



Human Papilloma Virus and Oral Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Oral cancer is the most common cancer that affects people all over the world. Oral squamous cell carcinoma affects about 40 to 50 percent in people of India. Tobacco, alcohol, and smoking are the causes of this condition. In addition, the association of human papilloma virus (HPV) with Oral cancer is being greatly discussed. The high-risk HPV 16 and 18 viruses are considered as the most prevalent causes of oral squamous cell cancer however the link is less well-established in terms of epidemiologic and molecular evidence. The role of vaccination for human papilloma virus in cancer prevention, etio-pathogenesis of transmission of infection and carcinogenesis as well as the limitations of HPV molecular analysis could be a matter of exploration. Oral Squamous Cell Carcinomas linked to Human Papillomavirus have been observed to be radiation sensitive, have better results, and have higher rate of survival.

Keywords: Oral cancer; human papillomavirus; transmission; cocarcinogen; vaccine.

1. INTRODUCTION

Squamous cell carcinoma (SCC) of head and neck region are greatly prevalent in the given category of malignancies. Squamous cell carcinoma is account for ninety percent of head

and neck region of cancers, which rank sixth amongst all cancers globally [1,2]. Oral squamous cell carcinoma (SCC) has greater frequency in the Indian population which is about 40–50% of amongst all cancers [3].

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Tobacco usage, alcohol intake, and infection with excessive-hazard human papillomavirus genotypes are a number of the threat factors related to OSCC. The association between HPV and OSCC was first proposed in 1983, but in situ hybridization required another two years to confirm the presence of viral DNA. Although, the relation among HPV and OSCC first proposed in 1983, but in situ hybridization (ISH) requires two years to verify the presence of viral DNA [4].

The human papillomavirus is a 7.9-kb round Deoxyribonucleic Acid virus. Tumour protein53 gene is the most usually discovered genetic mutation in oral malignancies (pRb) [5,6]. The etiology of oral and oro-pharyngeal cancer appears to be related to HPV.

HPV oncogenes work in concert with chemical cancer agents observed in alcohol, quid and tobacco to purpose malignant changes of oral keratinocytes in most people of HPV-related oral malignancies [7] HPV E6 and E7 activity may be responsible in minor proportion of HPV-related oral malignancies [7,8]. HPV16, 8, 31, 33, 35, 45, 51, 52, 56, 58, 59 are taken into consideration with higher chance [9,10,11].

2. HUMAN PAPILOMA VIRUS GENOMIC STRUCTURE

Human papilloma viruses are one of the types of the Papillomaviridae virus. Human papillomavirus (HPV) is a circular DNA virus with a diameter of 52–55nm that is nonenveloped and double stranded [12]. The genomic structure contains a double-stranded Deoxyribonucleic Acid molecule which is bound to histones of cells and enclosed in a capsid of protein without an envelope [9,10,11]. Eight ORF (oral reading frames) are encoded within the Human Papilloma Virus DNA genome.

The Open studying Frames is split into three useful parts: the early (E) place, which covers 45 percent of the genome, the late place, which covers forty percentage of the genome, and a region of lengthy control, which covers the final 40 percent of the genome (LCR) [9,10,11]. E1 to E7 proteins are encoded by using early Open analyzing frames, and they may be important for viral replication, mobile transformation, and transcription regulation. Early ORFs code for the proteins E1, E2, E4–E7, which are needed for viral replication, cellular transformation, and transcription regulation. E1 is vital for the replication of viral DNA. Early 2 is active in the

replication and transcription of viral genes [13-18]. E4 protein helps in viral assembly and releases via interacting with the keratin cytoskeleton and intermediate filaments. The E5 protein which binds to boom element receptors and promotes cell proliferation whilst inhibiting programmed cell death. E6 promotes DNA synthesis, inhibits cellular differentiation, and engages with proteins of tumour suppressors and restore elements, whereas E7 promotes mobile proliferation and interactions with cell cycle's negative regulators and protein of tumour suppressor. E6 and E7 proteins are oncogenes that might be related to the improvement of most cancers [13-18].

The capsid proteins or structural proteins in virion meeting are encoded in late region. The main protein of capsid is encoded via the Late1 ORF, whilst the minor capsid protein is encoded with the aid of the L2 ORF wherein "L" is late open reading frames. Among the early and past due areas is a non coding upstream regulatory area that contains the starting place of replication, the E6 and E7 gene promoter, and enhancers and silencers. [9-11]

HPVs 1, 2, 4, 6, 7, 11, 13, 16, 18, 30, 32, and 57 have all been detected in oral lesions. HPV-16 and -18 have been found in cases of eighty percent. High-risk Human Papilloma viruses detected 2.8 more chances than chances of low-risk types. HPV16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59 are excessive risk, whilst HPV 6, 11, 42, 43,44 are low risk [9-11].

3. CELL MARKER OF HUMAN PAPILOMA VIRUS

Premalignant lesions, cancer-derived cell traces, and metastases of lymph node have all been determined to include HPV DNA. Viral load of HPV, that's a degree of the quantity of viral DNA in a biopsy cloth might also help to elucidate the involvement of HPV in oral most cancers whether or not used by myself or in aggregate with well-characterized HPV serological tests.

Antibodies to Human Papillomavirus E6 and E7 are associated with symptoms of invasive HPV-associated malignant lesion, in contrast to antibodies to Humanpapilloma Virus Deoxyribonucleic Acid virus-like debris that is a sign of continuous, lifelong infection of HPV and are related to HPV-related illnesses. When comparing times with high viral hundreds to

those with low viral hundreds, those seromarkers were proven to be considerably greater [19,20].

4. HPV AS A COCARCINOGEN

The relative threat of OSCC related to infection of HPV is identical to the hazard associated with tobacco use [21,22] The E2 protein of the ORF is disrupted with the aid of the HPV genome, ensuing the lack of E2 repressive activity. This pastime permits E6 and E7 proteins to freely transactivate, ensuing in more desirable manufacturing of oncoproteins [18-23].

In HPV-related malignancies, the viral genome is incorporated into the host of cell genome, and tumour suppressor genes like p53 and pRb lose their essential activities. This causes anomalies in programmed cell death, DNA repair processes, cellular cycle control, and ultimately cell immortalization [23].

5. TRANSMISSION OF HUMAN PAPILOMA VIRUS

The ordinary mucosa of oral cavity may function as a resource for brand new Humanpapilloma Virus infections and/or a motive of new oral lesion of HPV-associated lesions. Human papilloma virus is determined in 0.6 - 81%of regular oral mucosa [24,25]. The variety of new oral intercourse and open mouth kissing partners were proven to be extra definitely linked with oral HPV acquisition than the wide variety of vaginal sex companions. Horizontal transmission of HPV because of sexual activity is the most standard form of transmission and acquisition for human papillomavirus (HPV) [26,27]. Vertical transmission (from mom to kid), fomites, and skin touch are all feasible routes [28-30].

Keratinocytes are a type of squamous epithelial cell that HPV have an unique affinity for the amount of differentiation of keratinocytes affects the production of the expression of viral genes [31,32]. The viral genome undertakes episomal replication throughout the early degrees of contamination, and only some copies of viral DNA in step with host mobile are detectable. Despite the truth that HPV is frequently transmitted via direct contact [13-18,33].

Following epithelial squamous differentiation, genes of viral are expressed regularly from early to late genes where elements of the early viral genome are developing toward epithelial layers with the production of full virion.[31][34] HPVs

might enter via epithelial breaches which infect the basal layers of epithelial cell, where the early virus is retained within the nucleus of inflamed cells [33,35].

HPV is transmitted inside the infected epithelium's basal cells as they proliferate and become squamous cells. three styles of contamination can occur after HPV inoculation: A)Plasmid replication, which takes place in lower epithelial cells and may be divided into two levels: 1) DNA of viral amplification up to 50 to 400 couples per diploid genome, and 2)maintaining a constant range of pairs for several generations of cells. B) Vegetative replication, takes place in cells that have differentiated from the epithelial cells and is connected to viral gene expression. C) productive replication, in which the virus is discharged from epithelial cells as a result of direct or indirect contact (particularly genital warts)[36].

The replication factors of E1 and E2 are among the earliest proteins of viral to be expressed. E2 mediates the transfer of certain HPV DNA copies to daughter cells as the basal cells divide, while some versions stay as episomes in the progenitor cells [37-40]. The developed epithelial cells in HPV-inflamed epithelium exhibit Human Papilloma virus Early 6 and 7 proteins in the suprabasal layers. Early6 suppresses programmed cell death, whereas Early7 initiates the DNA replication, which causes mature cells of epithelial to enter in Synthesis phase of the cell cycle and permitting viral DNA replication to take location [37,38,40,41]. The virus sooner or later hide out from the cells of shedding epithelial, spread by way of Late1 and Late2 proteins [37-39].

6. MECHANISM OF HUMAN PAPILOMA VIRUS CAUSED CARCINOGENESIS

The genome of virus gets included into genome of a host in the case of high-chance Human Papilloma Virus infection and underneath beneficial situations, which is required for the keratinocytes to live forever. The various type of virus, and their mechanism of action with various physical, chemical, and organic retailers, and the host's immune defense mechanisms, can alter the route of HPV contamination [10]. The introduction of a benign papilloma or wart is the second possible end result of HPV infection. A significant thickening of the spinous layer and proliferation of capillary characterizes these

tumours. There is no medical or histological indication of illness for genitalia infected with HPV.

The round form of the genome of viral breaks down on the E1 and E2 sections at some stage in this system of integration. E6 and E7 control are lost due to the lack of E2 in the course of this integration manner [9-11]. The E6 protein's most apparent feature is to set off p53 degradation by way of interacting with a protein of cell called E6 associated protein (E6AP). The E6AP has a right away position inside the mobile cycle with the aid of blocking p53 and pRb's regular activities. After DNA damage, the protein p53 tumour suppressor gene controls growth arrest and cell death. E6 additionally prevents apoptosis by means of interfering with different proapoptotic proteins as Bak and procaspase eight [42-44]. The product from the notch1 gene changed into these days was discovered to be a brand new p53 target [42,45,46].

During the last decade or so, a developing quantity of extra proteins were located to be E6 goal proteins which could play a position in cell transformation, with telomerase being one possibly essential example. 2015 The tumour suppressor gene product, that is retinoblastoma pRb, and their own type, p107 and p130, were shown to bind to E7. Fact E7 attach to non-phosphorylated product of Retinoblastoma, which may lead cells to enter in S phase early via breaking pRb-E2F complexes. HPV replication is enabled by utilizing E7 protein activity inside the epithelium's better layers, where diseased satellite cells to differentiate and leave the cell cycle. when HPV E7 inhibit pRb, the gene P16INK4a is over expressed, which precludes phosphorylation of pRb circle of relatives members. As an end result, p16INK4a overexpression might be a valuable biomarker for assessing HPV pathogenicity [42,47].

6.1 Mode of action of HPV in Tumorigenesis

A breakpoint within the E1/ E2 series permits HPV to integrate into the host genome and dramatically boosts its carcinogenicity via overexpression of Early6 and Early7 expressed in the early open reading body of virus.

- Early2 protein, which is encoded in the virus's early open reading body, inhibits E6, E7 expression.

- HPV E6, E7, disrupts the tumour suppressor genes p53 and pRb, as well as a various cell proteins implicated in carcinogenesis, with the aid of enhancing host genome functioning.
- Inflamed cells have abnormalities in expression of gene that govern programmed cell death, DNA repair, and the cell cycle, allowing for cell transformation.

7. CONNECTION OF HUMAN PAPILLOMA VIRUS AND ORAL CANCER

The connection between HPV and oral cancer was first studied in 1960s. In 1985, Lüning and co-worker proposed that HPV may also have a role within the genesis of malignancies in diverse parts of the pinnacle and neck [48-50]. Human papillomavirus is a double-stranded DNA virus that has been linked to a spread of oral lesions, most of which are benign/hyperplastic and more common in oral [50].

High-threat HPV, inclusive of HPV16 and 18, has been linked to OPMDs and OSCC [26]. The presence of viral Early6 and Early7 mRNA is needed for a Human papilloma virus to be taken into consideration oncogenic. These genes code for oncoproteins and are created while genome of virus is integrated into the DNA of the host cell [51]. Molecular determinants OSCCs inflamed with the HPV appear to have a awesome molecular profile than HPV-negative cancers. Furthermore, HPV malignancies are corresponding to cervical carcinoma in positive methods. p53 and bcl2 expression aren't related to HPV-nice OSCC, and p53 mutations are uncommon in HPV-nice tumours in comparison to HPV-poor tumours. HPV effective OSCC has been tested to have awesome genetic signatures than HPV poor OSCC [52].

The primary laboratory investigation of the human papilloma virus is:

- conventional polymerase chain response
- quantitative polymerase chain response
- In situ hybridization
- 4. p16 immunohistochemistry.

8. HPV VACCINE

The new HPV vaccination is powerful against a few subtypes of HPV which can be linked to genital warts, cervical cancers and oropharyngeal most cancers [53,54]. Gardasil (HPV-four) is a quadrivalent vaccine that protects

in opposition to HPV-6, HPV-eleven, HPV-sixteen, and HPV-18 contamination. This vaccine was used in female of age 9 to 26 years and found to be efficacious in preventing genital warts in males and female [55]. The role of vaccine in prevention of oral cancer needs to be explored more [56-60].

9. CONCLUSION

The importance of comprehending the link between the human papillomavirus and oral cancers is growing considering the observed association of HPV and oral cancer. The oral cancer is due to human papillomavirus may involve the tongue, the tonsils, and the oropharyngeal places in oral cavity. The Early 6 and Early 7 mechanisms play a crucial event in activating the p53 and pRb proteins in causing the malignancy. HPV vaccines are licensed to defend against the low-risk virus and may protect from vaginal and oral infection however its role in oral cancer prevention is yet to be clearly established and hence suggests the need for further research.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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