salivary glands, among which mucoepidermoid carcinoma, composed of mixtures of sqamous and mucous cells, is the most common malignant tumor. Mucoepidermoid carcinoma is reported to disregulate the Notch signaling pathway. Both pre-malignant and malignant lesions of oral cavity are mainly caused by tobacco, a great risk factor for different diseases. Tobacco specific nitrosamines have been detected in saliva of tobacco chewers. These nitrosamines are carcinogen that modify DNA and cause mutagenesis. The underlying mechanisms for OSCC still remain unknown. Several reports documented the involvement of several proteins, including P53, Rb, ICAM-5, TGFR, MMP-8, and TIMP-1 in development of OSCC. Moreover, OSCC develops frequently in immune-suppressed individuals, because the disease aggressiveness is directly associated with altered immune responses. Several approved drugs, targeting diverse factors of cancer are clearly not enough for the present times (Figure 7). New drugs are being developed targeting each of the enabling signaling molecules that are contributing in cancer development, thus hold promise as cancer therapeutics. Moreover, social awareness against tobacco and self-awareness for early diagnosis are required worldwide for oral cancer prevention.

8. Table

Table 1: Current trend of tobacco smoking among young people aged 15 years and over in India [16].

CURRENT TOBACCO SMOKING (%)										
Year	Men			Women			Both sexes			
	Lower 95% CI	Point estimate	Upper 95% CI	Lower 95% CI	Point estimate	Upper 95% CI	Lower 95% CI	Point estimate	Upper 95% CI	Estimated no. of current smokers
2000	23.7	33.8	46.9	3.7	5.7	7.8	14.0	20.2	28.0	138,505,200
2005	22.1	28.0	34.3	2.9	3.8	4.7	12.8	16.3	19.9	124,176,100
2010	19.1	23.5	28.1	1.9	2.5	3.0	10.7	13.3	15.9	111,856,400
2015	13.7	19.9	26.3	1.2	1.7	2.2	7.6	11.0	14.6	101,399,700
2020	9.5	17.0	25.3	0.7	1.1	1.7	5.6	9.3	13.8	91,913,300
2025	6.4	14.6	25.1	0.4	0.8	1.3	3.5	7.9	13.5	83,514,000
Voluntary target (30% relative reduction from 2010 to 2025		16.5			1.8			9.3		

Men - Fitted current tobacco smoking (%) Women - Fitted current tobacco smoking (%)

9.Figures

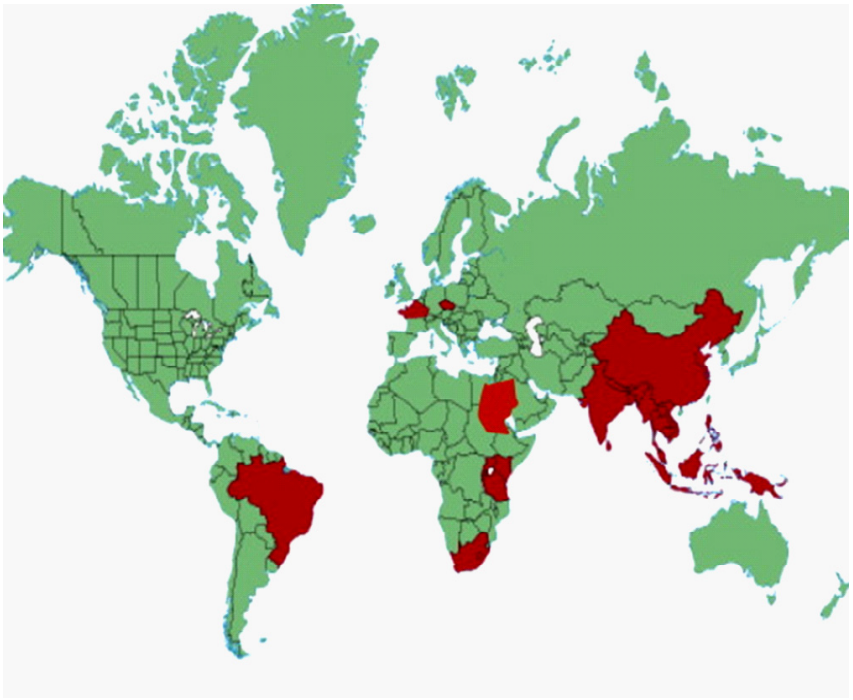

Figure 1: Countries with high incidence and mortality from oral cancer (in red). The areas characterized by high incidence rates for oral cancer (excluding lip) are found in the South and Southeast Asia (e.g. Sri Lanka, India, Pakistan and Taiwan), parts of Western (e.g. France) and Eastern Europe (e.g. Hungary, Slovakia and Slovenia), parts of Latin America and the Caribbean (e.g. Brazil, Uruguay and Puerto Rico) and in Pacific regions (e.g. Papua New Guinea and Melanesia) [15].

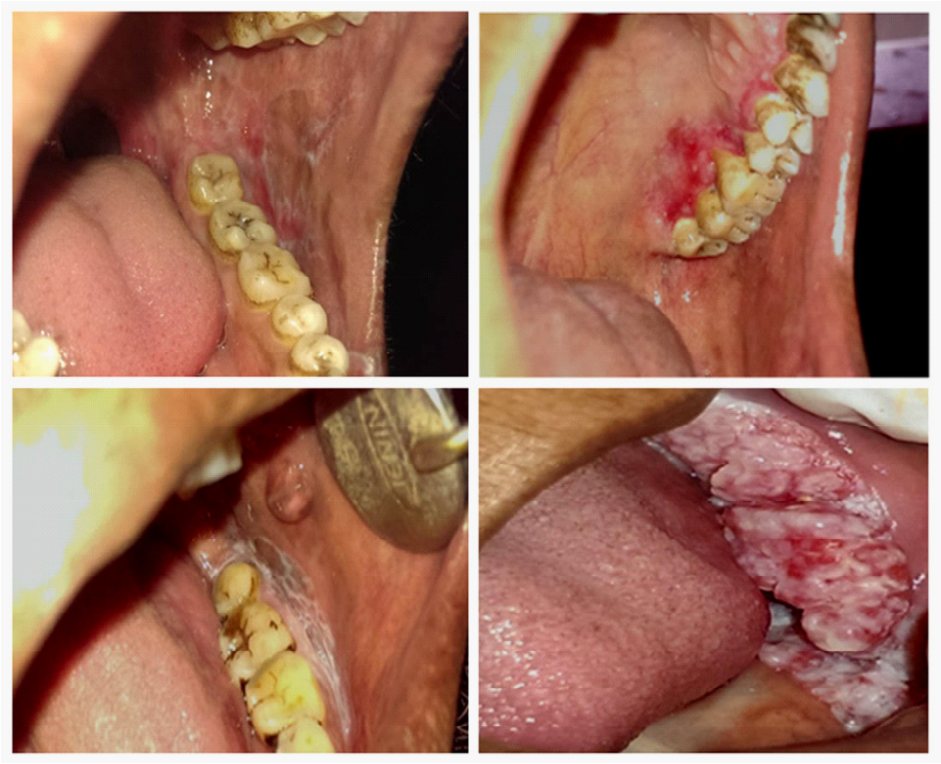

Figure 2: (in clockwise manner) Reticular lichen planus in the left buccal mucosa of a patient; erosive lichen planus in the upper left palatal aspect of an immunocompromised patient; proliferative verrucous leukoplakia in a patient having habit of retaining 'gutkha' in the buccal vestibule; speckled leukoplakia in the left buccal vestibule (all pictures were taken in the Dept of OP&OD of Burdwan Dental College & Hospital).

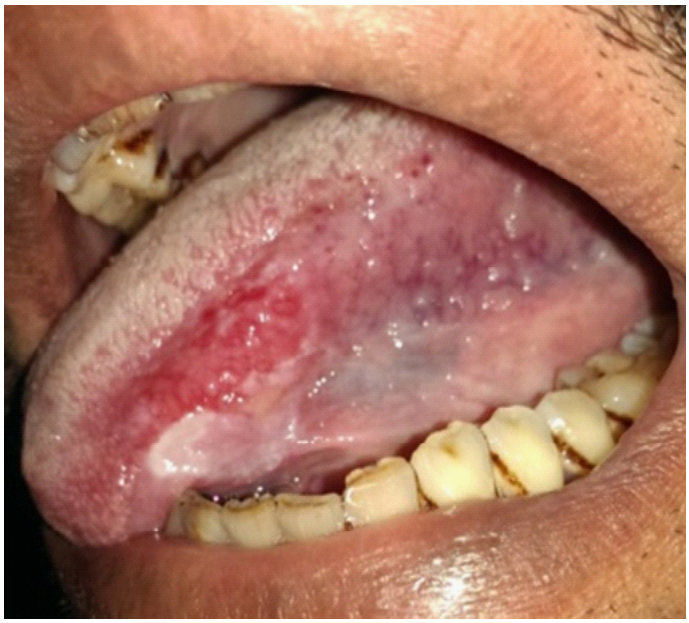

Figure 3: An ulcerated area on the left lateral border of the tongue of a patient suggestive of erythroplakia with areas of leukoplakic growth situated posterior to the reddened area (pictures taken in the Dept. of OP&OD of BDC&H)

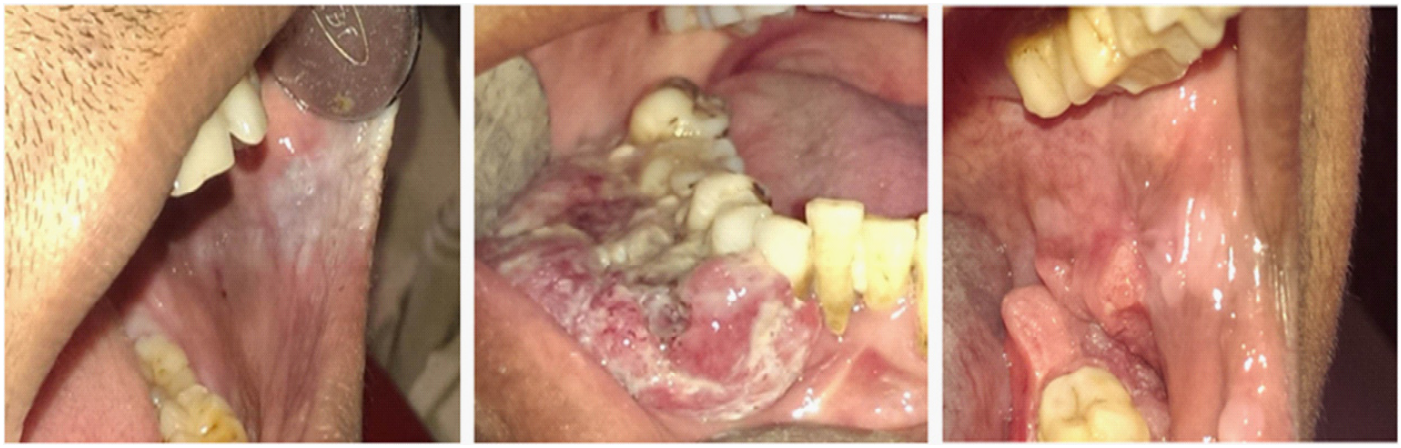

Figure 4: (from left to right) Hyperkeratotic area significant of epithelial dysplasia seen in the left buccal mucosa; Carcinoma in situ of the left buccal mucosa; Squamous Cell Carcinoma of the right buccal mucosa and associated alveolus. The lesion was associated with extensive bone loss, (pictures taken in the Dept. of OP&OD of BDC&H)

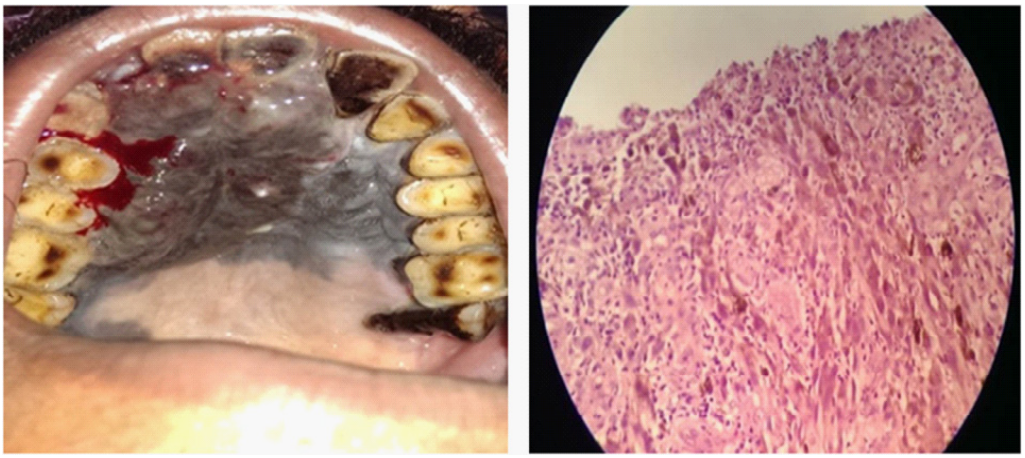

Figure 5: Malignant melanoma of the hard palate(left); Histological section stained with H&E showing malignant melanoma from sample collected from the same patient (right) (slide picture taken in the Dept. of OP of BCD&H).

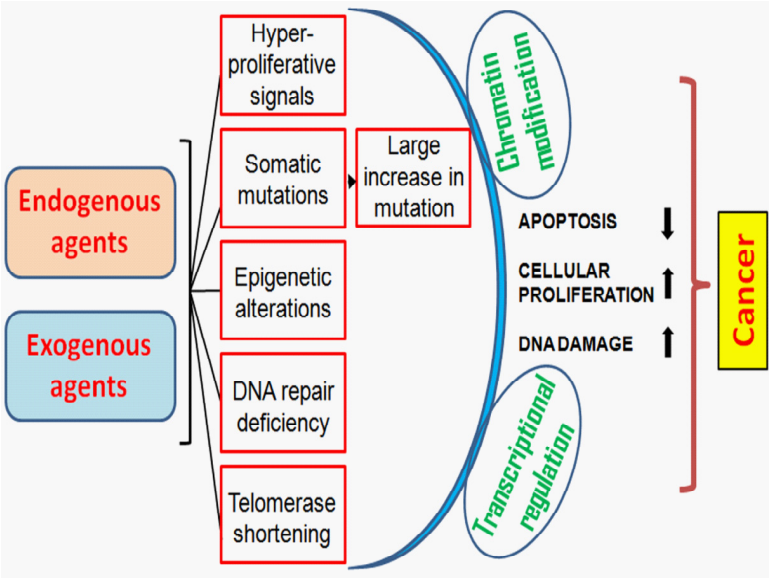

Figure 6: Endogenous and exogenous agents affecting somatic mutations, epigenetic alterations, telomerase shortening and DNA damage that leads to cancer progression through chromatin modifications and transcriptional regulation of oncogenes.

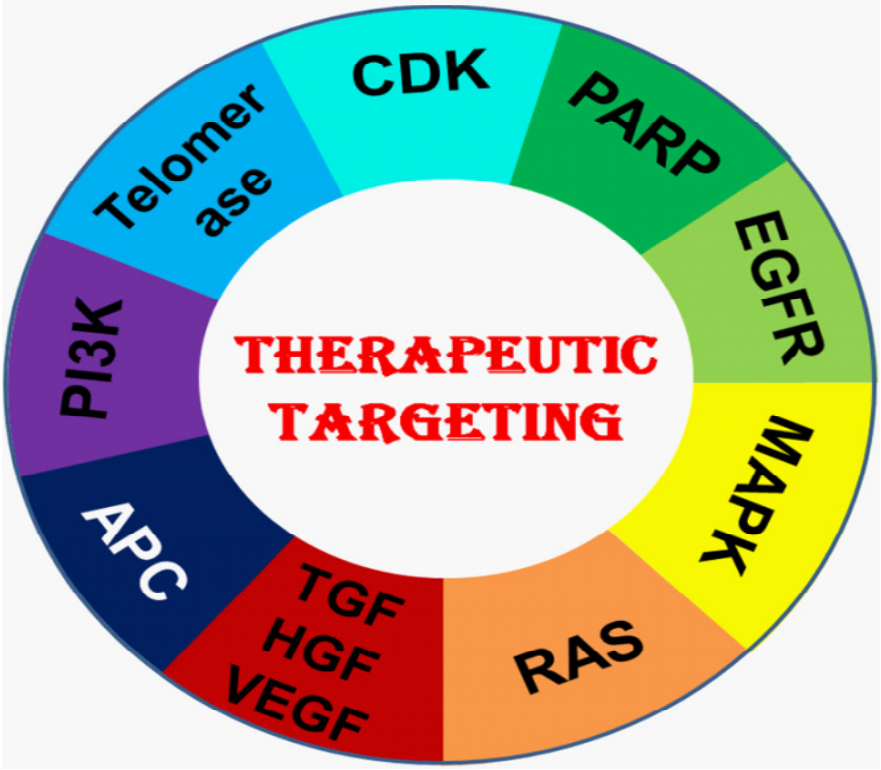

Figure 7: Different signaling molecules associated to cancers that are targeted for therapeutic purpose. CDK, Cyclin-Dependent Kinase; PARP, Poly ADP-Ribose Polymerase; EGFR, Epidermal Growth Factor Receptor; MAPK, Mitogen-Activated Protein Kinase; TGF, Transforming Growth Factor ; HGF, Hepatocyte Growth Factor; VEGF , Vascular Endothelial Growth Factor; APC, Anaphase-Promoting Complex, PI3K, Phosphatidylinositide 3 Kinase.

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