SYSTEMATIC REVIEW

Prevalence of human papilloma virus 16 and 18 in oral squamous cell carcinoma patients: A systematic review

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ABSTRACT

Background: HPV 16 and 18 are the two strains of Human Papillomavirus that have been associated with the development of OSCC. The aim of this study was to assess the prevalence of HPV 16 and18 in Oral Squamous Cell Carcinoma patients in comparison to controls.

Data Sources: Literature search was conducted on PubMed, Scopus, and Google Scholar. The search strategy combined Medical Subject Headings and relevant keywords. PRISMA guidelines were followed.

Study Selection: Studies conducted on OSCC patients in which prevalence of HPV 16 and 18 was studied in comparison to controls were included. Studies that assessed the prevalence of HPV 16 and 18 in HNSCC, pre-malignant lesions, any other carcinoma and or strain of HPV other than 16 and 18 were excluded.

Data Extraction: Data included publication title, year, authors, study design, sample size, prevalence of HPV 16 & 18 in cases and controls, number of cases and controls and detection methods. Quality assessment was done using Newcastle Ottawa scale.

Data Synthesis: HPV 16 had higher prevalence in OSCC patients as compared to controls. Both the virus strains were seldom found in healthy controls.

Conclusion: HPV 16 can have a significant role to play in OSCC development. HPV 16 (and HPV 18 to a lesser extent) is more prevalent in OSCC. Therefore, it may not be the primary cause but it has role to play in the development of OSCC.

Keywords: Oral Squamous Cell Carcinoma, Human Papilloma virus, Polymerase chain reaction

BACKGROUND

Oral squamous cell carcinoma is the sixteenth most common type of malignancy across the globe.[1] Not only that, it also accounts for 95% of all head and neck malignancies.[2] Despite advances in cancer related treatment modalities, OSCC is associated with severe disease and treatment related morbidity, poor disease-free survival and with high recurrence rates.[3,4] OSCC usually results from exposure of tobacco associated carcinogens that amass a series of genetic and epigenetic alterations resulting in oncogene activation and inactivation of tumor suppressor gene.[5,6] The resultant genetic changes impart proliferative and survival adaptations to the mutated cells characterized by cell division independent of growth factors, resistance to apoptotic signaling and an increased ability to invade adjacent structures by moving through the tissues of the extracellular matrix.[5,7,8]

But even in the absence of these established risk factors of tobacco and alcohol 15% to 20% of patients still develop OSCC(9). Also younger patients have a short exposure time to these risk factors so their role in these patients is yet not fully understood.[9,10] Keeping this in view it has been suggested that there might be other causes of OSCC such as genetics, diet and viral agents.[9] Exposure to Human papilloma virus or HPV is an established risk factor for anogenital and oropharyngeal squamous cell carcinoma.[9] But its role in the pathogenesis of OSCC remains controversial.[9]

HPV is a double stranded DNA virus that exhibits tropism for squamous epithelium. Till date 202 subtypes of HPV have been identified.[11] Based on its oncogenic potential it is subcategorized into high risk (hr) or low risk (lr) types. High risk HPV which

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includes subtypes 16, 18 and 33 is associated with malignant proliferation.[11] While low risk HPV including subtypes 6, 11 and 32 is associated with benign mucosal lesions.[11] The mechanism through which high risk HPV induces malignancy is primarily by viral integration whereby the virus integrates its genome into that of the host.[12] The specify fragments to be inserted are E6 and E7.[12] This insertion leads to the inhibition of tumor suppressor gene functions resulting in unregulated cell proliferation, apoptosis and genetic stability.[12]

HPV 16 and 18 has been associated with and established as an etiological factor of cervical cancer.[13] Their pathogenesis includes integration of viral DNA into epithelial cells of host.[14] This leads to the disruption of tumor suppressor genes. These genes include p53 and Rb.[14] If dysplasia caused by these viral strains are left undetected or un-treated, it can progress to neoplasia of the cervical intra-epithelial cells which culminates in invasion of the carcinoma.[15]

Studies have shown the presence of human papilloma virus DNA in oral squamous cell carcinoma, nevertheless these studies have shown great variability in viral prevalence that is explained by several factors.[9] There can be discrepancies in the sample collection and preservation methods, the sensitivity of tests conducted to detect the virus, and there is little proof of the actual oncogenic potential of HPV since the presence of HPV DNA alone is insufficient evidence for an association.[9] This review was conducted to assess the prevalence of HPV 16 and 18 in OSCC patients and healthy controls. The objective of this systematic review was to assess the prevalence of HPV 16 and18 in Oral Squamous Cell Carcinoma patients in comparison to health controls.

MATERIAL AND METHODS

1. Data sources: An extensive search of literature was conducted across the databases of PubMed, Scopus, and Google Scholar. A search of grey literature was carried out through ProQuest. No language, publication year and geographical restrictions were applied. The search strategy combined Medical Subject Headings (MeSH) and relevant keywords including: "Oral Squamous Cell Carcinoma (OSCC)," "Human Papillomavirus," "HPV 16," "HPV 18," and "Polymerase Chain Reaction (PCR)." Boolean operators such as AND and OR were applied to refine the search. Reference lists from relevant articles and previously conducted reviews were manually screened. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure 1 outlines the PRISMA flow diagram used for study selection. All database searches, article screening, and data extraction were independently performed by two reviewers to ensure methodological rigor and minimize bias.

2. Study selection: The process of search was conducted by two reviewers who were independent. The preliminary search was carried out based on titles and abstracts. This was done in order to select articles for full text review. Full text articles were re-assessed based on the inclusion criteria and the selected articles were then subjected to quality assessment.

Inclusion criteria: The inclusion criteria were:

1. Studies conducted on diagnosed cases of Oral Squamous Cell Carcinoma patients
2. Studies in which prevalence of HPV 16 and 18 was studied in Oral Squamous cell carcinoma patients in comparison to healthy controls.

Exclusion criteria: The exclusion criteria were:

1. Studies that assessed the prevalence of HPV 16 and 18 in Head and Neck Squamous cell carcinoma and not specifically on Oral Squamous Cell Carcinoma patients.
2. Studies that assessed the prevalence of HPV 16 and 18 in oral potentially malignant lesions or pre-malignant lesions.
3. Studies that included any strain of HPV other than 16 and 18.
4. Studies that assessed the prevalence of HPV 16and 18 in any other cancer

3. Data extraction: An extensive search of literature was conducted across the databases of PubMed, Scopus, and Google Scholar. A search of grey literature was carried out through ProQuest. The key terms used for searching data were Oral Squamous Cell Carcinoma (OSCC), Human Papilloma virus 16 and 18 and polymerase chain reaction (PCR). The retrieved data from studies including title of publication, year of publication, authors, study design, sample size, prevalence of HPV 16 in cases and controls, HPV 18 prevalence in cases and controls, number of cases and controls and HPV detection methods.

4. Quality Assessment: New castle Ottawa scale (NOS) was the scale used for quality assessment of the studies included in this systematic review. Based on this scale the studies were assessed on the points of comparability

(2 points), selection (4 points) and exposure (3 points). The studies are then classified as high, moderate and low quality based on the points. Studies with a score of 7-9 are considered high quality, 4-6 are moderate while <4 are low quality studies.

All the studies included in this systematic review were high quality studies. They were assessed on the New Castle Ottawa scale and it was seen that they fulfilled all three criteria. The criteria of selection were fulfilled as the recruitment and selection of cases and controls was done using the appropriate methodology. By controlling the confounding factors of age, gender and tobacco use, the criteria of comparability were also addressed. Lastly, the exposure assessment was appropriately carried out as PCR technique was used to detect Human Papilloma virus. The details of scoring of the included study based on NOS has been shown in Table-I.

5. Data Synthesis: Table-II shows a comparison of the prevalence of HPV 16 and 18 in patients with Oral Squamous Cell Carcinoma and healthy controls. These studies assess if these two strains of HPV are more prevalent in OSCC patients as compared to healthy individuals without OSCC.

It was seen that HPV 16 had high prevalence in OSCC patients as compared to controls. The overall prevalence of HPV 18 was less as compared to HPV 16 except in a study conducted by Purwanto et al[17] in Indonesia where the prevalence of HPV 18 was higher than HPV 16 in OSCC patients as compared to controls. A similar trend was seen in the study conducted by Rubab et.al.[19] Both the virus strains were seldom found in healthy controls. While the occurrence can be quoted as a less frequent, it cannot be reported as zero. This low prevalence of the viral strains in controls and higher prevalence in OSCC patients suggests that they do have a role to play in etiology of OSCC. The analysis of these studies revealed that the prevalence of HPV 16 and 18 across all the countries. The prevalence was much higher in countries like Iran and China.[16,20] The prevalence was much lower in Pakistan and Indonesia among OSCC patients.[17,19] While majority of the studies used PCR, the most sensitive detection technique for HPV, some also employed the techniques of hybridization and DNA sequencing to confirm the presence of the virus.

Excluded Studies: A total of 20 studies were excluded from the systematic review. The list of these studies and the reason for exclusion have been mentioned in the Table-III.

Table-I: Quality assessment of the included study based on New Castle Ottawa scale

S #	Study (Author, Year)	Country	Selection (total score 4)	Comparability (total score 2)	Exposure (total score 3)	Total Stars (total score 9)	Quality Rating	Reference
1.	**Tabatabai *et al*., 2015**	Iran	4	2	3	9	High	(18)
2.	**Purwanto *et al*, 2020**	Indonesia	4	2	3	9	High	(20)
3.	**Chowdary *et al, 2018***	India	3	0	2	5	Moderate	(21)
4.	**Baig *et al, 2018***	Pakistan	4	1	2	7	Good	(22)
5.	**Gan *et al,2014***	China	4	1	2	7	Good	(23)
6.	**Phu Singha *et al*, 2017**	Thailand	4	2	3	9	High	(24)

Table-II: Comparative analysis of the included studies.

Sr #	Study (Author, Year)	Country	Sample Size (OSCC/Control)		Detection Method	HPV-16+ only in OSCC (%)	HPV-16+ only in Controls (%)	HPV-18+ only in OSCC (%)	HPV-18+ only in Controls (%)	HPV 16 & 18 co-infection		Key Findings	Reference
			OSCC cases	Controls						OSCC	Controls		
1.	**Tabatabai et al., 2015**	Iran	39	27	PCR	12 (30.7%)	0 (0%)	0 (0%)	0 (0%)	5 (12.8%)	0 (0%)	HPV-16 and -18 present in OSCC, none found in controls	(18)
2.	**Purwanto et al., 2020**	Indonesia	78	79	PCR	1 (1.3%)	3 (3.8%)	12 (15.4%)	0 (0%)	1 (1.3%)	0(0%)	HPV-18 more common in OSCC; HPV-16 more in controls	(20)
3.	**Chowdary *et al,2018***	India	20	20	PCR	6 (30%)	3 (15%)	3 (15%)	1 (5%)	2 (10%)	2(10%)	Prevalence of HPV 16& 18 higher in OSCC cases	(21)
4.	**Baig *et al,2018***	Pakistan	100	200	PCR	4 (4%)	2 (1%)	5 (5%)	4 (2%)	23 (23%)	3(1.5%)	Relatively higher prevalence of both strains in OSCC cases. Co-infection of HPV 16 and 18 was highly prevalent.	(22)
5.	**Gan *et al, 2014***	China	200	68	PCR	39(19.5 %)	0 (0%)	15(7.5%)	2(2.9%)	0(0%)	0(0%)	Both viral strains prevalent in OSCC cases more than the controls. HPV 16&18 co-infection was not seen	(23)
6.	**Phu Singha *et al*, 2017**	Thailand	80	100	PCR + Hybridization	13 (16.3%)	11 (11%)	1(1.3%)	0(0%)	0(0%)	0(0%)	HPV-16 higher in OSCC as compared to controls.	(24)

Table-III: Record of the studies excluded from the systematic review.

Sr #	Article excluded	Reason for exclusion	Reference
1.	Kulkarni *et al*	Study was conducted on carcinoma of the cervix and not only on OSCC	(8)
2.	Kaewmaneenuan et. al	Oral potentially malignant lesion	(25)
3.	Jalouli *et al*	Oral potentially malignant lesion	(26)
4.	Xhang *et al*	Oral potentially malignant lesion	(27)
5.	Chang *et al*	• HPV strains other than 16 and 18 were studied • Study did not include healthy controls	(28)
6.	Laco *et al*	• HPV strains other than 16 and 18 were studied • The study included oropharyngeal Squamous cell carcinoma as well.	(29)
7.	Popvi`c *et al*	Study did not include healthy controls	(30)
8.	Shroyer *et al*	Oral potentially malignant lesions were included	(31)
9.	Menezes *et al*	Study did not include healthy controls	(32)
10.	Rajesh *et al*	Study did not include healthy controls	(33)
11.	Shaikh *et al*	Study did not include healthy controls	(34)
12.	Kreimer *et al*	Study was conducted on Head and Neck Squamous cell carcinoma and not OSCC in particular	(36)
13.	Quintero *et al*	Study was conducted on Head and Neck Squamous cell carcinoma and not OSCC in particular	(37)
14.	Kabagenyi *et al*	Study was conducted on Head and Neck Squamous cell carcinoma and not OSCC in particular	(39)
15.	Azhar *et al*	Study did not include healthy controls	(41)
16.	Sri *et al*	Oral potentially malignant lesions were included	(42)
17.	Yang *et al*	Oral potentially malignant lesions were included	(43)
18.	Khasawneh et. al	Study was conducted on Head and Neck Squamous cell carcinoma and not OSCC in particular	(44)
19.	Parshad et. al, 2015	Study did not include healthy controls	(45)
20.	De Abreu *et al*, 2018	Study did not include healthy controls	(46)

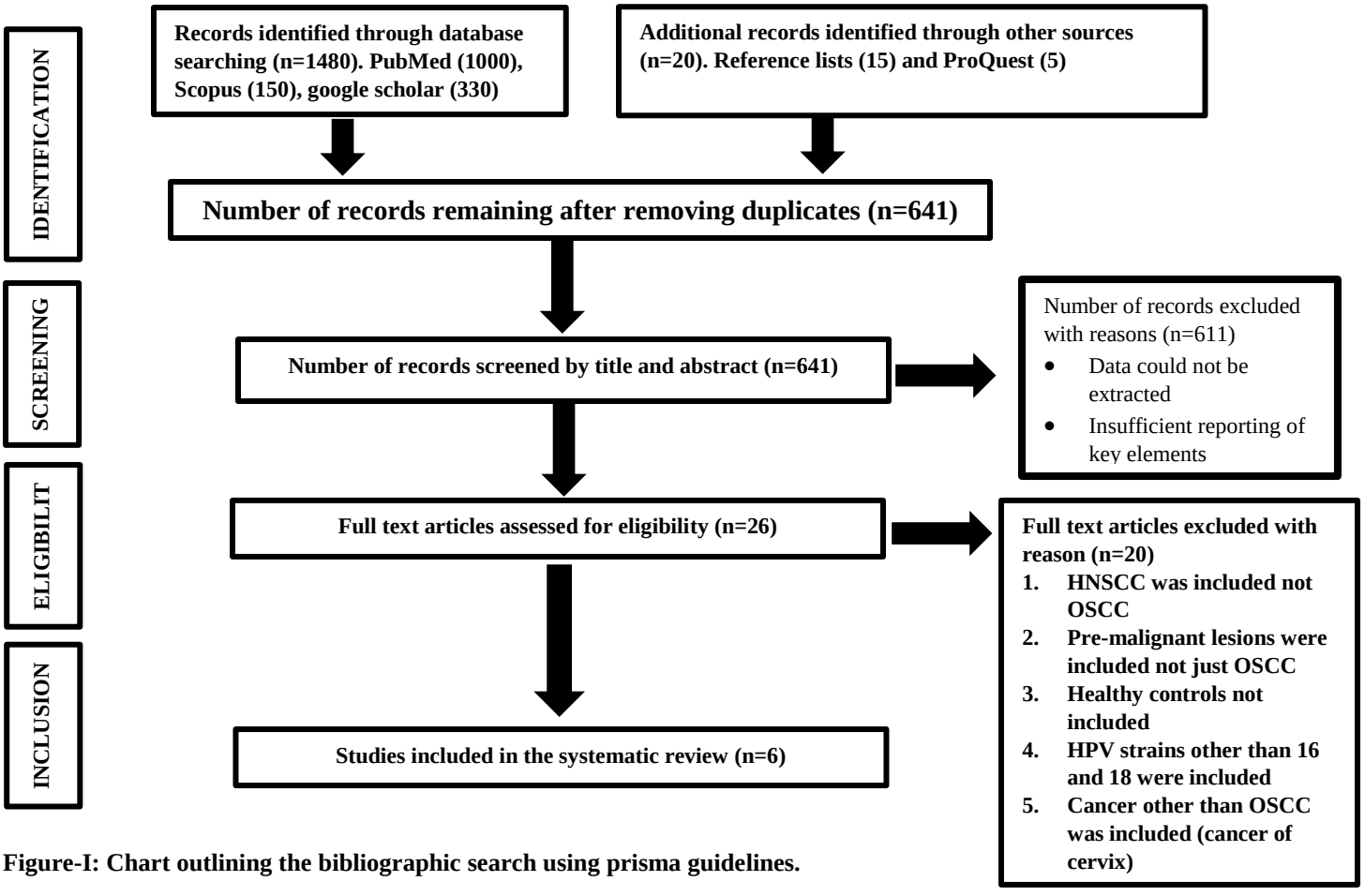

Figure-I: Chart outlining the bibliographic search using prisma guidelines.

DISCUSSION

In this systematic review most of the studies reported that the prevalence of HPV 16 was much higher in OSCC patients as compared to controls. For example, according to a study conducted in Iran by Tabatabai et al, the prevalence of HPV 16 in OSCC patients was 15% as compared to 3.7% controls.[16] Similarly, Purwanto et al reported a similar trend with a 23% prevalence of HPV 16 in cases as compared to 1.5% controls.[17] This indicates a very strong association between occurrence of this virus strain and OSCC. These findings are similar to those reported by a metanalysis, where the HPV 16 prevalence was 20.1% as compared to a very negligible prevalence in controls further solidifying the evidence that there may be an association between OSCC pathogenesis and HPV 16.[41]

Regarding the prevalence of HPV 18, it was seen that in this systematic review, studies revealed variable results. While one study conducted by Purwanto et al reported a higher prevalence of HPV 18 (15.4%) in OSCC patients as compared to control, where there was no detection of the virus.[17] Many studies have reported findings similar to these. A study conducted in China reported 19.5% prevalence of HPV 16 and 7.5% of HPV 18 in OSCC patients as compared to controls (2.9%).[20] The high prevalence of HPV 18 in OSCC cases indicates that there can be a role of this virus in the pathogenesis of OSCC.

The prevalence of HPV is influenced by geographical variation as well.[42] Among our included studies, it was seen that in studies included form China[20] and Iran[16], the prevalence of both viral strains was substantially higher in patients with OSCC. On the contrary a study conducted in Indonesia by Parwanto et al reported a higher prevalence of HPV 16 in controls as compared to OSCC cases.[17] These differences in prevalence due geographical variations can be attributed to the varying risk factors. These include a genetic predisposition to development of disease, oral health and hygiene, sexual practices and use of tobacco.[43]

Polymerase chain reaction is a standardized detection test used for HPV.[11] The sensitivity and specificity of this test has long been established and is widely used for detection purposes.[11] In this systematic review also, PCR technique was the most widely used technique. While this is true, some studies also used DNA sequencing for confirmation. One such study was that conducted by Lima et al in China.[12] Employing various detection techniques can also be responsible for the variation in results across our included studies.

The association of HPV 16 with OSCC across different studies highlights the important issue of HPV vaccination.[44-47] The high prevalence of HPV 16 and comparatively variable prevalence of HPV 18 indicates their potential role in the pathogenies of OSCC and underscores the importance of development of a vaccine for this virus which could lead to substantially reducing the incidence of OSCC.

CONCLUSION

The comparative analysis of our selected studies with additional literature revealed that HPV 16 can have a significant role to play in OSCC development, with HPV-18 also playing a role, albeit with variable prevalence. HPV 16 (and HPV 18 to a lesser extent) is more prevalent in OSCC. This supports the hypothesis that while it may not be the primary cause but it has role to play in the development of OSCC. Additionally, the variation in prevalence of both virus strains in cases and controls can be attributed to geographical variations and detection methods. Two main factors imparted strength to this systematic review. Firstly, the inclusion of healthy controls in studies allowed us to draw more meaningful information regarding role of HPV in OSCC. It allowed for a comparison of the prevalence of virus in OSCC cases in comparison to healthy controls. Secondly, studies from various geographical regions were included which enabled us to get an insight in prevalence of and association of HPV with OSCC across different regions. One weakness of this study was that since this was not a meta-analysis, due to the lack of quantitative analysis the findings of this systematic review is not statistically supported and therefore, the results and conclusion are mainly descriptive.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTION:

Ahmer Bilal Tariq: Concept & design, Literature review, manuscript write-up

Noor ul Huda: Literature review & manuscript write-up

Muhammad Aman: Literature review & manuscript write-up

Hira Butt: Concept & design, literature review,

manuscript write-up, supervision, critical revision and final approval

Dur E Shumyle: Literature review & manuscript write-up

Nauman Rauf Khan: Concept& design, Literature review, supervision and final approval

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