How to Cite:
Vijayan, A. K., Muthukrishnan, A., Nair, A. M., & Jo, S. (2022). Role of human papillomavirus in the pathogenesis of oral lichen planus: A systematic review. *International Journal of Health Sciences*, *6*(S2), 5928–5937. https://doi.org/10.53730/ijhs.v6nS2.6532

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 exactaetiologyremains unclear. Autoimmunity, viruses like Hepatitis C Virus (HCV), Human Papillomavirus (HPV), and stress have all beenhypothesized 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 remissionswith 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 analyse 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.
- Studies not done on Human papillomavirus.
- 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 PathogenesisAND 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, 4articles 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. Twostudies 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.[5,8-21]Twelve studies used Polymerase chain reaction (PCR) to detect the prevalence of HPV in OLP.[5,8-18] One study had used a Luminex-based assay for the detection of HPV[19]and two studies had used IHC(immunohistochemical staining).[20,21]
Three studies reported a higher prevalence of HPV 18[16-18]and five studies reported a higher prevalence of HPV 16.[13-15,20,21]One studycompared 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.[5]

A total of three studies reported the association of HPV with OLP (e).[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.[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.[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.[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).[19]The authors also reported that cell proliferation index was higher in HPV positive samples and also associated with topoisomerase Iiα,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.[5]

Two studies evaluated the association of HPV in the malignant transformation of OLP.[10,13]One study compared the presence of HPV in dysplastic and non-dysplastic OLP.[10]Onestudy evaluated and compared the presence of HPV in OLP not malignized and OLP that turned to malignancy.[13] Sahebjamiee et al had reported that the HPV prevalence was higher in dysplastic than non-dysplastic OLP lesions.[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.[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 containsapproximately 8000 base pairs, bound to cellular histones and contained in a protein capsid without an envelope.[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.[23,24]The virus traffics through the major capsid protein L1 and the minor capsid protein L2help deliver viral genome to epithelial

cells.The third region isthe long control region(LCR) which is anon-coding region that controls viral transcription.HPVs are classified into low-risk and high-risk typesbased on the nucleotide sequence of E6 and E7.[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 areexpressed.The HPV E6 and E7 proteins are oncogenic.Bothbind and degrade p53 and pRb respectively.This gradually contributes to the progression of malignancy by inducing genomic instability.[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.[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.[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 andOral Potentially Malignant Disorder(OPMD) is still under debate.[30] HPV is detected asymptomatically in oral mucosa but the origin or reservoir of oral HPV is still unknown.[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.23The frequency of HPV in OLP varied from 0% to 80%.[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 typesand type of HPV detection method.[35,14]The 15 articles includecountries in Asia, Europe, and North America. There is a considerable variation in the geographical distribution of HPV in OLP in different parts of the world.Arirachakaran et al in their study showed a low prevalence of HPV infection in Thai patients with OLP(OR: 3.08).[9]A study from Iran detected HPV DNA in 11 of 40 (27.5%)OLP cases.[10]There was nosignificant relationship between HPV and OLP instudies conducted in Italy (OR: 1.12,4.18,6.12) and the U.K. (OR: 2.00). [8,11,12,19]

According to Khovidhunkit SO et al HPV prevalence is higher in Asia and Africaand lower in the north and east.35 In Asia it is strongest in India[14,20] (OR: 138.05,120.71), followed by Turkey[21] (OR: 8.73), Iran[17](OR: 5.85), and Thailand (OR: 3.08).[9] Theassociation of OLP and HPV varies across different genotype and OLP clinical types. HPV 16 is the most frequently reported genotype,followed by HPV 18.[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.[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.[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 demonstratedbut the pathogenic influence of HPV infection could not be elucidated.[16]In their investigation on HPV infection in OLP, Razavi SM et al. found a high positivity for HPV 18 (73.3%).[17] 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 couldalso help in understanding the malignant potential of OLP.[18]

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.[37]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.[5]

There are a wide array of assays used for the detection of HPV including PCR,ISH,(Insituhybridization), and IHC(Immunohistochemistry).PCR is considered the most sensitive and widely used approach in thedetection of HPV. However, the detection methods can also be influenced by the quality of the sample.[37]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.[38]

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.[39] Chronic use of high-potency topical steroids suppresses the immune systemresulting in up-regulated HPV replication.[19]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.[19,39]

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 studiesare needed to elucidate the role of HPV in thepathogenesis of OLP. Furthermore, auniform research standard should be established to producemore convincing results.

References

1. Pindborg JJ, Reichart PA, Smith CJ, Sobin LH. WHO International Histological Classification of Tumors: Histological Typing of Cancer and Precancer of the Oral Mucosa. Berlin: Springer; 1997.
2. Miller CS, Epstein JB, Hall EH, Sirois D. Changing oral care needs in the United States: the continuing need for oral medicine. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2001;91:34- 44.
3. Silverman S, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. Oral Surg Oral Med Oral Pathol 1985;60:30-4.
4. Gorsky M, Raviv M, Moskona D, Laufer M, Bodner L. Clinical characteristics and treatment of patients with oral lichen planus in Israel. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 1996;82:644-9.
5. Szarka K, Tar I, Feher E, Gall T, Kis A, Toth ED, et al. Progressive increase of human papillomavirus carriage rates in potentially malignant and malignant oral disorders with increasing malignant potential. Oral Microbiol Immunol. 2009; 24(4):314–8.
6. van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med 2003;32:507–12.
7. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol 2007;43:742–8
8. Campisi G, Panzarella V, Giuliani M, Lajolo C, Di Fede O, Falaschini S, *et al.* Human papillomavirus: Its identity and controversial role in oral oncogenesis, premalignant and malignant lesions (review). Int J Oncol 2007;30:813-23.
9. Arirachakaran P, Chansaengroj J, Lurchachaiwong W, Kanjanabud P, Thongprasom K, Poovorawan Y. Oral lichen planus in that patients have a low prevalence of human papillomavirus. ISRN Dent. 2013; 2013:362750.
10. Sahebjamiee M, SandL, KarimiS, Jalil Momen et al J Oral MaxillofacPathol 2015 May-Aug; 19(2): 170–174.
11. Giovannelli L, Campisi G, Colella G, Capra G, Di Liberto C, Caleca MP, et al. Brushing of oral mucosa for diagnosis of HPV infection in patients with potentially malignant and malignant oral lesions. Mol Diagn Ther. 2006; 10(1):49–55.
12. Giovannelli L, Campisi G, Lama A, Giambalvo O, Osborn J, Margiotta V, et al. Human papillomavirus DNA in oral mucosal lesions. J Infect Dis. 2002; 185(6):833–6.
13. Maitland NJ, Cox MF, Lynas C, Prime SS, Meanwell CA, Scully C. Detection of human papillomavirus DNA in biopsies of human oral tissue. Br J Cancer. 1987; 56(3):245–50.
14. Debanth S, Singh PA, Mehrotra R, Singh M, Gupta SC, Pandya S, et al. Human papillomavirus infection and premalignant lesions of the oral cavity: A cross-sectional study in Allahabad, North India. Asia- Pac J Clin Oncol. 2009; 5(2):111–8.
15. OFlatharta C, Flint SR, Toner M, Butler D, Mabruk MJ. Investigation into a possible association between oral lichen planus, the human herpesviruses, and the human papillomaviruses. Mol Diagn. 2003; 7(2):73–83.

16. Sand L, Jalouli J, Larsson PA, Hirsch JM. Human papillomaviruses in oral lesions. Anticancer Res. 2000; 20(2B):1183–8.
17. Razavi SM, Ghalayani P, Salehi MR, Attarzadeh H, Shahmoradi M. Humanpapillomaviruss as a possible factor in the pathogenesis of oral lichen planus. Dent Res J (Isfahan). 2009; 6(2):82–6.
18. Sameera A, Kotikalpudi R, Patel RK, et al. Molecular detection of human papillomavirus DNA in oral lichen planus patients. J Clin Diagn Res 2019;13:Zc20-4.
19. Mattila R, Rautava J, Syrjänen S. Human papillomavirus in oral atrophic lichen planus lesions. Oral Oncol. 2012;48:980-84.
20. Pol CA, Ghige SK, Gosavi SR. Role of human papilloma virus-16 in the pathogenesis of oral lichen planus—an immunohistochemical study. Int Dent J. 2015; 65(1):11–4.
21. Yildirim B, Senguven B, Demir C. Prevalence of herpes simplex, Epstein Barr and human papillomaviruses in oral lichen planus. Med Oral Patol Oral Cir Bucal. 2011; 16(2):e170–4.
22. Harden me, Karlmunger k. Human papillomavirus molecular biology. Mutat Res Rev Mutat Res 2017; 772: 3– 12.
23. De Villiers EM, Fauquet C, Broker TR, Bernard HU, ZurHausen H. Classification of papillomaviruses. Virology 2004;324:17–27.
24. Bernard HU, Burk RD, Chen Z, Van Doorslaer K, Hau- sen H, DE Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010; 401: 70–79.
25. Bernard HB. Regulatory elements in the viral genome. Virology 2013; 445: 197–204.
26. Weissenborn SJ, DE Koning MN, Wieland U, Quint WG, Pfister HJ. Intrafamilial transmission and family-specific spectra of cutaneous beta-papillomaviruses. J Virol 2009; 83: 811–816.
27. Ragin C, Edwards R, Larkins-Pettigrew M, Taioli E, Eckstein S, Thurman N, *et al.* Oral HPV infection and sexuality: A cross-sectional study in women. Int J Mol Sci 2011;12:3928-40.
28. Kreimer AR, Alberg AJ, Daniel R, Gravitt PE, Viscidi R, Garrett ES, *et al.* Oral human papillomavirus infection in adults is associated with sexual behaviour and HIV serostatus. J Infect Dis 2004;189:686-98.
29. D'Souza G, Wentz A, Kluz N, Zhang Y, Sugar E, Youngfellow RM, Guo Y, Xiao W, Gillison ML. Sex differences in risk factors and natural history of oral human papillomavirus infection. J Infect Dis 2016; 213: 1893–1896.
30. Syrjänen S, Lodi G, von Bultzingslöwen I, Aliko A, Arduino P, Campisi G, *et al.* Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: A systematic review. Oral Dis 2011;17 Suppl 1:58-72.
31. Parsons RJ, Kidd JG. Oral papillomatosis of rabbit: a virus disease. J Exp Med 1943; 77: 233–250.
32. 32.Young SK, Min KW. In situ DNA hybridization analysis of oral papillomas, leukoplakias, and carcinomas for human papilloma- virupapillomaviruss. Oral Surg Oral Med Oral Pathol 1991;71:726-9
33. Cox M, Maitland N, Scully C. Human herpes simplex-1 and papillomavirus type 16 homologous DNA sequences in normal, potentially malignant and malignant oral mucosa. Oral Oncol 1993;29B:215-9.

34. Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: A meta-analysis, 1982-1997. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2001;91:622-35.
35. Khovidhunkit SO, Buajeeb W, Sanguansin S, Poonsawat S, Weerapradist W. Detection of human papillomavirus in oral squamous cell carcinoma, leukoplakia and lichen planus in Thai patients. Asian Pac J Cancer Prev. 2008;4:771-75.
36. Braakhuis BJ, Brakenhoff RH, Meijer CJ, Snijders PJ, Leemans CR. Human papilloma virus in head and neck cancer: The need for a standardised assay to assess the full clinical importance. Eur J Cancer 2009;45:2935-9.
37. Ma J, Zhang J, Zhang Y, et al. The magnitude of the association between human papillomavirus and oral lichen planus: a meta-analysis. PLoS One 2016;11:e0161339.
38. Smith EM, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, *et al.* Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. J Natl Cancer Inst 2004;96:449-55.
39. Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Current TK. Controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. Oral Surg Oral Med Oral Pathol Oral RadiolEndod 2005;100:164-78.

Table 1: Characteristics of 15 included studies

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

Campisi G	2004	Italy	EA-OLP non-EA-OLP	PCR	14/71	5/90	HPV 16,18,31,6
Oflatharta C	2003	Ireland		PCR	10/38	0/20	HPV 16
Giovannelli L	2002	Italy		PCR	9/34	5/90	NA
Sand L	2000	Sweden		PCR	6/22	0/12	HPV 18

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.

Figure 1:PRISMA flowchart describing the identification, screening, eligibility and inclusion of studies.