An update on oral human papillomavirus infection

Ankit H. Bharti, Kiran Chotaliya, Y. S. Marfatia
Department of Skin and VD, Baroda Medical College, Raopura, Vadodara, Gujarat, India

Address for correspondence:
Dr. Ankit H. Bharti, Baroda Medical College, Raopura, Vadodara - 390 001, Gujarat, India. E-mail: ankitbharti@gmail.com
Dr. Y. S. Marfatia, Department of Skin and VD, Baroda Medical College, Raopura, Vadodara - 390 001, Gujarat, India. E-mail: ym11256@gmail.com

Abstract

Human papillomavirus (HPV) constitutes the majority of newly acquired sexually transmitted infections (STIs) in United States as per the centers for disease control factsheet 2013. Genital HPV is the most common STI with incidence of about 5.5 million world-wide, nearly 75% of sexually active men and women have been exposed to HPV at some point in their lives. Oral Sexual behavior is an important contributor to infection of HPV in the oral mucosa especially in cases known to practice high risk behavior and initiating the same at an early age. HPV infection of the oral mucosa currents is believed to affect 1‑50% of the general population, depending on the method used for diagnosis. The immune system clears most HPV naturally within 2 years (about 90%), but the ones that persist can cause serious diseases. HPV is an essential carcinogen being implicated increasingly in association with cancers occurring at numerous sites in the body. Though there does not occur any specific treatment for the HPV infection, the diseases it causes are treatable such as genital warts, cervical and other cancers.

Key words: Human papillomavirus, oral human papillomavirus, oral infection

INTRODUCTION

Human papillomavirus (HPV) constitutes the majority of newly acquired sexually transmitted infections (STIs) in United States as per the centers for disease control factsheet 2013. There are nearly 20 million new STI every year, of this HPV is the most common sexually transmitted virus and infection in the United State. There are nearly 200 different strains of HPV, most of which are harmless and more than 40 HPV types that can infect genital and oral mucosa in both males and females, out of all these, 9 are known to cause cancers. Every day in the US, about 12,000 people ages 15‑24 are infected with HPV. The vast majority of them will clear the virus naturally and never know that they were exposed or had it. Sexual partners who have been together for a while tend to share HPV. This means that the partner of someone who tests positive for HPV likely has HPV already, even though they may have no signs or symptoms. Like most Americans, their immune system will clear it in under 2 years. India has one of the world's highest incidence of oral cancer. The major limitation of the current review was a dearth of adequate HPV related data in Indian population, which can establish precise facts and help to plot a strategy for its management and verify the role of HPV in the head and neck squamous cell carcinoma (HNSCC).

VIROLOGY

HPV is a 55 nm deoxyribonucleic acid (DNA) virus, which belongs to papillomaviridae family. The virion consist of a non‑enveloped, singular double stranded DNA with nearly 5500 nucleotide base pairs. More than 120 genotypically different forms, with each type having nearly 90% of them sharing...
a similar DNA base pair homology.[9] Nearly 40 HPV types are known to infect the genital tract mucosa and 14 are detected in the majority of biopsies, of invasive cervical carcinoma and are therefore considered “high risk” [Table 1] or “oncogenic.”[1]

IMUNOPATHOGENESIS
The precise mechanism of entrance of HPV into the cell are not yet validated. It is known that the HPV capsid proteins play an essential role in host epithelial cell entry and delivery of the viral DNA to the nucleus.[9]

HPV CLEARANCE
Acquiring new HPV infection is now strongly being associated with sexual behavior with female and male sexual partners. So is the probability of clearing existing HPV infection is also being strongly associated with sexual behavior. No association has been found with age and incidence of any, oncogenic, or non-oncogenic HPV types, although the probability of clearing these infections increased with age. The risk of HPV infection decreases with increasing age in women,[10,11] men on the other hand seem to have a constant risk for acquiring new HPV infections throughout their life.[12] A study of men in the USA, noted that the incidence of HPV infection was constant over the age range 18‑44 years.[13] and yet another study, claims that the incidence was constant in men aged 18‑70 years and residing in Brazil, Mexico and USA.[12]

Markowitz et al. reported faster clearance of oncogenic HPV infections in men with increasing age,[12] thus more rapid clearance noted in older men might be related to a higher prevalence of HPV antibodies in older men.[14]

In consensus to what has been reported in women, the median time to clearance of HPV 16 is nearly 2 times longer (about 12 months) than with other oncogenic HPV types (e.g. 6·3 months for HPV 18). Clearance of specific HPV types by age group needs to be further assessed in Indian population especially by meta-analysis studies. The median time for clearance of any type of HPV infection was significantly longer in men aged 18-30 years as compared to other age groups.[12]

| Table 1: HPV genotypes and oncogenic risk |
|------------------------------------------|
| Risk type                  | HPV type       |
| High                      | 16, 18         |
| Intermediate              | 31, 33, 35, 39, 45, 51, 52, 58, 59, 68 |
| Low                       | 6, 11, 42, 43, 44 |
| **HPV=Human papillomavirus** |               |

TRANSMISSION
HPV infection of oral and oropharyngeal mucosa are associated with oro-genital sex and high risk sexual behavior of cohabiting numerous partners, particularly when initiated at an early age.[15‑18]

HPV infection is more strongly related to couples who practiced oral sex as against couples who solely practiced vaginal sex.[17,20]

Oral and oropharyngeal HPV infections are primarily acquired through sexual activities, mouth to mouth contact between partners or family members, autoinoculation and vertical transmission during birth are also some of the known routes which can establish HPV infection.[17,21,22] Mucosotropic HPV strains are capable of causing benign lesions in the upper aerodigestive tract.[23]

CLINICAL MANIFESTATIONS
Focal epithelial hyperplasia (heck disease)
Heck’s disease or focal epithelial hyperplasia was first described in 1965, it is seen most commonly in Alaska Eskimos and in American native or Indians, South Africa and occasionally in Israel. It affects oral mucosa, lips, tongue, notably lower lip and more rarely the palate, floor of the mouth and oro-pharynx more commonly in the age group of 3-18, but can be seen in all age groups.[24] It is strongly associated with HPV types 13 and 32 which are seen in about 90% of infections.[25,26] Usually regresses spontaneously but treatment is often taken to mitigate esthetic problems or repeated bite injuries.

Oral squamous papilloma
Oral Squamous papilloma is a benign tumor seen in all age groups, more commonly in 30-50 years of age. The lesions in children are commonly seen in the laryngotracheobronchial complex and in the oral mucosa over soft palate, lingual, frenulum, lower lip and uvula among adults.[24] It is mainly related to HPV 6 and 11. Surgical removal is the first choice of treatment, but electrocauterization, cryosurgery and interferon injections are also used.

Oral condyloma acuminata
Condyloma is derived from the Greek word “kondilus” i.e. round tumors and acuminate from the Latin word “acuminare”; i.e. to become pointed. The sexual route remains the main route of transmission (20%)[27] and people who have oral sex have a 50% chance to acquire the oral infection. Incubation period ranges from 2 to 8 weeks. It is
characterized by little pinkish or whitish nodules, which proliferate over tongue, lips, palate and floor of mouth which can be sessile or pedunculated. The surface contour is usually cauliflower like. HPV types 6 and 11 have commonly been detected with immunohistochemistry and by hybridization with 75-85% positivity.[28,29]

Common warts (Verruca vulgaris)
Verruca vulgaris is one of the most common manifestation seen mainly in children can infect oral mucosa.[24] It is usually seen on lips, hard palate, gingival and dorsal surface of tongue. The most common HPV types affecting the musocostrofics (6, 11 and 16) and the cutaneoustrofic (1, 2, 4 and 7) and HPV-2 and HPV-4 are detected in more than 55% of oral lesions.[30] Usually warts are self-limited and resolve within 2 years. Treatment is sought usually because of esthetic discomfort or to avoid bite injuries.

Oral lichen planus
OLP chronic immunomediated disease with unknown etiology, which is seen commonly in relation with skin and mucosal lesions associated with HPV.[31,32] It is commonly seen in age group of 30-60 years predominantly in females, though it can also be seen in children and adolescents. The lesions of OLP are generally bilateral and symmetrical, affects the oral mucosa, gingival, the dorsum of tongue and lip mucosa. HPV types 11 and 16 are commonly found in about 87% of patients. Treatment with corticosteroids reduces the symptoms but does not cure the condition, treatment with calcineurin inhibitors, topical retinoids are also used as additive therapy.[33,34]

Oral verrucous carcinoma
A variant of squamous cell carcinoma (SCC), which is benign with well-distinguished morphology and clinical presentation. It is a rare tumor described by Ackerman in 1948 as a cancer that commonly involves lips, oropharynx and laryngeal mucosa. It is also known as Acherman’s tumor, florid papilomatosis, epithelioma cuniculatum and carcinoma cuniculatum[35] and Buschke – Loewestein. Commonly caused by HPV types 6, 11, 16 and 18.[24] The treatment of choice is surgical resection, Radiotherapy with resection, cytostatic drugs like interferon – α. Recurrence rate is high when isolated surgical resection or radiotherapy is performed.[35]

Oral leukoplakia
Martorell-Calatayud A. described oral leukoplakia as “a white patch or plaque that cannot be characterized clinically or histologically as any other disease.” It is considered to be premalignant lesion of oral cavity and has a potential of 16-62% of getting converted into oral SCC.[36] Oral leukoplakia is commonly caused by HPV types 6, 11 and 16.[37] No consensus as to the best treatment course and prevention remains the best approach. Non-surgical treatment based on topical bleomycin and systemic retinoids. Invasive treatment includes cryosurgery, CO₂ laser and surgical resection. They are effective in the short run, nut lesions may relapse in the long run.

Oral squamous cell carcinoma
In 1976, the first description of relation between OSCC and HPV was described by Zur Hausen, since then it has been as an exclusive cause for Cervical Carcinoma.[38] HPV was seen in association to 20% of OSCC cases as reported in 1983 by Syrjanen.[39] HNSCC are a major cause of morbidity and mortality world-wide especially in the Indian subcontinent with > 90% of which are SCC and rank sixth among all malignancies worldwide.[40]

More than 90% HNSCC and anogenital cancers are caused by HPV-16 type. It represents 3% of malignant transformation, i.e. more than 5,000 diagnosed cases a day and more than 90% of oral cancers. HPV infection influences the prognosis of the SCC [Table 2]. The similarities between the oral and genital injuries along with the following factors point toward a role of HPV infection in oral mucosa, i.e. Affinity to epithelial cells, type of genital and oropharyngeal epithelia and oncogenic potential of HPV.[40]

Recurrent respiratory papillomatosis
It is characterized by the proliferation of benign squamous papillomas within the aerodigestive tract.[41-43] In 75% of children with RRP, the diagnosis was made before the child’s 50th birthday and in adults in fourth decade.[44] It is mainly caused by HPV-6 and HPV-11, found usually over oral mucosa, trachea and bronchi and esophagus. In 1998, Wang et al. reported this disease presenting in age < 5 years it is referred as Juvenile Onset RRP is thought to be vertically transmitted during the childbirth, although transplacental transmission has also been reported.[45] Treatment modalities include cold steel excision, CO₂ laser and adjuvant modalities such as interferon, ribavarin, cidofovir, photodynamic therapy, HPV vaccine etc.

WHIM syndrome
It is a rare Autosomal Dominant syndrome characterized by warts, hypogammaglobulinemia, infections and retention of mature neutrophils in
the bone marrow (myelokathexis) also associated with increased susceptibility to HPV infections is also reported. The occurrence of HPV related SCC in two sibling with WHIM syndrome was reported by Cipriani et al. A mutation in chemokine receptor CXCR4, a 7-transmembrane protein expressed in a variety of stem cells and progenitor cells, but its role is not well-characterized.[46]

**RELATION TO HUMAN IMMUNODEFICIENCY VIRUS**

Sikora et al. proved that seropositive individuals show a higher prevalence of oral infection with high oncogenic risk HPV, which increase with age, male gender and infection by Virion Host Shutoff – 2 protein.[29]

Seropositive individuals also have a higher risk of getting oral HPV infection from more than one HPV types, further increasing the oncogenic potential of the infection.[21] The risk of infection by high oncogenic types of HPV is 13 times greater in HIV positive individuals who practiced oral sex with more than one person during the previous year.[29, 47]

**RELATION TO PREGNANCY**

Genital warts in pregnancy flourish well with increase in size and number, which is believed to be due to hormonal influence, increased vascularity and relative immune-deficiency. Elective caesarean is advised in case of genital warts as vertical transmission of HPV DNA from an HPV infected mother to a neonate is increased if the infant is delivered through an infected cervix. However the absence of persistent infections infection infants at 6 months after delivery may suggest temporary inoculation rather than true vertical infection.[48]

Despite the overwhelming evidence for a sexual transmission of high-risk HPVs, other routes of transmission have been proposed. Several studies have explored whether HPVs can be vertically transmitted from mother to child by direct contact during labor, or horizontally through manipulation of the child with infected hands, bathing, towels and fomites. 19.7% of the 66 infants born to HPV positive mothers and 16.9% of the 77 infants born to HPV-negative mothers tested HPV-DNA positive at some point during follow-up thus Children of mothers’ who were HPV-positive at the post-partum visit are nearly 5 times more likely to test HPV-positive than children of corresponding HPV-negative mothers.[49] The oncogenic HPV types 16, 18, 31, 33 and 35 are common, whereas HPV types 6 and 11 are rarely seen. The interaction between oral HPV and Pregnancy is yet to be studied.

**CONCLUSION**

Oropharyngeal HPV infection is primarily associated with sexual activities especially oro-genital sex

### Table 2: Difference between oropharyngeal cancer HPV+ and HPV−

|                      | HPV positives | HPV negatives |
|----------------------|---------------|---------------|
| **Age**              | Younger       | Older         |
| **Risk factors**     | Oral sex, french kiss, high number of sexual partners | H/O tobacco and/or alcohol consumption |
| **Incidence**        | Increasing    | Decreasing    |
| **Location**         | Base of tongue, amygdae | Oral mucosa |
| **Field cancerization** | No           | Yes           |
| **Histology**        | Poorly differentiated - basaloid | Clearly differentiated |
| **Stage of diagnosis** | T3-4, N2-3    | Variable      |
| **Biomarkers**       | Over-expressed P16, inactivation of P16 and pRb | Loss of P16; P53 and pRb mutation; cyclin - D1, EGFR and survivine overexpression |
| **Chromosomal mutations** | Less frequent | Frequent      |
| **Prognosis**        | Very good, increased sensitivity to radiotherapy and chemotherapy | Poor |
| **Distant metastasis** | Rare         | Frequent      |
| **Second primaries** | Rare          | Frequent      |
| **Five years survival rate %** | 60-90 | 20-70 |

**HPV=Human papillomavirus; EGFR=Epidermal growth factor receptor**

### Table 3: Laboratory investigations

**Laboratory investigations for detection of human papilloma virus**

| Method                     | Drawbacks                                                                 |
|----------------------------|---------------------------------------------------------------------------|
| Direct method              | Light microscopy: Microscopic cellular features. Low sensibility and does not indicate HPV types |
|                           | Electron microscopy: HPV particles can be identified                     |
|                           | HPV types cannot be detected                                             |
| Molecular methods          | *In situ* hybridization                                                   |
|                           | Southern blot and dot blot                                               |
|                           | Amplified technique                                                      |
|                           | Target amplification                                                     |
| Hybrid captured technology |                                                                           |

**HPV=Human papillomavirus**
and vertical transmission during birth. High risk sexual behavior of cohabiting numerous partners, particularly when initiated at an early age play a major role in its pathogenesis. HPV infection is more strongly related to couples who practiced oral sex as against couples who solely practiced vaginal sex.

Considering the Indian Scenario, no significant data is available regarding the changing trends of sexual practices and its impact on currently prevalent STI’s especially HPV infection. The spectrum of manifestations of HPV infection range from focal epithelial hyperplasia, OLP, squamous papilloma to SCC. High level of suspicion for HPV infection in undiagnosed persistent oral lesions especially in high risk group can facilitate diagnosis can facilitate diagnosis [Table 3] of oral HPV.

Role of HPV in oropharyngeal cancer needs to be evaluated further. The limitation is scarce availability of polymerase chain reaction as a diagnostic technology to pick up oral HPV.

REFERENCES

1. STI Estimates Fact Sheet 2013: CDC. Available from: http://www.cdc.gov/std/statas/STI-Estimates-Fact-Sheet-Feb-2013.pdf. [Last visited on 2013 Sep 16].
2. Genital HPV Infection – Fact Sheet: CDC. Available from: http://www.cdc.gov/std/HPV/STDFact-HPV.htm. [Last visited on 2013 Sep 16].
3. Feller L, Khammissa RA, Wood NH, Lemmer J. Epithelial maturation and molecular biology of oral HPV. Infect Agent Cancer 2009;4:16.
4. Saini R, Khim TP, Rahman SA, Ismail M, Tang TH. High-risk human papillomavirus in the oral cavity of women with cervical cancer, and their children. Virol J 2010;7:131.
5. Michl P, Pazdera J, Prochazka M, Pink R, Stosova T. Human papillomavirus in the etiology of head and neck carcinomas. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010;154:9-12.
6. Mannarini L, Kratochvil V, Calabrese L, Gomes Silva L, Morbini P, Betka J, et al. Human papilloma virus (HPV) in head and neck region: Review of literature. Acta Otorhinolaryngol Ital 2009;29:119-26.
7. D’Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML, et al. Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus. J Infect Dis 2004;189:686-98.
8. Fakhry C, Dsouza G, Sugar E, Weber K, Goshu E, Minkoff H, et al. Relationship between prevalent oral and cervical human papillomavirus infections in human immunodeficiency virus-positive and -negative women. J Clin Microbiol 2006;44:4479-85.
9. Esquenazi D, Russolillo Filho I, Carvalho Mda G, Barros FS. The frequency of human papillomavirus findings in normal oral mucosa of healthy people by PCR. Braz J Otorhinolaryngol 2010;76:78-84.
10. Castro TP, Russolillo Filho I. Prevalence of human papillomavirus (HPV) in oral cavity and oropharynx. Braz J Otorhinolaryngol 2006;72:273-82.
11. Vera-Iglesias E, García-Arpa M, Sánchez-Caminero P, Romero-Aguilera G, Cortina de la Calle P. Focal epithelial hyperplasia. Actas Dermosifiliogr 2007;98:621-3.
12. Delgado Y, Torrela A, Colmenero I, Zambrano A. Focal epithelial hyperplasia. Actas Dermosifiliogr 2005;96:697-9.
13. Castro TM, Duarte ML. Condyloma in tongue: a case report. Braz J Otorhinolaryngol 2004;70:565-8.
14. Scully C, Prime S, Maitland N. Papillomaviruses: Their possible role in oral disease. Oral Surg Oral Med Oral Pathol 1985;60:166-74.
15. Sikora AG, Morris LG, Sturgis EM. Bidirectional association of anogenital and oral cavity/pharyngeal carcinomas in men. Arch Otolaryngol Head Neck Surg 2009;135:402-5.
16. Chang F, Syrjänen S, Kellokoski J, Syrjänen K. Human papillomavirus (HPV) infections and their associations with oral disease. J Oral Pathol Med 1991;20:305-17.
17. Kumaraswamy KL, Vidhya M. Human papilloma virus and oral diseases: Their possible role in oral disease. Oral Surg Oral Med Oral Pathol 1985;60:166-74.
18. Edwards PC, Kelsch R. Oral lichen planus: Clinical presentation and management. J Can Dent Assoc 2002;68:494-9.
19. Nicos MM, Fernandes JD, Lourenço SV. Oral lichen planus. An Bras Dermatol 2011;86:633-41.
20. Bharti and Marfatia: An update on oral human papillomavirus
Bharti and Marfatia: An update on oral Human papillomavirus

36. Martorell-Calatayud A, Botella-Estrada R, Bagán-Sebastián JV, Sanmartín-Jiménez Q, Guillén-Barona C. Oral leukoplakia: Clinical, histopathologic, and molecular features and therapeutic approach. Actas Dermosifiliogr 2009;100:669-84.

37. Sand L, Jalouli J, Larsson PA, Hirsch JM. Human papilloma viruses in oral lesions. Anticancer Res 2000;20:1183-8.

38. Castro TM, Neto CE, Scala KA, Scala WA. Oral manifestations associated with human papillomavirus (HPV) current concepts. Rev Bras Otorrinolaringol 2004;70:546-50.

39. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153-6.

40. Termine N, Panzarella V, Falaschini S, Russo A, Matranga D, Lo Muzio L, et al. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: A meta-analysis (1988-2007). Ann Oncol 2008;19:1681-90.

41. Bennett RS, Powell KR. Human papillomaviruses: Associations between laryngeal papillomas and genital warts. Pediatr Infect Dis J 1987;6:229-32.

42. Mounts P, Shah KV, Kashima H. Viral etiology of juvenile- and adult-onset squamous papilloma of the larynx. Proc Natl Acad Sci U S A 1982;79:5425-9.

43. Silverberg MJ, Thorsen P, Lindberg H, Ahmed-Grant L, Shah KV. Clinical course of recurrent respiratory papillomatosis in Danish children. Arch Otolaryngol Head Neck Surg 2004;130:711-6.

44. Cohn AM, Kos JT 2nd, Täber L-H, Adam E. Recurring laryngeal papilloma. Am J Otolaryngol 1981;2:129-32.

45. Dyrstad SW, Rao KA. Recurrent respiratory papillomatosis (RRP)-Juvenile onset. Clin Med Oncol 2008;2:481-6.

46. Cipriani NA, Blair E, Taxy JB. WHIM syndrome and oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:105-8.

47. Heck JE, Berthiller J, Vaccarella S, Winn DM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: A pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2010;39:166-81.

48. Park H, Lee SW, Lee IH, Ryu HM, Cho AR, Kang YS, et al. Rate of vertical transmission of human papillomavirus from mothers to infants: Relationship between infection rate and mode of delivery. Virol J 2012;9:80.

49. Castellsagué X, Drudis T, Cañadas MP, Goncè A, Ros R, Pèrez JM, et al. Human Papillomavirus (HPV) infection in pregnant women and mother-to-child transmission of genital HPV genotypes: A prospective study in Spain. BMC Infect Dis 2009;9:74.

Source of Support: Nil. Conflict of Interest: None declared.

Announcement

“QUICK RESPONSE CODE” LINK FOR FULL TEXT ARTICLES

The journal issue has a unique new feature for reaching to the journal’s website without typing a single letter. Each article on its first page has a “Quick Response Code”. Using any mobile or other hand-held device with camera and GPRS/other internet source, one can reach to the full text of that particular article on the journal’s website. Start a QR-code reading software (see list of free applications from http://tinyurl.com/yzh2tc) and point the camera to the QR-code printed in the journal. It will automatically take you to the HTML full text of that article. One can also use a desktop or laptop with web camera for similar functionality. See http://tinyurl.com/2bw7fn3 or http://tinyurl.com/3ysr3me for the free applications.