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REVIEW ARTICLE **OPEN ACCESS**

Pathogenesis of Oral Squamous Cell Carcinoma: A Concise Review

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ABSTRACT
Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy and is a major cause of cancer morbidity and mortality worldwide. Oral carcinogenesis is associated with cumulative gene alterations. In addition to genetic insult by tobacco-associated intra-oral carcinogens, several additional factors, such as genetic susceptibility of individuals and external agents, such as alcohol, dietary factors and viruses (Human papilloma virus HPV, and Epstein–Barr virus, EBV), may play a synergetic role in oral tumorigenesis.
Key words: *HPV, HNSCC, OSCC, EBV*

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy and is a major cause of cancer morbidity and mortality worldwide. The neoplastic process is a beginning, with normal epithelium progressing through hyperplasia to dysplasia to carcinoma in situ and finally invasive carcinoma. Oral carcinogenesis is associated with cumulative gene alterations. In neoplasms, cell proliferation is excessive, autonomous and uncoordinated with the normal tissues. These neoplastic cells ultimately enter lymphatic vessels and metastasize to regional lymph nodes [1]. The biological activity of oral squamous cell carcinoma is usually evaluated by classifying the tumors as highly, moderately, or poorly differentiated according to a system primarily developed by Broders. The Broders's system based on the proportion of differentiated cells to undifferentiated or anaplastic cells [2].

EPIDEMIOLOGY

The highest rates of oral cancer in people of all ages occur in developing countries such as south and south-east Asia where oral cancer is often the first or second most common site of malignancy. The incidences of OSCC, reported from institutional databases, in patients under 40 years of age vary between 0.4 - 3.6% of all cancer cases. The incidence of OSCC varies considerably both between and within countries according the criteria included.

Although the incidence of oral cancer at any age is comparatively low in western countries at 2-6% of all malignancies, in the Indian subcontinent the rate is as high as 30-40%. The rising incidence is also reflected in the population under 40 years of age who, it is estimated, make up between 16 and 28% of all oral cancer patients seen at various institutions in India. This displays an alarming rise in the incidence rate of cancer in younger people [3].

Gender distribution

Conflicting evidence on the gender distribution of oral cancer in the young has been reported. Carcinoma of the tongue has widely been regarded as a disease predominantly affecting males. The difference seen previously was probably a reflection of the differences in habits between males and females, but this gap is narrowing as habits such as smoking and drinking are becoming more socially acceptable amongst women [4].

Nevertheless, further studies report conflicting evidence towards a male bias in the incidence rate of SCC of the head and neck, showing no gender difference between those under 40 years of age and older patients.

ETIOLOGY

Alcohol and tobacco

Tobacco smoking and alcohol drinking are probably the two most important known risk factors for the development of oral squamous cell carcinoma. Tobacco, whether smoked, chewed or taken as snuff, is undoubtedly a major carcinogen causing both initiation and promotion of cancer in the oral cavity [5].

Betel quid chewing

Betel quid chewing is widely prevalent oral habit in India, Taiwan, Papua New Guinea, South Africa and other South-east Asian countries. The oral cancer is increasing in India due to young people chewing pan masala products often containing tobacco, which is responsible for the carcinogenicity of the betel-quid.

Occupation

Epidemiological evidence exists for an association between workers exposed to formaldehyde, and other manual workers such as printers, electronics workers, textile workers etc and an increased risk of oral cancer.

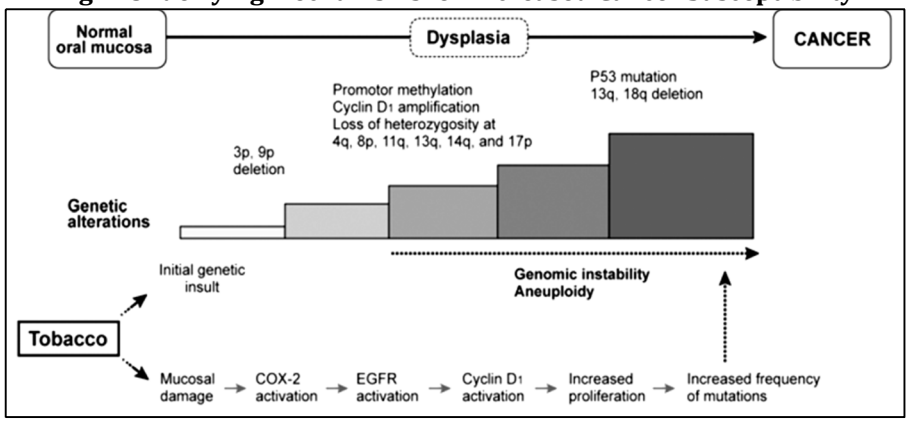
Immune defence

The lymphocyte subsets and found an elevation in NK cells and a decline in B cells in patients with oral precancerous lesions compared with those in healthy subjects, suggesting an impairment of humoral immunity in patients with oral pre-cancers.

Dietary factors

Diet is an important factor in cancer a etiology and prevention in India. The protective effects of antioxidant micronutrients against oral cancers and precancers have also been accumulating worldwide via micronutrient studies and chemoprevention trials using Vitamins A, C, E and carotenoids.

Fig 1. Underlying Mechanisms for Increased Cancer Susceptibility



Genetic progression model of multistep oral carcinogenesis (fig 1). Transformation of normal epithelium by multiple genetic alterations leads to dysplasia and invasive carcinoma. The accumulated genetic changes that occur in oral carcinogenesis include activation of the epidermal growth factor receptor (EGFR), alterations of tumor suppressor's p53 and p16, and cyclin D1 overexpression.

Mutagen sensitivity

Although the predominant cause of HNSCC is exposure to tobacco and alcohol, there is a clear disparity between the number of people who develop tumors and the total number exposed. Differences in carcinogen metabolism and DNA repair due to genetic polymorphisms have been suggested as a possible cause for this variation in susceptibility. Mutagen sensitivity is the best documented of these phenotypic assays which tests whether specific mutagenic agents interfere with chromosome integrity [6].

METABOLIC ENZYME POLYMORPHISMS

Individuals may be at increased cancer susceptibility due to less efficient detoxification of carcinogens or more efficient activation of co-carcinogens or a failure to maintain adequate DNA repair after carcinogen exposure. Tobacco smoke comprises at least 50 known carcinogens, and polymorphisms in some carcinogen-metabolizing enzyme genes have been well-documented in molecular epidemiology studies.

DNA repair mechanisms

Nuclear DNA is under constant DNA damage stress induced by both endogenous (such as reactive oxygen species) and exogenous sources (such as radiation and environmental carcinogens). Proper recognition

and repair of the DNA damage are essential for homoeostasis and normal functioning of multicellular organisms [7]. DNA repair activities are maintained by the presence of different DNA damage sensor and repair mechanisms

Cancer-predisposition genes

Cancer-predisposition genes may play a role in the genetic susceptibility to HNSCC. Most cancer predisposition genes identified so far are tumor suppressor genes. The only clear exception to this at present is the tyrosine kinase family of oncogenes, such as RET, which predisposes to multiple endocrine neoplasia (MEN) type 2.

Somatic Genetic Abnormalities in Hnscc

CDKN2A: Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4), also known as CDKN2A, is a tumor suppressor protein, which in humans is encoded by the CDKN2A gene. P16 plays an important role in regulating the cell cycle, and mutations in p16 increase the risk of developing a variety of cancers, notably melanoma.

P53 and TP53: The TP53 gene, located on chromosome 17p13, was the second tumor suppressor gene to be recognized and deletions and /or mutations in the TP53 gene has been found in tumor tissue from sporadic osteosarcomas, soft tissue sarcomas, brain tumors, leukemia's and carcinoma of the breast [8].

FHIT and other chromosome 3 genes: Bis (5'-adenosyl)-triphosphatase is an enzyme that in humans is encoded by the FHIT (Fragile histidine triad) gene. This gene, a member of the histidine triad gene family, encodes a diadenosine 5', 5'''-P1, P3-triphosphate hydrolase involved in purine metabolism.

Retinoblastoma gene (RB): The prototype tumor suppressor gene, RB, was cloned 9 years ago, in 1986. Despite the clear benefit to families with retinoblastoma of identification of the mutation in RB predisposing to disease, and the apparent economic benefits, relatively few mutations have been identified and applied in clinical medicine.

BRCA2: BRCA2 (Breast Cancer Type 2 susceptibility protein) is a protein that in humans is encoded by the BRCA2 gene. BRCA2 orthologs have been identified in most mammals for which complete genome data are available. BRCA2 belongs to the tumor suppressor gene family and the protein encoded by this gene is involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double strand breaks.

P27 gene: Cyclin-dependent kinase inhibitor 1B is an enzyme that in humans is encoded by the *CDKN1B* gene. It encodes a protein which belongs to the *Cip/Kip* family of cyclin dependent kinase (Cdk) inhibitor proteins.

Microsatellite instability (MSI): Microsatellites are repeated sequences of DNA. Although the length of these microsatellites is highly variable from person to person, each individual has microsatellites of a set length. These repeated sequences are common, and normal. The most common microsatellite in humans is a dinucleotide repeat of CA, which occurs tens of thousands of times across the genome.

ONCOGENES/ GROWTH FACTORS

The oncogenes comprise a family of genes that act dominantly to induce or maintain cell transformation. Oncogenes were first demonstrated in RNA tumor viruses, and further research revealed that they are derived from normal cellular genes called proto-oncogenes [9].

Epidermal growth factor receptor and Erb-B-1: The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4).

Erb-B-2: HER2/ neu (also known as ErbB-2) stands for "Human Epidermal growth factor Receptor 2" and is a protein giving higher aggressiveness in breast cancers. It is a member of the ErbB protein family, more commonly known as the epidermal growth factor receptor family. HER2/neu has also been designated as CD340 (cluster of differentiation 340) and p185. It is encoded by the *ERBB2* gene.

Transforming growth factors: Transforming growth factor (sometimes referred to as Tumor growth factor, or TGF) is used to describe two classes of polypeptide growth factors, TGFα and TGFβ. The name "Transforming Growth Factor" is somewhat arbitrary, since the two classes of TGFs are not structurally or genetically related to one another, and they act through different receptor mechanisms.

Int-2 / FGF-3: INT-2 proto-oncogene protein also known as FGF-3 is a protein that in humans is encoded by the *FGF3* gene. FGF-3 is a member of the fibroblast growth factor family. FGF3 binds to Fibroblast Growth Factor Receptor 3 (FGFR3) to serve as a negative regulator of bone growth during ossification [10].

Bcl-1: The BCL1 gene encodes for a 36-kDa nuclear protein of 295 amino acids, cyclin D1, which belongs to the cyclin G1 family. The main mechanisms of BCL1 gene activation include translocation and

amplification, both of which result in overexpression of normal RNA of 1.5 and 4.5 kb and of intact 36 kDa cyclin D1 protein.

Myc: Its codes for a protein that binds to the DNA of other genes and is therefore a transcription factor. When a gene like Myc is altered to cause cancer, the cancerous version of the gene is called an oncogene.

Ras: Ras is a family of genes encoding small GTPases that are involved in cellular signal transduction. Activation of Ras signaling causes cell growth, differentiation and survival. Ras is the prototypical member of the Ras superfamily of proteins which are all related in structure and regulate diverse cell behaviors.

Multiple oncogenes: Multiple oncogenes may be involved in oral carcinoma, particularly *c-myc* with *H-ras* or *c-erb B-1*, especially in later stages. None of the oncogenes *fes*, *abl, sis* or *mos*, however, are amplified or over expressed in oral carcinoma.

Tumor suppressor gene changes

A tumor suppressor gene, or anti-oncogene, is a gene that protects a cell from one step on the path to cancer. When this gene is mutated to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.

VIRUSES INVOLVED IN SCC

Adenoviruses

Adenovirus 12 can (with simian virus 40) induce immortality in keratinocytes *in vitro* and superinfection with Kirsten sarcotna virus induces tumorigenicity, possibly due to the acquisition of the *K-ras* oncogene [11].

Epstein-Barr virus (EBV) - EBV is clearly associated with anaplastic nasopharyngeal carcinoma and Burkitt's lymphoma, and the oncogenicity is not in doubt.

Cytomegalovirus (CMV) – There is, at least on serological evidence, an association between CMV and oral carcinoma but there are no other reliable data yet available.

Varicella-zoster virus (VZV) – As with CMV there is, at least on serological evidence, no association between VZV and oral carcinoma but again there are no other reliable data yet available.

Human herpes virus 6 (HHV-6) - There is a higher prevalence of serum antibodies to HHV-6 in patients with oral carcinoma compared with controls and significantly raised titres.

Herpes simplex viruses (HSV)- In contrast to the data concerning most herpes viruses and oncogenicity, HSV can under certain circumstances cause cell transformation and, at least in animals, can be oncogenic.

Human papillomaviruses (HPV)- HPV are dependent on terminally differentiating epithelial cells. HPV may be implicated in oral carcinoma. HPV was detected in pre-cancerous oral mucosa two to three times more often and in OSCC and 4.7 times more often than in normal mucosa.

DISCUSSION

Oral cancer refers to any epithelial malignancy located in the mouth. It may arise as a primary lesion originating in any of the oral tissues, or by metastasis from a distant site or origin, or by extension from a neighboring anatomic structure, such as the nasal cavity or the maxillary sinus [12]. Oral cancers may originate in any of the tissues of the mouth, and may be of varied histological types such as, adenocarcinomas, melanomas or even teratomas.

Use of chewing tobacco, alcohol or snuff causes irritation from direct contact with the mucous membranes. Their risk is greatly increased compared to a heavy smoker, or a heavy drinker alone. Human papilloma virus (HPV0 particularly versions 16 and 18) is a known risk factor for oral cancer [13].

It is now believed that OSCC follows a similar pattern in its development, and thus is preceded by premalignant lesions such as leukoplakia, dysplasia, erythroplakia, lichen planus and oral sub-mucous fibrosis. Five-year survival rates for mouth, tongue, oropharynx and laryngopharyngeal cancers seldom exceed 40% and involvement of regional lymph nodes is one of the more important prognostic factors for oral cancer [14].

CONCLUSION

The etiology of HNSCC has been clearly defined in terms of the environmental factors that predispose to this condition but it appears that genetic factors should also be a consideration. Further work is needed to clarify the interactions between genetic and environmental factors. Increased knowledge of molecular alterations can be used as an additional aid to current diagnostic and staging techniques and may provide the basis for new therapeutic approaches.

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