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REVIEW ARTICLE

Smoking associated risk and Molecular Pathogenesis of Oral Cancer

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ABSTRACT:
Smoking of tobacco is widely practiced worldwide. It all begins as try, becomes habit and gradually lead to dependence due to addictive nature of tobacco. Use of tobacco and tobacco products is linked to various forms of cancer. "Cancer," a word which once heard triggers fear and anxiety, reason being this illness has caused many people to lose their lives. Oral and pharyngeal cancer is ranged sixth most common cancer for both the genders worldwide. Use of tobacco products with poor dietary habits, alcohol intake and stressful lifestyle is the reason for increasing cases of oral cancer. Men are more likely to have oral cancer as compared to women. Tobacco is loaded with a lot of carcinogens and highly addictive alkaloid nicotine which is the main reason of its popularity and dependence. Carcinogenesis is the result of accumulation of genetic alterations in somatic cells. The carcinogens in tobacco include nitrosamines, nitroproline, nitrosodiethanoalamine, polycyclic aromatic hydrocarbons. This article focuses on the smoking associated risks and molecular pathogenesis of oral cancer along with cancer risk value of tobacco compounds.

Key words: Smoking, Nicotine, nitrosamines, tumour suppressor genes, proto oncogenes.

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Introduction

"Cancer," a word which once heard triggers fear and anxiety, reason being this illness has caused many people to lose their lives.[1] Use of tobacco and tobacco products is linked to various forms of cancer. Tobacco's use since its discovery is increasing many fold; the reason being the addictive nature of the easily available substance, increasing stress, workload, and laziness or just to escape the fear, anxiety, nervousness, tiredness, frustration associated with today's lifestyle or just may be a reason to socialize or to look cool. Whatever it is, it costs you. Here it's not only the money you are spending but you are exposing yourself to nearly 7000 toxic chemicals and carcinogens which cost you your life and its quality. Also being highly addictive like cocaine and heroine, so it's difficult to abstain oneself from smoking. Approximately, each cigarette smoked contains 2-3 mg of nicotine and 20-30 ml of carbon monoxide (CO) which penetrates the body. The substances which are affective in the smoke of tobacco are nicotine, CO, and nitrosamines.[2]

What's packed in a smoking tool?

There are approximately 600 ingredients in cigarettes. The basic components of most cigarettes are tobacco, chemical additives, a filter, and paper wrapping. When burned, they create more than 7,000 chemicals and at least 69 of these chemicals are known to cause cancer, and many are poisonous.[2]The main constituent Tobacco is obtained from the plant **Nicotiana tabacum**, the cultivated tobacco plant which is a native of Sub Tropical America but now cultivated worldwide. Traditionally, tobacco is classified into types which differ in the conditions of growth, processing, and eventual use; the major cigarette types used in the United States and Europe are flue-cured ("bright," "Virginia"), hurley, Maryland, and Turkish ("Oriental").[3] Tobacco contains potent carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, nitrosodiethanolamine, nitrosoproline, and polonium. The addictive nature of tobacco is due to an alkaloid Nicotine which is as addictive as cocaine or heroin. It is so addictive that smokers who want to quit smoking cannot. Smokers report that cigarettes help them to relax.

Nicotine is a cholinergic agonist and stimulates the brain. Smokers experience withdrawal symptoms when trying to quit smoking. Over time, a person becomes physically and emotionally addicted to, or dependent on, nicotine. Nicotine is pharmacologically a weak base and penetrates the biological membranes depending on the pH. The absorption of nicotine occurs in the lower respiratory tract and the alveolus of the lungs. Rapid penetration of nicotine occurs in brain. Diverse effects of nicotine occur as a result of both stimulant and depressant actions on

various central and peripheral nervous system pathways. This drug can increase the heart rate by excitation of the sympathetic nervous system, or by paralyzing the parasympathetic nervous system. Nicotine affects the medulla in the brain to increase heart rate causing a discharge of epinephrine from the adrenal medulla, which raises blood pressure.[4]

To properly assess the human health risk of a smoking, data on its smoke yield and inhalation risk value is necessary. Human inhalation risk value for cancer or another endpoint has been studied for 98 components. These 98 components were selected from list of hazardous smoke components, as their potential hazard contribution can be assessed. Table below lists these components, together with their inhalation risk values and the institute that published this value. There are nearly 5800 components that are identified as hazardous but are not mentioned here in. Exposure to the components on this list forms a potential health risk to develop cancer and/or other diseases, primarily cardiovascular and respiratory illnesses.[5]

List of hazardous tobacco smoke components with their cancer and non-cancer inhalation risk values.[5]

Smoke component	Cancer risk value[1] (mg m^{-3})	Institute	Non-cancer risk value[2] (mg m^{-3})	Endpoint	Institute
1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane (DDT)	1.0E-04	U.S. EPA			
1,1-Dimethylhydrazine	2.0E-06	ORNL			
1,3-Butadiene	3E-04	U.S. EPA	2E-03	Reproduction	U.S. EPA
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TEQ)	2.6E-04	Cal EPA			
2-Amino-3-methyl-9H-pyrido[2,3-b]indole (MeAaC)	2.9E-05	Cal EPA			
2-Amino-3-methylimidazo[4,5-b]quinoline (IQ)	2.5E-05	Cal EPA			
2-Amino-6-methyl[1,2-a:3′,2″-d]imidazole (GLu-P-1)	7.1E-06	Cal EPA			
2-Aminodipyrido[1,2-a:3′,2″-d]imidazole (GLu-P-2)	2.5E-05	Cal EPA			
2-Aminonaphthalene	2.0E-05	Cal EPA			
2-Nitropropane		Cal EPA	0.02	liver, focal vacuolization and nodules	U.S. EPA
2-Toluidine	2.0E-04	Cal EPA			
3-Amino-1,4-dimethyl-5H-pyrido [4,3-b]indole (Trp-P-1)	1.4E-06	Cal EPA			
3-Amino-1-methyl-5H-pyrido[4,3-b]-indole (Trp-P-2)	1.1E-05	Cal EPA			
4-Aminobiphenyl	1.7E-06	Cal EPA			
5-Methylchrysene	9.1E-06	Cal EPA			
7H-Dibenzo(c,g)carbazole	9.1E-06	Cal EPA			
2-Amino-9H-pyrido[2,3-b]indole (AaC)	8.8E-05	Cal EPA			
Acetaldehyde	4.5E-03	U.S. EPA	9.0E-03	nasal olfactory epithelial lesions	U.S. EPA
Acetamide	5.0E-04	Cal EPA			
Acetone			30	neurological effects	ATSDR
Acetonitrile			0.06	Mortality	U.S. EPA
Acrolein			2.0E-05	nasal lesions	U.S. EPA
Acrylamide	8E-3				
Acrylic acid			1.0E-03	nasal olfactory epithelium degeneration	U.S. EPA
Acrylonitrile	1.5E-04	U.S. EPA	2.0E-03	respiratory effects	U.S. EPA
Ammonia			0.1	respiratory effects	U.S. EPA
Aniline	B2—probable human carcinogen	U.S. EPA	1E-3	immune-related	U.S. EPA
Arsenic	2.3E-06	U.S. EPA			
Benz[a]anthracene	9.1E-05	Cal EPA			
Benzene	1.3E-03	U.S. EPA	9.8E-03	decreased lymphocyte count	ATSDR
Benzo[a]pyrene	9.1E-06	Cal EPA			
Benzo[j]fluoranthene	9.1E-05	Cal EPA			
Beryllium	4.2E-06				
Cadmium	5.6E-06	U.S. EPA			
Carbazole	1.8E-03	NATA			
Carbon disulfide			0.1	effects on CNS	HC
Carbon monoxide			10	Cardiotoxic	Cal EPA
Chloroform,	4.3E-04	U.S. EPA	0.1	liver changes	ATSDR
Chromium VI	8.3E-07	U.S. EPA	1.0E-04	lower respiratory effects	U.S. EPA
Chrysene	9.1E-04	Cal EPA			
Cobalt			5.0E-04	respiratory functions	RIVM
Copper			1.0E-03	lung and immune	RIVM

				system effects	
Di(2-ethylhexyl) phthalate	4.2E-03	Cal EPA			
Dibenzo[a,i]pyrene	9.1E-07	Cal EPA			
Dibenzo[a,h]acridine	9.1E-05	Cal EPA			
Dibenzo[a,h]anthracene	8.3E-06	Cal EPA			
Dibenzo[a,j]acridine	9.1E-05	Cal EPA			
Dibenzo[a,h]pyrene	9.1E-07	Cal EPA			
Dibenzo[a,l)pyrene	9.1E-07	Cal EPA			
Dibenzo[a,e]pyrene	9.1E-06	Cal EPA			
Dibenzo[c,g]carbazole	9.1E-06	Cal EPA			
Dimethylformamide			3.0E-02	digestive disturbances; minimal hepatic changes	U.S. EPA
Ethyl carbamate	3.5E-05	Cal EPA			
Ethylbenzene			0.77	liver and kidney effects	RIVM
Ethylene oxide	1.1E-04	Cal EPA			
Ethylenethiourea	7.7E-04	Cal EPA			
Formaldehyde	7.7E-04	U.S. EPA	1.0E-02	nasal irritation	ATSDR
Hexane			0.7	Neurotoxicity	U.S. EPA
Hydrazine	2.0E-06	U.S. EPA	5E-3	fatty liver changes	ATSDR
Hydrogen cyanide			3.0E-03	CNS and thyroid effects	U.S. EPA
Hydrogen sulphide			2E-3	nasal lesions	U.S. EPA
Indeno(1,2,3-c,d)pyrene	9.1E-05	Cal EPA			
Isopropylbenzene			0.4	increased kidney, adrenal gland weights	U.S. EPA
Lead	8.3E-04	Cal EPA	1.5E-3	not applicable	U.S. EPA
Manganese			5.0E-05	neurobehavioral	U.S. EPA
m-Cresol			0.17	CNS	RIVM
Mercury			2.0E-04	nervous system	U.S. EPA
Methyl chloride			0.09	cerebellar lesions	U.S. EPA
Methyl ethyl ketone			5	developmental toxicity	U.S. EPA
Naphtalene			3E-3	nasal effects	U.S. EPA
N-nitrosodi-n-butylamine (NBUA)	6.3E-06	U.S. EPA			
N-nitrosodimethylamine (NDMA)	7.1E-07	U.S. EPA			
Nickel			9.0E-05	chronic active inflammation and lung fibrosis	ATSDR
Nitrogen dioxide			1.0E-01	not applicable	U.S. EPA
N-nitrosodiethanolamine	1.3E-05	Cal EPA			
N-nitrosodiethylamine	2.3E-07	U.S. EPA			
N-nitrosoethylmethylamine	1.6E-06	Cal EPA			
N-Nitrosonornicotine (NNN)	2.5E-05	Cal EPA			
N-Nitroso-N-propylamine	5.0E-06	Cal EPA			
N-nitrosopiperidine	3.7E-06	Cal EPA			
N-nitrosopyrrolidine	1.6E-05	U.S. EPA			
n-Propylbenzene			0.4	increased organ weight	U.S. EPA
o-Cresol	C- possible human carcinogen	U.S. EPA	0.17	decreased body weight, neurotoxicity	RIVM
p-, m-Xylene			0.1	respiratory, neurological, developmental	U.S. EPA
p-Benzoquinone	C- possible human carcinogen	U.S. EPA	0.17	CNS	RIVM
p-Cresol	C- possible human carcinogen	U.S. EPA	0.17	CNS	RIVM
Phenol			0.02	liver enzymes, lungs, kidneys, and cardiovascular system	RIVM

Polonium-210	925.9	ORNL[3]			
Propionaldehyde			8.0E-03	atrophy of olfactory epithelium	U.S. EPA
Propylene oxide	2.7E-03	U.S. EPA			
Pyridine			0.12	odour threshold	RIVM
Selenium			8E-4	respiratory effects	Cal EPA
Styrene			0.092	body weight changes and neurotoxic effects	HC
Toluene			0.3	colour vision impairment	ATSDR
Trichloroethylene	82	HC	0.2	liver, kidney, CNS effects	RIVM
Triethylamine			7.0E-03	n.a.	U.S. EPA
Vinyl acetate			0.2	nasal lesions	U.S. EPA
Vinyl chloride	1.1E-03	U.S. EPA			

[1]Cancer inhalation risk values provide an excess lifetime exposure risk, in this case the human lung cancer risk at a 1 in 100,000 (E-5) level.
[2]Noncancer inhalation risk values indicate levels and exposure times at which no adverse effect is expected; here values for continuous lifetime exposure are listed.
[3]Unit risk in risk/pCi = 1.08E-08.

The list above of hazardous smoke components includes all nine components reported in mainstream cigarette smoke that are known human carcinogens (IARC Group I carcinogens), as well as all nine components that are probably carcinogenic to humans (IARC Group 2A carcinogens). In addition, it contains 34 of the 48 components that are possibly carcinogenic to humans (IARC Group 2B carcinogens).[5]

The WHO Study Group on Tobacco Product Regulation (TobReg) recently published an expert advice on smoke component regulation (based on research by a joint WHO and IARC working group). A list of 43 priority toxicants was composed from three smoke component emission level datasets which were all based on the Hoffmann list. All components of this TobReg initial group of priority toxicants are present on the list, with the exception of catechol, crotonaldehyde, hydroquinone, and nicotine derived nitrosamine ketone. Those components are not on the current list as no human inhalation risk values were found. Catechol has been classified by IARC as possibly carcinogenic to humans (Group 2B); hydroquinone and crotonaldehyde have been classified by IARC as not classifiable as to its carcinogenicity to humans (Group 3).[5]

Thus, shortlist of 98 potentially hazardous smoke components includes all important smoke components from these previous lists. Compared to the Hoffmann list, this list included many new components including acetone, acetonitrile, cadmium, methyl chloride, methyl ethyl ketone, propionaldehyde and toluene.[5]

How it all begins..

The excessive use of tobacco products has been associated with various lesions in the oral cavity. Tobacco associated lesions include tooth stains, abrasions, smoker's melanosis, acute necrotizing ulcerative gingivitis and other periodontal conditions, burns and keratotic patches, black hairy tongue, nicotinic stomatitis, palatal erosions, leukoplakia, epithelial dysplasia and squamous-cell carcinoma. It has been established that there is a dose-response relationship between the amount of tobacco product used and the development of oral cancer. The mucous-secreting epithelial lining (i.e., mucosa) is separated into two types: masticatory (keratinized) and lining (nonkeratinized).[6]

The masticatory mucosa is thick, with a denser, less vascular connective tissue component. Keratin is a protective barrier against stimuli, such as traumatic forces of the everyday activities of eating foods, drinking liquids, speaking, and swallowing or noxious stimuli from ill-fitting dentures or tobacco use. Stimulation of the masticatory tissue may result in increased keratin formation and the appearance of a white lesion (i.e., leukoplakia). Masticatory mucosa is found on the hard palate, dorsum of the tongue, and keratinized gingival. The lining mucosa will form very little keratin and has a less fibrous, more vascular connective tissue. Lining mucosa is found on the floor of the mouth, ventrolateral surface of the tongue, soft palate complex, labial vestibule, and buccal mucosa. Tobacco use affects mainly the surface epithelium, resulting in changes in the appearance of tissues. The changes may range from an increase in pigmentation to a significant thickening of the epithelium (hyperkeratosis), resulting in leukoplakia.[6]

The most deadliest consequence of smoking is Cancer. Smoking causes multiple organ cancers, which include cancers of the lung, oral cavity, esophagus, larynx, throat, kidney, bladder, liver, pancreas, stomach, cervix, colon, and rectum, as well as acute myeloid leukemia.

Cancer, for the most part, is caused by multiple somatic mutations in a single cell and its progeny. However in some individuals, constitutional genetic alterations may also play a role. Depending on the specific cell type, the affected cell and the progeny accumulate sequential mutations and sustain multiple genetic alterations over decades. The defective genetic anomalies lead to disabled critical cellular pathways, which with DNA replications in between, evolve clonally and expand into a malignant phenotype. Additional mutations in some genes confer a further selective growth advantage and neoplastic process progresses to invade surrounding tissues and metastasise

to other organs. The most common type of oral cancer is squamous cell carcinoma, which develops from the stratified squamous epithelium that lines the mouth and pharynx. This form of cancer accounts for 90% of the oral malignancies.[6] Epidemiologic studies have shown that up to 80% of oral cancer patients were smokers. In addition to the risk of primary cancers, the risk of recurrent and second primary oral cancers is related to continuing smoking after cancer treatment. Of patients who were observed for 1 year, 18% developed a recurrence or a second primary oral cancer, and those who continued to smoke had a 30% risk.[7] The effect of smoking on cancer risk diminishes 5 to 10 years after quitting. Almost 30 percent of the Indian population older than age 15 uses some form of tobacco. Men use more smoked tobacco than smokeless tobacco. Women are more likely to use smokeless (chewed) tobacco.[8]

Molecular pathogenesis of oral cancer

Carcinogenesis is a genetic process that is result of a change in morphology and in cellular behavior. The assessment of molecular change is the primary mean of diagnosis and may guide management. Major genes involved in head and neck squamous cell carcinoma (HNSCC) include proto-oncogenes and tumor suppressor genes (TSGs). TSGs negatively regulate cell growth and differentiation. Functional loss of TSGs is common in carcinogenesis.[8]

Both copies of a TSG must be inactivated or lost (LOH) for loss of function (the "two-hit" hypothesis) **Knudson's two-hits model** is in a familial form, so the affected person inherits a mutated gene from one parent and a somatic mutation in the target tissue inactivates the normal gene given from the other parent. In non-hereditary cancers, both of the inactivating mutations have to occur within the same somatic cell. Heterozygous mutation in the germline are more likely to develop malignancy.[9]

Inheritance of the predisposition follows a dominant pattern even though transmission occurs by recessive mutations. Multiple hits to the DNA are necessary to cause carcinogenesis, but inheritance of just one genetic defect predisposes a person to cancer but does not cause it directly as a second event is needed, explaining why two hits are required.[9]

Factors that play a role in the progression of disease may include allelic loss at other chromosome regions, mutations to proto-oncogenes and TSGs, or epigenetic changes such as deoxyribonucleic acid (DNA) methylation or histone deacetylation. Cytokine growth factors, angiogenesis, cell adhesion molecules, immune function, and homeostatic regulation of surrounding normal cells are also contribute in it.[8]

Chromosomes are numbered (1 to 23), and the arms of each chromosome are divided by the centromere into a short arm (designated P) and a long arm (designated Q). TSGs have been associated with sites of chromosome abnormalities where LOH has been reported to commonly involve chromosome arms 3p, 4q, 8p, 9p, 11q, 13q, and 17p. TSGs involved are P53, Rb (retinoblastoma), and p16INK4A. Other genes involved are FHIT (fragile histidine triad), APC (adenomatous polyposis coli), DOC1 VHL (gene for von Hippel-Lindau syndrome), and TGF- R-II (gene for transforming growth factor type II receptor). Carcinogenesis is a multistage process. The loss occur on chromosome arms 3p and 9p early in the lesion's progress from benign to dysplastic, with additional losses later in the disease, often involving 8p, 13q, and 17p. Putative TSGs at these sites of loss are P16 loss at 9p and P53 gene loss at 17p. Chromosome arm 3p may code for FHIT and is involved in epithelial cancers. Diadenosine tetraphosphatemay accumulate in the absence of FHIT, which may lead to DNA synthesis and cell replication. TSGs at another site of 3p may include the VHL gene, which encodes membrane proteins that function in signal transduction and cell adhesion. LOH on 9p is seen in 72% of lesions and may represent the site for P16, which encodes a cell cycle protein that inhibits cyclin-dependent kinases and that arrests the cell cycle at the G1–S phase, and loss may lead to cell proliferation. Later changes are seen on chromosomes 13 and 17, which are associated with progression to malignancy. LOH on 13q is identified in more than 50% of HNSCC.[8]

The involved TSGs are near the interferon locus and are close to the Rb locus. LOH on 13q has been associated with lymph node metastasis in HNSCC. LOH on 17p (the region of the P53 gene) is found in 50% of cases of HNSCC. The p53 and G1 and G2 cell cycle inhibition. Other genetic changes have been identified on chromosomes 4, 8, and 11. Loss on chromosome 4 occurs in up to 80% of HNSCC cases; the lost TSG may be the epidermal growth factor (EGF) gene. Loss on 8p occurs in up to 67% of HNSCCs and is associated with a higher stage and a poor prognosis; the related TSG is unknown. Loss on chromosome 11 is present in up to 61% of HNSCCs; the common site lost may code the cyclin D1 gene. [8]

LOH has been studied in oral premalignant lesions and predicts the malignant risk of low-grade dysplastic oral epithelial lesions**.** The importance of allelic loss has been confirmed in a prospective study of patents with dysplasia, where lesions with allelic loss at 3p, 9p, and 17p predict risk of progression to SCC, even in histologically benign or tissue with mild dysplasia. This is of importance as the majority of oral premalignant lesions (hyperplasia, mild and moderate dysplasia) do not progress to cancer. Lesions that progress to SCC appear to differ genetically from nonprogressing lesions, although they have similar histomorphologic findings. Molecular analysis, therefore, may become necessary in diagnosis. LOH on 3p and/or 9p is seen in virtually all progressing cases. LOH on 3p and/or 9p (but no other chromosome arms) has a 3.8 times relative risk of developing SCC, and if additional sites of LOH are present (4q, 8p, 11q, 13q, or 17p), a 33-fold increase in risk of progression to cancer is seen. Accumulation of allelic loss is seen in progressing lesions, and the majority of progressing dysplasias have LOH on more than one arm (91% vs 31% of nonprogressing dysplasias); 57%

have loss on more than two arms (vs 20% of dysplasias without progression). LOH on 4q, 8p, 11q, 13q, and 17p is common in severe dysplasia/carcinoma in situ or SCC.[8] Matrix metalloproteinase 2 and tissue inhibitor of metalloproteinase play an important role in cancer initiation and development. ICAM-5 (telencephalin) is an intercellular adhesion molecule reported to be expressed only in the somatodendritic membrane of telencephalin neurons.

The development of malignant epithelial neoplasms is associated with disruption of cell-to-cell and cell-to-matrix adhesion. Syndecans are a family of heparin sulfate proteoglycan receptors that are thought to participate in both cell-to-cell and cell-to-matrix adhesion. In a study of 43 SCCs, a reduction of syndecan 1 correlated to histologic grade, tumor size, and mode of invasion. The initiation or progression of oral cancer may be associated with polymorphism of the vascular endothelial growth factor gene.[8]

Role of Viruses

The potential role of viruses in oral cancer is under continuing study. The interaction of viruses with other carcinogens and oncogenes may be an important mechanism of disease. Smokers demonstrate higher antibody titers to HSV, suggesting reactivation. Neutralizing antibodies to HSV are present in the serum of patients with oral cancer at higher titers in those who have advanced cancer, and antibody response to HSV antigen is greater in patients than in controls.[8]

The association of HPV with anogenital and cervical dysplasia, carcinoma in situ, and invasive carcinoma has been well established. HNSCCs with transcriptionally active HPV-16 DNA are characterized by occasional chromosomal loss, whereas HNSCCs lacking HPV DNA are characterized by gross deletions that involve whole or large parts of chromosomal arms and that occur early in HNSCC development. These distinct patterns of genetic alterations suggest that HPV-16 infection is an early event in HNSCC development. In some studies, approximately half of OSCCs contain HPV types 16 or 18 (HPV-16 or -18). In one study, when assessed by polymerase chain reaction, 90% of oral carcinomas were found to contain HPV-16 or HPV-18. HPV is detected with increased frequency in oral dysplastic (2–3x) and malignant epitheilum (4.7x) than in beinign oral mucosa, and the probability of high-risk HPV was increased (2.8x). Oropharyngeal SCC, particularly involving the tonsil, base of the tongue, and larynx, has a higher prevalence of high-risk HPV-16 than oral SCC. Nonkeratinizing cancer of the base of the tongue and the tonsil associated with HPV appear to have an improved response to radiation sensitivity.[8]

Oncogenes and anti-oncogenes

Proto-oncogenes may code for growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, and transcription factors. Although proto-oncogenes increase cell growth and differentiation and are likely involved in carcinogenesis, few have been consistently reported in HNSCC. Proto-oncogenes associated with HNSCC include ras (rat sarcoma), cyclin-D1, myc, erb-b (erythroblastosis), bcl-1, bcl-2 (B-cell lymphoma), int-2, CK8, and CK19.[8]

The p53 tumour-suppressor gene may undergo mutation to contribute to the development of cancer. Mutant p53 proteins are stable and their concentration in cancer cell is considerably higher than that of normal p53 protein in non-neoplastic cells. Unlike normal, benign or premalignant mucosa, 54% of oral cancers may express stable p53 protein. However, the significance of detection of p53 protein and its role in carcinogenesis remains controversial, especially as the rate of detection of p53 protein overexpression is heavily dependent on technique.[10]

CONCLUSION

Tobacco use is the major cause of oral cancer worldwide. Smoking tobacco is not only harmful for the smoker but also to the people around. Passive smokers are also affected by the carcinogens and affect the overall health leading to increased morbidity and mortality rates. Due to this reason smoking is prohibited in public places around the world. Smoking is a deteriorating habit which leads to dependence and death. Tobacco is very addictive and Medical help is thus required to quit smoking completely.

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