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Mini Review

Etiology, risk factors and recent advances in molecular pathogenesis of oral cancer: a mini-review

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ABSTRACT:

Oral cancer is a cancer which arises from the lining of the lips, buccal cavity and oro-pharynx. It usually starts as a painless patch and progresses into a nodule or nodulo-proliferative growth. It is most commonly seen in people who are smokers, alcoholics and beetle nut or gutka chewers. Diagnosis is made by tissue biopsy of the concerning area, followed by investigation with Computerized Tomography (CT) scan, Magnetic Resonant Imaging (MRI) and Positron Emission Tomography (PET) examination to determine if it has spread to distant parts of the body. There are no hundred percent cures for the oral cancer, but there is hundred percent prevention of oral cancer by restricting tobacco and alcohol use. Human papilloma vaccination of risky individuals etc., There are many treatments available for oral cancers which include chemotherapy, and radiation therapy, wide local excision of the lesion and adjuvant chemotherapy. All these treatments are unique and depend on the size and location of the lesion and overall health status of the patient. In this review article, the authors have traced etiology, risk factors and recent advances in the molecular pathogenesis of oral cancer.

Keywords:
Oral cancer, Squamous cell carcinoma, Head and neck, Smoking, Alcohol.

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INTRODUCTION

Oral cancer or head and neck cancers are a group of malignancies which can start anywhere in the oral cavity, nasal cavity, oro-pharynx, larynx, paranasal sinuses or salivary glands. Symptoms for head and neck malignancy may present from a vague sore throat, hoarseness of voice to a swelling or lump. Sometimes, severe cases of head and neck carcinoma may experience unusual bleeding from the lesion or swelling, facial puffiness, or dyspnoea. Majority of the head and neck malignancies are caused by the use of alcohol or tobacco in various forms. Other risk factors include betel quid, certain types of human papilloma virus, radiation exposure, certain workplace exposures and Epstein-Barr virus. In 2015, head and neck cancers affected more than 50 lakh people universally and it had lead to over 4 lakh deaths (GBD, 2015a; GBD, 2015b). In the United States, $1/100^{th}$ of the general population is affected and males are most commonly affected than females. The average 5 year survival following diagnosis of head and neck cancer in the developed world is just above 50 % (SEER, 2016; Beyzadeoglu *et al.*, 2014). In India, cancer is responsible for increased morbidity and mortality and each year around one million new cancer cases are diagnosed and around 6,00,000–7,00,000 Indians died due to cancer by the year 2012 (Mallath, 2014). Epidemiological studies highlighted that overall cancer incidence in India was lower as compared to developed countries (Sinha, 2003). About 90% of head and neck cancers are squamous cell cancers. The diagnosis is confirmed by tissue biopsy and histopathology examination. The degree and the extent of spread may be determined by various medical imaging tests and blood tests. Head and neck cancer often is curable if it is diagnosed early; however, outcomes are typically poor if it is diagnosed late. Treatment may include a combination of surgery, radiation therapy, chemotherapy and targeted therapy.

Etiology and risk factors

Divergent chemical and biological agents were listed by various researches and scientists in the causation of the head and neck malignancies. Chemical compounds containing products like tobacco and alcohol, biological agents like human papillomavirus (HPV), *Treponema pallidum*, poor dental hygiene and dentures, lack of folate and high homo cysteine in diet, diabetes with chronic candidiasis and other viruses of the oral cavity have been shown to be remarkably integrated with oral cancer.

Literature and many survey on many research articles showed evidences suggesting that tobacco use in various forms, including smoking, chewing and in betel quid etc., have carcinogenic impact in oral cavity. The commonest form of tobacco use across the globe is smoking. The various forms in which tobacco is used as smoke are - cigarettes, cigars, pipe and beedi etc. Hookah or chillum (a clay pipe used to keep the burning tobacco) are other common forms of smoking in some countries of Asia including India. In some part of India like Mizoram, tobacco smoke is dissolved in water ('smoke on the water') which is another peculiar form of tobacco use.

Various authors in their respective studies have indicated that alcohol is a prime harmful factor for oral carcinogenesis. Several epidemiological studies also proved that dual use of tobacco and alcohol intake in the study animals showed high incidence of cancers. Few studies have shown that individuals with daily alcohol consumption of greater than 170 g of whisky are prone to have ten times higher risk of oral cancer than the occasion and light drinkers (Wynder, 1957). The mechanism of damage by alcohol *in-vivo* is by damaging the metabolism of the oral mucosal cells which ultimately assists the entry of carcinogenic substances (McCoy, 1978).

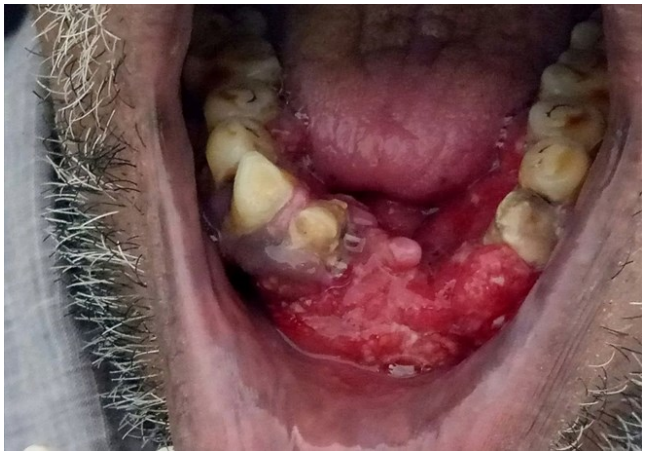

Figure 1. Clinical photograph showing proliferative growth (Source: author)

The function of cancer causing viruses in humans is a bright and emerging area of research; these viruses are competent enough in hijacking host cellular framework and can cause DNA aberrations and induce proliferative changes in the affected cells. Human Papilloma Virus (HPV) and Herpes Simplex Virus (HSV) were proved to cause oral cancers due to poor oral hygiene, diabetes changes in oral-sexual practices and other associated factors, globally. HPV has been documented in more than 25% of the oral cancers cases (Ha, 2004; Kreimer *et al*., 2005).

The most frequently detected variant of HPV in squamous cell carcinoma of the head and neck (HNSCC) is HPV-16 and constitutes more than 90% of HNSCC cases, followed by variants HPV-18, HPV-31 and HPV-33. The prognostic importance of HPV in pre-malignantoral lesions is not transparent. However, few studies have found better disease-specific survival and better prognosis for HPV positive oral malignancies.

Herpes Simplex Virus-1 or ‘‘oral herpes’’ is frequently linked with sores and ulcers around the mouth and lip and has been proved by few authors as a causative agent of oral cancer (Schildt *et al*., 1998). Epidemiological studies showed significantly greater levels of Immunoglobulin G and Immunoglobulin M antibodies of HSV-1 in oral cancer patients when matched with the control group (Shillitoe *et al*., 1982). Kassim *et al.* (1988) also documented cancer causing potential relationship between HSV-1 and oral squamous cell carcinoma (OSCC) (Kassim *et al.,* 1988). According to Starr *et al*. (2001), herpes simplex virus-1 in association with smoking and human papilloma infection increases the risk of carcinogenesis of oral squamous cell carcinoma. Immune-deficient patients such as human immuno deficiency virus positive patents has 2-3 fold increased risk of oral cavity cancers, as the HIV virus suppresses the immune system directly and also these patients are prone to various viral and fungal infections of the oral cavity such as HSV-1, HPV and candidiasis (Chidzonga, 2003; Grulich *et al*., 2007). Epstein Barr Virus (EBV), Human Herpes Virus-8 (HHV-8) which is mostly associated in AIDS patients and cytomegalovirus have also been reported as risk factors of OSCC in different studies (Al-Moustafa *et al.*, 2009; Atula *et al*., 1998). These are more frequently observed in HIV and AIDS patients.

According to the experimental and clinical studies by few authors in the field of oral cancer research, leukoplakia and nodular leukoplakia with co-infection with candida species have a comparative greater chance of squamous metaplasia, dysplasia and malignant transformation. Incidence of oral cancer was observed in patients with poor dental hygiene and prolonged irritation by sharp and irregular tooth which constantly erodes mucosa of the oral cavity. Eroded mucosal area becomes the site of entry for the microbes which leads to dental sepsis and ultimately on long term it can promote carcinogenesis. Deficiencies of vitamins, minerals and trace elements in the diet can also promote carcinogenesis. Lot of experimental animal studies must be done to accurately mention the factors which are responsible and which can prevent oral cancer. Some researchers have reported lower risk of oral cancer with higher intake of fruits and vegetables in normal subjects; however they did not do a comparative study with the people who have smoking and tobacco habits.

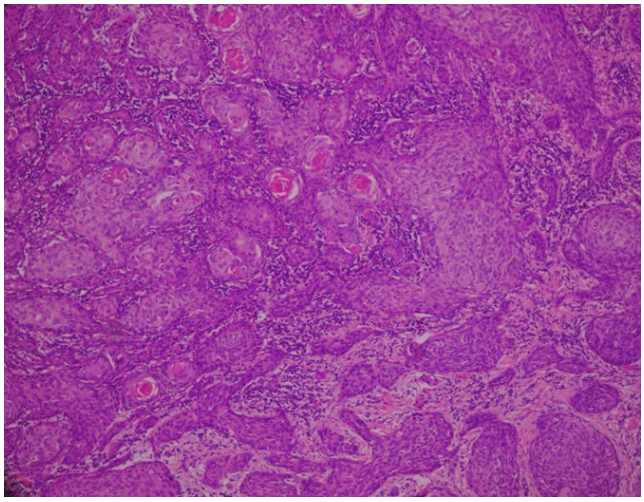

Figure 2. Microphotograph showing the features of well differentiated squamous cell carcinoma (Source: author)

Betel quid chewing is frequently seen in various parts of India and South East Asia, this habit is seen both in men and also in women with predominance in men, chewing of betel quid for year's leads to a premalignant condition in the oral mucosa known as oral submucous fibrosis which can be graded from 1 to 3. Oral sub-mucous fibrosis is characterized by recurrent and chronic mucosal inflammation and fibrosis of the submucosal tissues which leads to difficulty in opening mouth.

Molecular pathogenesis

The p53 gene is popularly known as tumour-suppressor gene which encodes a transcription factor which has a charecteristic role in maintaining genomic stability, cell cycle and cell division, DNA repair, apoptosis and cell ageing (Sullivan *et al*., 2018; Bykov *et al*., 2017; Kaiser and Attardi, 2018). Greater than eighty percentages of HPV-negative head and neck squamous cell carcinomas (HNSCC) have p53 mutations resulting in the loss of function (Lawrence *et al*., 2015). A mutation in p53 gene usually occurs in the primary stage of carcinogenesis and is almost always associated with HPV negative cases, due to the degradation of p53 by the HPV E6 oncoprotein (Castellsagué *et al*., 2016).

Molecular characterization advance proved that in HNSCC, PI3K/Akt/mTOR seems to be the most customarily down regulated pathway. In HNSCC, approximate rate of mutations of PIK3CA gene is 16% (Kang *et al*., 2015). Cellular growth, cell differentiation and cell survival is determined by PI3K group of enzymes and activated by Receptor Tyrosine Kinase (RTKs), such as Epidermal Growth Factor Receptor (EGFR).

The epidermal growth factor receptor such as EGFR, HER1 or ErbB1 belongs to the HER/ErbB family of Receptor Tyrosine Kinase (RTKs). EGFR is over-expressed in 80-90% of head and neck squamous carcinoma cases and has reciprocal correlation with prognosis and treatment outcomes (Solomon *et al*., 2018). EGFR signaling is a complex network, involving many individual genes and mutations and overlap with other pathways. As such, the potential for therapeutic targeting of EGFR signaling is vast, representing both a daunting challenge and tantalizing opportunity for HNSCC research. Resistance to EGFR targeted therapies was seen in the recent trials due to up-regulation or activation of other RTKs, such as c-MET (hepatocyte growth factor receptor). C-MET encodes mesenchymal–epithelial transition factor which is associated with increased migration of tumor cells, invasion of the local and distant tissue or organs and metastasis in cancer (Madoz-Gúrpide *et al*., 2015). C-MET mutations are reportedly rare in HNSCC (2–13%), while gain in MET copy number and over-expression of its ligand Hepatocyte Growth Factor (HGF) is common in HNSCCs (Cho *et al*., 2016).

The cancer genome atlas of the national cancer institute, expressed that inactivate mutations in NOTCH1/3 was seen in 17% of human papilloma virus positive cells and 26% of human papilloma virus negative head and neck squamous cell carcinoma and these are missense mutations occurring in functional regions of NOTCH-1 and non-sense mutations which are the result of truncated proteins, frame shift insertions and deletions (Nowell and Radtke, 2017). In the latest cohort

studies done by Sun *et al*. (2017) and Zhao *et al*. (2016) , it was disclosed that over-expression of downstream genes such as HES1 and HEY 1 in NOTCH1 mutation leads to poor and bad prognosis in head and neck squamous cell carcinomas.

Signal Transducer and Activator of Transcription (STAT) plays a definite role in both HPV-positive and negative head and neck squamous cell carcinomas; up-regulation of STAT3 and its genetic targets were believed to contribute to the aggressive behavior and malignant potential making the tumor or lesion resistant to chemotherapy, EGFR-therapy and radiation therapy (Geiger *et al*., 2016; Seo *et al*., 2017).

Association of human papilloma virus is seen with carcinoma of the tonsils and oro-pharynx and the incidence has been increasing for the last three decades and now it has exceeded the incidence of HPV- induced cervical cancer of women (Leesmans *et al*., 2018). HPV positive patients usually develop small tumors but they have high chance of regional metastasis to the lymph nodes and it is more common in young white males according to Maxwell *et al*. (2016). Though there is regional metastasis, HPV-positive patients demonstrate favorable prognosis when compared to HPV-negative patients (Zhang *et al*., 2016). HPV positive patient also show better and improved response to chemotherapy and radiotherapy when compared to HPV-negative patients (Coordes *et al*., 2016) and this may be due to the molecular make-up and pathogenesis or age related or may be due to the overall health of the patients, which still remains unclear.

Diagnosis

Detection of oral cancer in the initial stages is one of the most efficient ways to reduce death from this particular disease. Early detection can minimize the morbidity of the disease and its treatment, which is associated with a severe loss of function, disfigurement, depression and poor quality of life. Various screening tests such as cytology techniques, brush biopsy, saliva microscopic examination, DNA analysis, Immuno-histo-chemistry, laser capture micro-dissection, lab-on-a-chip and various imaging techniques are available for early detection. Recent study done by Erugula *et al*. (2016) showed that elevated homocysteine and decreased folate levels which gets altered by smoking can lead to oral cancers. So, continuous observation of homocysteine and folate levels would also contribute to the diagnosis of oral cancers in correlation with other risk factors.

Prevention and treatment

Occurrence and progression of oral carcinogenesis can be done by eliminating the use of tobacco, alcohol and betel nuts. The oral carcinoma risk can be reduced by limiting the exposure to UV light and dietary modifications like eating more of fruits and green leafy vegetables (Chainani-Wu *et al*., 2011). The current therapies employed for oral cancer patients include surgery like excision and wide local excision, radiation therapy alone or chemotherapy plus radiation, and chemotherapy alone. These therapies are recommended in combination or alone based on the TNM staging like tumor size, underlying or overlying structures involved extent of spread or metastasis, overall general health of the patient and life style of the patients. Usually the therapy plan is discussed and developed by multidisciplinary team depending upon the case, which include general and plastic surgeons, surgical and medical oncologists, radiologist, maxillofacial surgeons and dentists, and rehabilitation specialists.

CONCLUSION

Carcinoma of the oral cavity or head and neck carcinomas overall have multi-factorial etiology and arises commonly due to chronic use of tobacco and alcohol addiction, which can lead to divergent biochemical changes and molecular abnormalities in the oral cavity. A thorough dental examination of the oral cavity for various predisposing factors and precancerous lesions to be done once in six months in the persons who

have dental problems and have a habit of tobacco use and alcohol intake.

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