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Review Article

A Review on the Role of Human Papilloma Virus in Oral Squamous Cell Carcinoma

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ABSTRACT

Head and neck squamous cell carcinoma is 6th most common cancer worldwide. Main etiologic factors are cigarettes, alcohol consumption also tobacco products such as ghutka, pan masala and betel quid also responsible for development of OSCC. The key role of Human papilloma virus as a major etiology factor of Squamous cell carcinoma is patients who do not have habit of smoking or alcoholism has emerged recently. HPV has a main role in emergence of cervical carcinoma. It was also reported to be associated with Head and neck squamous cell carcinoma in 1995. In this article we have analyzed the role of HPV in OSCC.

Keywords: Human papilloma virus; Oral squamous cell carcinoma; Oral cancer

INTRODUCTION

"Oral squamous cell carcinoma" is worldwide public health illness with an increased death rate. "Oral squamous cell carcinoma" is malignant epithelial abnormal mass of tissue showing squamous differentiation originating from mucosa of the oral cavity. Oral squamous cell carcinoma shows more predilections towards males with the ratio of 1.7:1. It is the 10th most frequent cancer in males. Risk factors of "oral squamous cell carcinoma" are cigarettes, ghutka, chewing of betel nut, alcoholism, viruses, age related or chronic irritation. Among which the most common are tobacco and alcohol abuse. HPV is also one of the predisposing features for oral squamous cell carcinoma.

In India most cancers have tobacco as an etiological factor but initially the role of HPV is also considered as cause of HN-SCC. HPV has a definite impact on prognosis of OSCC, so it is very crucial to know the procedure of HPV related HN-SCC. International Agency for Cancer Research found substantial proof for HPV-16 playing a causative role in pathophysiology of oral and pharyngeal carcinoma and a smaller group of oral neoplasms [1]. Many foreign studies have given the incidence of HPV from 22%-50% but predominance of HPV in India has not been seen [2]. A simple oral health impact assessment instrument might aid in determining quality of life, and its usage in the initial stages of oral neoplasms could aid the physician in determining the best treatment option for enhancing quality of life [3].

The HPV involvement was first given by Syrjanen in 1983 while they discovered koilocytotic atypia in neoplastic oral lesion and then supported by other authors. Evidences for involvement are 1) HPV's well-documented wide epithelial tropism. 2) The oropharyngeal and vaginal epithelium share morphological similarities. 3) The ability to *in vitro* immortalize human oral keratinocytes. 4) The etiological function of high-risk HPV in the cervical-SCC is well-established. 5) Recognizing HR-HPV genotypes in oral squamous cell cancer samples [4]. HPV transmission in oral cavity is mainly due to sexual behavior. Vertical birth transmission, oral contact and auto inoculation being the modes of transmission. HPV is rarely transmitted through direct touch, skin, or mucosa. Because the oral mucosa is constantly exposed to diseases and stress, it develops an abraded surface that allows HPV to enter the basal cells. HPV is usually eliminated by the immune system of human within 2 years, but those that remain might cause serious problems. HPV has a terminal need. For replication, differentiated epithelial cells like squamous cells are required.

HPV is a risk factor to many cancers giving the indices of cervical cancer (91%), vaginal (75%), vulva (69%), penis (63%), anus (91%), oropharynx (70%), breast cancer [5].

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Human papilloma virus is non-capsulated; double helical virus comprising of more than fifty subtypes. Among those 50 variations "HPV-16" and "HPV-18" are identified as a causing agent of oral squamous cell carcinoma. "E6 and E7" genes are the chief contributors in development of oral malignancy. Positive human papillomavirus person with high risk of human papilloma virus can damage DNA which will lead to cells to divide and grow out of control resulting in cancer. High-risk HPV positive oral squamous cell carcinoma person would have survival of 5 years than the low risk HPV positive person having oral squamous cell carcinoma.

PREVALENCE OF HPV IN OSCC

Both the incidence of HPV in OSCC and its predictive impact were found to be the reason in meta-analysis. Due to a variety of factors, prevalence may vary. Despite its name, "Oral squamous cell carcinoma" is type of carcinoma which affects oral cavity [6].

Gillison and Andrews, et al. and other authors may use the terms base-of-tongue and cancer interchangeably for Oral malignancies and pharyngeal malignancies in studies performed by the above authors, where the majority of cases, HPV infection is more common in trials comparing the prevalence of subsites [7,8].

STRUCTURE OF HPV

Human papillomaviruses (HPV) infect squamous epithelial tissue such as the dermis and the epithelial linings of the anogenital tract and oropharynx, causing warts and papillomas throughout many cases. The viral particles are made up of eight thousand base pair DNA molecules linked to intracellular histones and housed in a protein coat made up of seventy two pentameri capsomers. The capsid contains 2 structural proteins-late L1 and L2 which are encoded. Protein combination of L1 and L2 or L1 alone is seen in appearance of virus like particles in human body. Occurrence of HPV-33, HPV-45 and HPV-52 is observed but HPV-16 and HPV-18 are frequently found among the cases of OSCC. Nearly eight open reading frames are encoded in the HPV-DNA genome. The Open reading frames are organized into three sections: The early region covers 45 percent of the genome, while the late region covers 40 percent.

HPV-INDUCED CARCINOGENESIS

The elevated-risk HPV E6 and E7 oncoprotiens, which are generated in HPV-infected squamous epithelial cells, are linked to enhanced proliferation and aberrant differentiation. The Genetic material from high-risk HPV-16 and HPV-18 is found in <70% of HPV DNA positive tissue biopsies. Frequency of HPV infection of the uterine cervix is substantial, while the occurrence of squamous cell cancer of cervix is very rare in same people discussed above. Aside from the duration of HPV infection, with several HPV genotypes, viral DNA is detected episomally and the amount of intracellular viral load may all play a role in tumor development. HPV is clearly a necessary factor, but it is insufficient to cause squamous cell carcinoma of the cervix of uterus by itself. HPV DNA is identified in the more than ninety percent of squamous cell carcinoma of the cervix biopsy specimens.

Tobacco related oral squamous cell carcinoma Tobacco use is generally acknowledged to be one of the leading causes of early death around the world. There are more than '130 crore' smokers in the globe, according to estimates. Tobacco is estimated to cause approximately more '63 crore' deaths and hundreds of crore of dollars in economic harm annually by the World Health Organization (WHO) [9-11].despite the fact that greater number of individuals are aware that ghutka is harmful to their well-being, the majority of the people continue to consume tobacco as part of their daily lives, unknowing that nicotine contains over six dangerous compounds, which includes substances producing cariogenic effect and cancer-promoting substances that can infiltrate the body's numerous methodology.

"Oral squamous cell carcinoma" is a kind of oral carcinoma that accounts for more than ninety percent of all 'oral malignancies' [12].Oral and oropharyngeal malignancies are accounted for more than about 220000 new cases each year. And globally, 5% of all malignancies [13]. (Age, food, sex, gender, betel nut, nutrition, race, alcohol, cigarettes) are all etiology for OSCC, according to the study [14].

CONSIDERATION ABOUT ORAL AND OROPHARYNGEAL TOPOGRAPHY

The accurate definition of 'oral and oropharynx carcinoma' is other aspect that acknowledges us about the presence of true HPV in lesions of oral cavity. In terms of anatomy, the border between the oral cavity and the oropharynx is the most important point to consider. Posterior 3rd of the tongue is way to differentiate it. However cannot clinically characterize it, and as a result, certain cancers of a particular location may be incorporated into the other and examined [15].

HPV HEAD AND NECK CANCER (HPV-HNC)-A DIFFERENT ENTITY

According to Ha and Califano in a present day analysis on toxicological and molecular bases, HPV determines a significant key role in 'oral carcinogenesis. HPV malignancies are a distinct form of tumor with multiple major differences reported in: High-risk patient category (usually, unmarried males under 40 years old) [15]. According to a recent meta-analysis, in addition to the traditional horizontal transmission during sexual life, the presence of HPV-DNA in fluid present in amniotic cavity, membrane of fetus and placental cells implies HPV infection inside uterus i.e. prenatal transmission. Also, a new research has demonstrated that HPV plus alcohol have a statistically significant synergistic effect. The incidence of head and neck carcinoma was statistically seen more among in heavy alcohol abusers who tested positive for the virus than among HPV-negative cancer drinkers. Alcohol has the ability to alter mucosal cells biologically [16].

DETECTION METHOD

Following are the methods to detect HPV in the lesion. 1: RT-PCR (detect E6 and E7), 2: Immunohistochemistry (overexpression of P16 protein), 3: *In situ* hybridization, 4: Hybrid capture II. 5: Frozen diagnosis [17]. Diagnosis of oral carcinoma and premalignant lesion relies mostly on visual evaluation of the oral cavity [18].

Some authors have assessed appropriate detection methods and found a number of probable blunders. Boy S discovered HPV utilizing simply the polymerase chain reaction, rather than two *in situ* hybridization approaches [19]. 'p16' is referred good surrogate marker [20-22].It does not provide appropriate support for some authors [23] other people's outcomes When Kingma weighed the pros and cons of various options; He got the best general outcome using E6 HPV subtype-specific PCR [24]. As said by Chaudhary the Hybrid Capture II test yielded only marginally better results. However, the E6 PCR test yielded positive results [25]. Several publications in the 1990s underlined the worth of PCR in order to discover HPV infection [26-29].

AFFIRMATION CONFIRMING THE CHARACTER OF HPV

The verdict that confirms involvement of HPV in oral squamous cell carcinoma is spotting of greater risk genotypes-HPV 16, HPV 18. Increased presence of these virus in oral cancer as compared to normal oral mucosa is an high risk genotype shows 'HPV' as an self-sufficient causative agent for 'oral squamous cell cancer' [30-33].

Based on the evidence so far, Miller and White [31] conclude that HPV presence in the malignant process is obvious, but caution that a few genotypes may still be involved. What would explain why they haven't been found in oral lesions? Because to the low prevalence If HPV was only temporary, at least one person would be infected. It's a good idea to double-check the following characteristics: 1. Comparable HPV frequency in tumor and normal mucosa samples and non-tumoral specimens, as well as pre-neoplastic lesions taken from areas far away from the tumors in patients who have been diagnosed with squamous carcinoma; 2. Because of probable selectivity of HPV-negative cells during culture, viral incidence discrepancies in autopsy specimen and oral squamous carcinoma cell lines.

When evaluating the modified Koch's postulates, Syrjänen et al. state that at least three requirements must be met.1. The detection of viral genome in tumor or tumor cell; 2. The viral protein's ability to change cells outside their normal biological context; 3. The pathogen or pathogenic protein ability to transform cells *in vivo* encourage the growth of tumors in animals the remaining criteria are as follows; 4. Cancer development follows Pathogenic infection not withstanding limited consideration, the work of Lind et al. should not be overlooked. In certain cases of infected leukoplakia, cancer developed within a ten-year time frame; 5. Epidemiologic link between virus and disease. In autopsy specimen and oral squamous cancer cell lines, viral prevalence appears to be different as owing to probable selectivity of HPV -ve cells in the course of culture. HPV is commonly seen in pre-malignant lesions and cancerous lesions in comparison to normal oral mucosa 6. Prevention of HPV vaccination would abolish oral squamous cell carcinoma-the true impact of a vaccine programme would only be known years after it is implemented. A disparity in the recurrence of high, low-risk genotypes in the population.

BRADFORD HILL CRITERIA OF CAUSATION

In 1965 Bradford gave the criteria, to come-up with proof of casual relation between causes and clinical effect. The Bradford Hill criterion must be met to support HPV's causal role in oral cancer. The standards for each and every criterion have been refitted to encompass integrated data out of both "epidemiological" and "experimental" investigations from the emergence of current microbiology tools [34]. Each criterion is evaluated using data from published sources.

CRITERIA

1. Strength of association
2. Consistency
3. Stability
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

UNDERSTANDING MOLECULAR MECHANISMS OF HPV CARCINOGENESIS

As it is understood cancerous type of 'HPV' may lead to unproductive infection and remain in low number in the cells. HPVs are known to play an oncogenic function following Deoxyribose Nucleic Acid integration, chromosomal expression of E5, E6, E7 loci, inhibition of the p53/pRb proteins, which results in more proliferation of cells and contributes to the carcinogenesis [32,33]. According to some authors only DNA genotype is not enough to show cancerous role of HPV in carcinoma from association of mRNA is also important. In some cases where HPV-positive but E6 mRNA-negative cancer was closer prognosed as HPV-negative tumors [35,36].

CONCLUSION

HPV is clearly a necessary factor, but it is insufficient to cause squamous cell carcinoma of the cervix of uterus by itself. HPV DNA is identified in the more than ninety percent of squamous

cell carcinoma of the cervix biopsy specimens. The abnormal action of these genes, together with the cumulative effects of one or more co-factor, results in preferred development of the afflicted cells, which characterizes cancer's progressive abnormal growth. Oral health and oncotherapy can have an impact on a patient's quality of life if they have oral cancer.

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