ORIGINAL ARTICLE

Review on the Most Important Viruses in Oral Squamous Cell Carcinomas

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ABSTRACT

Background: Head and neck squamous cell carcinoma (HNSCC) accounts for nearly 5% of all cancers and is a serious issue in public health globally. HNSCC includes a large group of tumors that are categorized as oropharyngeal squamous cell carcinomas (OPSCC) or oral squamous cell carcinomas (OSCC). Also some Studies have reported possibilityassociation between some of important virus such as human papilloma virus (HPV) and EBV infection in OSCC.
Aim: To combine the findings of previous studies to assess important viruses in OSCC.
Methods: We searched Web of science, PubMed and Scopus using key words such as oral squamous cell carcinomas, head and neck squamous cell carcinoma, squamous cell carcinoma, infection and virus. The search period was 2000 -2020. Standard laboratory test and standard methods should be used in the studies articles.
Result: Of the 33 selected studies, 19 studies were related to HPV, 9 studies were related to EBV and 5 studies were both viruses, respectively. The prevalence of HPV infection in OSCC varied from 4 to 51.4% and the prevalence of EBV infection in OSCC ranged from 7 to 72.7%. These two types of HPV are high risk. In these studies, 28 studies indicated the possibility of HPV and EBV viruses affecting patients with OSCC, and the results of 5 studies indicate no effect.
Conclusion: The findings of this study indicate that HPV and EBV infections are significantly associated with OSCC based on epidemiological studies. This finding implies that HPV can be a possible cause for OSCC. However the mechanism for HPV and EBV transmission to the oral cavity is yet unknown and there is a need for further research in this regard.
Key words: Oral squamous cell carcinomas, Head and neck squamous cell carcinoma, Squamous cell carcinoma, Infection, Virus

INTRODUCTION

The global prevalence of head and neck cancer is more than 650,000 cases. The annual mortality due to head and neck cancers was reported to be 330,000 in 2018[1]. Head and neck squamous cell carcinoma (HNSCC) accounts for nearly 5% of all cancers and is a serious issue in public health globally[2].. HNSCC includes a large group of tumors that are categorized as oropharyngeal squamous cell carcinomas (OPSCC) or oral squamous cell carcinomas (OSCC). OSCC accounts for more than 90% of oral tumors[2]. The prevalence of oral cancers is variable. For instance the prevalence of oral cancers was reported to be 22.72% in the United States, while the prevalence was 20.45% in Europe, 5.76% in Africa, and 0.84% in Australia[3].

While environmental, lifestyle, infectious, and genetic factors can have a role in the development of OSCC, the major risk factors for OSCC include smoking and alcohol abuse[4].. Chemical risk factors have also been widely studied in OSCC. Studies have also shown that human papilloma virus (HPV) infection has a role in some subtypes of HNSCC[5]. The role of HPV infection in OSCC was first described by Syrjänen et al. (1983)[6]. Various molecular epidemiology studies showed that HPV infection might be etiologically involved in subtypes of head and neck cancers including oral cavity cancers[7,8]. Various studies have been conducted on the mechanism of cancer development due to HPV infection[9]. The role of HPV E6 and E7 genes have been documented in the development of HPV related cancers. Bothe E6 and E7 genes inhibit tumor suppressor activity proteins like p53 and retinoblastoma protein (pRB). The E6 protein interacts with E6 associated protein (E6AP) and inactivates p53, while E7 protein binds with pRB and disrupts complex formation of a group of genes in the transcription factors family with E2F. One of the roles of pRB is preventing cellular over-proliferation though inhibition of cell cycle progression. Therefore, inactivation of pRB by binding to E7 may result in cancerdevelopment. The role and mechanism of HPV in the development of oral cancer is not yet well understood. HPV infection might produce oral cancer through different mechanisms.

Epstein-Bass virus (EBV), also known as human herpes virus 4 (HHV-4), with a double stranded DNA genome belongs to the *Herpesviridae* family[10]. EBV is linked with nasopharyngeal and gastric carcinoma, squamous cell carcinoma, Hodgkin and Burkitt lymphomas[11]. EBV can infect B lymphocytes and epithelial cells. Temporary reactivation of the EBV infection and virus proliferation in nasopharynx results in virus spread and

latent infection in B lymphocytes[11,12]. Studies have reported association between EBV infection and local oral diseases including gingivitis, periodontitis, pulpitis, periapical inflammations and periodontal abscesses[13]. A number of studies have also reported HPV and EBV co-infection in OSCC cases[14,15]. Although the mechanism of OSCC induction by HPV is not yet clear, epidemiological studies have reported a significant relationship between HPV infection and OSCC. On the other hand, the findings of previous studies regarding the relationship between HPV infection and OSCCare being debated.

OSCC has affected a large number of people worldwide and is considered a serious problem. The treatment of OSCC is very difficult and puts a great economical and psychological burden on patients and their families. Furthermore, no study has recently assessed the viral causes of OSCC. Therefore, the aim of this review study was to combine the findings of previous studies to assess the important viruses, including HPV and EBV, on OSCC.

METHODS

We searched Web of science, PubMed and Scopus using key words such as oral squamous cell carcinomas, head and neck squamous cell carcinoma, squamous cell carcinoma, infection and virus. The search period was 2000 -2020.Standard laboratory test and standard methods should be used in the studied articles.

RESULT

In the initial search, 1300 articles were found.After deleting the unrelated, duplicate, and incomplete information, 33 studies were eventually classified as the main study. The studies were selected from 24 different countries, with the largest number being in India with five studies.Of the 33 studies, 19 studies were related to HPV, 9 studies were related to EBV and 5 studies were both viruses, respectively.The prevalence of HPV infection in oral squamous cell carcinoma (OSCC) varied from 4 to 51.4% and the prevalence of EBV infection in OSCC ranged from 7 to 72.7%.Studies have shown that the most common type of HPV, commonly seen in OSCC, is HPV-16 and 18. These two types of HPV are high risk. In these studies, 28 studies indicated the possibility of HPV and EBV viruses affecting patients with OSCC, and the results of 5 studies indicate no effect.The sample size was very variable in these studies, with 11 in the Broccolo study and 409 in the Lingen study. In all of the studiesReviewed, the number of men with OSCC was higher than that of women, and the prevalence of HPV and EBV was higher.

Virus	AUTOR NAME	Contry	Gender				Number of OCSCC	AJCC tumor stage				virus expression positive		Detection method	Type of virus	Conclusion
			male		female											
			N	P	N	P		T_1	T_2	T_3	T_4	N	%			
HPV	Lingen et al. 2013(16)	USA	236	21	173	3	409	132	126	44	86	24	5.9	PCR	16,18,31,33, 35,39,45	The etiologic fraction for HR-HPV in OCSCC was 5.9%
HPV	Krüger et al. 2014(17)	Germany	37	5	51	-	88	33	20	1	31	5	6	DNA-PCR	11,16,18,51, 59,68	HPV infection might play a less important role in oral carcinogenesis
HPV	de Abreu et al. 2018(18)	Brazil	66	2	21	1	90	36		51		3	less than 4%	PCR	16	HPV is not involved in the genesis of oral cavity SCC in Brazilian population
HPV	Niv et al. 2000(19)	Israel	17	3	6	1	24	-	-	2	2	4	17.3	PCR	16	the presence of HPV DNA type 16 within cells from oropharyngeal SCCa
HPV	Elango et all. 2011(20)	India	41	22	19	7	60	19	11	13	17	29	48	PCR, IHC and ISH	16	This study confirms a positive correlation of HPV infection with oral tongue cancer
HPV	Kaminagakura et al. 2011(21)	Brazil	81	-	33	-	114	26		88		22	19.2	PCR	total of 17 HPV types were analyzed	The higher prevalence of high-risk HPV types, especially HPV16, may be a contributing factor to oral carcinogenesis in younger individuals
HPV	Lee et al. 2010(22)	Korea	-	-	-	-	36	36		-		13	36	Real-time PCR	16	HPV-16 may be one of the causative factors in early squamous cell oral tongue carcinoma and be associated with its depth of invasion
HPV	Chaudhary et al. 2010(23)	India	146	-	76	-	222	80		142		72	32.43	PCR, HC II	16	in case of malignant oral lesions such as OSCC, 32.4% HPV 16 E6 positive by PCR and 31.4% by the HC-II assay and the HC II assay seemed to have better sensitivity in case of OSCC.
HPV	Zhao et al. 2009(24)	China	35	15	17	6	52	22		30		21	40.4	PCR	6,11,16,18	HPV infection can act as an independent predictor for the survival and prognosis of OSCC
HPV	Verma et al. 2016(25)	India	110	27	25	7	135	20	5	37	73	31	22.9	PCR, IHC	16,18	may serve as molecular signature of HPV-positive lesions or more broadly the tumors that show better prognosis
HPV	Chen et al. 2016(26)	China	110	-	68	-	178	-	-	-	-	25	14.04	color reaction of hybridization and PCR	16,18	Oral HPV infection (specifically type 18) is an independent risk factor for OSCC in Fujian area
HPV	Duray et al. 2012(27)	Belgium	130	49	32	16	147	38	27	28	54	65	44	Real-time qPCR	16, 18, 31, 33, 35, 39, 45, 51, 52, 53,	A high prevalence of HPV infections was detected in the OSCC patients included in the study. Also decreased 5-year

															56, 58, 59, and 66	disease-free survival rate.
HPV	Saghravanian et al. 2015(28)	Iran	58	8	56	7	114	-	-	-	-	15	13.1	PCR	6,11,16,18, 31	In the Iranian population, we found no significant association between HPV and malignant transformation
HPV	Lee et al. 2012(29)	Taiwan	156	27	7	1	163	20		113		28	22	PCR	16,18	HPV infections in advanced OSCC patients are not uncommon and clinically relevant
HPV	Saini et al. 2010(30)	Malaysia	51	24	54	30	105	-	-	-	-	54	51.4	PCR	16, 26, 31, 33, 35, 45, 51 and 58	This study indicates that high-risk HPV infection is one of the contributing factors for OSCCs
HPV	Lacau St Guily et al. 2011(31)	France	151	12	58	10	209	-	-	-	-	22	10.5	INNO-LiPA	16,18,39	HPV is common among oral cavity carcinoma cases in France and emphasize the predominance of HPV 16
HPV	Castillo et al. 2011(32)	Japan,Pakistan and Colombia	45	-	26	-	71	-	-	-	-	40	56	PCR,INNO-LiPA	16,51,68	there was no significant difference of HPV prevalence in SCC of the UDT among populations at different risk of HPV exposure
HPV	Anaya-Saavedraet al. 2007(33)	Mexico	33	-	29	-	62	-	-	-	-	27	43.5	PCR	16,18	Oral HR-HPV was strongly associated with OSCC, suggesting that HPV-16 and -18 are risk factors for oral cancer in Mexican patients.
HPV	Gheit et al. 2017 (34)	India	176	-	76	-	252	-	-	-	-	30	11.9	multiplex PCR and bead-based Luminex Technology	HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68a and b, 70, 73 and 82	HR-HPV typesassociated with HNC
EBV	Kis et al. 2009(35)	Hungary	51	-	14	-	65	-	-	-	-	48	73.8	PCR	-	Although a high prevalence of EBV was found in OSCC, comparable carriage rates on healthy mucosa of patients indicated that an aetiological role of EBV is unlikely.
EBV	Acharya et al. 2014(36)	Thailand	38	-	53	-	91	-	-	-	-	41	45.5			Epstein-Barr virus prevalence is associated with OSCC
EBV	Prathyusha et al. 2019(37)	India	12	3	8	1	20	-	-	-	-	4	20	PCR	-	The prevalence of EBV was significantly high in controls than OSCC cases
EBV	Saleem et al. 2019(38)	Pakistan	115	33	35	1	150	-	-	-	-	34	22.6	Chi-square test	-	acantholytic tumor, a rare histological subtype of OSCC, tended to be EBV related
EBV	Sand et al. 2002(39)	Sweden	23	9	6	2	29	-	-	-	-	11	37.9	Nested PCR	-	EBV is present in oral diseases such as OSCC and OLP
EBV	Higa et al. 2002(40)	Japan	50	36	4	3	54	11	15	15	12	39		NISH ,PCR	A,B	In Okinawa, EBV infection was frequently demonstrated in oral squamous cell carcinoma
EBV	AlfrazdagMohamedahmed Abdalla Abdalrazig et al. 2017(41)	Sudan	66	-	41	-	107	-	-		-	35	32.7	PCR	-	This study result revealed that EPSTEIN-BAAR VIRUS could be one of the causative factors that lead to squamous cell carcinoma
EBV	Heawchaiyaphum et al.2020(42)	Thailand	58	-	107	-	165	-	-	-	-	68	41.2	PCR,ISH	-	EBV can infect squamous cells and establish latent infection
EBV	Jiang and Dong 2012(43)	USA	-	-	-	-	26	-	-	-	-	11		real-time PCR	-	The findings suggest that dysplasia may make cells more susceptible to infection by EBV
HPV, EBV	Broccolo et al. 2018(44)	Italy	-	-	-	-	11	-	-	-	-	1, 8	9.1,72.7	PCR, IHC	20 high-risk HPV types	Single HPV or EBV positivity was higher in OSCC than in OPSCC
HPV, EBV	Badrawy et al. 2015(45)	Egypt	9	-	6	-	15	-	-	-	-	2, 3	13.3, 20	real time PCR	-	This study may provides a role of HPV and EBV infection in the etiology of oral SCC
HPV, EBV	Higa et al. 2003(46)	Japan	118	-	59	-	177	-	-	-	-	-	78, 72	PCR	-	The prognosis for (mostlyEBV/HPV infected) squamous cell carcinomas in Okinawa was better than that in the mainland where most cases were negative for EBV and/or HPV.
HPV, EBV, HPV and EBV	Polz-Gruszka et al. 2015(47)	Poland	75	-	17	-	92	-	31	19	42	28 ,-, 6	30.4,26. 1, 6.5	PCR	16, 51,52,59,66 ,68,71,74	IN oral cavity cancer other mixed infections were observed (i.e. 51, 52, 59, 66, 68, 71, and 74).The pathogenesis of oral squamous cell carcinoma may be connected with EBV infection.
EBV, HPV	Delavaian et al. 2010(48)	Iran	12	-	9	3	21	-	-	-	-	3, 1	-	PCR	-	This virus had no important role in OSCC

DISCUSSION

The aim of this study was to assess the oral infection with important viruses, including HPV and EBV,among patients with OSCC. A meta-analysis by Miller and Johnstone (2001) on OSCC cases proposed that HPV infection may be a significant and independent risk factor for OSCC. They also reported that the variety in the prevalence of HPV infection among OSCC cases depends on geographical differences, as well as differences in type of sampling, methodology and HPV detection techniques in the studies[49]. Similarly, the highest prevalence of HPV infection was reported in Africa and Asia, especially in Chinese provinces with high prevalence of OSCC[50]. The findings of a meta-analysis in 2017 revealed that EBV infection was associated with a statistically significant increase in the risk of OSCC[51].

In the current review, 33 original articles were assessed. The findings of the current review indicated that the prevalence of HPV among OSCC cases was varied and ranged from less than 4% to 51.4%. Furthermore, the prevalence of EBV among OSCC cases ranged from 7 to 72.7%. The most prevalent types of HPV in OSCC cases were HPV-16 and HPV-18, which are considered as high-risk serotypes.The results of all reviewed studies except 5 indicated that HPV and EBV infections might affect OSCC. The possible mechanisms for this effect are discussed as follows.

The relationship between oral infections and oral cancers was first assessed on HPV. Epidemiological studies have been conducted on HPV infection and its relationship with oral cancers. Kreimer et al. (2010) assessed the prevalence of oral HPV infection and reported that oral HPV infection might be related with oral cancers[52]. The prevalence of HPV among American men and women was reported to be 7.3% by Sanders et al. (2012)[53]. These findings resulted in conducting studies that assessed the relationship between oral sex and oral HPV infection[54,55,56]. The findings of these studies indicated that oral sex and opened-mouth kissing were related to oral HPV infection. Therefore, it is suggested that oral sex might be one of the causes of oral HPV infection. HPV is transmitted through sexual intercourse and may result in cervical and anal cancer and that oral transmission of HPV infection might be due to high-risk sexual behaviors and oro-genital contact.

One of the mechanisms related to development of OSCC in oral HPV infection the destruction of p53 by HPV E6 through ubiquitin pathway. Although p53 was found to be active in tumors with HPV 16 positivity[57,58]. The other mechanism might be due to over-synthesis of P53 due to DNA damage. Pillai et al. (1999) found that expression of defective high-risk HPV 16/18 E6 protein is an important event in HPV carcinogenesis[59]. The expression of E7 and the presence of pRB indicate complex formation between these proteins that result in the destruction of pRB. Therefore, E7 protein might have a role in mild carcinogenesis of HPV.

The mechanisms that may involve in the carcinogenesis of EBV might include the following. Malignancy due to EBV is related to the virus proteins that regulate cell proliferation, immune response and apoptosis[60]. RNAs and Epstein–Barr virus-encoded small RNAs (EBERs) are small non-coding proteins that act in the active EBV infection. Latent membrane proteins (LMPs) help in the activation of signaling pathways linked to EBV stability, while EBV-determined nuclear antigens (EBNA) regulate gene expression. EBV oncoprotein (LMP-1), activates nuclear factor-kappa B (NF-κB). NF-κB has an important role in EBV-immortalized B-cells survival. Regarding the EBV encoded proteins, BHRf1protein sequence is 25% homologous with the oncogene protein BCL-2 protein and prevents apoptosis in cells.LMP-1 and EBNA-5 protein inhibit p53-mediated apoptosis. NPS is also related to EBERs, EBNA-1, LMP-1, LMP-2 and BARFO[60,61]. Sustained expression of LMP-2A at RNA level in both primary and metastatic tumors indicate that this protein is a stimulating factor in EBV related malignancies. LMP-2A might cooperate with aberranthost genome and interfere with signaling pathways in various cell functions, especially cell cycle and apoptosis pathways, and have a role in malignancy transmission[62].

The products from the mentioned genes affect cell immortalization and virus genome proliferation[11]. The findings of some studiesindicated that the expression of EBV DNA, mRNA and proteins were present in majority of OSCC cells[63,64]. However, the carcinogenic effect of EBV on oral mucosa is yet unknown.

Majority of studies used PCR or in situ hybridization (ISH)for virus detection. The findings of these studies are debated as there is the possibility that differences in diagnostic methods might affect the diagnosis of EBV and HPV infections in OSCC. Various diagnosis techniques exist for EBV, including PCR, Nester PCR, RT-qPCR, IHC and ISH.

Sample sizewas also different in the studies ranging from 11 subjects in the study by Brocclo et al. to 409 subjects in the study by Lingen et al[16,44].. This variability in sample size makes it difficult to have a proper judgment. One of the limitations of this study was variable sample size in reviewed studies. The moving nature of oral cavity and the washing effect of saliva can have a limited effect on the low detection rate of HPV, which might be another limitation of this study. The other limitations might include differences in the detection methods, publication year, study location, country where the study was conducted, and the economic level of the study region. Furthermore, some studies did not take into

CONCLUSION

The findings of this study indicate that HPV and EBV infections are significantly associated with OSCC based on epidemiological studies. This finding implies that HPV can be a possible cause for OSCC. Increase in HPV prevalence might result in an increase in the incidence of

OSCC. Regarding the fact that OSCC is the second HPV related cancer and also the increasing prevalence of HPV infection, the effect of HPV vaccination on OSCC should be considered. However, the mechanism for HPV and EBV transmissionto the oral cavity is yet unknown and there is a need for further research in this regard.

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