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Review Article

The Burden of Oral Cavity Squamous Cell Carcinoma Associated with High-Risk Human Papillomavirus in Indian Population

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Abstract

Age standardised incidence and mortality rate of Lip and Oral cavity cancer in India is 9.1 & 5.6/100000 population. The low-income group are affected the most due to wide exposure to risk factor such as tobacco chewing and insufficient exposure to newly diagnostic aids resulting in delay in reporting of oral cancer. Geographic variations in incidence rates 2008–12 by subtype is Mouth cancer was the most frequent cancer, with incidence rates elevated in India/Chennai. The most recent figures estimate that 25.6% of all oropharyngeal cancer and 23.5% of Oral cavity squamous cell carcinoma are attributable to HPV infection. In this review article we included histopathologically proven oral cavity squamous cell carcinoma cases and provide type specific prevalence of High-risk HPV. We have included 20 studies of oral cavity squamous cell carcinoma reported from 1995 to 2020, comprising a total of 1948 samples found that 434 (22.2%) sample attributed to HPV Infection. In Inconsistent results regarding HPV Prevalence it has been obtained so for which account for these discrepancies may be related to the site of sample collected or origin, detection method and sample size.

Keywords: High-risk human papillomavirus; Polymerase Chain Reaction (PCR); Oral cavity squamous cell carcinoma; Genotypes; International classification of disease

Abbreviations

HPV: Human Papillomavirus; HR-HPV: High-risk human papillomavirus; OCSCC: Oral Cavity Squamous Cell Carcinoma; OPSCC: Oropharyngeal Squamous Cell Carcinoma; ICD: International Classification of Disease; PCR; Polymerase Chain Reaction; RT PCR: Real-Time Polymerase Chain Reaction

Introduction

Cancer of lip & oral cavity squamous cell carcinoma is the 16th rank and most common malignancy globally represented 355,000 new cases and 177,000 death estimated in 2018 but in India the scenario is much worse having 2nd rank with almost 119,992 (10.4%) new cases and death 72,616 (9.3%) [1,2]. It is generally more prevalent in men than women. Age standardised incidence and mortality rate of Lip and Oral cavity cancer in India is 9.1 & 5.6/100000 population (https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets). The low-income group are affected the most due to wide exposure to risk factor such as tobacco chewing and insufficient exposure to newly diagnostic aids resulting in delay in reporting of oral cancer. Geographic variations in incidence rates 2008–12 by subtype is Mouth cancer was the most frequent cancer, with incidence rates elevated in India/Chennai (7.1) [2]. In head and neck, Human Papillomavirus (HPV) attribute cancer represents 38,000 cases of which 21,000 Oropharyngeal cancer occurring in more developed countries. HPV and infection of the head and neck region is associated with 25% (average) of HNC cases worldwide; nevertheless, this percent contribution varies between anatomical sites (Figure 1) [3]. The most recent figures estimates that 25.6% of all oropharyngeal cancer are attributable to HPV infection with HPV 16 being the most frequent type [4]. And In systematic Review (2005) by Kreimer and colleague, HPV DNA was detected in 23.5% of Oral cavity squamous cell carcinoma [5]. In India (Table 1) approximately 5,900 cases of oral cavity cancer attribute to HPV [4]. The prognosis for patients with Oral Squamous Cell Carcinoma (OSCC) remains poor with 5-year survival rate. On the basis of International Agency for Research on oral cancer recognized that High-Risk Human Papillomavirus (HR-HPV) 16/18 is risk factor for Oropharyngeal carcinoma (posterior one third of tongue, soft palate and tonsils) but Role of HPV Marker in Oral cavity squamous cell carcinoma is somewhat controversial [6]. The oral cavity includes the lip, buccal mucosa, gingiva anterior two 3rd of tongue, floor of the mouth as well as hard palate and is defined as the cancer of lips, mouth and tongue adapted by International Classification of Disease (ICD) coding. The overall prevalence of HPV associated Oral Cavity Squamous Cell Carcinoma (OCSCC) globally varies from 0-30%. Indian studies have reported wide variation in prevalence of HPV associated OCSCC between 15-70% in northeast, eastern and southern part. [7–9]. HPV is a non enveloped, double stranded DNA virus belonging to Papillomaviridae family which infects the basal epithelial cells of mucosa and skin. Nearly 120 types of HPV have been completely sequenced which are broadly divided into “low risk” and “HR” types, based on their oncogenic potential. The viral DNA contains “early” genes encoding 6 proteins, namely, E1, E2, E4 E7, and “late” genes encoding 2 proteins, namely, L1 and L2. E6 and E7 are mainly responsible for the oncogenic activity of

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Table 1: Estimated numbers of HPV infection-attributable cancer cases in 2018, by, cancer subsite, and Gender [4].

Human papillomavirus	New cases (Men)	New cases attributable to HPV (Men)	New cases (Women)	New cases attributable to HPV (women)	Total cases	New cases attributable HPV pathogens
Oropharyngeal carcinoma	110000	34000	26000	8100	140000	42000
Oral cavity cancer	190000	3900	91000	2000	280000	5900

the virus. E6 degrades p53, thereby limiting its activity of suppressing the cell cycle progression and inducing apoptosis. E7 destabilizes Rb protein there by activating the cyclin-dependent kinases at G1 S phase checkpoint of the cell cycle, thus promoting cellular proliferation. Disruption of these major regulatory pathways ultimately leads to cellular transformation and immortalization [10,11].

Methods

We have taken The PubMed, Medline, Scopus, database to perform a comprehensive literature search on high-risk human papillomavirus associated oral cavity squamous cell carcinoma published 1995 to 2019 in India. The search was conducted using both Mesh terminology HPV, oral cavity cancer, oral cavity squamous cell carcinoma, biopsy, Polymerase Chain Reaction (PCR). Reference cited in the collected article were also reviewed. Based on research studies reported HPV proportion in oral cavity squamous cell carcinoma identified. In this review article we included histopathologically proven oral cavity squamous cell carcinoma cases and provide type specific prevalence of High-risk HPV. 20 Oral cancer studies reported during 1995-2019, comprising total of 1948 samples of oral cancer. Method of detection of these studies was Polymerase chain reaction (Conventional PCR, Real-Time PCR) and only three studies have both PCR as well as hybrid capture-2, southeren blot hybridization of L1 PCR product, & EIA [6,12–14].

Proportions of Human papillomavirus associated Oral cavity squamous cell carcinoma in Indian studies (Table 2).

Balram et al 1995, collected 91 patients (50 male & 41 female) histologically proven cases of oral cavity squamous cell carcinoma from regional centre Trivandrum, Kerala and stated that over all prevalence of HPV positivity of the lesions was 73.6% (67/91). The separate infection rate of cancerous oral lesions with HPV 6/11/16 and HPV 18 was 13% (12/91), 20% (18/91), 42% (38/91) and 47% (43/91) respectively. HPV-16 was seen in a higher percentage of the lesions of the lower alveolus and floor of the mouth (75%), while HPV-18 was more commonly seen within the lesions from the buccal mucosa (69%) and combined infection with HPV-16 and HPV-18 was found in 24% of well differentiated SCC lesions, 60% of Moderate differentiated SCC lesions, 19% of Poorly differentiated SCC lesions [7]. Jenice D'Costa, 1998 observed 100 untreated patients, 72 males and 28 females aged between 22 and 83 years (median age of 50 years), histopathological proven cases of oral cavity squamous cell carcinoma from Tata memorial hospital Mumbai. Stated that over all prevalence was 15/100 (15%). In this studies, correlation was not observed between HPV presence and tumour stage, grade and size of the tumour [9]. Kalavatthyjaypalelango et al, observed 60 cases of tongue squamous cell carcinoma aged from 28 to 83 years was seen HPV 16 (29/60) 48.3% and positive correlation of HPV 16 and tongue cancer. In this study anatomical site of lesion (anterior/posterior/base/dorsum of the tongue) is not defined so that it is very difficult to classify OCSCC or OPSCC [28]. Nagpal JK et al, 2002 Studied a total of 110 patients of oral squamous cell carcinoma from AH Regional cancer Research centre Cuttack, Orissa showed the prevalence of HPV 33.6% (37/110) cases of OCSCCs. Majority of the cases from maxillary region (not specified) and subsequent slot-blot analysis and Southern blot hybridization of L-1 PCR products probed with type-specific sequences revealed the presence of HPV-16 in 22.7% (25/110) and HPV-18 in 14.5% (16/110) of the cases [12]. Rolando Herrero et al, 2003 studied histopathogically proven Oral cavity squamous cell carcinoma from multicentre including India (Bangalore, Trivandrum and Chennai) 547 cases of Oral cavity, off these 267 used for detection of HPV by using consensus primer, showed HPV Prevalence was only 8/267 (3.01%) following HPV 16 was 2.7% [6]. Alok Mishra et al, 2006: Studied OCSCC and precancerous lesion from Department of ENT Surgery, Lok Nayak Hospital, New Delhi, showed the prevalence of High-risk HPV infection in oral cancer was 18/66, (27.3%). Among different grade of oral cancer majority 12/66 (18%) of HPV infection was seen in Well Differentiated Squamous Cell Carcinoma (WDSCC) followed by 6% (4/66) in moderate differentiated squamous cell carcinoma while the least positivity 2/66 (3%) in Poorly differentiated squamous cell carcinoma. This showed a significant proportion of oral cancer patients harbour only high risk HPV types 16, which is highest in the well-differentiated squamous cell carcinomas [16].

Paul Sebastian et al 2014, Analysed 22 histopathological confirmed anterior tongue carcinoma patients from Regional cancer centre, Thiruvananthapuram were found, all sample assayed were negative for HPV and subtypes of High-risk [17]. Claudie laprise et al 2016, investigated 250 oral brush biopsy sample for the association between HPV and oral cancer in a case–control study in Kerala, South India. The absence of HPV DNA in all oral cavity cancer cases and controls implies that HPV infection is not an influential risk factor on the burden of oral cancer in this study population from Kerala, South India [18]. Pooja Dalakoti et al, 2019 stated that fifty tissue sample were tested negative for HPV DNA by conventional nested PCR and Taq Man real-time multiplex PCR [19]. Adrija Pathak et al, 2018 studied 6 cases of histologically proven of oral cavity squamous cell carcinoma, were found 1/6 (16.6%) HPV infection [20]. A K Singh et al, 2016, Studied 43 histologically proven cases of OCSCC from RML Institute of medical sciences Lucknow from 2013-2014, were confirmed in only 3/43 (7%). HPV positivity did not find any statistical correlation with age, gender, residence, addiction habit, stage, tumour size, nodal status, tumour grade, and number of sexual contacts [25].

Rupesh Kumar et al, 2015, analysed hr-HPV status in oral cavity cancers alone from Dr. Bhubaneswar Borooah Cancer Institute (BBCI), Regional Cancer Centre, Guwahati, India were found 24/88 (72.7%) and compared with smoking, tobacco, alcohol, betel nut use and found that there was significant association of hr-HPV positivity and alcohol consumption (OR = 2.98; 95% CI. 0.95–9.43, p = 0.03) [21]. Kulkarni SS et al, 2011Studied 34 Oral rinses sample tested for High-risk HPV associated Oral cavity squamous cell carcinoma were

Table 2: Studies on HPV Prevalence among cases of oral cavity cancer in India.

S. no	Ref Study	Sample	Method of detection & Primer set	No of tested sample	Overall HPV Positivity	Type specific Genotypes
1	Balram et al. [7]	Fresh frozen and paraffin-embedded tissue	PCR-MY09/MY11 (L1) GP5+/GP6+ (L1) /GP17+/GP18+ (L1)	91	(67) 73.6	HPV18 (47.3%) HPV16 (41.8%) HPV11 (19.8%) HPV6 (14.3%)
2	D'Costa et al. [9]	Fresh frozen tissue	MY09/MY11 (L1) SBH (6,11,16,18,33)	100	(15) 15.2	HPV16 (15.2%)
3	Kalavathy Jayapal Elango et al. [15]	Tissue biopsy	MY09/MY11(L1) GP5+/GP6+ (L1) PCR	60	(29) 48.3	HPV16 (48.3%)
4	Nagpal JK et al. [12]	Fresh frozen and paraffin embedded tissue	MY09/MY11 (L1)-PCR/ MY09/MY11 (L1)-PCR/	110	(37) 33.6	HPV16 (22.7%) HPV18 (14.5%)
5	Herrero et al. [6]	Oral exfoliated cells, fresh tissue, Blood	GP5+/GP6+ (L1) Hybridization with EIA oligonucleotide probes (2. 6. 11. 16. 18. 31. 33. 35. 39. 40. 42. 43. 44. 45. 51. 52. 56. 58. 59. 66. 68)	262	(8) 3.01	HPV16 (2.7%)
6	Mishra et al. [16]	Fresh frozen	MY09/MY11 (L1) Amplification with TS primers (16. 18)	66	(18) 27.3	HPV 16 (27.3%)
7	Sebastian et al. [17]	Tissue biopsy	PCR, LBA (HPV 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84)	22	0	0
8	Pooja Dalakoti et al. [19]	Tissue (Not defined)	PGMY09/11/GP51/61-PCR Conventional nested PCR and Taq Man-based Realtime Multiplex PCR	50	0	0
9	Adrija Pathak et al. [20]	Paraffin embedded tissue	PCR	6	(1) 16.6%	HPV16
10	Abhinav Arun sonker et al.	Fresh tissue	PCR	43	(3) 7.0	Unknown Genotypes
11	Rupesh Kumar et al. [21]	Fresh frozen	PCR-GP-E6-3F GP-E6-6B	86	(24) 27.9%	HPV16 (22%) HPV18 (6.9%)
12	Suyamindra S Kulkarni et al. [22]	Saliva rinse	PCR	34	(24) 70.6%	HPV16 (41.7%) HPV18 (54.2%)
13	Priya Koppikar et al. [8]	Tissue	PCR	83	(28) 34%	Unknown Genotypes
14	Ajaykumar Chaudhary et al. [13]	Oral cells Tissue	Hybrid capture-2 PCR	222	(32) 52.5%	Unknown genotypes
15	Tarik Gheit et al. [23]	Paraffin-embedded tissue	PCR	252	(30)11.9%	HPV16 (9.1%) Other HPV (2.8%)
16	Raghu Dhanapal et al. [24]	Tissue	PCR	14	(3) 21.4%	HPV18 (21.4%)
17	Abhishek kumarsingh et al. [25]	Paraffin-embedded tissue	PCR	43	(3) 7%	Unknown
18	Gaurav Verma et al. [26]	Paraffin-embedded tissue	MY09/MY11(L1) GP5+/GP6+(L1	102	(18) 17.6%	HPV 16 (29%) HPV 18 (16.1%)
19	Vinayak Palve et al. [27]	Tissue	PCR Digital PCR QPCR	136 106	(59) 43% (35) 33%	HPV16 (43%) HPV16 (30%) HPV18 (18%)
20	Rajesh Deepa et al.	Tissue	GP5+/GP6+(L1) PCR	60	(0) 0%	0%

found 24/34 (70.6% 0) HPV positivity followed by HPV 16 (41.7%) and HPV 18 (54.2%) and HPV 16/18 multiple infection in 4.18% [22]. Priya Koppikar et al, 2004, studied 83 oral cavity cancer from Tata memorial hospital parel Mumbai, describes the frequency of HPV infection were 28/83 (34%) [8]. Ajay Kumar Chaudhary et al 2010, describes Oral cavity squamous cell carcinoma associated with HPV by using both techniques PCR as well as Hybrid capture were 32/222 (14.4%). In this study anatomical site tongue and hard palate were not included in the oral cavity squamous cell carcinoma [13]. Tarik Gheit et al 2017, Studied 252 cases of OCSCC from MGIMS, Sewagram Maharashtra, were found of the 30 cases of HR-HPV (11.9%) followed by HPV 16 (9.0%) [23]. Raghu Dhanpal et al,2016, Analysed HPV in 14 histologically confirmed cases of OCSCCs, were found only 3 cases of HPV 18 Genotype (21.4%) [24]. Abhishek Kumar Singh et al, 2016, studied 43 Clinically & histologically proven cases of OCSCC from 2013-2014, Department of Surgery, KGMC Lucknow, were

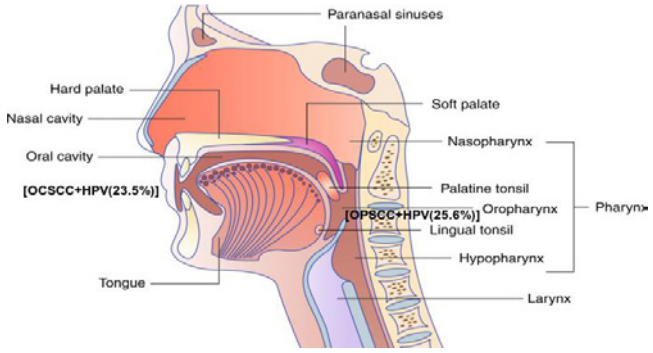

Figure 1: Distribution of human papillomavirus-associated between anatomical sites of OCSCCs and OPSCCs with 23.5% and 25.6%.

found only 3/43 (7%) HPV positivity and did not find any statistical correlation with age, gender, habit, stage, grade and sexual contact [25]. Gaurav Verma et al, 2016, examined 102 tissue biopsy clinically and histologically OCSCC constituted by Buccal mucosa, Alveolar/ gingival. Vestibular, Retromolar space, Floor of the Mouth, and anterior tongue showed HPV positivity of 17.6% (18/102) and type specific HPV 16 positivity of 29% (9/31) and HPV 18, 16% (5/31). But did not display any specific distribution differences with respect to the clinical stage of histopathological grade [26]. Vinayak palve et al, 2018: Quantitative PCR (qPCR) was performed on oral cavity tumors (n = 106) proven cases were indicated that 33% of tumours (35 of 106) were positive for HPV DNA. Although we found a higher incidence of HPV16 (30%) and HPV 18 (18% [19 of 106]) type. When the results from all of the assays (p16 IHC, HPV DNA, and HPV RNA) were combined, we found that 6% to 48% of the tumours were positive in various assays combined with PCR [27]. Deepa Rajesh et al, 2018, tested a total of 60 DNA samples and failed to find a HPV-positive reaction in any. Approximately, 20% of the samples were randomly chosen and retested. The result of the second test was 100% concordant with the first test.

Discussion

The wide variation in detection rates of Oral HPV infection has been found in studies. In most of the studies, the exact anatomical site for sample of oral mucosa is not mentioned and thus the origin of HPV infection whether oral or oropharyngeal is nearly impossible to trace. Anatomically, the oral cavity and oropharynx are separated from each other at junction of the hard and soft palate, and by the circumvallate papillae. In this review article we have included only oral cavity squamous cell carcinoma and excluded base of the tongue, tonsil and soft palate cases (OPSCC). Sample are obtained mostly tissue biopsy (FFPE, Frozen tissue) and Oral rinses. All off the studies used polymerase chain reaction techniques that uses the primer which is targeted to the viral capsid L1 gene. The commonly used L1 consequences primers are PGMY09/11, and GP5+/6+. The prevalence of HR-HPV in cancer of the oral cavity shows high variability, we have included 20 oral cavity squamous cell carcinoma studies reported from 1995 to 2020, comprising a total of 1948 samples found that 434 (22.2%) sample attributed to HPV Infection.HPV prevalence in Squamous Cell Carcinomas (SCC) of the oral cavity in India from Southern region indicated no HPV infection [29]. Whereas the prevalence of HPV in Oral cavity squamous cell carcinoma has been reported to be different across the various regions with 6% in western region [8], 33.6% in the Eastern region [12], and 28%-43.5% in North-eastern region [21].The higher HPV prevalence in North-east India as compared to other regions of subcontinent is very likely due to the relatively higher consumption of tobacco products [30]. Some Studies indicate that the most likely explanation for the origin of this distinct form of Oral cavity cancer associated with HPV is a sexually acquired Oral HPV infection that is not cleared, persists and evolve into a neoplastic lesion.

Conclusion

In Inconsistent results regarding HPV Prevalence it has been obtained so for which account for these discrepancies may be related to the site of sample collected or origin, detection method and sample size. Many of the studies are limited sample size. Therefore, clear estimate of the prevalence of High-risk HPV genotypes in OCSCC lesions is not available in south India population. Specific anatomical site of the oral cavity must be considered and classified in order to avoid any independent results. Virus positivity often determined by viral DNA detection through PCR techniques, but this approach might indicate a transient infection that is unrelated to oral carcinogenesis. Although there still is a certain skepticism about association of HPV and OCSCC. Solid clinical data are urgently needed to evaluate the E6/E7 m RNA, Hybrid capture-2 and p16ink4a, confirm the diagnosis of High-risk HPV associated Oral cavity squamous cell carcinoma in South Indian Population.

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