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Original Article

Looking beyond tobacco and alcohol for oral squamous cell carcinoma

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Abstract

Squamous cell carcinoma is the most common malignant neoplasm of the oral cavity. Betel nut chewing, cigarette smoking and alcohol drinking are thought to be the major environment risk factors responsible for the development of oral squamous cell carcinoma (OSCC).

Reports of OSCC in patients who never used tobacco and alcohol are infrequent.

The aim of this article is to review the current data concerning the possible etiological factors causing OSCC other than tobacco like viral infections, diet, nutrition, chronic irritation, genetic mutations and other. Although it is well known that the incidence of OSCC increases with age, recent trends for a rising incidence particularly relates to cancer in young individuals. Investigations can be routine ranging from simple oral examination, blood test, bone marrow analysis, diet chart analysis as well as molecular analysis through techniques like PCR, ISH (in situ hybridization), DNA sequencing, southern blot and antibody test.

This review critically examines numerous publications devoted to oral cancer in young individuals who never used tobacco and alcohol. Most studies suggest that 4-6% of oral cancer occur in such individuals.

Awareness of this possibility is important since it can lead to potentially fatal consequences.Thus providing clinicians a broader vision for diagnosis which will lead to effective treatment and prevention in the future.

Keywords : Viral infections, chronic mechanical trauma, diet

Introduction

Sixth most common type of cancer in the world is oral squamous cell carcinoma (OSCC).[1]The effect of some etiological factors such as usage of tobacco and alcohol has been well established in the literature[2]

However, numerous cases of OSCC occurring in non-smokers and non-alcoholic consumers or patients who were not associated with the traditional risk factors were seen in approximately 15-20% of all oral cancer cases as reported in some literature. [2] Identification of these uncommon risk factors is vital for the diagnosis of oral squamous cell carcinoma especially in cases where there is a long-standing ulcer or a smaller tumour size.[3]

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The factors are as following

1.) Chronic Mechanical Trauma

It has been shown in the literature that causation of oral squamous cell carcinoma can be due to chronic mechanical trauma from sharp remaining teeth, improper dental fillings, ill-fitting dentures and loose anchoring attachments.

A report by Randhawa et al describes a case of squamous cell carcinoma, involving the posterolateral border of the tongue of a young female patient, with no deleterious habits usually associated with oral cancer. The report focuses on the etiological factors and prognosis related to the case. The elucidating factor in the patient was the history of chronic trauma due to sharp edges of the carious broken lower first molar which was considered as one of the possible mechanism of her tongue cancer. [4]

2.) Diet and Nutrition

The significance of diet and nutrition has been identified in numerous epidemiological studies. Iron which is a very crucial constituent of our diet has a very crucial role in maintaining the thickness of the epithelium and its deficiency may cause epithelial atrophy and the Plummer Vinson (Patterson brown Kelly) syndrome seen in iron deficiency anemia which is associated with dysphagia, gastric achlorhydria, splenomegaly, spooning of nails, esophageal web formation and most importantly it may lead to the cancer of upper respiratory tract and food passages. There are food items present in fruits and vegetables which could be protective or risky in oral neoplasia. The risk factors in diet could be the excessive usage of red chilli powder and meat.[5]

3.) Viral Infection

Viruses like Human papillomavirus and its subtypes, Herpes group viruses,

Adenoviruses and the Hepatitis C viruses can infect the oral cavity and develop cancer [6].

Human papilloma virus (HPV)

Studies have shown oral cancer patients with no exposure to smoking and/or drinking were 6.1 times more likely to have HPV DNA in the tumors than the Non Smoking/Non Drinking benign controls.

Predictors of oral HPV infections have increased in recent population as a result of high-risk sexual behaviour in the form of practice of premarital sex, average number of lifetime sex partners, oral sex, and a history of sexually transmitted diseases. It may arise from the oropharynx, including the base of tongue and tonsil as HPV has been found out to be an etiological agent specifically in those areas.

With more than 120 different types identified till now. HPV's are epitheliotropic, oncogenic DNA viruses. Low-risk, episomal HPV's (HPV6/11) induce benign proliferation of epithelium whereas, high-risk oncogenic types HPV16/18, are commonly found integrated with the host DNA. In 20% of HNSCCs overall High-risk HPV DNA has been consistently detected and in 20–72% of the OSCC subset.[3] High-risk HPV has been closely associated in many benign and malignant oral lesions like condyloma, squamous papilloma, focal epithelial hyperplasia and malignant lesions.

HPV Test

Many head and neck oncologists consider p16 overexpression as an indirect marker of HPV infection in stratifying patient and thus considers it to be the most important marker as it negatively regulates cell proliferation by suppressing inactivation of pRb protein. Only p16-positive patients undergo further investigation with a more specific HR-HPV detection method, and p16-negative patients are considered HPV-negative. Thus, p16 can be used as a first-line assay provided that its sensitivity approaches 100%. These detection methods must be technically feasible, accurate and cost effective in order to provide a widespread clinical implementation.

The strategy behind HPV detection lies in its ability to recognize the High-risk type HPV-E6 and E7 oncoproteins target the p53 and pRB tumor suppressor pathways. The final goal of any presence of HPV is the detection of these high- risk proteins as they have an important role in oncogenesis since they render these pathways dysfunctional in the majority of HPV-related human cancers. Thus, inhibition of TP53 and pRb by E6 and E7 viral oncogenes respectively, play a key role in the ablation of cell cycle control, apoptosis, and promotion of

instability in the genetic makeup contributing towards the development of cancer[6]. HPV testing is mainly based on PCR method. Others tests which can

be used for HPV testing are in-situ hybridization and in situ oncogenic protein staining techniques as they also have shown increased sensitivity and specificity[6].

When dealing with limited amounts of tissue or nucleic acid the use of multiplex real-time PCR comes as a potential diagnostic tool as it is able to multiplex providing a significant advantage.

HPV Serology is not that precise as it only provides data based on prior exposure to HPV. They are useful in identification of a subset of HPV-associated oral cancers in which HPV is active biologically. HPV viral load in oral biopsies is used in conjunction with serological markers. It is believed that some viruses, mostly the high-risk HPVs, have significant roles in the initiation as well as progression of cancers and their continued expression of their viral transforming activities is necessary in the maintenance of the transformed phenotype[6]

The most widely used techniques include viral DNA detection, with polymerase chain reaction (PCR) or In Situ Hybridization, and p16 detected by

immunohistochemistry The latest developments in HPV testing, such as the RNAscope HPV test are also reported these days.[7]

Herpes Simplex Virus

Exists in two forms HSV1 and HSV2 .HSV1 is mainly involved with oral and ocular infections whereas HSV2 is involved with genital infections. pathogenesis by HSV involves the following steps namely:

a.) Induction of cellular protein: HSV induces the expression of stress or heat shock proteins which might transform cells.

b.) Host cell shutoff process: Protein synthesis is ceased and RNA is degraded located in the same region where the genome which mediates in cell transformation is located.

c.) Stimulation of other viruses: HSV may act as co-carcinogen along with other viruses such as HPV as seen in cervical carcinogenesis.

d.) Chromosomes as targets: HSV target chromosome at restricted sites such as on chromosome 1q and on chromosomes 3,9 and 16 and possibly cause chromosomal rearrangements and ultimately cell transformation.

Although its presence has been detected in various studies and the fact that it could transform some animal cells to a malignant phenotype in vitro, still its carcinogenic activity is unknown.[6]

HSV can be detected by PCR/DNA sequencing, immunohis to chemical detection of HSY-2 protein, IgA and IgM antibodies against HSV[6]

Epstein-Barr virus

EBV is known to cause nasopharyngeal carcinoma, Burkitt's lymphoma, post-transplant lymphoma and gastric carcinoma. It is believed that EBV encodes viral proteins that have transforming potential.

Several epidemiological studies done in finding the role of EBV in HNSCC have been successful in identifying EBV DNA or EBV-encoded small messenger RNA either through PCR or in situ hybridization.[6]

4.) Genetic and Familial Factors

Family history possibly could be a risk factor as there have been cases reported in some patients of Head and neck squamous cell carcinoma(HNSCC) where the ability to repair DNA damage is defective.[5] Villaret et al using cDNA assay identified genes such as keratin 17 and 19,laminin-5,connexin-26 and VEGF
which were differentially expressed in HNSCC cases in comparison with normal tissue.[8]

5.) Immune Deficiency

Transplant recipient undergoing immunosuppressive therapy developing OSCC of the lip has been seen to occur in individuals.[5] However, similar defective response as seen in HIV individuals developing oral cancer like Kaposi sarcoma caused due to HHV-8 and Non-Hodgkins B –cell lymphoma due to EBV has not been able to be involved in the causation of OSCC.

Conclusion

In the light of evidence of an absence of traditional factors in significant proportion of younger patients and the relatively short time span for these behaviour to exert a detrimental effect, it is now of importance to examine and investigate other potential risk factors such as chronic mechanical trauma, diet and nutrition, previous viral infections, familial episodes of cancer. These investigations may prove to be valuable in future for an insight of the risk factors other than the commonly known risk factors for oral squamous cell carcinoma.

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