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Human Papillomavirus associated burden of Oral Squamous Cell Carcinoma in an Indian inhabitants

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ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is the eighth most common global malignancy and one of the leading cancer in Indian inhabitants. Gujarat is considered nowadays to be the high-risk region for oral cancer. The occurrence of OSCC mainly due to tobacco addiction; however 15-20% of overall oral cancer incidence in the non-smoker and non-alcoholic patients. Previous studies indicated that oral cancer might be caused by infection of Human Papillomavirus (HPV) along with consumption of tobacco. We have combined “PubMed” and “Medline” articles published from 1983 to 2017 and retrospective review has been done to identify the association of HPV and oral cancer. There are > 100 types of HPV have been found in oral lesions, including type 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, and 73. The prevalence of HPV in OSCC has been reported the overall prevalence ranges between 20-50%. The risk difference of OSCC with HPV infection varies ethnicity to ethnicity. The meta-analysis has shown HPV 16 and 18 strain found to be associated with the higher risk of developing OSCC in the Indian subcontinent. In view of the relationship between HPV and OSCC, further studies are required to reveal the role of HPV onset of oral neoplasm especially the oral cancer patients without the history of tobacco in any form.

KEYWORDS: HPV, OSCC, Oral cancer, India, Tobacco, PCR.

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INTRODUCTION:

Oral cancer is a perilous and emergent malignant neoplasm in many parts of the globe [1], it represents the carcinoma of the tongue, lip, buccal mucosa, soft palate, hard palate, tonsil, alveolus and gingival[1,2]. It has been reported that 90% of cases are Squamous Cell Carcinoma [3, 4]. Oral cancer is the eight most common fatal disorder worldwide [5]. In the Indian subcontinent, it is the leading malignancy among men and third most common type of cancer among women. Annually ~128,000 deaths occur from >260,000 new cases of Oral Squamous Cell Carcinoma (OSCC) [6].

Tobacco and alcohol consumption are the well-established risk factors for oral cancer [7]. In the Asia-Pacific region, the concomitant and current form of tobacco is composed of areca nut, slaked lime, catechu, betel leaf and betel quid [8]. Chewing betel quid is a common dietary habit widespread in many parts of the world[1,3]. The frequent use of betel quid leads to a 50-fold increase in reactive oxygen species generated [2, 9]. Another risk factor for developing OSCC is smoking cigars, pipes, and cigarettes [3]. The western part of India, Gujarat is the tobacco growing belt, and it is obvious to be a high-risk region for OSCC due to the habit of chewing tobacco in various forms like pan, bidi and Gutkha. In our previous study we found 80% patients found to be associated with the history of tobacco in form of chewing and smoking, out of 71% patients had a history of tobacco chewing only, it clearly indicates the higher amount of tobacco consumption in form of chewing leads to OSCC[8]. However, approximately 20% of oral cancers developed in patients lacking these traditional risk factors [10, 11].

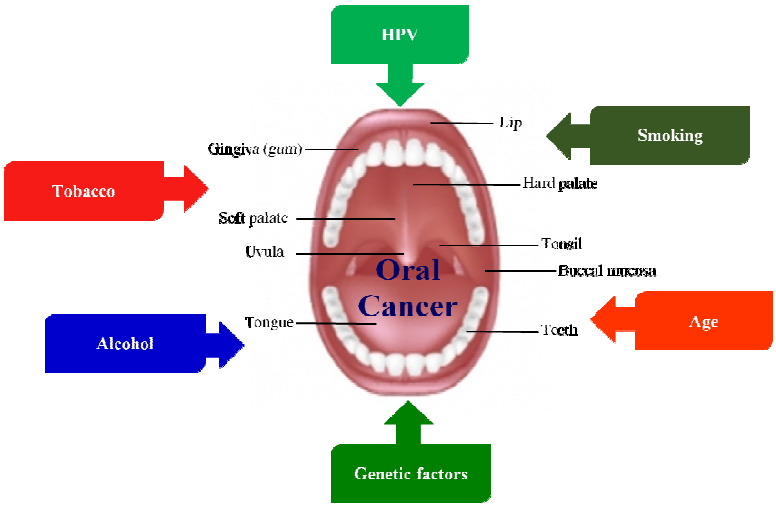

Figure 1: Various risk factors for developing OSCC.

There is increasing evidence that Human Papillomavirus (HPV) is an etiologic agent for developing oral cancer along with tobacco and alcohol addiction [11]. The co-existence of HPV in oropharyngeal and oral carcinoma was first studied [12], and then supported the notion by many studies

[13,14]. HPV is a small, non-enveloped, icosahedral, double-stranded DNA virus with the genome of 8 kb and it belongs to papillomaviridae family [15-18]. HPV genome comprised of three distinct regions: The early region, the late region and URR (upstream regulatory region). The early part contains seven early proteins (E1, E2, E4, E5A, E5B, E6, and E7), the late includes two late proteins (L1, L2). The URR comprised promoter and enhancer DNA sequences that regulate viral replication [19]. There are more than 150 different subtypes of HPV has been reported, and approximately 120 types are entirely sequenced [20].

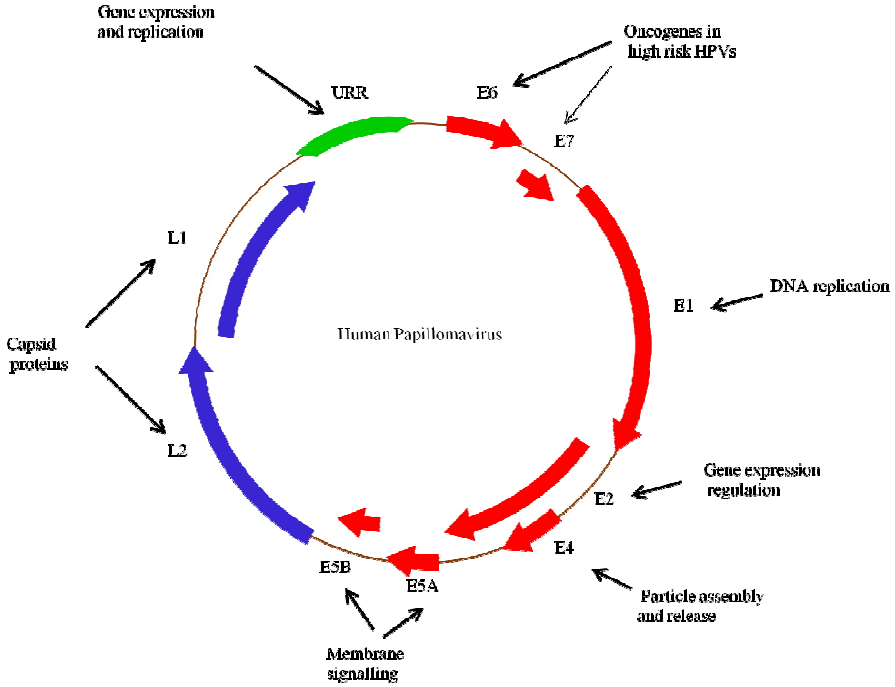

Figure 2: HPV structure and function of viral proteins[111]

More than 10% of human cancers are developed by infection of HPV [21]. On the bases of potential oncogenic HPVs can be categorized into two subsets: low-risk type and high-risk type [3]. It causes both benign and malignant tumors of squamous epithelia [22]. There are 24 types of HPV have been associated with benign lesions of OSCC including 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, and 73, and 12 types with malignant OSCC lesions including 2, 3, 6, 11, 13, 16, 18, 31, 33, 35, 52, and 57 [23]. The most predominant type detected in oral cancer is the HPV type 16[24, 25].

ROLE OF HPV IN OSCC PATHOGENESIS:

HPVs are mostly transmitted by close contact, especially oro-genital sex and high-risk sexual behavior through oral sexual activities such as the number of oral sex partners, and self-inoculation [26, 27].

The buccal mucosa is the most exposed site to chemical carcinogens, infections, and trauma end up with carcinogenesis. The continuous exposure cause abrasion leads the mucosal surface more susceptible to HPV by penetration into the basal cells [28, 29].

The life cycle of HPV initiated through micro lesions in the epithelium and characterized by a special trophism keratinocytes, a specialized differentiation program of the infected squamous epithelial cell. Capsid proteins are linked to viral DNA synthesis and expression in keratinocytes. Usually, infection initiates in the basal and para-basal cells of the squamous epithelium. For a productive cell replication, a suitable micro-environment provided by the changes in the keratinocytes from the basal layer to the surface of the epithelium. .Late and early promoter activation and synthesis of capsid occur when the basal layer is infected by virions released from the stratum corneum and granulosum[30].

The early and late proteins have a different function. E1 initiate viral DNA replication and transcription. E2 regulates DNA replication and viral transcription by controlling ORFs E6 to E7. E4 interacts with cytoskeleton proteins due to altering extracellular matrix cells. E5 interact with cellular proteins and down regulates MHC class I molecules; subtypes E5A and E5B, both have a role in membrane signaling. E6 degrades *p53*, which is tumor suppressor gene, and E7 binds to pRb oncoprotein. L1(major viral capsid proteins) and L2(the minor viral capsid proteins) in the late region, require for viral capsid formation in the final stage of replication [31].

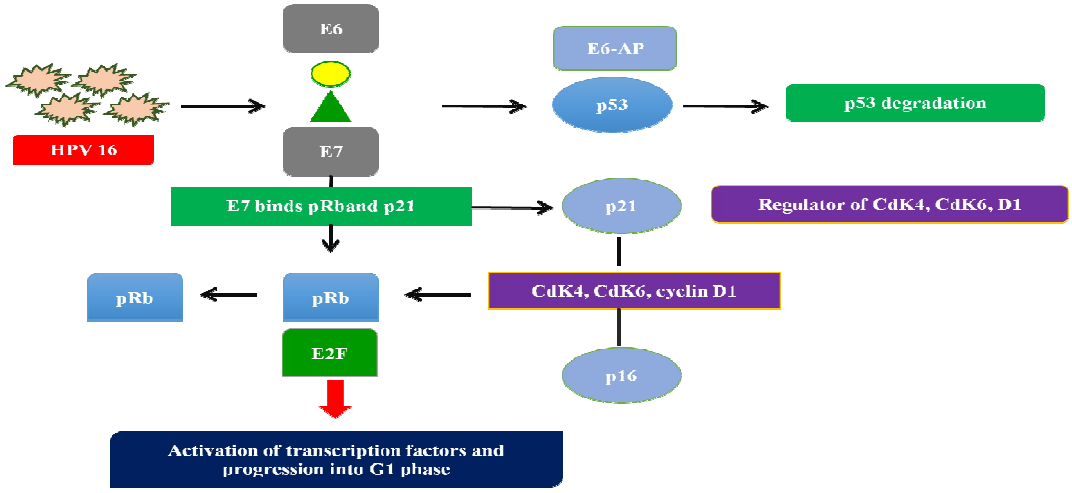

Figure-3: The proposed mechanism of high-risk HPV oncogenes in tumorigenesis

HPV integrates into the host genome at the E1/E2 sequence, hence up regulates E6 and E7 (encoded in an early open reading frame) and increase its tumor igenicity. E2 protein negatively regulates E6 and E7 protein expression encoded by the ORF of the virus. *p53* and *pRb* are the tumour suppressor genes that disrupted by E6 and E7 proteins by altering its host genome leads to cell proliferation and tumour formation.[112]

MATERIALS AND METHODS:

We collected the information using “PubMed” and “Medline” database from 1983 to 2017 and the retrospective reviewhas been done to check the association between HPV and oral cancers and its occurrence at multiple sub-sites in the oral cavity like tongue, buccal mucosa, soft palate, hard palate, lips and gingiva. The keywords searched for the data collection are “HPV”, “OSCC”, “oral cancer”, “HNSCC”, “Indian population”, “Human Papillomavirus”, “cervical cancer” and “prognosis”, etc. Meta-analysis of HPV screening was done by type-specific PCR-based assays or in situ hybridization (ISH) [15, 32-35].

AGE AND GENDER:

Oral cancer is a lethal disorder that occurs mainly in the elder age. However, most of the cases of oral cancer prevalence between 50 and 70 years of age [36], There are certain cases where, occurrence of OSCC identified as early as ten years of age without any type of history[37]. In most of the countries, the mean age of OSCC prevalence is usually between 51-55 years of age (Table-1). Around 17% of the patients are younger below 40 years of age [38]. The younger patients are affected three times more with the high-risk HPV types than elders, due to viral transmission by direct physical contact [39]. Considering all the age groups, men are more affected than women for oral cancer [40].

SITE:

There has been an extensive variation of HPV positive rates in cancers at different sites of the oral region. Approximately 40% of gingivobuccal cancers have tested HPV positive [41]. Previously 43% of tonsilar cancers were found positive for oncogenic subtypes of HPV [42], In contrast, the other study has reported 66% of tonsilar cancer, followed by the base of tongue 34% [43]. The earlier research has shown the prevalence of HPV ranged from 70% in the case of buccal mucosa, 67% in the case of the floor of the mouth and 82% in the case of tongue [44]. The previous study has reported 61% head and neck cancer samples were positive for HPV [45]. The number of studies has indicated HPV 72.5-91% prevalence of HPV in tongue cancers [46]. According to these results, oncogenicity of HPV should be considered as a high risk for tongue cancer. The tongue is the foremost among all sites contributing up to 42% of all oral cavity sites in Japan, Taiwan, Thailand, Yemen, India and Iran [40]. The Indian scenario is showing high occurrence of buccal mucosa SCC, which is due to tobacco chewing at specific buccal site[8].

PREVALENCE OF HPV IN ORAL CANCERS IN INDIA:

Overall 23.5% of prevalence of HPV was reported from the geographic region [47]. In an Indian scenario, petite data is available for HPV induced oral carcinomas. In Western countries, the floor of mouth and tongue are the generic sites for developing squamous cell carcinomas (SCC). The most exposed site observed was buccal mucosa due to tobacco chewing site for OSCC in Indian subset.[48]. The earlier research demonstrated 33.6% prevalence of HPV in OSCC patients in Eastern India [49], in contrast, the studying the same region reported 69% HPV prevalence [50]. As etiology differs, the study in Western India showed 15% HPV prevalence[14]. The incidence of HPV in South India was reported higher as compared to Eastern and Western India. The earlier study identified 16.8% of HPV prevalence in South Indian region[51] whereas, the same region showed 31% and 74% prevalence of HPV [52, 45]. The study performed in western India has shown 0% HPV prevalence in OSCC while 59.6% HPV prevalence found in cervical cancer[10]. A petite study has been performed in the Western region of the India regarding OSCC, as it is the leading neoplasm, the further study need to be validated for the HPV detection.

Table 1: Role of HPV and its association with OSCC- Global incidence rate

References	Year	Country	OSCC Cases	Mean age	Tobacco	Smoking	Alcohol	HPV (+ve)	HPVgenotype	
									HPV 16	HPV 18
15	2016	India	47	-	13	10	5	19	-	-
44	2015	Netherlands	176	63	-	33	-	47	42	1
66	2014	China	312	-	265	272	227	52	13	6
67	2014	Germany	88	-	-	54	64	5	3	-
68	2014	Germany	93	57	-	73	72	25	-	-
69	2014	China	200	81	100	-	71	55	39	15
70	2013	China	400	52	225	222	195	87	20	18
10	2013	India	97	46.7	86	-	-	0	0	0
71	2013	Colombia	67	65.9	-	-	-	33	27	6
72	2013	Mexico	80	63	38	-	33	4	2	2
73	2013	USA	409	-	-	-	-	24	15	2
74	2012	China	103	49	79	90	72	31	16	7
75	2012	Belgium	162	57	-	52	44	65	-	-
76	2012	China	173	51	-	-	-	28	16	12
77	2012	China	65	53	-	-	-	24	-	-
78	2012	Brazil	114	-	36	-	28	22	15	-
3	2012	Malaysia	30	30	6	6	-	1	-	1
79	2012	Hradec-Kralove	24	63	-	9	-	5	4	-
80	2011	Carolina	25	30	-	-	-	11	2	-
81	2011	India	60	55	-	-	-	30	29	-
32	2011	India	34	-	-	-	-	24	10	13
82	2011	France	209	59	-	-	-	22		
83	2009	China	52	-	-	31	21	21	33	16
84	2008	Brazil	29	23	26	-	18	5	-	-
85	2007	Japan	66	-	-	23	24	66	24	-
86	2007	Japan	20	-	-	-	-	20	8	13
12	2006	Italy	63	68.89	-	11	6	24	8	10

[87]	2006	South- Africa	59		-	-	-	7	-	7
[88]	2006	USA	94	56.6	-	-	-	12	10	-
[89]	2005	Belgrade	50	32	-	30	27	32	10	6
[90]	2004	Japan	73	-	42	-	14	54	43	18
[91]	2004	Sweden	110	-	-	-	-	12	9	-
[92]	2004	Venezuela	16	-	-	-	-	8	-	-
[52]	2003	India	42	-	-	-	-	13	9	-
[93]	2003	USA	141	-	114	-	106	29	24	1
[94]	2003	Japan	86	-	-	-	-	30	28	2
[94]	2003	Brazil	46	-	-	-	-	18	-	-
[96]	2003	Japan	103	51.1	-	-	-	51	-	-
[49]	2002	India	110	-	-	-	-	37	25	16
[97]	2002	Taiwan	29	-	19	18	-	24	24	20
[34]	2001	USA	254	54.2	-	-	-	62	62	-
[33]	2001	Venezuela	50	-	-	26	19	30	-	-
[98]	2000	Japan	83	-	-	-	-	47	-	-
[17]	2000	Greece	53	52.7	-	-	-	48	24	11
[51]	1999	India	61	-	-	-	-	17	-	-
[99]	1999	Greece	81	-	-	-	-	40	5	22
[29]	1998	USA	284	-	-	-	-	64	41	2
[100]	1998	Venezuela	50	55	-	-	-	35	13	-
[101]	1998	Korea	42	-	-	-	-	22	15	6
[102]	1998	Sudan	88	-	-	-	-	0	0	0
[103]	1996	USA	64	-	-	-	-	20	11	2
[104]	1996	Netherland	35	-	-	-	-	19	15	-
[105]	1995	South- Africa	66	-	-	-	-	1	0	1
[106]	1995	Japan	77	-	-	-	-	24	23	1
[107]	1993	USA	39	-	-	-	-	7	7	1
[108]	1991	Spain	15	-	-	-	-	0	0	0
[109]	1990	USA	100	-	10	-	-	6	-	-
[110]	1990	Finland	40	-	-	-	-	16	10	1
[35]	1988	Finland	51	-	-	-	-	6	5	-

[OSCC= Oral Squamous Cell Carcinoma, HPV= Human Papillomavirus,- = Unknown]

OTHER CANCERS:

HPV infections have been found in many other cancers. Globally, 99.7% prevalence of HPV has been reported in cervical cancer [53]. The rate of cervical cancer is maximum in South-Eastern Asia with an especially large burden in India, Latin America and sub-Saharan Africa [54]. The previous study showed a prevalence of HPV in 71% of invasive anal cancers [55]. Serological studies have confirmed HPV-16 and HPV-18 are the etiologic agent, and HPV-DNA is detectable in about 40–50% of all penile cancers. Overall, 17.5% HPV prevalence reported in patients with ovarian cancer [56].Approximately 13,000 cases of penile cancer, 35,000 of anal cancer, 8,500 of vulvar cancer and 12,000 of vaginal cancer are attributable to HPV worldwide. Globally, ~ 38,000 cases of head and neck cancer are attributable to HPV, and HPV 16/18 are responsible for 85% of the head and neck carcinoma [57]. The prevalence of HR-HPV in the esophageal squamous cell carcinoma was reported 24.8% in Chinese population[58]. The overall prevalence of HPV was reported 28.0% in laryngeal cancer[59]. A study screened for HPV DNA and found 65-85 %of HPV infection in breast cancers positive[60]. An association between HPV and SCC of the urinary bladder ranging from 0% to 17% in present outcomes [61]. The prevalence of HPV has been reported 37.57% among lung cancer patients in China[62].

FUTURE DIRECTION:

Global survey of HPV infection and oral cancers has been reported. According to an Indian data,20-50% of the HPV prevalence detected in OSCC in the different region of the India[112]. The variation in the data showed, there is a strong recommendation of the new hypothesis to screen the HPV, especially in the western part of the India, as it has found higher number of OSCC patients compared to other region of the India. The number of studies has reported that overall survival significantly higher among HPV-positive patients as compared to patients with HPV-negative tumour[63-65]. If the percentage of the HPV affected patients have known, the prognosis of the patients could be better.

The further study needs more polishing touch, which includes 1) The investigation of the epidemiological profile of oral HPV infection and occurrence of OSCCs, 2) HPV transmission into oral cavity and how it causes oral cancers, 3) To investigate whether the HPV vaccines are biologically effective for preventing infection of oral HPV and related disease, 4) Complete examination is needed on the effects of HPV vaccines for preventing HPV positive oral carcinoma, and 5) analyze the status of HPV whether it should be used in clinical examinations for anti-cancer

treatment throughforthcoming studies. Understanding the etiological importance of HPV in oral carcinoma might be required in prognosis, treatment and prevention of disease.

CONCLUSION:

In the Indian subcontinent, oral cancer is a major personal tragedy and public health problem. The meta-analysis has shown HPV 16 and 18 strain found to be associated with the higher risk of developing OSCC. In view of the relationship between HPV and OSCC, it is must to design additional studies to validate its role in development of oral carcinomas especially the oral cancer patients without the history of tobacco in any form. The future studies should be carried out to screen HPV infection in oral cancer patients in Gujarat region especially as it is the blazing dilemma in the current area.

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