Role of human papillomavirus in the pathogenesis of oral lichen planus: A systematic review

Dr. Aswathy K. Vijayan  
Reader, Department of Oral Medicine and Radiology, PMS College of Dental Science and Research, Vattapara, Thiruvananthapuram, India  
Corresponding author email: aswathykvijayan4@gmail.com.

Dr. Arvind Muthukrishnan  
Professor and Head, Department Of Oral Medicine and Radiology, Saveetha Dental College and Hospital, Saveetha Institute Of Medical and Technical Sciences, Saveetha University, Chennai, India  
Email: arvindmuthukrishnan@yahoo.com

Dr Aparna M. Nair  
Reader, Department of Periodontics, PMS College of Dental Science and Research, Vattapara, Thiruvananthapuram, India  
Email: aparnamnair3@gmail.com

Dr Shiana Jo  
Assistant Professor, Department of Oral Medicine and Radiology, PMS College of Dental Science and Research, Vattapara, Thiruvananthapuram, India  
Email: shianajohn@gmail.com

Abstract---Oral Lichen Planus (OLP) is a chronic inflammatory disease with a cell-mediated immunopathologic response. Although OLP has been studied extensively for decades, its exact etiology remains unclear. Autoimmunity, viruses like Hepatitis C Virus (HCV), Human Papillomavirus (HPV), and stress have all been hypothesized in recent articles. HPVs are epitheliotropic viruses with an affinity for keratinocytes and are principally found in the anogenital tract, urethra, skin, larynx, tracheobronchial and oral mucosa. This article aimed to review the frequency of HPV prevalence in OLP. A computer database search was performed through the use of PubMed from 1987 to 2021. The summary showed that the association of HPV and OLP varied significantly by geographic population. The correlation of HPV and erosive-atrophic oral lichen planus was comparable and well above that of HPV and non-EA-OLP.
Among HPV genotypes, HPV 16 showed an extremely strong association with OLP, and HPV 18 showed a relatively strong one.

**Keywords**—HPV, OLP, DNA, oral cavity, premalignant lesion.

**Introduction**

Oral lichen planus (OLP) is a chronic inflammatory disease with relapses and remissions with a debatable malignant transformation (MT) potential.\[^1,2^\] OLP prevalence in the general population is approximately 1% to 2%.\[^1,2^\] OLP appears as bilateral lesions involving the buccal mucosa, gingiva, lateral borders of the tongue and floor of the mouth.\[^3,4^\] All types of OLP can be grouped into two clinical groups: erosive-atrophic forms (EA-OLP), including erosive, atrophic, bullous, and mixed erosive-atrophic; and non-erosive-atrophic forms (NON-EA-OLP), including papule, reticular, plaque, and mixed non-erosive atrophic.\[^5^\] OLP is a cell-mediated immune condition of unknown aetiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa. An increase in differentiation of the stratified squamous epithelium will lead to hyperkeratosis and erythema with or without ulceration.\[^6,7^\] In addition to diabetes, stress, and trauma, viruses like the Human Papillomavirus (HPV) have been implicated in the pathogenesis of OLP.\[^4,5^\] This review analyses the role of HPV in the malignant transformation of oral lichen planus.

**Materials and Methods**

**Design**

A review was undertaken using objective and transparent methods as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, to identify, evaluate and summarize all relevant research findings.

**Selection Criteria of studies**

**Inclusion Criteria:**

- Original studies on Human papillomavirus in Oral Lichen Planus.
- Original case-control or cross-sectional studies.
- Clinical or histological diagnosis of OLP specified.
- Studies in English language.

**Exclusion criteria:**

- Studies not done in Oral lichen planus.
- Reviews and incomplete data.
Search Category

A systematic search was performed in Pub Med (www.ncbi.nlm.nih.gov/pubmed), Google and Medline to screen relevant literature. Moreover, reference lists of previous meta-analyses and other relevant papers were manually searched to identify additional studies. The article search included only those from English Literature from the period 1987 till December 2021 entering the following terms: HPV or Human papillomavirus, AND oral precancer or oral premalignancy or oral lichen planus, or oral dysplasia AND Pathogenesis AND Malignant potential, as both medical subject heading (MeSH) terms and text words. In addition, an internet search was also done using the keywords “Oral lichen planus” and “Human papillomavirus,”, and “Dysplasia” and “Pathogenesis” and “Malignant transformation”.

Study selection

Study selection was conducted by two authors who independently screened titles and abstracts against the inclusion/exclusion criteria and identified relevant papers. Then the same two authors independently reviewed the full-text studies unable to be excluded by title and abstract alone. Comparison of papers was completed between the two authors with no disagreements regarding inclusion.

Results

A meticulous search in PubMed, Medline and Google scholar yielded a total of 44 articles. On reading the abstract, 23 articles were excluded for insufficient data. From the remaining 21 articles, 4 articles were excluded as they do not meet the inclusion and exclusion criteria. From the remaining 17 articles, two were excluded after reading the full text. Hence, a list of 15 articles was chosen for the final analysis. The selection procedure is presented as a flowchart in Figure 1 as per PRISMA guidelines. The following details were recorded from each study: first author, publication date, clinical type of OLP, detection methods, number of OLP patients and healthy controls, and HPV genotypes. The details of the selected studies are given in Table 1.

A total of 15 studies and 645 patients discussed the role of HPV in the pathogenesis of OLP. The study had middle-aged women as the predominant participants. Three studies had detected both high risk and low-risk type HPV DNA in OLP and nine studies had reported the association of only high-risk HPV types with OLP. All of the studies had not compared the results with normal buccal mucosa. Two studies had compared the association of HPV with leukoplakia. One study had compared the HPV association with OSCC. Three studies discussed the association of HPV and the magnitude of malignant transformation in the erosive variant of OLP. Two studies compared the association of HPV in dysplastic and non-dysplastic OLP. The purpose of the current article is to discuss a possible association between HPV infection and OLP lesions.
Study characteristics and interpretation of the results

All the 15 studies evaluated the prevalence of HPV in OLP.\textsuperscript{5,8-21} Twelve studies used Polymerase chain reaction (PCR) to detect the prevalence of HPV in OLP.\textsuperscript{5,8-18} One study had used a Luminex-based assay for the detection of HPV\textsuperscript{19} and two studies had used IHC(immunohistochemical staining).\textsuperscript{20,21} Three studies reported a higher prevalence of HPV 18\textsuperscript{16-18} and five studies reported a higher prevalence of HPV 16.\textsuperscript{13-15,20,21} One study compared HPV DNA in OLP with Oral Leukoplakia (OL) and OSCC and had reported that HPV prevalence increased gradually with increasing severity of lesions as in OLP, OL, and OSCC respectively.\textsuperscript{5}

A total of three studies reported the association of HPV with OLP (e).\textsuperscript{5,8,19} Two studies were undertaken to examine the presence of HPV in OLPe and to determine the different DNA types compared to the normal oral mucosa.\textsuperscript{5,8} The study by Mattila et al assessed HPV genotype in OLP (e) as related to DNA content and repair, proliferation activity, apoptosis, cell adhesion and lymphocyte infiltration.\textsuperscript{19} One study investigated the potential role of HPV in OL, erosive-atrophic OLP (EA-OLP), non-erosive atrophic OLP (non-EA-OLP), OSCC and healthy oral mucosa.\textsuperscript{5}

One study by Mattila et al analyzed the HPV association with a subgroup of erosive OLP and reported that HPV is associated with OLP (e).\textsuperscript{19} The authors also reported that cell proliferation index was higher in HPV positive samples and also associated with topoisomerase lia, caspase-3 and CD20 markers. Szarka et al had reported that there was an increase in HPV DNA in both erosive-atrophic OLP (EA-OLP) and non-erosive atrophic OLP (non-EA-OLP) with significantly higher numbers in EA-OLP than non-EA-OLP. The authors have also compared the prevalence of HPV DNA with OL and OSCC and had reported no significant difference between EA-OLP and OL.\textsuperscript{5}

Two studies evaluated the association of HPV in the malignant transformation of OLP.\textsuperscript{10,13} One study compared the presence of HPV in dysplastic and non-dysplastic OLP.\textsuperscript{10} One study evaluated and compared the presence of HPV in OLP not malignized and OLP that turned to malignancy.\textsuperscript{13} Sahebjamiee et al had reported that the HPV prevalence was higher in dysplastic than non-dysplastic OLP lesions.\textsuperscript{10} The study by Mattila et al says that HPV prevalence was higher in non-dysplastic OLP than in dysplastic OLP lesions. However, the authors also reported the presence of HPV in OLP that turned malignant during follow up.\textsuperscript{13}

Discussion

HPV is a small, nonenveloped, circular double-stranded, deoxyribonucleic acid (DNA) virus with 52–55 nanometres(nm) diameter. This double-stranded DNA molecule contains approximately 8000 base pairs, bound to cellular histones and contained in a protein capsid without an envelope.\textsuperscript{[22]} The HPV genome encodes for eight open reading frames(ORFs). The early (E) ORFs encode E1, E2, E4, E5, E6, and E7 proteins that control viral replication. The late (L) ORF contains the structural proteins L1 and L2.\textsuperscript{[23,24]} The virus traffics through the major capsid protein L1 and the minor capsid protein L2 help deliver viral genome to epithelial
cells. The third region is the long control region (LCR) which is an non-coding region that controls viral transcription. HPVs are classified into low-risk and high-risk types based on the nucleotide sequence of E6 and E7.\textsuperscript{[25]}

HPV exhibit a tropism for squamous epithelium. The virus traffics the abraded epithelium through major capsid protein L1 and minor capsid protein L2 by delivering the viral genome to the epithelial cell nucleus. E1 and E2 are the first viral proteins that are expressed. The HPV E6 and E7 proteins are oncogenic. Both bind and degrade p53 and pRb respectively. This gradually contributes to the progression of malignancy by inducing genomic instability.\textsuperscript{[26,27]} HPV 16 genotypes are the most common HPV genotype to present in oral and oropharyngeal mucosa. The prevalence site of HPVs includes the epithelium of the vagina, vulva, penis anal canal, cervix, perianal region, the crypt of the tonsil, and oropharynx.\textsuperscript{[28]} Multiple pathways for HPV transmission to the oral cavity can exist. There is growing evidence that HPV infection can be transmitted by vertical transmission from mother to child. Horizontal HPV infection could be a mode of transmission either than oral sex.\textsuperscript{[29]}

OLP is a chronic inflammatory disease of dysregulated cell-mediated immunity in which T lymphocytes accumulate beneath the epithelium. The specific role of HPV in the development of OSCC and Oral Potentially Malignant Disorder (OPMD) is still under debate.\textsuperscript{[30]} HPV is detected asymptotically in oral mucosa but the origin or reservoir of oral HPV is still unknown.\textsuperscript{[31]} The rate of HPV in OLP was twice as high as in normal cases. Based on these studies, the case-control studies of HPV and OLP correlation were increasingly growing.\textsuperscript{[23]} The frequency of HPV in OLP varied from 0% to 80%.\textsuperscript{[31,32,33,34]}

The prevalence of HPV in OLP varies depending on several parameters such as geographic differences in population, HPV genotype, OLP clinical types and type of HPV detection method.\textsuperscript{[35,14]} The 15 articles included in the study showed a low prevalence of HPV infection in Thai patients with OLP (OR: 3.08).\textsuperscript{[19]} A study from Iran detected HPV DNA in 11 of 40 (27.5%) OLP cases.\textsuperscript{[10]} There was no significant relationship between HPV and OLP in studies conducted in Italy (OR: 1.12, 4.18, 6.12) and the U.K. (OR: 2.00).\textsuperscript{[8,11,12,19]}

According to Khovidhunkit SO et al, HPV prevalence is higher in Asia and Africa and lower in the north and east.\textsuperscript{35} In Asia it is strongest in India\textsuperscript{[14,20]} (OR: 138.05, 120.71), followed by Turkey\textsuperscript{[21]} (OR: 8.73), Iran\textsuperscript{[17]} (OR: 5.85), and Thailand (OR: 3.08).\textsuperscript{[9]} The association of OLP and HPV varies across different genotype and OLP clinical types. HPV 16 is the most frequently reported genotype, followed by HPV 18.\textsuperscript{[36]} A study by OFlatharta et al., showed 26.3% (9/38) prevalence of HPV-16 in OLP samples using PCR indicating a statistical association between HPV-16 and OLP.\textsuperscript{[15]} An immunohistochemical study to demonstrate the role of human papilloma virus-16 in the pathogenesis of oral lichen planus was done by Pol et al 2015. They concluded that HPV-16 may have a role in the pathogenesis of OLP. The authors also stressed the significance of screening the patients with OLP for HPV-16, considering the oncogenic potential of HPV-16.\textsuperscript{[20]}
Sand L et al., demonstrated 27.3% HPV DNA positivity in OLP using PCR of which five OLP were positive for HPV 18 and one OLP for nonspecific primers. None of the controls turned HPV positive. The authors concluded that an association between OLP and HPV was demonstrated but the pathogenic influence of HPV infection could not be elucidated. In their investigation on HPV infection in OLP, Razavi SM et al. found a high positivity for HPV 18 (73.3%). In a study by Sameera et al., high rates of HPV type 18 were observed in Indian patients compared to those of eastern and western continents. The authors concluded that the presence of HPV type 18 could be associated with the pathogenesis of OLP and could also help in understanding the malignant potential of OLP.

The most common clinical forms of OLP are EA-OLP and non-EA-OLP. Ma et al. reported that the association between HPV and EA-OLP (OR: 9.34) was comparable and stronger than the association of HPV and non-EA-OLP (OR: 4.32) in a meta-analysis. Szarka et al. reported that HPV was detected significantly more frequently in OLP (32.8%) lesions than in controls ($P < .001$). Furthermore, the prevalence differed significantly between the more risky atrophic and erosive forms of OLP, compared with reticular OLP (42.6% and 22.4%, respectively) according to these authors.

There are a wide array of assays used for the detection of HPV including PCR, ISH, (In situ hybridization), and IHC (Immunohistochemistry). PCR is considered the most sensitive and widely used approach in the detection of HPV. However, the detection methods can also be influenced by the quality of the sample. Some recent studies have found HPV in saliva and oral exfoliated cells, however, the sensitivity and specificity are too low. The role of HPV detection in saliva is still uncertain.

The traditional first-line treatment of symptomatic OLP is the use of immunosuppressive medication. The use of these drugs brings relief from symptoms. The use of immunosuppressive drugs in the management of OLP, on the other hand, may increase viral replication in the oral cavity. Chronic use of high-potency topical steroids suppresses the immune system resulting in up-regulated HPV replication. As a result, topical steroids should be administered with caution and close clinical follow-up is needed. Antiviral therapy along with topical steroids should be considered if there is a possible association between HPV and OLP.

**Conclusion**

HPV is found to have an association with OLP, which has previously been hinted at in the literature. However, this association should be regarded with caution as it is not a universal finding in OLP and could be a chance occurrence. More prospective cohort studies are needed to elucidate the role of HPV in the pathogenesis of OLP. Furthermore, uniform research standard should be established to produce more convincing results.
References


Table 1: Characteristics of 15 included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Clinical type</th>
<th>Detection method</th>
<th>OLP (n/N)</th>
<th>Control (n/N)</th>
<th>HPV genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sameera A</td>
<td>2021</td>
<td>India</td>
<td></td>
<td>PCR</td>
<td>13/15</td>
<td>0/15</td>
<td>HPV 18</td>
</tr>
<tr>
<td>Sahebjamiee</td>
<td>2015</td>
<td>Iran</td>
<td></td>
<td>PCR</td>
<td>11/40</td>
<td>5/40</td>
<td>HPV16,18</td>
</tr>
<tr>
<td>Pol CA</td>
<td>2015</td>
<td>India</td>
<td>EA-OLP</td>
<td>IHC</td>
<td>21/30</td>
<td>0/30</td>
<td>HPV16</td>
</tr>
<tr>
<td>Mattila R</td>
<td>2012</td>
<td>Finland</td>
<td>EA-OLP</td>
<td>Luminex assay</td>
<td>13/82</td>
<td>NA</td>
<td>HPV 16,6,11,31,33,58,66</td>
</tr>
<tr>
<td>Arirachakaran P</td>
<td>2013</td>
<td>Thailand</td>
<td></td>
<td>PCR</td>
<td>1/37</td>
<td>0/37</td>
<td>NA</td>
</tr>
<tr>
<td>Yildrim B</td>
<td>2011</td>
<td>Turkey</td>
<td></td>
<td>IHC</td>
<td>14/65</td>
<td>0/15</td>
<td>HPV16</td>
</tr>
<tr>
<td>Debnath S</td>
<td>2009</td>
<td>India</td>
<td></td>
<td>PCR</td>
<td>6/6</td>
<td>3/35</td>
<td>HPV16</td>
</tr>
<tr>
<td>Razavi SM</td>
<td>2009</td>
<td>Iran</td>
<td></td>
<td>PCR</td>
<td>9/29</td>
<td>¼</td>
<td>HPV18</td>
</tr>
<tr>
<td>Szarka K</td>
<td>2009</td>
<td>Hungary</td>
<td>EA-OLP</td>
<td>PCR</td>
<td>39/119</td>
<td>3/72</td>
<td>NA18,31,33</td>
</tr>
<tr>
<td>non-EA-OLP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maitland NJ</td>
<td>2009</td>
<td>UK</td>
<td></td>
<td>PCR</td>
<td>7/8</td>
<td>5/12</td>
<td>HPV 16</td>
</tr>
<tr>
<td>Giovannelli L</td>
<td>2006</td>
<td>Italy</td>
<td></td>
<td>PCR</td>
<td>12/49</td>
<td>11/49</td>
<td>NA</td>
</tr>
</tbody>
</table>
Figure 1: PRISMA flowchart describing the identification, screening, eligibility and inclusion of studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Type of OLP</th>
<th>PCR</th>
<th>HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campisi G</td>
<td>2004</td>
<td>Italy</td>
<td>EA-OLP</td>
<td>14/71</td>
<td>16,18,31,6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>non-EA-OLP</td>
<td>5/90</td>
<td></td>
</tr>
<tr>
<td>Oflaharta C</td>
<td>2003</td>
<td>Ireland</td>
<td>PCR</td>
<td>10/38</td>
<td>16</td>
</tr>
<tr>
<td>Giovannelli L</td>
<td>2002</td>
<td>Italy</td>
<td>PCR</td>
<td>9/34</td>
<td>18</td>
</tr>
<tr>
<td>Sand L</td>
<td>2000</td>
<td>Sweden</td>
<td>PCR</td>
<td>6/22</td>
<td>18</td>
</tr>
</tbody>
</table>

n: numbers of HPV positive subjects; N: numbers of total subjects; IHC: immunohistochemical staining; PCR: polymerase chain reaction; NA: not available; EA-OLP: erosive-atrophic oral lichen planus; non-EA-OLP: non-erosive-atrophic oral lichen planus.