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Association of uncommon sexual practices with Human Papilloma Virus in Head and Neck Squamous Cell Carcinoma

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Abstract
Head and Neck Squamous Cell Carcinoma (HNSCC) are the most common cancers in India. Association of uncommon sexual practices, clinical presentations & pathology of Human Papilloma Virus (HPV) infection in 50 HNSCC patients were assessed and compared with 50 patients having benign Head & Neck lesions in a prospective study. Punch biopsy from the lesion in all the patients was used for confirmation of the diagnosis and HPV DNA isolation by PCR assay.
All HNSCC patients had poor oral hygiene and 28% of them had uncommon sexual practices. 88% of patients were smokers while 68% were alcoholic. Out of 21 HPV positive HNSCC patients 9 (42%) had history of uncommon sexual practices as compared to 2 out of 29 (6.8%) in HPV negative HNSCC patients. Association of HPV in HNSCC was 42% as compared to 8% in benign lesions (p=0.001). 21 of 50 HNSCC patients tested positive for HPV, of which 20 were HPV 16, and 1 was HPV 18 whereas only 4 out of 50 patients with benign lesions were HPV positive, all of which were HPV 16.
It is concluded that the association of HPV in HNSCC was significantly high and significant number of HPV positive HNSCC patients were associated with uncommon sexual practices as compared to HPV negative HNSCC. A larger study is recommended to further confirm this high association of HPV in malignancy and defining role of vaccination programme for primary prevention of HNSCC.
Keywords: *Human Papilloma Virus; Head and Neck Squamous Cell Carcinoma; Aetiology; Prevention; Association.*

Introduction

Human Papilloma Virus (HPV) 16 and 18 are well established etiological agents in cervical cancers, and an effective vaccination program has also been developed for prevention of carcinoma cervix. Recent epidemiology and molecular data has also suggested that chronic HPV infection of the upper airway may promote head and neck tumorigenesis [1] [2]. Oral squamous cell carcinoma is the most common malignancy in India [3]. Although excessive tobacco and alcohol use are important risk factors for head and neck squamous cell carcinoma(HNSCC), epidemiologic studies suggest that more than 25% of HNSCC are now caused by HPV, the prevalence of which is increasing, while that of tobacco and alcohol-induced cancer is declining. Since the survival of HPV-positive HNSCC patients is notably better than that of HPV-negative HNSCC patients, it highlights the need to understand the oral HPV infections causing these cancers. However, only few studies have been done to prove the association of HPV in HNSCC, which may form

the basis for vaccination program in prevention of HNSCC in developing countries.

Methodology

In this prospective study, total of 100 consecutive patients presenting with growth/lesion in head & neck, at S.P Medical College & P.B.M Hospital Bikaner, from period of April2015 to September 2015 were randomized into two groups of 50 patients each. Group I consisted of 50 patients of head & neck cancers, while group II comprised of 50 patients having any benign lesion in head and neck. Patients who had received radiotherapy or chemotherapy in the past due to any cause, or head and neck cancer other than squamous cell histology were excluded from the study. Informed written consent from each patient was taken before being made part of the study. Biopsy samples of all patients were analyzed for the presence of HPV subtypes 16 & 18 DNA. Detection of Human Papilloma Virus in the biopsy sample was carried out by Polymerase Chain Reaction (PCR) study in the Department of Veterinary Microbiology and Animal Biotechnology, College of Veterinary and Animal Science, Bikaner, Rajasthan.

Association of HPV in HNSCC was assessed and compared between the two groups. Association between abnormal sexual practices like multiple sexual partner and oral sex with human papilloma virus and head and neck squamous cell cancer was studied. HPV positive HNSCC were compared with HPV negative HNSCC to see if there was any difference in their clinical presentation. The data were entered and analyzed in SPSS version 20 (IBM Inc) and results were drawn. As the data was not normally distributed hence statistical significance was determined by non-parametric Mann-Whitney U test and Kruskal-wallis test. Confidence interval (CI) was higher than 95% and $p<0.05$ was considered statistically significant.

Results

1) 11 out of 50 HNSCC patients (22%) admitted to having abnormal sexual practices like multiple sexual partner and oral sex. Among HPV positive patients, 9 out of 21 (42%) had history of uncommon sexual practices as compared to 2 out of 29 (6.8%) HPV negative HNSCC patients.
2) Association of HPV in HNSCC patients (case group) was 42% with 21 out of 50 patients of HNSCC being HPV positive (Fig 1), whereas association of HPV in control group with benign diseases was 8% with 4 out of 50 positive for HPV.
3) HPV subtypes 16 and 18 DNA were detected in 21 (42%) of 50 patients of HNSCC by PCR assay. HPV 16 was the predominant subtype present in 20 (95.2%) while HPV 18 was detected only in 1 (4.7%) patient. (Table 1)
4) All the 50 HNSCC patients had poor oral hygiene and 14(28%) had uncommon sexual activity like multiple sexual partners and oral sex. 44(88%) patients were tobacco smokers / chewers and 34(68%) had history of regular alcohol intake.
5) Base of tongue 16(32%) followed by tonsil 15(30%) were the two most common sites of HNSCC in this study.

Fig 1 HPV 16 PCR Assay of HNSCC Cases 1-27 & 28-50

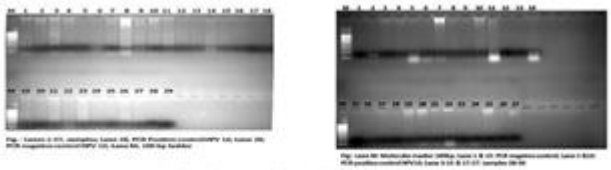

Fig 1 Cases of HNSCC 1-27 & 28-50

Table 1: HPV status in HNSCC patients

HPV Status		Number of patients	Total
HPV Negative		29 (58%)	29
HPV Positive	HPV 16	20 (40%)	21
	HPV 18	1 (2%)	
Total			50

Table 2: Prevalence of HPV in various western studies.

Studies	Total number of patients	HPV positive patients	Prevalence of HPV
Hammarsted et al[4]	203	99	49%
Hong et al[5]	489	230	47%
Chaturvedi et al[6]	271	120	44.1%
Present study	50	21	42%
Fakhry et al[13]	96	38	40%
Gan et al[14]	200	55	27.5%
Gillison et al[8]	253	55	22%
Benjamin et al[7]	167	25	15%

Table 3: Prevalence of HPV in various Indian studies.

Studies	Total number of patients	HPV positive patients	Prevalence of HPV
Balaram et al[9]	91	67	74%
Elango et al[10]	60	29	48.3%
Present study	50	21	42%
Nagpal et al[15]	110	37	33.6%
Barwad et al[12]	111	36	32.4%
Koppikar et al[11]	102	32	31%

Table 4: Prevalence of HPV in cases and control

Study	Prevalence of HPV in cases	Prevalence of HPV in control
D'Souza et al[17]	37%	6%
Gan et al[14]	27.5%	2.9%
Smith et al[16]	26%	7%
Present study	42%	8%
Elango et al[10]	48.3%	0%
Koppikar et al[11]	31%	5%

Discussion

Although Tobacco and Alcohol are the main risk factors causing more than 75% of oral cancers in developed countries but there are 20% of HNSCC patients who are not exposed to these traditional risk factors and therefore, other risk factors have been proposed in them. HPV 16 and HPV 18 have been extensively studied, as possible etiological agents. The prevalence of HPV in HNSCC has been increasing in the west and is thought to be probably related to their sexual behavior. The role of HPV as an etiologic factor for HNSCC has been repeatedly proven in various studies worldwide but interestingly few studies have shown that HPV infection is also a significant factor in India as tobacco and alcoholism have been thought to be the main etiological factors in this country.

The route of transmission of HPV is sexual, more specifically oral sex and having multiple sexual partners. In our study out of 21 HPV positive HNSCC patients 9 (42%) gave history of such sexual practices whereas among 29 HPV negative HNSCC patients only 2 (6.8%) patients admitted to have these practices (p=0.003). Smith et al said that HPV positive HNSCC is associated with oral-genital sexual practice.[16] D'Souza et al said, a high lifetime number of vaginal-sex partners (26 or more) as was a high lifetime number of oral-sex partners (6 or more) was associated with oropharyngeal cancer.[17] Gillison et al showed that in his study out of 92 HPV positive HNSCC patients 93% patients had multiple oral sex partners. Association increased with increasing number of oral sex partners. [18]

21 out of 50 HNSCC patients were found to contain HPV DNA by PCR assay (Fig 1) hence HPV association in our study was 42%. These were either HPV16 or HPV18 as we did not look for other subtypes. HPV 16 was the major subtype being present in 20 of 21 (95.2%) cases, whereas HPV 18 was detected in 1 of 21 (4.8%) of HPV positive cases (Table 1). As compared to HNSCC patients, only 4 patients from control group (Benign lesions of Head and Neck) were found to contain HPV DNA and all 4 had HPV 16. Thus the association of HPV in benign diseases of head and neck was 8%. This difference in association of HPV in HNSCC and control group was found to be statistically highly significant (p=0.01).

SCC of Tonsil had higher prevalence of HPV. Hammarsted et al and Hong et al studied on Tonsillar SCC only and they detected HPV in 49% and 47% of their patients respectively.[4][5] Similarly Chaturvedi et al also studied exclusively in Oropharyngeal squamous cell carcinoma and the prevalence of HPV in their study was 44.1%.[6] On the other hand Benjamin et al had low prevalence of HPV in their study and the reason for this may be because apart from Oral cavity and Oropharynx he also selected patients of SCC of Esophagus, Hypopharynx and Pyriform sinus where prevalence of HPV is low. He found that the prevalence of HPV was maximum in tonsillar fossa i.e. 60%, whereas none of the patients of

SCC from Esophagus, Hypopharynx and Pyriform sinus was positive for HPV DNA.[7] Similarly Gilison[8] et al also studied on patients with SCC of Larynx, Hypopharynx and Nasopharynx apart from Oral cavity and Oropharynx. He also suggested that the prevalence of HPV was more in oropharyngeal SCC. He detected HPV in 57% of Oropharyngeal SCC and 94% in Tonsillar SCC. Prevalence of HPV in various western studies is given in Table 2.

Studies from various regions in India show wide geographical variation in the prevalence of HPV ranging from 31% to 74%. South Indian HNSCC patients were found to have maximum HPV prevalence, 74% in the study by Balaram et al[9] and 48.3% by Elango et al.[10] The reason for such a high prevalence of HPV in the study done by Balaram et al is because he detected HPV 6 and HPV 11 also apart from oncogenic subtypes HPV 16 and HPV 18. The prevalence of HPV 16 was 42% and HPV 18 was 47% in his study which is similar to present study.[9] Koppikar et al showed the prevalence of HPV was 31% but prevalence of oncogenic HPV i.e. HPV 16 & 18 was less.[11] Present study shows that the association of HPV is 42%. This present study was done in a Tertiary care centre in north western India and another study was done in north India at PGIMER Chandigarh by Barwad et al. It was based on FNAC from involved lymph nodes and the prevalence of HPV was 32.4%. [12] Prevalence of HPV in various Indian studies is given in Table 3.

Many researchers have compared the prevalence of HPV in benign lesions of head and neck to prevalence of HPV in HNSCC. They found out that as compared to control, the cases are more significantly associated with HPV infection. This further strengthen the idea of HPV as an etiological factor for HNSCC. Our study proves that association of HPV in HNSCC is significantly more than association of HPV in control. This association is in concordance with the literature.[10],[11],[14],[16],[17] (Table 4).

Age of the HNSCC patients in our study ranged from 35 years to 75 years. 34 (68%) of the patients were in the age group 51-70 years. Mean age of patients was 55.32±10.20. 44 (88%) patients were males forming male to female ratio of 7.3:1. Majority of patients (80%) were from oropharynx. Most common presenting complaint was Odynophagia (80%). 50% of patients complained of pain and 8% complained of ulcer as their chief presenting complaint. Majority of patients were advanced when diagnosed as 35 (70%) patients belonged to stage III and IV in our study population. Out of 50 HNSCC patients 44 (88%) were smokers and 34 (68%) were alcoholic. All the patients had poor oral hygiene. HPV positive HNSCC patients were compared with HPV negative HNSCC patients for various clinical presentation and pathology. HPV positive HNSCC and HPV negative HNSCC were found to be similar with respect to age at presentation and there was no anatomical site predilection for HPV positive HNSCC in our study.

Conclusion

It is concluded that the association of HPV in HNSCC was significantly high and significant number of HPV positive HNSCC patients were associated with uncommon sexual practices as compared to HPV negative HNSCC. HPV 16 & 18 in HNSCC was associated in 42% as compared to 8% in benign head & neck lesions in western India which is comparable to the available global literature. A larger study is required to further clarify any predilection of HPV infection for a particular anatomical site, specific clinical features, pathological features and outcome of the HPV positive HNSCC patients. This high association if confirmed by other studies may form the basis for starting a vaccination program for primary prevention of HNSCC.

References

1. Franceschi S, Talamini R, Barra S, Baron AE, Negri E, Bidoli E, et al. Smoking and drinking in relation to cancers of the oral cavity, pharynx, larynx and esophagus in northern Italy. Cancer Res1990;50:6502-7.

2. Mashberg A, Boffetta P, Winkelman R, Garfinkel L. Tobacco smoking, alcohol drinking and cancer of the oral cavity and oropharynx among U.S. veterans. Cancer 1993;72:1369-75.
3. Nair MK, Gangadharan P, and Padmanabhan TK. Cancer in Kerala. In: A. Gjogora and M. Ismail (eds) Cancer prevention in developing countries. Pergamon New York 1986;65-7.
4. Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J et al. HumaSn papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int. J. Cancer 2006;119: 2620–3.
5. Hong AM, Martin A, Armstrong BK, Lee CS, Jones D, Chatfield MD et al. Human papillomavirus modifies the prognostic significance of T stage and possibly N stage in tonsillarcancer.Ann Oncol 2013;24:215-9.
6. Chaturvedi AK, Eric AE, Ruth MP, Brenda YH, Weihong X, Esther K et al. Human Papillomavirus and Rising Oropharyngeal Cancer Indcidence in the United States. J ClinOncol 2011;29:4294-301.
7. Benjamin P, Nathan C, Tamara OM, Yuan X, Sharon PW. Human papillomavirus (HPV) in head and neck cancer. Cancer 1997;79(3):595-604.
8. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Li Wu et al. Evidence for a Casual Association Between Human Pappilomavirus and a subset of Head and Neck Cancers.JNatl Can Inst 2000;92(9):709-20.
9. Balaram P, Nalinakumari KR, Abraham E, Balan A, Hareendran NK, Bernard HU et al. Human papillomavirus in 91 oral cancers from Indian Betal quid chewers-high prevalence and multiplicity of infections. Int. J. cancer 1995;61:450-4.
10. Elango KJ, Suresh A, Erode EM, Subhadradevi L, Ravindran HK, Iyer SK et al. Role of Human Papilloma Virus in Oral Tongue Squamous Cell Carcinoma. Asian Pacific J Cancer Prev 2011;12:889-96.
11. Koppikar P, deVilliers EM, Mulherkar R. Identification of human papillomaviruses in tumors of the oral cavity in an Indian community. Int. J. Cancer 2005;113:946–50.
12. Barwad, A., Sood, S., Gupta, N., Rajwanshi, A., Panda, N. and Srinivasan, R. Human papilloma virus associated head and neck cancer: A PCR based study. Diagn. Cytopathol 2012;40:893–7.
13. Fakhry C, Westra WH, Li S, Anthony C, Ridge JA, Pinto H et al. Improved survival of patients with Human papillomavirus positive Head and Neck squamous cell carcinoma in a prospective clinical trial. J Natl cancer Inst 2008;100:261-9.
14. Gan LL, Zhang H, Guo JH, Fan MW. *Prevalence of human papillomavirus infection in oral squamous cell carcinoma* [*: a case-control study in Wuhan, China. Asian Pac J Cancer Prev. 2014;15 (14): 5861-5.*
15. Nagpal JK, Patnaik S, Das BR. Prevalence of high-risk human papillomavirus types and its association with p53 codon 72 polymorphism in tobacco addicted oral squamous cell carcinoma (oscc) patients of eastern india. Int. J. Cancer 2002:97:649–53.
16. Smith EM, Rubenstein LM, Haugen TH, Pawlita M, Turek LP. Complex etiology underlies risk and survival in head and neck cancer human papillomavirus, tobacco, and alcohol: a case for multifactor disease. J Oncol. 2012; 571862.
17. [D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM et al. Case- control study of Human

Papillomavirus and Oropharyngeal cancer. N ENGL J MED 2007;356:1944-56.

18. Gillison ML, D'Souza G, Westra W, Suger E, Xiao W, Begum S et al. Distinct risk factor profiles for Human Papillomavirus type 16- positive and human papillomavirus 16 negative Head and Neck cancers. J Natl Cancer Inst 2008;100:407-20.