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Unification of Dental Science and Molecular Biology: A Better Approach for Oral Cancer Prevention

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ABSTRACT

Oral cancers are one of the most common cancers worldwide today. The five-year survival rate of oral cancer still remains low and delayed diagnosis is the major documented reason. Oral cancer satisfies the criteria for a suitable disease for screening. A dentist is the point of contact in heath system for any illness in oral cavity. The initial screening of oral cancer is done by visual examination. However this cannot efficiently screen patients at a probable risk. Hence, it is imperative to diagnose the disease at a molecular level. The detection and diagnosis are currently based on clinical examination, histopathological evaluation of the biopsy material and molecular methods. Several diagnostic aids have been developed over the years for early detection of oral cancer. Neither of the methods have individually proven to meritoriously screen oral cancer. Therefore, an integrative approach of dental science and molecular biology fraternities will aid in effectively combat oral cancer. The present article reviews the current trends in oral cancer diagnosis and screening and the beneficiary approach of amalgamation of dental science and molecular biology.

Key words: dental science, molecular biology, oral cancer prevention

Oral Cancer: A major health hazard in India

Oral cancer is one of the most fatal health problems faced by the mankind today. The incidence of the disease varies enormously all around the world (Figure-1). [1] Oral cancer accounts for 30–40% of all the malignant tumors in India, which accounts for only about < 2–4% in western countries. [2]

Although oral cancer ranks as the 17th most common cancer across the globe with 354 864 cases and 354 864 deaths, it is the major concern for India. In our country, it is the *second* most prevalent cancer with 119 992 cases and 72 616 deaths in 2018. [1] The frequency is high due cultural, ethnic, geographic factors and the popularity of addictive habits. Being India-centric problem, it needs our special attention. A rising trend in oral and oropharynx cancers is observed in young patients. [3] The 5-years survival rates are low, probably because most lesions are not diagnosed in the initial stages. Oral cancer poses significant mortality and morbidity in the patients, especially when discovered late in the course of the disease and depict higher rate of lymph-node metastasis. [4] However, if detected early, the probability of survival from oral cancer is remarkably better than most other cancers. [2]

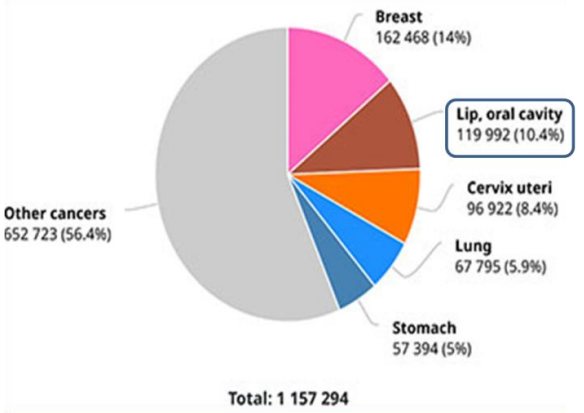

Figure 1: Oral cancer Incidence (India)
(Source: Globocan, 2018)

Why oral cancer prevention is important?

The overall goal of cancer prevention and control is to reduce the incidence and mortality of cancer and to improve the quality of life of cancer patients and their families. A well-conceived national cancer control programme is the most effective instrument to bridge the gap between knowledge and practice and achieve this goal. Prevention frequently offers the most costeffective long-term strategy for cancer control. Furthermore, cancer preventive measures are beneficial as they can also contribute to preventing other chronic diseases that share the same risk factors. Implementation of effective, integrated and multisectoral preventive strategies targeting multiple risk factors for cancer will reduce in the long-term the incidence of cancer in sites such as oral cavity, stomach, liver, breast, uterine cervix, colon and rectum. Although primary prevention in the form of advice and education about risk factors is important, this is largely ineffectual as evidenced by increased tobacco use despite knowledge of the risks, and the lack of evidence of effectiveness of mass education programmes in improving oral health. There is clearly a large gap between knowledge and behavior change. One way forward is to improve early detection of oral cancer, either by case finding or by organized screening programmes. The rationale for this is that oral cancer may be preceded by a clinically detectable potentially malignant lesion (leukoplakia or erythroplakia) or that it may begin as a small, localised, often asymptomatic lesion in the early part of its natural history. If detected when small, these lesions can be treated thus avoiding the notoriously high mortality and morbidity associated with this cancer. It is unlikely however that population screening for oral cancer will ever be instituted. [5] Recent pilot studies of oral cancer screening programmes using a simple oral examination showed that dental screeners in a hospital, medical practice or industrial setting could detect relevant lesions with a sensitivity and specificity equivalent to that achieved in other screening programmes. However, the compliance for screening following a postal invitation was only about 25%, leading the researchers to conclude that such a programme may not be cost effective. A viable alternative might be to carry out screening opportunistically, especially if high-risk groups could be targeted. Initially, the most obvious place to evaluate opportunistic screening or case finding is in a general dental practice environment. At present however, there are no data on the prevalence of lesions, or of high risk habits in a population of dental attenders, and there have been no attempts to evaluate oral cancer screening in primary dental care. [6]

In addition, screening for oral cancer in India can reduce mortality by over 80% in tobacco and/or alcohol users. [7] Screening by oral examination followed by tissue biopsy, the gold standard, has only 64% sensitivity for oral cancer [8]and 31% specificity for oral dysplasia or cancer. [9] Molecular tests including hypermethylation, RNA, and protein-based panels are under development, but not validated. Other technologies that use dyes, autofluorescence, or exfoliative cytology as adjuncts to the physical examination are used in clinical practice but have not improved early detection rates. Thus, amalgamation of oral examination (by a

dentist) and molecular methods (by a biologist) is anticipated to be an ideal approach for early detection of oral cancer. [10]

What are the methods for oral cancer screening by a dentist?

Commonly, a thorough visual and digital examination is the basis of oral cancer/pre-cancer detection strategies. An oral examination accompanied with various methodologies has been shown to be an effective way of detecting relevant lesions in the oral cavity, and a goodunderstanding of clinical presentation of high risk lesions is required to avoid over-diagnosis (Figure-2).

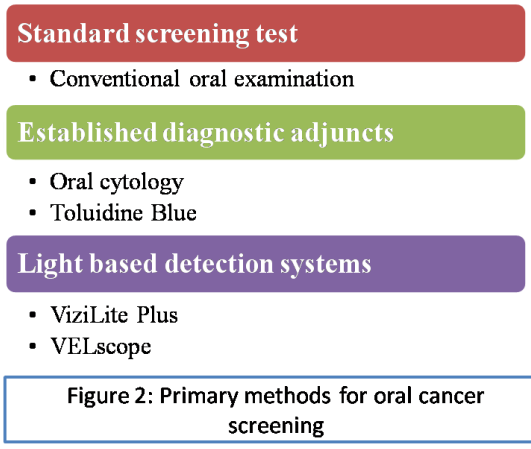

Figure 2: Primary methods for oral cancer screening

Chairside tests: The chairside adjuncts that have been developed for oral cancer/ precancer detection include methods that utilise vital stains and a number of light-based detection systems. [11]

Toluidine blue: Vital staining of the oral mucosa with toluidine blue (as a one per cent rinse or application)has been suggested as a means of surveillance in patients at risk of developing oral cancer, and for those who have had a confirmed neoplasm in other parts of the aerodigestive tract. The results and accuracy of these studies have been variable, with differing false positive and false negative rates. [12] Toluidine blue is most useful in secondary care for delineating the extent of lesions and for surveillance of patients at risk of recurrent disease.

Autofluorescence (VELscope®): The phenomenon of autofluorescence is based on the interaction of various fluorescent tissue compounds (fluorophores) that occur naturally in the body. When excited by an appropriate light stimulus, these compounds emit visible fluorescent light in the violet to green region of the spectrum. VELscope® is a portable device comprising a light source and a viewing handpiece. The technology is based on the direct visualization of tissue fluorescence. Both keratinized and non-keratinized squamous epithelium with a normal sub mucosa shows a typical homogeneous, pale green fluorescence. Sharply circumscribed areas of decreased auto-fluorescence might indicate areas of mucosal abnormalities that should definitely be monitored or investigated by tissue biopsy. [13]

Chemiluminescence: Examination of the oral cavity with the aid of chemiluminescent blue/white light has been suggested in several studies to improve the identification of mucosal abnormalities in comparison with normal incandescent light. Following a rinse with one per cent acetic acid for one minute under the chemiluminescence light, the normal mucosa appears blue, whereas abnormal mucosal areas reflect the light and appear more “acetowhite” with brighter, sharper margins. [13]

In addition to above mentioned major methods, there exists a large literature. However; sensitivity and specificity of these approaches have always remained compromised; and the search for better tactics to detect oral cancer at early stage is still on.

Why a dentist’s role is vital in oral cancer prevention?

Dentists are typically the first professionals who are approached to treat ailments within the oral cavity, making them uniquely placed to perform opportunistic screening for oral cancer and to provide advice and counseling interventions during routine examination. [14] There exist opportunities

during a patient's visit to a dental clinic for risk habit intervention services as it is well established that dental patients are traditionally receptive to preventive health messages and further, as some risk factors including smoking and betel quid chewing leave oral effects, visible evidence of the benefits of cessation can serve as a strong motivation for patients to quit.[15]

It is well-established fact that oral cancer is largely related to lifestyle and as health care providers, practitioners should be well aware of these factors. Further, they play a central role in providing information about the benefits that could result from the changing of lifestyle habits.[16] However, a large percentage of the dentists in UK, Ireland, Europe and USA found providing tobacco and alcohol cessation advice to their patients challenging [16-20]and further perceived themselves insufficiently trained to incorporate these interventions within their practices.[20] In a study conducted by Saleh et al; 2014[14], it was reported that up to 80% of the dentists have provided cessation advice to their patients indicating that they feel responsible, and want to be actively involved in oral cancer prevention not only through early detection but also through cessation of risk habits.

The knowledge and perception of dentists' in prevention and early detection is an important aspect for better management of oral cancer. With the increasing number of oral cancer among younger individuals with no established risk habits [21] and with the emergence of new risk factors such as human papillomavirus (HPV) infection,[22-23] it is clear that high risk individuals are not limited to only those who are associated with traditional risk factors and therefore awareness amongst primary healthcare professionals including dentists will be crucial particularly in detecting the disease early.

In India, there is a significant contribution of dentists in detection of oral cancer, however; the documentation and well-organized programme are lacking.

Why a biologist's role is vital in oral cancer prevention?

Oral carcinogenesis is a molecular and histological multistage process featuring genetic and phenotypic molecular markers which involves enhanced function of several protooncogenes, oncogenes and/or the deactivation of tumor suppressor genes, resulting in the over activity of growth factors and its cell surface receptors, which could enhance messenger signaling intra-cellularly, and/or leads to the increased production of transcription factors.[24] Alone oncogenes are not responsible for carcinogenesis, genes having tumor suppressor activity, leads to a phenotypic change in cell which is responsible for increased cell proliferation, loss of cellular cohesion, and the ability to infiltrate local tissue and spread to distant sites.[24] Understanding the molecular interaction of both oncogenes and tumor genes will permit more accurate diagnosis and evaluation of prognosis, which might lead the way for novel approaches to treatment.

Normal cells transform into pre-neoplastic cells and then to cancer after a series of clinical and histopathological stages involving genetic and molecular changes. Genetic alterations occurring during the carcinogenesis may present in the form of point mutations, amplifications, rearrangements, and deletions.[25]

Molecular changes in oral cancer

The multi-step progression of cancer involves a combination of acquired and inherited alterations in the DNA sequence. Genetic changes in keratinocytes cause a progressive acquisition of a malignant phenotype from premalignant to cancer, characterized by invasion across the epithelial basement membrane and eventual metastasis (Figure 3). The overexpression of oncogenes causes a disruption in the cell cycle driving to abnormal cell proliferation, while the expression of the tumor suppressor genes, especially the proteins p53 and p16 in the dysplastic epithelium are

significant markers to detect pre-neoplastic lesions in the oral cavity.[26]

Oncogenes

Genes whose protein products have been found to be important for normal cell growth signaling and whose overexpression or mutation leads to unchecked cell growth and tumorigenesis are defined as 'oncogenes'. Epidermal Growth Factor Receptor (EGFR) and its ligands have been studied extensively in squamous cell carcinoma of the oral cavity.[27]TGF-α m-RNA was found at 5 times higher levels in 96% of histologically normal tissue from patients with OSCC and at 5 times higher levels in 87.5% of tumors when compared with normal mucosa. Amplification and over-expression of c-myc/N-myc has been observed in 20–40% oral cancers.[28] K-ras/ N-ras amplification and a point mutation at H-ras, as well as loss of the H-ras allele, has been associated with chewing-tobacco-induced oral cancer.[29] Several studies on Western patient groups have also shown amplification of 11q13, containing the int-2, hst-1, cyclin D1 (prad-1/ bcl-1) oncogenes, in 30–50% of OSCC [30], and these amplifications are associated with poor prognosis.[31] Recently, constitutive activation of Stat-3 has been proposed to be an early event in oral carcinogenesis.[32] 82.2% of oral tumors showed Stat-3 expression and activation, whereas no expression of Stat-3 was observed in normal epithelium and premalignant lesions.[32]

Tumor Suppressors

Tumor Suppressor Genes (TSG) serve as transducers of negative growth signals [46]. These genes are involved in cell cycle regulation, including cell cycle arrest and apoptosis. The p53 gene located on chromosome 17p13.1 is the most important TSG and has been called the 'Guardian of the Genome'.[33]The p53 gene can be inactivated by several mechanisms, including point mutations, deletion, and binding with cellular and viral proteins.[34]A high percentage of oral cavity cancers have also been found to have abnormally high levels of p53 expression (15–60%). The loss of the heterozygosity of the p53 allele has been reported in 20% of oral cancer cases, as well as in 22% of premalignant oral leukoplakia lesions.[27] Rearrangement in the coding and the 5' region of the p53 gene has also been observed in oral tumors.[27] The p16 gene encodes a protein kinase that phosphorylates and thereby inactivates cyclin-dependent kinase 4, whose activity is essential for cell cycle progression by phosphorylation of pRB. Several studies show frequent p16 gene mutations or the loss of itsexpression in dysplastic and neoplastic oral lesions, which suggests that this is an early step in oral carcinogenesis.[27]

Genomic Instability

Genomic instability reflects the propensity and susceptibility of the genome to acquire multiple alterations, such as loss of heterozygosity (LOH) and microsatellite instability (MSI) at the repeat sequences, which can contribute to inactivation of TSG.. Frequent LOH on chromosomes 3p, 9p, 13q and 17p has been demonstrated as an early event in OSCC,[35] and has been associated with the progression of pre-malignant lesions to squamous cell carcinomas.[36]In addition to this, more recently novel molecular target agents have been developed as treatment options. Until now, inhibitors of the epidermal growth factor (EGFR), such as Cetuximab, anti-VEGF (e.g., Bevacizumab), m-TOR inhibitors and other VEGF or EGFR kinase inhibitors and multi-kinase inhibitors represent a curative targeted therapy in combination with radiotherapy and/or chemotherapy.[37]

The advances in the understanding of the molecular basis of oral carcinoma will help in the identification of new markers. The study of the carcinogenic process of the oral cavity, including continued analysis of new genetic alterations, along with their temporal sequencing during initiation, promotion and progression, will allow us to identify new

diagnostic and prognostic factors, which will provide a promising basis for the application of more rational and efficient treatments.

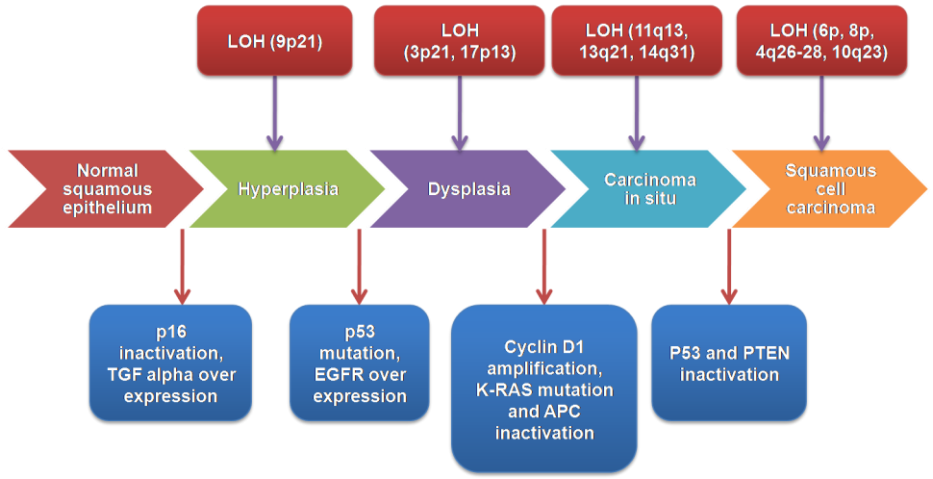

Figure 3: Molecular pathogenesis of oral cancer

Integration of dental science and molecular biology

As oral cancer is an aggressive and highly metastatic disease its early detection can aid in better disease management and treatment. There are two approaches in the early detection of oral dysplasia and cancer: 1) oral cancer screening programs that identify asymptomatic patients with suspicious lesions and 2) employing specific diagnostic tools to identify dysplasia and early oral cancers in asymptomatic patients with an oral abnormality.

Screening for oral cancer implies searching for oral precancerous and cancerous lesions, typically before symptoms occur. Thus visual screening requires the expertise of dental science; hence dentists can play a vital role in oral cancer screening. However, several investigators have demonstrated that oral cancer screening has limited value as a method for detecting precancerous or early cancerous lesions.[38] Oral cancer screening is fraught with problems including the fact that approximately 5-15% of the general population may have an oral mucosal lesion. While the majority of these lesions are benign, clinical inspection alone cannot differentiate which lesions are potentially precancerous and cancerous and which ones are benign.[38] Thus, it is vital to conduct cytological or molecular confirmation of the malignant transformation of the oral lesions. Here the role of molecular biologists comes into play. There are many tests that can be conducted in the laboratory for early detection of oral carcinoma. From cytological examination of biopsies to DNA analysis many techniques have been developed to detect oral precancerous lesions. Furthermore non-invasive methods such as salivary and plasma-based detection of oral cancer biomarkers are also on the horizon as promising tools for early detection.

However, there is a dearth of patients who are willing to attend these extensive screening programmes. Thus an initial screening using visual expertise of dentists can aid in sorting out the population which can be included for molecular screening programmes. Thus, a screening module using the integration of dental science and molecular biology can ensure systematic and equitable implementation of control strategies across the continuum of

prevention, early detection, treatment and palliative care (Figure 4).

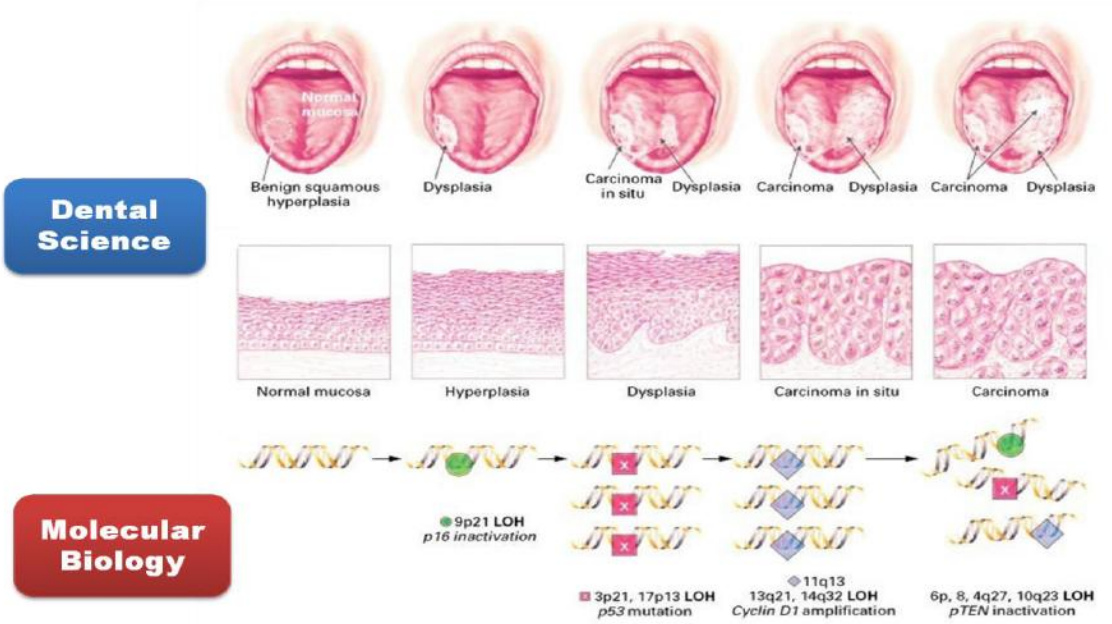

Figure 4: Differential view of experts to study progression of oral carcinoma
Source: adapted from Zhou et al., 2016 [39]

CONCLUSION

Since the advent of screening in oral cancer, many techniques have been employed for early detection of precancerous lesions, where dentists rely on the visual inspection of the malignant transformation. Whereas molecular scientists promote early diagnosis at the molecular levels, both these school of thoughts have their own advantages and limitations. Therefore, integration of both the fraternities remains only anticipated successful approach to effectively combat oral cancer in India.

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