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Current Novel Concept of Carcinogenesis to Combat Oral Cancer

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Abstract

One of the greatest public health threats around the world is oral cancer. Field cancerization and carcinogenesis are two steps in the multistep and multifocal tobacco-related process of oral cancer development. The rationale for molecularly targeted oral cancer prevention at the molecular level is promising. Aneuploidy and allelic imbalance are two biomarkers of genomic instability that can be used to estimate cancer risk of oral premalignancies. Understanding the biology of oral carcinogenesis can help us make significant advances in pharmacogenomics, cancer risk assessment, identification of high-risk patients, monitoring of preventive measures, and cancer diagnosis in patients. In addition, research on appropriate animal models of carcinogenesis will lead to the development of new chemopreventive drugs against oral malignancies based on molecular signalling pathways and targets. Novel approaches, such as interventions with molecularly targeted agents and drug combinations in high-risk oral patients, are undoubtedly needed to reduce the devastating global consequences of oral malignancy.

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Introduction

Head and neck cancer is the sixth most common cancer in humans^[1], representing 3% of all cancers. Of these, 90% are oral squamous cell carcinomas, 48% of which occur in the oral cavity. They may occasionally be accompanied by precancerous lesions such as leukoplakia and erythroplakia. Worldwide, more than 300 000 new cases of squamous cell carcinoma of the oral cavity are detected annually^{[1][2]}. The tongue is the most typical site of intraoral cancer, accounting for approximately 53% of cases, and tongue tumours usually develop on the posterior lateral margin and ventral surfaces of the tongue. The second most common intraoral location is the floor of the mouth. The gingiva, buccal mucosa, labial

mucosa, and hard plate are less commonly affected^{[3][4]}. The incidence of oral cavity cancer shows considerable local variation. In India and other Asian countries, oral and pharyngeal cancers account for up to half of all malignancies, and this particularly high prevalence is attributed to the influence of carcinogens and region-specific epidemiologic factors, especially tobacco and betelquid chewing. Of particular concern is the increase in oral cancer prevalence among young adults^{[5][6][7]}. Despite advances in the treatment of oral cavity cancer (surgery, radiation, and chemotherapy), malignancies of the oral cavity, particularly tongue cancer, are associated with high morbidity and long-term survival rates of less than 50%. The survival rate of patients is still quite low, mainly due to the fact that they have an increased risk of developing a second primary malignancy. Therefore, early detection of oral cavity cancer and premalignancy as well as prevention are crucial^{[8][9]}. To prevent and detect oral cavity cancer early, this paper will concentrate on our understanding of oral carcinogenesis.

Oral carcinogenesis

When many genetic alterations affect the squamous epithelium, a very complicated multifocal process known as oral carcinogenesis occurs. The use of various molecular biology techniques to diagnose oral precancerous lesions and cancer can significantly improve the early detection of changes that are not visible under the microscope. In this way, patients at high risk for developing oral cancer could be identified^{[10][11]}. Methods exist to understand how oral cancer develops at the molecular level. These include proteomics, mitochondrial arrays, micro RNA arrays, methylation microarrays, gene expression microarrays, and array comparative genomic hybridization. Powerful methods are now being used to find biomarkers for oral cancer in biofluids (saliva and serum). The term "field cancerization" describes the potential occurrence of cancer at multiple sites. This has been observed in the development of cancer in tissues covered with squamous epithelium (head and neck tumour) and transitional epithelium (urothelial carcinoma)^{[12][13][14]}. It is clear that oral cavity cancer, like carcinomas in other tissues, develops over a long period of time and that the oral cavity undergoes several neoplastic changes during this time. Mutations of this gene have been found at different sites of premalignant leukoplakia and carcinoma in the same oral cavity. Smoking has been associated with both an increased risk of developing oral cancer and a decreased tumour suppressor function of the gene^{[15][16]}. Therefore, long-term (e.g., 20-40 years) exposure to multiple environmental and exogenous variables may result in multifocal presentations and mutated expressions of tumour suppressor genes. Persistence of mutations may also indicate alterations in DNA repair and apoptosis, increasing the risk of further transformation. The extent of resistance to therapeutic intervention may be further increased by mutational adaptations that alter the survival of specific clones of transforming cells. Recent genomic research has shown that multiple tumours in the oral cavity often arise from the same primary clone. Surgical removal of a premalignant lesion does not readily halt the progression of carcinogenesis due to the complexity of the oral carcinogenesis process^{[17][18]}.

Risk factors

Tobacco and alcohol use are the main risk factors for the development of oral cancer. Although drinking and smoking are independent risk factors, their cumulative effects significantly increase the risk. A large proportion of oral cancer cases in Asian countries are associated with the use of smokeless tobacco products such as gutkha and betel quid.^[19] Several studies have shown that the development of oral cancer is highly familial. A very small number of individuals with oral cancer have been found to have a familial clustering of the disease, possibly with an autosomal dominant mode of inheritance. CYP1A1 or the genes encoding glutathione S-transferase-M1 and N-acetyltransferase-2 are examples of genes of the xenobiotic pathway that may be polymorphic. Carriers of the rapid metabolising alcohol dehydrogenase type 3 (ADH3) allele may be particularly susceptible to the negative consequences of prolonged alcohol consumption and have a higher risk of oral cancer.^{[20][21][22]}

In particular, in individuals who neither smoke nor drink alcohol, human papillomavirus (HPV), especially HPV type 16, could be an etiologic factor. According to Ang et al, tumour HPV status is a significant and independent prognostic factor for survival of patients with oropharyngeal cancer. They also found that the risk of death increased significantly with each additional pack-year of tobacco smoking. Although it is not generally accepted that bacterial infections can cause oral cancer, there has been a substantial increase in the number of research papers supporting this theory.^{[23][24]} The common pathogenic bacterium *Helicobacter pylori* and its association with gastric cancer is the most notable example. The oral squamous epithelium is constantly exposed to a series of microbial challenges, both at the cellular and molecular levels, because the mouth harbours a wide variety of microorganisms, including more than 750 unique bacterial species. In this context, we should draw attention to how they may be related to the development of oral cancer. Oral premalignant lesions of oral cancer are clinically obvious. Leukoplakia, erythroplakia, tobacco pouch keratosis, nicotinstomatitis, lichen planus, and submucosal fibrosis are just some of them.^[25]

Leukoplakia is described as "a white spot or plaque that cannot be clinically or pathologically classified as any other disease by the World Health Organisation. Leukoplakia should therefore be used only in therapeutic contexts. The phrase should never be used for microscopic diagnosis because it has no specific histologic meaning. Leukoplakia is a clinical diagnosis of exclusion on examination of the patient. Sometimes a white spot previously thought to be leukoplakia turns out to be something else entirely after biopsy. In these cases, the lesion should no longer be classified as a leukoplakia. The incidence of leukoplakia increases with age and is most common in middle-aged and older men.^[26] Leukoplakia affects less than 1% of men under 30 years of age but increases to an alarming 8% of men over 70 years of age. In women over 70 years of age, the prevalence rate is 2%. The buccal mucosa, alveolar mucosa, and lower lip are the most commonly affected areas. However, lesions of the lateral tongue, lower lip, and floor of the mouth show dysplastic changes.^[27]

Erythroplakia is a clinical term that refers to a red spot that cannot be clinically or pathologically attributed to any other disease, similar to leukoplakia.^[27] This definition does not include inflammation-related conditions that may cause clinically visible redness. Older men are more likely to develop oral erythroplakia, which manifests as a red stain or plaque with a velvety, soft texture. The soft palate, retromolar pad, lateral tongue, and floor of the mouth are most commonly affected. Although the lesion is often well demarcated, in other cases it may gradually blend into the surrounding mucosa. In certain lesions, white areas may also be present (erythroleukoplakia). Erythroplakia is often asymptomatic, but some people may experience a painful, burning sensation.^[28]

Nicotin stomatitis is a thickened, hyperkeratotic change in the palatal mucosa most commonly associated with pipe smoking, but in milder cases can occur as a result of cigar smoking or, less commonly, cigarette smoking. The palatal mucosa thickens and becomes hyperkeratotic, occasionally cracking on the surface. Conspicuous elevations with red nuclei often form on the surface, representing inflamed openings of the minor salivary gland ducts. The ability of investigators to recognise often minor morphologic changes and their clinical expertise have always been key factors in the detection and diagnosis of oral neoplasms. However, some early malignant lesions cannot be distinguished from benign lesions by their appearance, and some people have carcinomas even if they do not have clinically obvious oral premalignant lesions. In addition, it can be difficult even for specialists to identify which premalignant oral lesions are more likely to develop into invasive carcinoma. To detect premalignant lesions and identify those at risk of developing into cancer, a reliable, objective, and noninvasive approach is needed^{[28][29][30]}.

Biomarkers

The evaluation of preventive measures or therapeutic interventions, as well as the early stages of malignant transformation of the oral mucosa, is supported by biomarkers. Early, intermediate, and late end stages in the course of oral carcinogenesis are revealed by biomarkers in the form of genetic and molecular alterations^[31]. The prognosis, diagnosis, and treatment of oral cavity carcinomas will be improved by these biomarkers. The efficacy and safety of chemopreventive drugs will also be determined by genetic and molecular indicators. Chemopreventive agents are either manufactured or are natural substances^[32]. Unlike other drugs that do not prevent disease, chemopreventive agents reduce the occurrence of diseases such as cancer before clinical symptoms appear. This development is critical to understanding early changes in the oral mucosa. In addition, biomarkers will reduce the duration of long-term follow-up and the number of patients needed to determine a better therapeutic response to a chemopreventive drug. Indicators can therefore help define the type, dosage, frequency, and regimen needed to get the most benefit from chemopreventive drugs. Another aspect driving biomarker development is the reduction of clinical trial costs. Biomarkers can be divided into broad categories that capture susceptibility to carcinogens, progression, exposure, and/or responses of target cell populations^{[32][33]}. Oral cavity cancer studies provide anatomical access to lesions that develop premalignantly and malignantly, which is a distinct advantage. To determine the amount of DNA adducts and oral cancer risk, one could simply analyse biopsies of the original lesion as well as areas of the mucosa that appear normal. Following DNA binding studies of nuclear proteins such as p53, DNA adduct studies and cytogenetic analysis may also reveal altered structure and function of susceptible regions in the DNA. As early biological indicators, several investigators have focused on microscopic cytogenetic and somatic mutational changes. Staining of micronuclei in exfoliated buccal mucosal cells is one method for detecting chromosomal abnormalities^[34]. In addition, the reversal of leukoplakia and the efficacy of retinoids, carotenoids, and vitamin E have been studied using micronuclei. Other techniques include the determination of aneuploidy and the evaluation of losses and gains of genetic material, particularly in the context of somatic and sex chromosomes. Sister chromatid exchanges and allelic variants identified by losses on chromosomes 3, 4, 5, 6, 8, 9, 11, 13, 17 and 19 are two other types of chromosomal aberrations^[35]. Molecular biomarkers with potential diagnostic value

include DNA content and chromosomal polysomy, loss of heterozygosity, nucleolar organisation regions, histo blood group antigens, proliferation markers, increased epidermal growth factor receptor (EGFR), and decreased expression of retinoic acid receptor, p16, and p53. Despite the lack of a valid, reliable panel of markers for clinically useful prognostic information in patients with premalignant lesions of the oral cavity, the development of high-throughput genomic and proteomic analysis techniques may soon lead to significant progress toward a prognostically relevant molecular classification system. Potential biomarkers for oral carcinogenesis are genomic, oncogenic, immunological, oxidative stress, apoptosis biomarkers.^{[35][36]}

Oral carcinogenesis in animal

Tumour development, the process of carcinogenesis, and studies of prevention and therapy have been studied in a variety of animals. Our understanding of the function of specific genes in tumorigenesis has improved with the progressive development of transgenic or knockout mice. The hamster cheek pouch model and the model of oral (tongue) carcinogenesis by 4-nitroquinoline-1-oxide (4-NQO) are the two most commonly used animal models for oral carcinogenesis^[36]. Although the hamster oral tumour model resembles some of the changes observed in human oral cancer, there are still a number of unique features that must be considered when evaluating the results of oral carcinogenesis studies. The hamster cheek pouch provides a very large surface area of oral mucosa for the growth of invasive cancer, whereas humans do not have this type of mucosal structure. Unlike humans, mice, or rats, the hamster cheek pouch does not have lymphatic drainage, which allows various drugs or molecules to accumulate in the pouch. In addition, the hamster may respond to antigenic tumour sources with a natural killer macrophage or granulocyte cytotoxicity rather than a T-cell response. The use of the water-soluble carcinogen 4-NQO in rats and mice is one of the newest animal models for the study of oral carcinogenesis. In rats, the carcinogen is delivered either via water (20 ppm) or by application in mice. While topical application of the carcinogen to the mouse palate over a period of up to 16 weeks, similar to the hamster model, leads to the development of palatal tumours within 49 weeks, administration of 4-NQO in drinking water (20 ppm) over a period of 8 weeks leads to tongue lesions, including squamous neoplasms, in rats and mice within 32 weeks. Since the most common site for intraoral carcinoma is the tongue and the drinking water administering of 4-NQO is a simple and easy method, the 4-NQO-induced tongue carcinogenesis model is quite useful for investigating oral carcinogenesis and identifying cancer chemopreventive agents.^{[36][37]}

A number of chemical carcinogens including coal tar, 20-methylcholanthrene, DMBA, and 4- NQO have been used in experimental oral carcinogenesis. However, 4-NQO is the preferred carcinogen apart from DMBA in the development of experimental oral carcinogenesis. 4-NQO is a water-soluble carcinogen, which induces tumors predominantly in the oral cavity. It produces all the stages of oral carcinogenesis and several lines of evidences suggest that similar histological as well as molecular changes are observed in the human system.^[37]

Chemoprevention

Chemoprevention is the use of organic or inorganic substances to slow down, stop, or reverse the evolution of malignancy in tissues that are at risk of developing invasive cancer. The most well researched chemopreventive medicines for oral cancer are retinoids. Only 3 months of 13-cis retinoic acid administration resulted in a clinical response rate of 67% compared to 10% with placebo. A relatively high risk of recurrence within 3 months after ceasing therapy was documented, however toxicity were significant. Clinical and pathologic response rates to retinoids in individuals with oral premalignant lesions have been validated in further investigations, however toxicities are still a concern. Translational investigations, however, revealed that genetic aberrations persisted in some individuals with full clinical and pathologic response to retinoid therapy indicating that cancer formation may have occurred in these patients.^{[38][39]} Other substances that have been tested in clinical studies for their ability to prevent the development of oral leukoplakia in patients include vitamin E, the soy-derived Bowman-Birk inhibitor concentration (BBIC), curcumin, and the polyphenol epigallocatechin-3-gallate from green tea. Small clinical studies utilising oral BBIC showed no apparent effects and a 32% response rate. The development of medicines that target certain stages in the molecular transition from normal to oral premalignancy to invasive cancer is the current focus of attention. Cyclooxygenase (COX)-2 inhibitors and epidermal growth factor receptor (EGFR) inhibitors are two examples of molecularly targeted drugs that have demonstrated promise in vitro, in animal models, or in preliminary human studies. The cyclooxygenase pathway is a promising target for the prevention of oral cancer, according to data from a number of sources. Inhibitors of COX-2 inhibited the development of oral cancer in animal models and COX-2 is overexpressed in head and neck squamous carcinoma. Patients with oral leukoplakia participated in a randomised placebo-controlled study of the COX-2 inhibitor ketorolac, which was given as an oral rinse. The results showed that the medication was well tolerated but had no larger clinical response than the control group. The high response rate (32%) in the placebo arm and the challenge in detecting whether topical application of the drug permitted penetration to the injured cells, however, make it difficult to analyse the trial's outcomes. Determining the degree of risk for cardiac toxicities associated with this class of drugs will also be important in determining the future of COX-2 inhibitors as chemoprevention medications.^[39]

A promising molecular target for treatment of oral cancer progression is the EGFR A receptor tyrosine kinase called EGFR is overexpressed in invasive cancers like head and neck squamous cell carcinoma and is linked to a poorer prognosis in such individuals. In clinical studies, EGFR inhibitors have demonstrated effectiveness against head and neck squamous carcinoma alone or in combination with chemotherapy and radiation, and side effects were typically well tolerated. Combination treatment that targets COX-2 and EGFR may be effective, according to the evidence. Despite the fact that chemoprevention seems to be a promising strategy for treating oral premalignancy, prospective clinical trials utilising particular agents, as well as robust corollary translational and laboratory investigations, are required to assess clinical, histologic, and molecular efficacy. In the future, it may be possible and necessary to individualize medical therapy to specific genetic abnormalities detected within the oral mucosa.^{[39][40]}

Conclusion

Human oral cancer is the sixth most common type of pregnancy globally. Premalignant lesions give rise to 70% of oral

malignancies. Multiple sites of premalignant alteration in the oral cavity lead to the development of oral cancer (field cancerization). Widespread use of animal models is intended to produce diagnostic and prognostic indicators. One distinguishing characteristic of human oral cancer is the emergence of these premalignant lesions. There are currently few indicators available to determine which of these lesions may progress to cancer. The main causes of oral cancer patients' poor prognoses are localised lymph node metastases and locoregional recurrence. One of the reasons for greater death rates is the lack of early diagnostic and prognostic indicators. We can better understand the dynamics and prevention of the development of oral cancer by identifying high- and low-risk individuals by the measurement of trustworthy biomarkers. Harvesting tissues and cells is necessary for the quantification of genetic and molecular alterations as well as their usage as markers for the early diagnosis and prevention of premalignant transformation. The fast development of promising technologies will help in the location of aberrant oral mucosa, the noninvasive and objective diagnosis and characterisation of found mucosal lesions, and the treatment of oral cancer patients. Without a doubt, the incidence of oral cancer would be significantly impacted by the avoidance or decrease of alcohol and cigarette use. The emergence of malignant alterations in the oral mucosa is also influenced by chemoprevention.

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