Etiology of oral cancer revisited
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Abstract
Incidence of oral cancer is increasing worldwide. World Health Organization published data shows India has the highest mortality rate in patients with oral cancer while other countries like the United Kingdom is showing a rise in the incidence. The main risk factors are consumption of tobacco in various forms and alcohol. Other risk factors are viral and fungal infections, genetic syndrome predisposing to oral cancer and potentially malignant lesions, or conditions. Viral infections are known to cause cancers. Human papillomavirus (HPV) is one such virus that has been strongly associated with oro-pharyngeal cancer in sites such as the base of the tongue, tonsils, and pharynx. Tests that can identify HPV in these sites are still under development. There has been some success in identifying salivary biomarkers to diagnose oral cancer however they are not specific and is currently not recommended. Treatment of oral cancer can cause serious morbidity, and hence prevention and early detection should remain the main goal. Prevention by educating public regarding ill effects of tobacco and excess alcohol consumption, political will in reducing the availability of these products, screening and monitoring will help in reducing the incidence of oral cancer.

Keywords:
Alcohol, human papillomavirus, oro-pharyngeal cancer, potentially malignant

Introduction
Oro-pharyngeal cancer is the 8th most common cancer. As per the cancer country profiles published by World Health Organization (WHO) highest mortality is in India; 18.3% of all cancer mortality in men and 6.8% in women is due to oro-pharyngeal cancer. The age-standardized incidence rate is 12.6 in 100000 in India and has the highest number of oral cancer per year. In the UK, oral squamous cell carcinoma (OSCC) with rising incidence has recorded 650,000 new cases and 350,000 deaths each year. In a period of 30 years, the incidence has increased by 250%. The 5 years survival rate for oral cancer is <54% and is associated with facial disfigurement, loss of vital function such as mastication, taste, and swallowing causing social inhibitions and poor quality of life. If detected early the survival increases to 90% for Stage 1 lesion.

The overall increase in incidence of oral cancer makes it more important to highlight the etiology that are known and research that can help develop effective screening methods and investigations to identify this condition early to improve morbidity and mortality.

Etiology and Risk Factors
WHO states that the aging population and increasing exposure to risk factors are the reason for oral cancer epidemic in developing countries. The increasing use of tobacco and alcohol accounts for 90% of all risk factors attributable to the cause of oral cancer. The other factors such as viruses, potentially malignant lesions, and genetic abnormalities form a smaller part of this massive health problem.

Tobacco
Smoking tobacco in the form of cigar, cigarettes, beedies, and rollups all increase the risk of oral cancer. The oral mucosa is exposed to at least 28 carcinogens present in the tobacco causing lesions ranging from epithelial dysplasia to frank cancer.

Spit tobacco
The risk of oral cancer is increased with use of snuff, betel quid with or without tobacco and other forms of smokeless tobacco. Carcinogens identified are tobacco-specific N-nitrosamine, N’-nitrosonornicotine (NNN), and 4 (methyl nitrosamino)-1-(3-pyridyl)-1-butanolone (NNK). NNN and NNK are formed from nicotine during curing, aging and fermentation of tobacco. Oral swabbing of a low concentration of a mixture of NNN plus NNK in water induced oral tumors in rats.

Betel quid
Betel quid consumption is considered one of the most riskiest habit in terms of oral cancer and stopping may show a reduction
of oral cancer incidence by half in India where the habit is widespread.\(^5\) The betel quid is made of arecanut, betel leaf, and lime with or without tobacco. Chewing quid releases carcinogens from the areca and tobacco into the buccal sulcus where it’s kept with continuous exposure to the chemical. Cancer associated with this habit is said to be more common in females as they tend to keep quid in buccal sulcus for a longer period of time. A study has found that the meta-relative risk for developing cancer with use of betel quid with tobacco is 7.74% and without is 2.56%.\(^6\)

**Alcohol**

Alcohol acts as an irritant and causes damage to cells that undergo DNA changes during cell repair. It acts as a solvent for harmful chemicals from other irritants like tobacco smoke to enter into cells. Excess alcohol causes nutritional deficiency by interfering with the absorption of folic acid, increases estrogen, and metabolic compound of alcohol: Acetaldehyde is carcinogenic and is linked with cancers that include colorectal and breast cancer.\(^6\)

**Infections**

Viral: Human papillomavirus (HPV) 16 is associated with oropharyngeal cancer. The high-risk HPV viruses 16, 18, and 31 are linked to the causation of several cancers, which include oropharyngeal site. The virus gets incorporated into cell and the HPV oncogenes: E6 degrades tumor suppressor gene P53, and E7 destabilises the retinoblastoma oncogene. E6 function loss leads to P53 expression and upregulates the downstream factors that induce programed cell death and stagnation of cell cycle. Loss of E7 allows increased Rb expression leading to arrest of cell division growth.\(^7\)

This has given the direction to researchers to concentrate on bacterial Cas9 RNA-guided endonuclease and single guide RNAs (sgRNAs) specific for E6 or E7, which can cause introduction of inactivating deletion or insertion of mutation in E6, E7 genome thus leading to P53 and Rb induction leading to cell cycle arrest and cell death. A vector-delivered Cas9/sgrRNA combination can lead to effective treatment modalities for HPV-induced cancers.\(^7\)

**Tests for HPV**

Currently, there are no sound methods, which can be used as screening method for HPV detection with high sensitivity and specificity. It is estimated that 5% of all cancers are caused by HPV. Cervical cancer is caused by HPV, and there is increasing evidence of HPV in the causation of oro-pharyngeal cancer. The sites involved are the base of the tongue, tonsils, and pharynx. Cervarix and Gardasil are the vaccines currently available against HPV 16 and 18.\(^8\) The PLOS One study of the NCI Costa Rica Vaccine Trial on 7,000 women between age group 18 and 25 years, showed that women who received the vaccine had 93% reduction in acquiring HPV after 4 years post HPV vaccination. This could be breakthrough for this site-specific oral cancer as 50-70% of all throat cancer is attributed to HPV.\(^8\) The presence of HPV in the oro-pharyngeal sites is a good prognostic indicator. Higher staged cancer with positive lymph nodes has a poorer prognosis compared to N0 oro-pharyngeal cancer. Whereas, if the cancer is positive for HPV 16 and is >N0 the prognosis is better. Lymph node positive nasopharyngeal cancer with HPV is categorized as Stage 2 cancer, considering this it is suggested that similar strategy should be applied to oro-pharyngeal cancer.\(^9\)

**Other viruses**

Epstein barr virus (EBV), human immunodeficiency virus, simian virus 40, polyoma virus, hepatitis B and C virus, human T lymphocyte virus 1, and human herpes virus (HHV) 8 are all implicated in various cancers that can affect human.\(^10\) The HPV is the only virus directly linked to oro-pharyngeal cancer. The other oral lesions associated with viruses: Hairy leukoplakia with EBV, Hepatitis C virus with oral lichen planus (OLP), and HHV 8 with Kaposi sarcoma.\(^10\)

**Fungal infection**

Candidiasis: Candidal infection causes epithelial hyperplasia and dysplasia, which can progress to cancer. A recent study proposes significant association between epithelial dysplasia, oral cancer, and yeast carriage.\(^11\) Chronic hyperplastic candidiasis may progress to dysplastic lesion in about 15% of the cases and 10% of these develop oral cancer.\(^11\) Therefore, recalcitrant lesions should be closely monitored. The number of patients with chronic muco-cutaneous candidiasis developing oral cancer is very small and theory that virulence of candida species may have a role than its mere presence suggests that further research is warranted to identify the genotype and phenotype of candidal species that might be responsible for the change.\(^13\)

**Precancerous oral lesions**

WHO defined a premalignant lesion as “A morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart.” A generalized pathological state of oral mucosa in which oral cancer is more likely to occur is called premalignant condition. In 2005, this changed and a common terminology for both these type of lesion is "potentially malignant.”\(^14\)

**Potentially malignant disorders**

**Leukoplakia**

“Leukoplakia is a white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease.” In studies from Western countries, an annual malignant transformation rate is 1-2% for all types of leukoplakia together. Non-homogenous lesions have higher tendency to turn into malignancy\(^15\) and verrucous leukoplakia tops the list and almost always transforms into squamous or verrucous carcinoma though it may take longer than other types. Some leukoplakia has more malignant potential than other, and some may not progress at all. Spontaneous regressions are also seen in leukoplakia but these changes are rare.\(^14\)
The site predominance of potentially malignant lesions does not always correlate with the site predominance of oral cancer. It was noted in studies on epithelial dysplasia that 21.8% of oral epithelial dysplasia occurred in the buccal mucosa, 13.7% on the palate, and 12.3% on the floor of the mouth.\(^\text{[16]}\) Shafer and Waldron found that leukoplakia was more common in the mandibular mucosa and sulcus (25.2%), followed by buccal mucosa (21.9%).\(^\text{[16]}\) The squamous cell carcinomas of the oral cavity occur predominantly in tongue, oropharynx, lip, and floor of the mouth. This directs the question as to if there is a subgroup of epithelial dysplasia, which have a lower rate of malignant transformation when they occur in sites like buccal mucosa.

Malignant potential of epithelial dysplasia is about 5-18%. Malignant change is associated with high risk factors such as, (1) Erythroplakia within a leukoplakia, (2) verrucous lesion, (3) high-risk anatomic sites like tongue or floor of mouth, and (4) the presence of multiple dysplastic lesions specifically, in the absence of risk factor like smoking.\(^\text{[16]}\)

**Erythroplakia**

"An erythroplakia is a red lesion that cannot be classified as another entity." Erythroplakia is not common as compared to leukoplakia but when present there is a high risk that this lesion is either dysplastic or cancerous with a probability of 91%. The clinical appearance is that of a flat, macular, velvety lesion that may be speckled with white spots representing keratosis.\(^\text{[16]}\)

**Oral lichen planus (OLP)**

Lichen planus is secondary to the cell-mediated immune response.\(^\text{[17]}\) The antigen is a self-peptide, which causes an autoimmune reaction in the mucosa and is manifested in a variety of forms; erosions to plaques.\(^\text{[18]}\) OLP manifests as striated lesion, papules, or plaques. It may also manifest in the form of vesiculo bullous lesion. It is also found with other diseases of altered immunity such as: Ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis. Hepatitis C virus infection, chronic active hepatitis, and primary biliary cirrhosis are also associated with some forms of lichen planus.\(^\text{[17]}\) Lichenoid lesion is changes in oral mucosa similar to that of lichen planus; this is due to drugs and chemical irritants that unmask the lichen planus peptide which in turn causes this reaction. The treatment is to stop the medication or to remove the irritant that has caused the reaction.\(^\text{[18]}\)

Various types of lichen planus are hypertrophic, atrophic, erosive/ulcerative, follicular, annular, linear, vesiculo-bullous, lichen planus pigmentosus, and lichen planus pemphigoides. patients with OLP develop coincident skin lesions in 44% of the cases whereas, 70% of patients with cutaneous lichen planus develop an oral lesion.\(^\text{[18]}\) Lichen planus rarely involves other epithelial structures like nail but may involve mucosal tissue of the esophagus, tympanic membrane, and larynx. OLP lesions either persist for many years with periods of exacerbation caused by stress and anxiety, showing erythema or erosion or with periods of quiescence with decreased pain and sensitivity. Sometimes it may totally burn out.

SCC develops in 0.2% of OLP patients each year. Less than 5% of OLP patients develop OSCC in the absence of use of tobacco, and when it develops it is usually in high-risk lesions such as atrophic, erosive, and plaque variety.\(^\text{[19]}\) All patients with lichen planus should be advised to stop smoking and reduce consumption of alcohol. Erosive and atrophic lesions are more notorious compared to reticular lesions. Treatment with steroids can change erosive variety to reticular variety, with a significant reduction in the risk of developing oral cancer.\(^\text{[18]}\)

**Oral submucous fibrosis (OSMF)**

This is a chronic fibrosing condition of oral mucosa with malignant potential. Betel quid is linked to the causation of this progressive disease. Other factors are poor nutrition, chilly consumption, and genetic and immunologic process. Arecoline, found in betel nuts is a fibroblast stimulant that increases collagen production by >100%. The study has found that arecoline elevates the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up-regulated in a variety of fibrotic diseases. This up-regulation is directly proportional to the dose in patients with OSMF.\(^\text{[20]}\)

Studies have shown that keratinocyte growth factor-1, insulin like growth factor-1, and interleukin 6 expressions that are implicated in tissue fibrogenesis are up-regulated in patients with OSMF due to areca in the quid. The arecoline found in arecanut also inhibits metallo-proteinases, which causes breakdown of collagen.\(^\text{[20]}\)

Flavanoid, catechin, and tannin in betel nuts causes collagen fibers to cross-link, making them resistant to degradation. Betel nut causes a change in gene expression in the fibroblast leading to irreversible affect on fibroblast, which then produces excess collagen. Areca quid stimulates collagen fibroblasts by activating NF-kappa B expression, leading to fibrosis.\(^\text{[20]}\)

Copper content in betel nut is high, and the suggested theory behind fibro-genesis is that the copper causes up-regulation of copper-dependent lysyl oxidase activity and this stimulates fibrogenesis.\(^\text{[20]}\)

**Genetic and immunologic processes**

The patients who are positive for human lymphocyte antigens (HLA)-A10, HLA-B7, and HLA-DR3 have increasing incidence of OSMF. Direct or indirect stimulation of the immune system causes the activation of CD4 lymphocytes with high ratio of CD4-CD8. This suggests an ongoing cellular immune response.\(^\text{[18]}\)

The disease manifests with fibrosis of submucosal tissue leading to difficulty opening mouth. This is a potentially malignant condition, which will require regular monitoring. The patients should be educated to see a dentist as soon as possible if they notice ulcer, lump in the neck, pain or increasing burning sensation in the mouth, and progressive difficulty in opening mouth.
Genetic syndromes

Inherited genetic syndromes such as Fanconi’s anemia and dyskeratosis congenita are both associated with very high risk of developing cancer of the mouth and throat at an early age.\(^{[21]}\) Monitoring is therefore essential.

Prevention and Modifying Risk Factor

Modifiable risk factors include lifestyle factors such as tobacco, alcohol, and areca chewing. Consumption of these is falling. India has the second highest number of tobacco consumers. In India, an index of industrial production data has shown output of tobacco reduction by 12.1% in March 2015 from a year ago. The stiff increase in taxes for tobacco products and stringent packaging norms has contributed to further decline in production of tobacco.\(^{[22]}\)

Tobacco products like Gutka are banned in some of the states in India. In the UK public adverts on benefits of stopping smoking, health care help that is available for de-addiction has shown reduction in the number of people smoking.

HPV 16 and 18 causes 70% of cervical cancers, and the bivalent and quadrivalent vaccine (Cervarix and Gardasil) reduce the HPV infection.\(^{[23]}\) This can have a significant impact on the prevalence of HPV related oral cancer.\(^{[6]}\)

Early detection

Screening of oral cancer by visual inspection can detect and classify potentially malignant lesions. The indications that the potentially malignant lesion can regress after the removal of etiologic factors such as tobacco and alcohol, the effectiveness of surgical treatment for removal of early cancerous lesion in the oral cavity, has lead to the success of screening. As per WHO, however, the screening has not lead to a decrease in overall cancer related mortality.\(^{[8]}\)

Biopsy remains the gold standard for diagnosis of dysplastic and cancerous lesions. Research has been progressing to device noninvasive techniques like salivary biomarkers, which can identify high-risk lesions. The use of this in diagnosing oral cancer is still under investigation. Some of them are validated and show their feasibility in the discrimination of OSCC from healthy controls. Individual cut-off values of these markers and their predictive value, standardization of obtaining and storing salivary sample, understanding unknown confounding factors, biomarker activity in patients with other cancers, and chronic inflammatory conditions are all still under investigation.\(^{[21]}\)

Conclusion

Government initiatives and public awareness forms an important part of the preventive program. Reduction of tobacco and alcohol consumption can reduce the number of new cases. It will be a prudent decision to implement HPV vaccination worldwide as it is now showing reduction in a number of HPV related infection since its initial trial.\(^{[8]}\)

It is said that stopping consumption of betel quid alone will reduce the burden of oral cancer by 50% in India where it is highly prevalent.\(^{[5]}\) Revisiting the etiology has helped to target the modifiable risk factors with effective prevention program to reduce the burden of this disease worldwide.

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