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REVIEW PAPER

Global Scenario of Research in Oral Cancer

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Abstract
Introduction With 300,000 new cases diagnosed worldwide, oral cancer continues to be a major global public threat. In Indian subcontinent, oral cancer accounts for 30–40% of all cancer types.
Methodology Early detection of oral cancer is still considered as the most effective way to improve survival. In this regard, early detection of oral premalignant lesions and conditions is quite important as it may help in prevention of oral cancer. Scientific evidence is available which clearly indicates that transition from normal epithelium to premalignancy to oral carcinoma is the result of accumulation of genetic and epigenetic alterations in a multi-step process.
Conclusion Proper oral screening and understanding of the genetic and environmental factors involved in oral carcinogenesis will allow the emphasis of cancer medicine to shift from the therapy of established oral cancer to the prevention of oral carcinogenesis.

Keywords Oral cancer · Oral oncology · Research · Future trends · Cancer screening

Introduction

With 300,000 new cases diagnosed worldwide, oral cancer continues to be a major global public threat. In Indian subcontinent, oral cancer accounts for 30–40% of all cancer types. Oral and pharyngeal carcinomas comprise up to half of all malignancies in India and other Asian countries. Based on the epithelial origin, majority are classified as oral squamous cell carcinomas (OSCC). Although OSCC which represents more than 90% of all oral cancers is the most common type of oral cancer, there are dozens of other pathologic diagnoses. The prognosis for patients with OSCC remains poor, with a 5-year survival rate that has not changed significantly for several decades, despite refinement of surgical and adjuvant treatment modalities. This is mainly attributed to delay in cancer diagnosis and development of second primary cancers. Early detection of oral cancer is still considered as the most effective way to improve survival. In this regard, early detection of oral premalignant lesions and conditions is quite important as it may help in prevention of oral cancer.

Oral Carcinogenesis and Field Cancerization Theory

Oral carcinogenesis is considered as a multi-step and multifocal process involving field carcinogenesis and intraepithelial clonal spread. According to the field cancerization theory, an area of mucosa can sustain an initial genetic injury and proliferates in a premalignant state. Additional genetic changes will result in progression to overt carcinoma in individual subsites.

The observation that oral cancer develops in multifocal areas of precancerous changes and the finding that histologically abnormal tissue surrounds the tumor has led to the field cancerization theory of oral carcinogenesis. Brakhuis and Brakenhoff [1] in 2005 had proposed the progression model for OSCC focusing on the genetic characterization of field cancerization. According to this model, initially a stem cell located in the basal cell layer of the mucosa

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acquires a genetic alteration which subsequently results in the formation of a patch, defined as a clonal unit consisting of the stem cell with its daughter cells that all share the part alterations.

This is accompanied by a series of histopathological stages from hyperplasia to dysplasia of varying degrees and to carcinoma in situ prior to the development of invasive squamous cell carcinoma [2]. The next crucial step in this process is the change of a patch into an expanding field as a result of additional genetic alterations. This mucosal field pushes the normal epithelium aside and can expand to a size of several centimeters. Even though fields are often macroscopically invisible, this may appear as oral patches. Finally clonal selection leads to the development of carcinoma within this field of preneoplastic cells.

Risk Factors

Tobacco chewing/smoking and alcohol consumption are considered as major etiologic factors in the development of oral cancer. Betel quid chewing (BQC) is a widespread habit in India, and 10–20% of world's population is considered to chew betel quid or areca nut in some form [3]. As far as Indian scenario is considered, tobacco chewing and smoking habits are responsible for many cancers of the oral cavity and oropharynx. Tobacco usage in the form of reverse smoking, i.e., smoking with the glowing end inside the mouth, confers a 5.19 times higher risk of oral and precancerous lesions of the palate than does use of chewing tobacco [4]. Diets low in vegetables and fruits and high in alcohol increase the risk of oral cancer [4]. In a rural cohort study from Kerala, Jayalekshmi et al. [5] analyzed oral cancer risk among women in relation to tobacco use and socioeconomic status. This study showed that oral cancer incidence was strongly related to daily frequency of tobacco chewing ($p < 0.001$) and was increased 9.2-fold among women chewing tobacco 10 times or more a day. The risk increased with the duration of tobacco chewing during the first 20 years of tobacco chewing.

Furthermore, high-risk human papillomaviruses have also been implicated as important etiologic agents, especially in the oral cancers with no tobacco or alcohol associations [6]. Human papillomavirus (HPV 16) has been branded as a risk factor in the new proportions of oral cancer victims. Multiple pathways for HPV transmission including perinatal transmission, sexual transmission by oral genital contact, and autoinfection from oral genital contact by hand have been proposed.

The current burden of oral cancer in the human population is partly due to the unique susceptibility of human genome to mutational changes and to the numerous environmental factors, including diet and lifestyle which reveal this susceptibility by increasing the opportunities for sustained mutational changes that drive carcinogenesis. Although environmental factors including lifestyle factors play an important role in etiology of oral cancer, genetic variation among individuals is also an important modulating factor in oral cancer susceptibility. It has been documented that some patients appear susceptible because of inherited trait(s) in their ability or inability to metabolize carcinogens or procarcinogens, possibly along with an impaired ability to repair DNA damage. Even though all humans are at risk of developing cancer, certain individuals and group of individuals, by virtue of genetic variations they possess, may be more or less susceptible to carcinogenesis.

In India, research on oral cancer has been mainly focused on identification of genetic susceptibility factors and molecular alterations in oral cancer tissues, with the hope of identifying biomarkers for early diagnosis and prediction of malignant transformation potential of oral precancerous lesions and conditions and prognosis.

Research on Genetic Susceptibility to Oral Cancer in India

It is becoming clear that inter-individual genetic variation plays a significant role in the ability of individuals to withstand exposure to exogenous carcinogens or to inhibit initiation, promotion, or proliferation in carcinogenesis. Genetic susceptibility to cancer is determined by two types of genes—high-penetrance genes and low-penetrance genes.

Familial or inherited high-penetrance genes account for only a small proportion (10–15%) of all cases. Despite this, no high-penetrance oral cancer susceptibility gene has been identified. In contrast, in the remaining majority of sporadic oral cancers, genetic variations in the form of low-to-moderate penetrance alleles interacting with environmental factors may predispose individuals to cancer. Even though individual low-penetrance-risk alleles are insufficient to cause cancer, these may influence cancer risk. Single nucleotide polymorphisms (SNPs) which are substitution of a single nucleotide along the DNA are the most common forms of genetic variations. SNPs represent a potentially vast arena for the detection of genetic alterations that seem to relate to medically important differences in disease susceptibility including cancer susceptibility. Functional SNPs may explain a significant portion of complex disease predisposition, treatment response, and prognosis, by acting as low-penetrance alleles. It is likely that individuals at differential risk of developing oral cancer are increasingly likely to be identified from germ line DNA, in the form of mutations or SNPs. SNPs in genes involved in DNA repair, cell cycle regulation, apoptosis, signal transduction process, etc., have been heavily investigated for their

contributing role in oral carcinogenesis, because of the mutator phenotype attributable to these genes and their frequent deregulation in carcinogenesis [7].

Molecular epidemiological studies have shown that an individual's susceptibility to oral cancer is modulated by both genetic and environmental factors. Genetic polymorphisms of phase I and phase II xenobiotic-metabolizing enzymes as well as DNA repair genes can modify an individual's response to carcinogens and hence, the carcinogenic potential of such exposures. There are several but conflicting reports on the association of various SNPs in genes encoding phase I and phase II metabolizing enzymes and DNA repair enzymes with oral cancer predisposition risk. From India, Sreelekha et al. [8] reported that CYP1A1 (Ileu/Val) genotype was associated with increased risk of oral cancer in Kerala population (South India), but Sikdar et al. [9] could not establish such an association with oral leukoplakia in Kolkata, Eastern part of the country. In Eastern Indian population, Sikdar et al. [9] reported that rare C allele at Dra I polymorphic site in CYP2E1 gene enhanced susceptibility to leukoplakia among tobacco users, while CYP2E1 PSt1 and Rsa1 polymorphisms were not associated with risk of leukoplakia in this population. In another study by Anantharaman et al. [10], it was observed that CYP1A1 MspI polymorphism does not independently confer risk to OSCC in Indian population, but confers risk only in association with tobacco exposure.

Several Indian research groups had studied the association of SNPs in genes encoding Phase II metabolizing enzymes. The GSTM1 null genotype was reported to be associated with OSCC susceptibility among tobacco habituals [8, 10]. While researchers from Eastern India reported risk association of GSTM3 (A/A) genotype with both oral cancer and oral leukoplakia in smokers [11], no such risk association was observed for oral cancer and oral leukoplakia from Western India [13]. Furthermore, Majumder et al. [12] reported that simultaneous presence of variant genotypes of GSTM3 and XRCC1 genes increased the risk of oral cancer. Few studies [8, 10] had reported GSTT1 null genotype to be associated with significantly increased risk of oral cancer in Indian tobacco habitual while another study: Buch et al. [11] reported no risk association, yet another study [10] reported GSTT1 null genotype to have a protective effect for oral cancer. For GSTP1 polymorphism also, conflicting results had been reported. Sikdar et al. [9] observed GSTP1 codon 105 polymorphism to have significant risk association with oral cancer.

Researchers had studied the association of SNPs of DNA damage repair genes with oral cancer susceptibility in Indian patients. In a South Indian population, the presence of polymorphic variants of XRCC1 codon 194 and 399 and XPD codon was independently associated with risk of oral cancer. But the study by Majumder et al. [12] reported that variant genotypes on three polymorphic sites of XRCC1 (codon 194, 280, 399) and one site on XRCC3 (codon 240) did not modulate risk of oral cancer independently, but simultaneous presence of variant genotypes of GSTM3 and XRCC1 (codon 290) increased the risk of oral cancer. But variant genotypes working in two different pathways when present in combination could modulate risk of oral cancer in this Eastern Indian population.

Oral cancer research group from Regional Cancer Centre, Trivandrum, evaluated the association of SNP C81T of H-Ras and the SNPs A870G and C1722G of Cyclin D1 and oral cancer susceptibility risk. H-Ras C81T polymorphic genotypes TC and CC showed higher risk of oral cancer susceptibility in Kerala population and the risk was more pronounced among men on stratified analysis. This study suggested that the variant "C" allele of the H-Ras C81T polymorphism could be considered as a genetic predisposition factor for oral carcinoma [13]. Sailasree et al. [14] investigated the role of MTHFR polymorphism C677T and A1298C on oral cancer susceptibility risk and its potential impact on prognostic outcome. The 677CT + TT genotype showed a significant threefold reduction in oral cancer risk and 1298CC genotype showed decreased cancer risk when compared to AA and AC genotypes. The 1298 CC and AC + CC showed increased risk of treatment failure and poor survival when compared with the wild-type AA genotype. So MTHFR C677T was reported to influence oral cancer susceptibility, while A1298C polymorphism was associated with patient prognosis.

From these studies, it can be observed that the effect of polymorphisms in genes encoding phase I and II xenobiotic-metabolizing enzymes and DNA repair enzymes shows wide variation in risk association in different populations groups. Conflicting results have been observed in different areas for the same gene polymorphism. The contradictory findings among studies could be attributed to the population-specific differences in allele frequencies of the SNPs studied, differences in environmental exposures, life style habits, and sample sizes and multiple subgroups analysis.

Research on Molecular Alterations in Indian Oral Cancer

Scientific evidences are available which clearly indicates that transition from normal epithelium to premalignancy to oral carcinoma is the result of accumulation of genetic and epigenetic alterations in a multi-step process [15]. Several single-gene studies carried out in 1990s worldwide showed

that changes in multiple markers were involved in transition steps from normal to precancer to cancer. Genetic alterations usually occur in two classes of genes classified as oncogenes and tumor suppressor genes. Genetic alterations in oncogenes and tumor suppressor genes had been implicated in oral carcinogenesis. All human cells have normal cellular genes known as proto-oncogenes which are involved in normal cellular functions, differentiation, and cell regulations. When proto-oncogene is activated by various mechanisms such as point mutation, chromosomal translocation, viral genome integration, and amplification, these proto-oncogenes become activated. Activated versions of proto-oncogenes are known as oncogenes which are involved in malignant transformation of a cell. Overexpression of oncogenes such as epidermal growth factor receptor (EGFR), C-jun, ki-67, Cyclin D and E, p53, Cox-1 and 2, loss of tumor suppressor genes such as c-erb2, pRB, underexpression of p53, p27 was reported as molecular markers which correlated with oral epithelial dysplasia and malignant transformation.

From India, an earlier study by Chakraborty et al. [16] in head and neck squamous cell carcinoma of Indian patients demonstrated high frequency of loss of heterozygosity (LOH) in chromosomal region 3p21.31, and this genetic alteration was found to be associated with development of early dysplastic lesions.

Ras genes play a crucial role in normal growth and transformation, and a high percentage of Ras mutation had been reported in Indian oral cancer patients [17] highlighting the important role of Ras pathway in oral carcinogenesis. Saranath et al. [17] reported H-ras mutations in 39% of betel-quid-induced oral cancers in Indian patients. But its validity in the context of oral premalignancy could not be established. So also, overexpression of Cyclin D1, a downstream member of the Ras pathway, has also been reported in a significant percentage of oral cancer patients, and Cyclin D1 overexpression was shown to be associated with poor prognosis.

In Indian oral cancers, a high prevalence of Ras and a lower frequency of P53 mutations were reported, thus indicating demographic variation in mutation spectra from the other parts of world. In another study, Sathyan et al. [13] analyzed the co-operative interaction between Ras and B-Raf genes in oral carcinogenesis in Indian patients. This study demonstrated that H-Ras mutation was associated with expression of key cell cycle regulatory proteins such as Cyclin D1, CDK4, RB, and p16 in vivo. Furthermore, this study suggested that H-Ras-mutated oral carcinoma could be defined as a molecular subtype with favorable outcome and unique biology.

From Regional Cancer Centre, Trivandrum, Sailasree et al. [14] evaluated the genetic and epigenetic status of p16INK4A and p14 ARF genes and assessed the prognostic significance of molecular aberrations in the INK4a locus. In this study, 62% of oral cancer patients had p16INK4A gene abnormalities, with deletion accounting for 33% and methylation for 29%. Furthermore, p14ARF gene alterations, either by deletion (12%) and/or by methylation (18%) were observed in 30% of the cases. On evaluating the prognostic correlation of these alterations, p16INK4A deletion was associated with aggressive tumors and initial treatment response. Promoter methylation of p16INK4A was associated with increased disease recurrence and emerged as an independent predictor of worse prognosis. However, p14ARF methylation was associated with lower recurrence in oral cancer patients with a good clinical outcome. From these results, the authors concluded that the molecular profile of INK4A/ARF locus both at DNA and at protein level could be used as a prognostic biomarker for assessing the aggressiveness of disease in oral carcinoma patients.

Tumor suppressor genes are major targets in sensing and responding to DNA damage in multi-step process of carcinogenesis. A lot of work has focused on p53 tumor suppressor gene, and these studies had shown that disruption of p53 pathway through mutations, loss of heterozygosity (LOH), or interaction with viral proteins, as the most frequent alterations in oral cancer. Although p53 changes had been detected [18] in premalignant lesions also, the applicability of p53 as a promising predictor could not be defined. In an earlier Indian study, Ralhan et al. [19] attempted to elucidate the relationship between the expression of retinoic acid receptors and cell cycle regulators such as p53, p21, and p16. This study revealed expression of retinoic acid receptors RAR-α, β, γ to be altered in premalignant lesions. Moreover, positivity of RAR-α in the epithelium was frequent in the phenotype significantly associated with pre-cancers that underwent malignant transformation.

Deletions in the retinoblastoma (RB1) gene were reported [20] to be infrequently altered in head and neck SCC patients and were especially associated with later stages in head and neck SCC development in Indian patients. Ghosh et al. [21] also demonstrated low frequency of RBI deletion in dysplastic lesions, but deletion frequency was significantly increased to stage I and II tumors.

Another group of Indian researchers demonstrated that alterations (deletions/methylation) of LIMD1 gene, a candidate tumor suppressor gene located at 3p21.3, were significantly associated with mild dysplastic lesions of head and neck cancers. In dysplastic lesions, LIMDI mutations were less frequent than deletion and methylation. Deletion and methylation of LIMDI were suggested as early event in oral carcinogenesis. LIMDI was reported to inhibit cell growth and metastases partly mediated through either an interaction of its N-terminal LEM domain (amino acid

18–68) with barrier to autointegration (BAF), a component of SWI/SNF chromatin—remodeling protein, or through interaction of its part of praline–serine-rich domain (amino acid 326–608) with C terminus of retinoblastoma protein pRB (amino acid 763–928) followed by transcriptional repression of E2F target genes [22].

Moreover Ghosh et al. [23] also demonstrated that co-alteration of both RBI and LIMDI was high in the late stage III and IV of head and neck lesions. Furthermore, patients with both LIMDI and RBI alterations showed worse prognosis and absence of RBI alterations did not change patient's survival considerably. This suggests that RBI inactivation might have some synergistic impact in HNSCC development. Ghosh et al. [23] proposed that the reduced level of LIMDI in oral cancer cells might be destabilizing the PRB-E2F interaction and chromatin remodeling complex resulting in deregulation of cell cycle.

The research data from this group demonstrated LIMDI inactivation as a primary event in HNSCC development and implicated LIMDI as a susceptible gene for HNSCC development. Furthermore LIMDI alterations, alone or with RBI alterations could be considered as an important prognostic marker in this cancer.

Worldwide, several other studies also had reported molecular alterations in oral cancer. Most of these studies highlighted alterations in genes/pathways which control cellular signaling, cell cycle, apoptosis, genomic instability, cytoskeleton, and angiogenesis to be significantly associated with progression of potentially malignant disorders of OSCC. However, these genetic tumors markers have so far not gained any use in routine diagnosis and their utility in the prediction of risk of malignant transformation remains unclear. But these studies have clearly indicated that multiple genes/pathways are involved in the progression from normal to metaplastic/dysplastic and subsequently to cancer.

Oral Cancer Screening

In a south Indian population, oral cancer screening employing visual inspection was reported [24] as cost-effective method for early detection of oral cancer which can significantly reduce the associated high morbidity and mortality. An analysis of oral cancer incidence from 1990 to 2005 in Chennai, India, has revealed the benefit of public health education and interventions demonstrating a significant parallel reduction in oral cancer incidence.

Future Prospective

The incidence of tongue cancer has been increasing during the last 10 years, especially among young adults, less than 40 years, who never smoke or chew tobacco and never consumed alcohol. In view of the rapidly increasingly incidence which is a matter of alarming concern, few research centers in India with international collaboration are studying the possible disease pathways, especially, the role of HPV16 and 18 and oral sex practices to elucidate the reasons for this phenomenon.

Further studies on the sequence of genetic alterations associated with oral cancer will help in understanding the molecular basis and natural history of oral cancer development. Undeniably embracing new high-throughput genomic technologies including microarrays, array comparative genomic hybridization, SNP arrays, methylation microarrays, gene expression arrays, proteomics mitochondrial arrays, and micro-RNA arrays offers exciting opportunities for advances in the broad area of oral carcinogenesis. Exploration of oral cancer biomarkers in biofluids such as saliva and serum are other promising approaches. Advances in next-generation sequencing and genomic technologies are unlocking the biology of disease in ways not previously possible, leading to a paradigm change in target finding, drug development, and patient treatment.

India is participating in International Cancer Genome Consortium (ICGC), with oral cancer as the site for research. Focusing on the gingiva–buccal cancer, the goal is to obtain a comprehensive description of genomic, transcriptomic, and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe. The lead institutions who are part of this project are National Institute of Biomedical Genomics (NIBMG) where most of the genomics work will be carried out, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai, where most of the patient characterization, tissue collection, and molecular genomic profiling will be done. The project is funded by Government of India through the Department of Biotechnology.

Genome-wide analysis may soon be capable of identifying not only genomic patterns associated with varying levels of cancer risk, but also the environmental susceptibilities that result from these genomic patterns. It is hoped that growing understanding of the genetic and environmental factors involved in oral carcinogenesis will allow the emphasis of cancer medicine to shift from the therapy of established oral cancer to the prevention of oral carcinogenesis.

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