

Oral Carcinogenesis- A Review

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ABSTRACT: *Oral cancer being the sixth most common malignancy over all in the world. Most common risk factors as we learnt are synergistic effect of smoking and alcohol though separately smokeless and smoking tobacco poses threat towards developing malignancy. Prevention and early detection of malignancy can cause reduction in mortality and improve patients' life expectancy. Efforts are being made to come out with new the technologies and biomarkers just to detect the genetic and molecular alterations that normal mucosa undergo during carcinogenesis. Here in this review we will discuss about factors affecting oral carcinogenesis, field cancerization, biomarkers regarding oral carcinogenesis and treatment plan.*

KEYWORDS: *oral carcinogenesis, field cancerization, biomarkers, alcohol*

INTRODUCTION: Cancer is not a single disease but a group of diseases which is affecting worldwide without any age or gender predilection. So far about 100 types of cancers have been detected all over the world of which commonly encountered ones are oral cancer, skin cancer, mammary cancer, lung cancer and cervical cancer. In spite of development of newer techniques to diagnose a cancer in early stage the rate of cancer is rising each and every year. Early diagnosis of cancerous lesion could definitely bring about better prognosis and low mortality rate. Its location, size, invasion, and metastasis all contribute to the symptoms of cancer. Reasons thought to be responsible for the rapid increase in cancer cases worldwide are major change in present human lifestyle, Increased inclination towards deleterious habits like consumption of alcohol, smoking and excess smokeless tobacco usage^[1]. Head and neck cancer is considered to be sixth most common cancer^[2] in human beings and represents 6% of all cancers. Oral cancer comprises of 48% of head and neck cancer of which 90% is squamous cell carcinoma^[3]. If it is evaluated in regional basis like in India and other Asian countries oral and pharyngeal carcinoma take about half of the major cancer cases occur in these regions due to the excessive betel quid chewing and tobacco abuse. The manifestations of premalignant lesions like leukoplakia and erythroplakia prior to the occurrence of oral carcinoma is also not uncommon here. This paper mainly focuses on the concept of oral carcinogenesis for better knowledge in order to prevent oral carcinoma by its early detection.

AGE AND SEX DISTRIBUTION: Generally the age range within 40-70 is reportedly having more cases of oral cancers. Predilection towards male gender is seen worldwide ^[11] which can be due to the wide range usage of smoke and smokeless tobacco, betel quid chewing, alcohol abuse etc. But in a developing country like India Male: Female ratio is about 1:1^[12].

SITE PREVALENCE: In developed country like U.S.A tongue is the most predominant site for oral cancer but in India, Buccal Mucosa is seen to be the dominant site for oral carcinoma. Other less common sites are floor of the mouth, lip, gingivae.

RISK FACTORS FOR ORAL CANCER: Oral cancer can be prevented or at least risk of its occurrence can be reduced if the risk factors are avoided cautiously. In western countries alcohol consumption and smoking are considered to be the most important risk factors which act synergistically to cause cancer in oral cavity ^[13,14]. Though in Asian country it has been seen that excessive use of smokeless tobacco like Gutkha and betel quid chewing ^[15] pose as an important risk factors in developing oral carcinoma.

Tobacco: If we compare smokers with non smokers the risk will be 3 times higher in smokers ^[16]. IARC in 2007, pointed out the carcinogenic property of snuff smoking as it is harmful for both oral and pancreatic mucosa thus can cause carcinogenesis of the same ^[17].

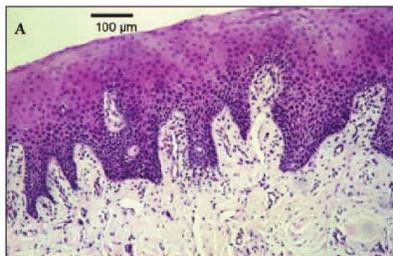
Interesting fact is that no difference in risk factors for developing oral cancer is noticed when comparison is made between non-smokers and smokers who didn't smoke for past 20 years. Whereas smokers who stopped the habit before 4 years have 35% less chance of getting cancer than the person who still holds on to the habit^[18]. It is 85% more risky to a person who is a non-smoker but is exposed to an environment of cigarette smoking than the person who neither smokes nor is exposed in the said environment ^[19]. Cigarette smoke in turn reduces the immunity of one person and may affect the oral cavity by eventually causing gingivitis, periodontitis and also oral cancer ^[20]. If cigarette smoking is tested on the composition basis this smoke itself contains certain compounds like nitrosamines, benzopyrenes and aromatic amines which actually results in developing cancer. These are grouped together and can be called as Precarcinogenes. These compounds often undergo oxidation by several oxidative enzymes which turn them into products which are poor in electrons and can covalently bond with DNA resulting in mutated region. They can also undergo non enzymatic metabolism to form carcinogens like reactive free radicals that in turn promote mutations by complex mechanisms ^[21]. The level of these free radicals can be seen increased in oral precancer and cancer. Consuming snuffs can interrupt the antioxidant defense systems and in turn make the oral epithelium vulnerable to free radicals of oxygen and nitrogen ^[22].

Alcohol: Permeability of oral mucosa is increased with excessive consumption of alcohol or alcohol abuse. The lipid in oral mucosa is dissolved which result in atrophy of epithelium and interfering with DNA synthesis and repair mechanism. Salivary flow is reduced owing to its genotoxic and mutagenic function thus affecting greatly the function of the liver to deal with toxic or potentially carcinogenic compounds. Immunity of body is hampered by the chronic alcohol abuse causing increased risk to infections and neoplasms ^[23].

Other risk factors of oral cancer:

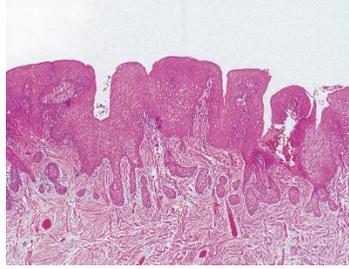
A positive association has been seen between periodontal disease and risk of oral cancer^[44] Dry snuff use shows an increased risk of developing carcinogenesis than moist snuff^[45] people working outside are continuously exposed to ultraviolet (UV) rays from sun thus in outdoor workers lip cancer is prevalently seen^[46]. Oral cancer from certain use of mouthwash and chronic irritation from poorly fitting dentures are few of those risk factors which still requires ample proof and thus still in controversy.^[47] Often it has been reported that first degree relatives of cancer patients are more prone to develop oral cancer. ^[48] Individuals with a defect in enzymes involved in the xenobiotic metabolizing pathway could be at enhanced risk to develop oral carcinoma^[49]

ORAL CARCINOGENESIS: Alteration in various genetic components of squamous cell carcinoma can give rise to Oral carcinogenesis. It is actually multifactorial process, early detection of which can improve the quality of life for the patient. Several molecular biological techniques have been introduced nowadays which can detect the underlying genetic changes of oral precancerous lesions that cannot be seen under microscope. These techniques thus eventually can point out those patients who are at high risk of developing cancers ^[4]. Sequence of genetic alterations and natural history of oral cancer are described in Figure 1⁵³.



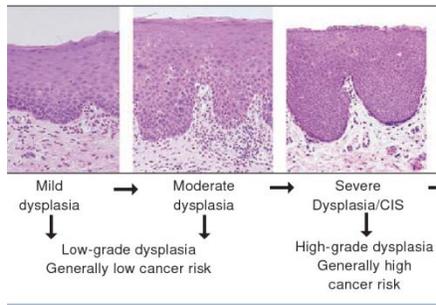
(a)

- Deletion 9q21(p16)



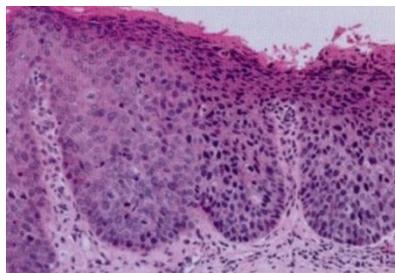
(b)

- Deletion 17 p13 (p53)
- Deletion 3p21
- Methylation p16 and MGMT



(c), (d),(e)

- Amplification 11 q13 and cyclin D 1
- Deletion 13 p21, 14 q24 and 14 q31
- Stromelysin-3 + VEGF



CARCINOMA IN SITU (f)

- Deletion 6p/8p23 and 4q26-28
- Hypermethylation p16 and p15

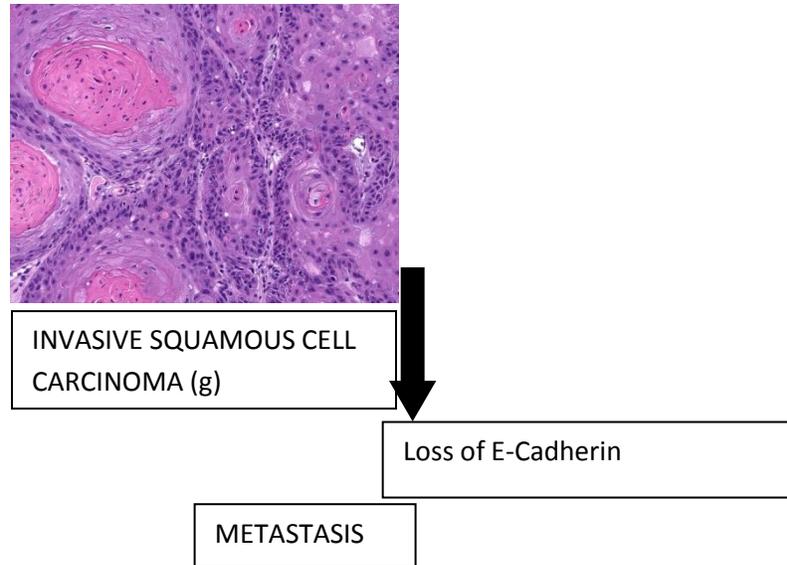


Figure 1: Natural history and genetic alterations of oral carcinogenesis. (a), Normal oral mucosa, (b) hyperplastic epithelium, (c) mild dysplasia, (d) moderate dysplasia, (e) severe dysplasia, (f) carcinoma in situ, and (g) invasive squamous cell carcinoma (well differentiated).

Various approaches at present are known through which molecular depth of oral cancer pathogenesis can be understand, these are as follows-microarray technology, methylation microarrays, gene expression microarrays, array comparative genomic hybridization, proteomics, mitochondrial arrays, and micro-RNA arrays^[5]. Potential of cancers to develop in multiple sites is termed as Field Cancerization^[6,7]. Can be observed in carcinoma related to squamous and transitional epithelium. Oral carcinoma like any other cancer in tissues can be insidious throughout its development and during this time multiple site of affected tissues can undergo neoplastic transformation. It is seen that underlying gene of the epithelium affected with precancerous lesion as well as carcinoma in same oral cavity have undergone mutation^[18]. Deleterious habit like smoking can increase the risk of oral carcinoma as it acts as an inducer in mutation of p53 gene along with blocking the tumor suppressing activity of the same^[9]. Prolonged exposure to different environmental and exogenous factors should also be taken in consideration regarding mutation of tumor suppressor genes and their multifactorial nature of presentation. Recurrency of these mutations can affect greatly which starts by alterations in DNA repair and apoptosis thus raising the chances of susceptibility for future transformation. These transforming cells soon undergo mutations to adapt themselves accordingly and able to enhance their resistance against therapeutic controls. Recently it is unveiled through genetic analysis that cancers forming at distant site within the oral cavity has its origin in same initial clone^[10]. Thus in most of the cases it is of no use to surgically remove premalignant lesion in order to stop the carcinogenesis progress because of field cancerization or multiplicity nature of oral carcinogenesis.

MICROENVIRONMENT:

For a compelling way to deal with malignant growth, it ought to be considered as an infection that includes complex connections among a network of heterotypic cells, described by the first cancerous tissue, the recently shaped tissue and cells encompassing it [24]. The TME of OSCC included disease related fibroblasts (CAFs), invulnerable cells and other supporting cells. Oncogenic changes in quality articulation profiles add to microenvironmental alterations, for example, ROS amassing, overproduction of cytokines and epithelial mesenchymal progress (EMT). CAFs are the absolute most basic components of TME, adding to proliferation,

attack and metastasis. Overexpression of cytokines, apoptosis initiated by White blood cells and adjustments in antigen preparing apparatus smother the versatile insusceptible reaction in OSCC[25]. The overexpression of cytokines appraisals, for example, changing development factor- β (TGF- β), contribute to the EMT, immunosuppression, and the advancement of the CAFs. Irritation and hypoxia are the dynamic powers of angiogenesis and changed digestion [26]. The glycolytic and oxidative digestion is utilized by OSCC so as to advance tumorigenesis through components coupled between territories of malignancy cell (parenchyma) and TME cells (stroma) [27].

POTENTIALLY MALIGNANT DISORDERS AND DYSPLASTIC CHANGES:

Capability of an oral mucosa to create oral premalignant sores like oral leukoplakia and erythroplakia may check as the sign for its plausible change to danger under reasonable conditions [28]. Leukoplakia is an unscrapable white sore and analyzed as a condition by barring different maladies or issues which are as of now not inclined to the danger of harm [29]. Microscopically, described by a few receptive epithelial changes, for example, hyperplasia, hyperkeratosis and acanthosis. Histologically, a differentiation is basic to be made among dysplastic and non-dysplastic leukoplakia. The term epithelial dysplasia alludes to cytological mixes and fluctuating degrees of atypia (like hyperchromatism, expanded atomic cytoplasmic proportion, pleomorphism, dyskeratosis, irregular mitotic figures or expanded mitosis). Mellow dysplasia is described by adjustments in the basal or parabasal keratinocytes, when the atypia is found in the center level is called moderate dysplasia; when changes are reached out to the surface layer, the terms progressed dysplasia and carcinoma in situ are applied (atypia is finished, from the base to the surface) [30]. About 1% may advance to harmful change [27]. Erythroplakia (high threatening potential) then again is characterized as a red injury that can't be described clinically or neurotically as other sickness [28]. Blend of red and white changes offer ascent to the injury called erythroleukoplakia. Erythroplakias have higher danger of harmful change as it shows differing degrees of dysplasia and carcinoma [28]. So a prompt biopsy in suspect of danger is suggested for a sore which remains unhealed for three weeks [31].

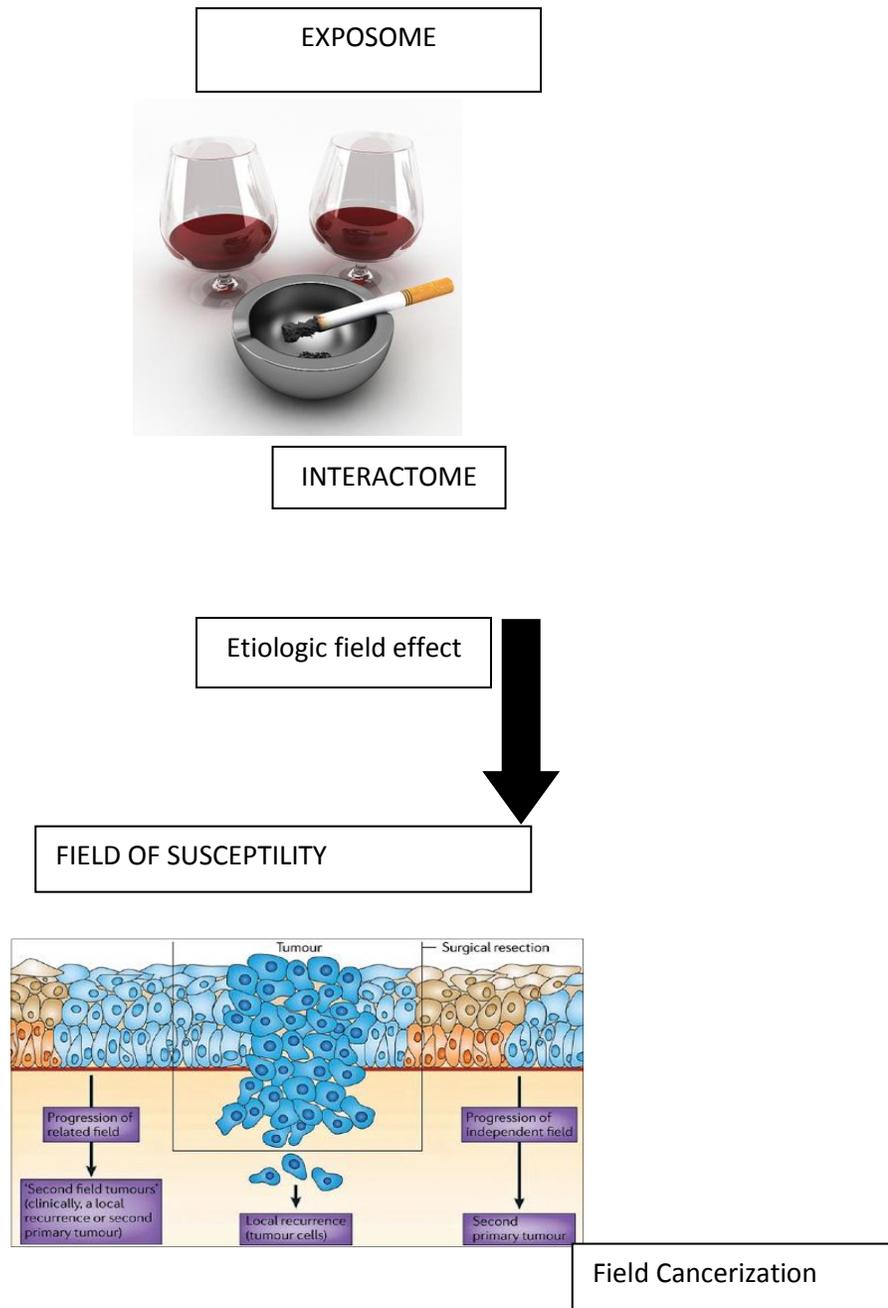
EXPERIMENT AND STUDIES ON ANIMAL MODELS FOR ORAL CARCINOGENESIS:

Suppositions are made relying on the conventional clinical and distinct example examines that oral disease can be tried from cell lines which are initially secluded from patients with carcinoma and furthermore from creature models of compound carcinogenesis and transgenic animals[32]. Over articulation of specific mixes are these days conceivable attributable to hereditary control of cells, which can likewise be gotten vitro or in vivo (creature models). Different reformist changes occurring all through oral carcinogenesis i.e its progress from typical tissues to obtrusive carcinoma through dysplastic changes can be concentrated through compound carcinogenesis [33]. Synthetic substances like dimethyl-1,2-benzanthracene (DMBA) and 4-nitroquinoline-1 oxide (4NQO) are most usually utilized synthetic substances. Despite the fact that utilization of DMBA presents impediment because of its restricting profoundly disturbing property for the investigation of OSCC. Aside from that it's fiery reaction and putrefaction of granulation tissue appearance makes it unsuitable for study [34]. 4NQO structure matches to those delivered via cancer-causing agents containing snuff; rather it is discovered more viable in creating carcinogenesis. When contrasted with DMBA it causes inescapable irritation [34, 35]. Hereditary methodologies are especially helpful for concentrating to get familiar with the nuts and bolts of oral malignant growth in its various stages hereditary methodologies are discovered to be valuable and proceed in getting new restorative techniques to deliver transgenic creatures in a huge size of creatures [36]

BIOMARKERS:

Biomarkers help in the assessment of anticipation or utilization of treatments if it ought to be utilized is surveyed for the most part by biomarkers. They help in identification of threatening progress from ordinary mucosa at its most punctual stages. Biomarkers uncover the hereditary and atomic adjustments in right on time, moderate, and late end focuses during the time spent oral carcinogenesis can likewise be uncovered by means of biomarkers [37]. Along these lines forecast, determination, and treatment of oral carcinomas will inevitably get refined with the utilization of biomarkers [38]. Adequacy and wellbeing of chemopreventive specialists likewise can be controlled by Hereditary and sub-atomic biomarkers. Thusly, explanations with respect to their sorts, dosages,

frequencies, and regimens which could assist them with accomplishing the greatest degree of advantage from these chemopreventive operators are normally controlled by these markers. Biomarkers will likewise Along these lines delayed subsequent methodology to decide the specific portion and clinical reaction to chemopreventive operators for that specific patient and hence less number of patients to treat which could prompt higher odds of treatment achievement [39, 40]. The Biomarkers can be arranged [41] into general gatherings which identify introduction, movement, powerlessness to cancer-causing agents, as well as the objective cell populaces reactions [40] as indicated by Board on Organic Markers of the Public Exploration Committee/Public Foundation of Sciences. As early biologic markers a few scientists noted and paid uncommon spotlight on adjustment in infinitesimal cytogenetic and physical changes. One of which is the recoloring of micronuclei that can be considered as a biomarker to decide chromosomal distortions on peeled mucosa.[42]. In spite of the fact that there are no clear biomarkers, neoplastic movement actually permits windows to discovering them [Fig 2]⁵²,[Table No1]⁵³



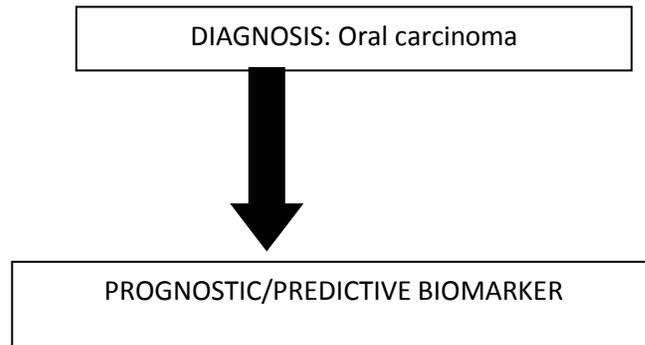


Figure 2. Opportunities for biomarkers in oral cancer. The “natural history” of oral cancer allows the study of different phases in the progression of malignancy. One opportunity is given by the generation of an etiologic field -influenced by risk factors “exposome” and their interactions “interactome” that promotes a state of susceptibility. The passage of this state to cancerisable field gives another opportunity for research. With the diagnosis may emerge prognostic and predictive biomarkers. Modified version ^[43]

Category	Measures
Genomic biomarker	Micronuclei, DNA adduct, DNA content, and chromosomal aberration (polymorphism, allelic loss, gain, and amplification)
Oncogenic biomarker	Oncogenic expression, modified tumor suppressor genes, and <i>Src</i> genes
Proliferation biomarker	Nuclear and cyclin-related antigens, mitotic frequency, ornithine decarboxylase (ODC), and polyamines
Differentiation biomarker	Cytokeratins, transglutaminase Type I, and transcription factor (AP)-1
Oxidative stress biomarker	Glutathione <i>S</i> -transferase, stress proteins (HSPs), and Superoxide dismutase Bcl-2 family, chromatin condensation
Apoptosis biomarker	factors, caspases, and nucleosome

POTENTIAL BIOMARKERS: TABLE 1

Immunologic biomarker	Cytokines
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TREATMENT

The anatomical constraint of the head and neck make the treatment of oral cancer difficult. The current treatment employed for oral cancer patients include surgery, radiation therapy, and chemotherapy. The treatment is recommended in combination or alone based on the severity of the tumor (tumor stage) and health status and life style of the patients.^[50] The treatment plan is discussed and developed by multidisciplinary team, which include surgeons, oncologist, radiologist, dentists, and rehabilitation specialists.^[51] Moreover, the concurrence from patients family should also be obtained before beginning the treatment. The patients have to face a lot of problems such as changes in appearance and organ dysfunctions, even after a successful treatment.

CONCLUSION:

Oral cancer being the sixth most common malignancy all over the world. Most common risk factors as we learnt are synergistic effect of smoking and alcohol though separately smokeless and smoking tobacco poses threat towards developing malignancy. Prevention and early detection of malignancy can cause reduction in mortality and improve patients' life expectancy. Efforts are being made to come out with new the technologies and biomarkers just to detect the genetic and molecular alterations that normal mucosa undergo during carcinogenesis. Oral cancer awareness within the common people is very important and initiative should be taken by government to make public learn about the deleterious effect of smoking and tobacco abuse.

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