ORIGINAL ARTICLE

FREQUENCY OF HUMAN PAPILLOMAVIRUS (HPV) WITH HEAD AND NECK CANCER: A SINGLE ONCOLOGY CENTER EXPERIENCE FROM KARACHI, PAKISTAN

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ABSTRACT

Background: The global incidence of head and neck cancer (HNC) is escalating. This research aimed to analyze the prevalence of human papillomavirus (HPV) in patients suffering from HNC.

Material and Methods: We conducted a forward-looking observational study at the Department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi, Pakistan, from January through September 2021. The study included patients above 15 years old, of any gender, with a confirmed diagnosis of HNC. HPV presence was determined via Polymerase Chain Reaction (PCR) for each patient. Socio-demographic data was collected using a pre-established proforma, and data analysis was executed using SPSS version 23.

Results: A total of 305 patients with HCNs were included. The mean age of patients was 46.46±12.58 years. The most common site of HNCs was found to be oral cavity (82%) and squamous cell carcinoma was the most common histological type (94.1%). Of 305 HNCs, 134 had tumor size of T3, 200 had nodal status of N1, 263 had grade II and only had metastasis (2.3%). Out of 305 patients with HNCs, 39 cases were found to be HPV positive. Statistically significant differences were observed between HPV and gender (p=0.048), naswar (p=0.018), betel nut consumption (p=0.020) and site of tumor (p=0.038).

Conclusion: The presence of HPV presents distinctive HNC characteristics and may serve as a survival indicator for these types of malignancies. Given the inherent genetic and socio-demographic disparities, along with differences in sexual behaviors and harmful lifestyle habits, the need for sex and race-specific clinical trials for HNC treatment is becoming increasingly evident.

Key Words: Cancer, Head and neck cancer, Human papillomavirus, Oral cavity cancer

BACKGROUND

Head and neck cancer (HNC) encapsulates a diverse array of neoplasms located in the head and neck region. As per the World Health Organization (WHO), HNCs can be classified based on site, etiology, and histology.[1] Squamous cell carcinoma, the most common type of HNC, ranks as the sixth most prevalent cancer in Pakistan.[2] Etiologically, HNCs can be categorized into two groups: Human papillomavirus (HPV) positive and HPV negative cancers.[3]

Existing data concerning HPV infection prevalence in Pakistan is not substantial or conclusive. Previous research provides conflicting perspectives on the extent of HPV infection among HNC patients. In the context of cervical HPV detection, studies report a prevalence rate ranging from 18% to 98%.[4-6] Another study specifically examined HPV prevalence in head and neck squamous cell cancers (HNSCC) across variables such as sex, race, tumor site, and HPV detection method. The findings showed that overall HPV prevalence in HNSCC was 47.4%, with higher rates observed in oropharyngeal tumors compared to non-oropharyngeal tumors. HPV positivity was also found to be more prevalent among men than women and white individuals compared to non-white individuals. Additionally, HPV detection rates varied depending on the method used, with p16 immunohistochemistry demonstrating the highest sensitivity and specificity. This study shed crucial light on the epidemiology of HPV-related HNSCC, underscoring the necessity for prevention and treatment strategies tailored to sex, race, and tumor site.[7]

HPV, a member of the Papillomaviradae family, is a non-enveloped, double-stranded DNA virus. Its size ranges from 52 to 55 nm, composed of seventy-two pentameric capsomers.[8] Although its role in causing cervical cancer is well-established, accounting for 5% of all cancers and nearly 113,400 cases annually, the connection between HPV and other cancers like HNC

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remains understudied.9 HPV-driven cancer stems from persistent HPV infections known to induce dysplastic and neoplastic changes.[10]

With limited research focused on HPV infection in HNCs, the need for further investigation is clear. This study, therefore, aims to evaluate the frequency of HPV-driven cancers, characterize the tumors associated with HPV infection, and understand the correlation between socio-demographic factors and HPV infection

MATERIAL AND METHODS

It was a prospective observational study conducted at the department of medical oncology, Jinnah postgraduate medical center, Karachi, Pakistan from January to September 2021. Sample size of 305 was estimated using proportion of HPV as 31.1% [11,12], taking margin of error as 5.2% and 95% confidence level. Patients of age more than 15 years of either gender with confirmed diagnosis of HNCs were included. Patients with non-HPV driven origins, patients with inoperable disease and palliative care cases were excluded from the study. Non-random probability consecutive sampling technique was applied for sample selection.

Ethical approval (ERC NO.F.2-81/2021-GENL/5845/JPMC) was taken from ERC of Jinnah postgraduate medical center, Karachi, Pakistan. Informed consent was obtained from all the eligible participants before collecting data. In this study, we used the p16 immunohistochemistry test, a surrogate marker for HPV infection, on tissue biopsies for HPV detection. This involved staining the tissues for the p16 protein, which is often overexpressed in HPV-related cancers. The test results were interpreted by experienced pathologists, who determined the presence of HPV based on the degree and pattern of staining. p16 positivity or negativity was determined by the intensity and extent of staining observed under the microscope. A sample was considered p16 positive when there was a strong and diffuse staining in the nucleus and/or cytoplasm of the cells in the tissue section. In the case of HNCs, p16 positivity was defined as staining in 70% or more of the tumor cells. Data on socio-demographics was collected on pre-designed proforma including sociodemographic, addiction, family history of cancer, smoking, tobacco, naswar, betel nut, betel leaf, alcohol, and tumor characteristics.

SPSS version 23 was used to analyze data. Mean and standard deviation (SD) were reported for quantitative data. Frequency and percentage were reported for categorical data. Association between HPV and socio-demographics was assessed using Chi-square test. A p-value<=0.05 was considered as statistically significant.

RESULTS

The study included 305 patients with HNCs from tertiary care hospitals of Karachi, Pakistan over a period of six months. The mean of the study participants was 46.46±12.58 years (range: 16-76 years). There were 227 males and 78 females diagnosed with HNCs. Most of the study participants were Urdu speaking (47.9%), urban area residents (72.1%), and illiterate (43.6%). The majority of participants (61.3%) in the study have a monthly family income less than 15,000 PKR, while 35.4% earn between 15,000-30,000 PKR and only a small fraction (3.3%) have income exceeding 30,000 PKR. In the study, 47 (15.4%) of participants reported a family history of any type of cancer, while the majority, 258 (83.6%), indicated no such history. A small proportion of the participants, 14 (4.6%), reported a family history of head and neck cancers (HNCs), while the vast majority, 291 (95.4%), had no family history of HNCs. There were 85 smokers and 106 were betel nut consumers. Almost 15.4% had a positive family history of any cancer and 4.6% had a positive family history of HNCs. The most common site of HNCs was oral cavity (82%), followed by larynx (7.9%). SSC was present in the majority of the cases (94.1%) and 5.9% had adenocarcinoma. Of 305 HNCs, 134 had tumor size as T3, 200 had nodal status as N1, 263 had grade II of tumor and only had metastasis (2.3%) (Table-I).

Out of 305 patients with HNCs, 39 (12.8%) cases were HPV positive and 266 cases were HPV negative. HPV was positive in 24 males (61.5%) and 15 females (38.5%). Statistically significant difference was observed between HPV and gender (p=0.048). We found HPV was positive in 2 naswar users (5.1%) and 37 non-naswar users. There was a statistically significant difference observed between HPV positivity and naswar consumption (p=0.018). Further, we found 20 HPV positive patients were betel nut consumers and 19 were non-betel nut consumers. We found a

statistically significant difference between HPV positivity and betel nut consumption (p=0.020). We observed HPV was positive in 36 patients with oral cavity tumors (92.3%), 1 patient with larynx (2.6%) and 2 patients with oropharynx (5.1%). There was a statistically significant difference observed between HPV positivity and site of tumor (p=0.038) (Table-II).

Table-I: Baseline characteristics of patients with HNCs (n=305).

Characteristics	Mean ± SD
Age in years	46.46±12.58
Gender	
Male	227 (74.4%)
Female	78 (25.6%)
Ethnicity	
Urdu	146 (47.9%)
Sindhi	66 (21.6%)
Punjabi	30 (9.8%)
Pashto	20 (6.6%)
Balochi	24 (7.9%)
Others	19 (6.2%)
Locality	
Urban	220 (72.1%)
Rural	85 (27.9%)
Education	
Illiterate	133 (43.6%)
Primary	89 (29.2%)
Matric	35 (11.5%)
Intermediate	32 (10.5%)
Graduate	14 (4.6%)
Post graduate	2 (0.7%)
Site of tumor	
Oral cavity	250 (82%)
Larynx	24 (7.9%)
Hypopharynx	8 (2.6%)
Oropharynx	4 (1.35)
Nasopharynx	19 6.2%)
Subtype of tumor	
Adenocarcinoma	18 (5.9%)
SSC	287 (94.1%)
Tumor size	
T1	5 (1.6%)
T2	64 (21%)
T3	134 43.9%)
T4	102 (33.45)
Nodal status	
No	43 (14.1%)
N1	200 (65.6%)
N2	61 (20%)
N3	1 (0.3%)
Grade	
I	26 (8.5%)
II	263 (86.2%)
III	16 (5.2%)
Metastasis	
Mo	298 (97.7%)
M1	7 (2.3%)

Table-II: Stratification of HPV with respect to socio-demographics and tumor characteristics.

Characteristics	HPV		P-value
	Yes (n=39)	No (n=266)	
Age in years	43.82±10.77	46.85±12.79	0.161
Gender			
Male	24 (61.5%)	203 (76.3%)	0.048*
Female	15 (38.5%)	63 (23.7%)	
Ethnicity			
Urdu	19 (48.7%)	127 (47.7%)	0.981
Sindhi	8 (20.5%)	58 (21.8%)	
Punjabi	3 (7.7%)	27 (10.2%)	
Pashto	3 (7.7%)	17 (6.4%)	
Balochi	4 (10.3%)	20 (7.5%)	
Others	2 (5.1%)	17 (6.4%)	
Locality			
Urban	24 (61.5%)	196 (73.7%)	0.114
Rural	15 (38.5%)	70 (26.3%)	
Education			
Illiterate	18 (46.2%)	115 (43.2%)	0.435
Primary	9 (23.15%)	80 (30.1%)	
Matric	7 (17.9%)	28 (10.5%)	
Intermediate	5 (12.8%)	27 (10.2%)	
Graduate	0	14 (5.3%)	
Post graduate	0	2 (0.8%)	
Monthly Family Income			
<15,000 PKR	29 (74.45)	158 (59.45)	0.199
15,000-30,000 PKR	9 (23.1%)	99 (37.2%)	
>30,000 PKR	1 (2.6%)	9 (3.4%)	
Addiction			
Smoking	7 (17.9%)	78 (29.3%)	0.139
Tobacco	5 (12.8%)	60 (22.6%)	0.166
Naswar	2 (5.1%)	56 (21.1%)	0.018*
Betel nut	20 (51.3%)	86 (32.3%)	0.020*
Betel leaf	7 (17.9%)	62 (23.3%)	0.455
Alcohol	0	9 (3.4%)	0.243
Family history of any cancer			
Yes	8 (20.5%)	39 (14.7%)	0.526
No	31 (79.5%)	227 (85.3%)	
Family history of HNCs			
Yes	3 (7.7%)	11 (4.1%)	0.322
No	36 (92.3)	255 (95.9%)	
Site of tumor			
Oral cavity	36 (92.3%)	214 (80.5%)	0.038*
Larynx	1 (2.6%)	23 (8.6%)	
Hypopharynx	0	8 (3%)	
Oropharynx	2 (5.1%)	2 (0.8%)	
Nasopharynx	0	19 (7.1%)	
Subtype of tumor			
Adenocarcinoma	2 (5.1%)	16 (6%)	0.589
SSC	37 (94.9%)	250 (94%)	
Tumor size			
T1	0	5 (1.9%)	0.454
T2	5 (12.8%)	59 (22.2%)	
T3	21 (53.8%)	113 (42.5%)	
T4	13 (33.3%)	89 (33.5%)	

Nodal status			
No	6 (15.4%)	37 (13.9%)	0.818
N1	27 (69.2%)	173 (65%)	
N2	6 (15.4%)	55 (20.7%)	
N3	0	1 (0.4%)	
Grade			
I	3 (7.7%)	23 (8.6%)	0.7
II	35 (89.7%)	228 (85.7%)	
III	1 (2.6%)	15 (5.6%)	
Metastasis			
Mo	39 (100%)	259 (97.4%)	0.601
M1	0	7 (2.6%)	

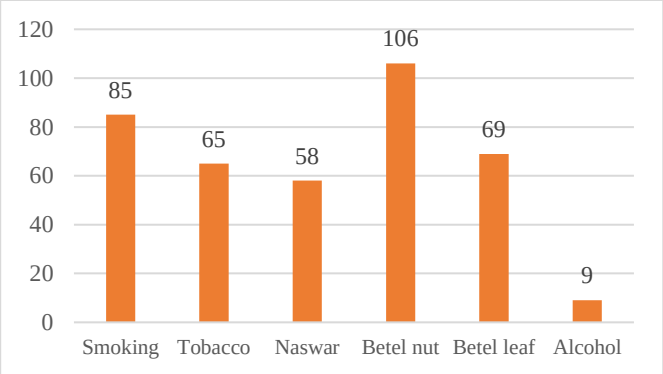

Figure-I: Frequency of substance use among participants (N=305).

DISCUSSION

The role of high-risk HPV in cervical cancer is well-established, yet recent decades have also seen emerging evidence of its involvement in other malignancies, including a subset of head and neck cancers.[13, 14] This latter group exhibits distinct clinical, epidemiological, and molecular characteristics compared to non-HPV head and neck carcinoma.[15]

While oropharyngeal squamous cell carcinoma (OPSCC), which represents approximately a quarter of all head and neck squamous cell carcinoma (HNSCC) cases, has been robustly linked to HPV, its association with other HNSCC types is less certain.[16, 17] High HPV prevalence is observed in oral malignancies in Western countries, with rates ranging from 70-90%.[18] However, our study reports a comparatively lower incidence of HPV-associated HNC at around 13%, a finding consistent with data from other regions.[19, 20]

Despite HPV's frequent detection in oral cavities, its contribution to oral cavity squamous cell carcinoma (OCSCC) remains limited (3.9% of cases), contrasting starkly with the 47% case contribution to OPSCC.[21] Interestingly, our findings revealed a high HPV prevalence of 92.3% in oral cavity cancer, compared to 5.1% in oropharyngeal and 2.6% in larynx cancer. Tobacco use, betel quid chewing, and alcohol consumption all pose potential risks for oral cavity malignancies.[22] Moreover, our study corroborates previous research indicating a higher HPV prevalence in men than women.[23,24] This may suggest gender-based transmission patterns, though the data remains inconclusive. Evidence points to potential protective roles of female hormones against HNSCC development.[25] Further, a study by Ochoa *et al*. underscored the survival advantage conferred by HPV positivity in HNSCC patients, with HPV-negative individuals exhibiting significantly lower survival rates.[26]

Our analysis also highlights the link between HPV infection and hazardous habits such as tobacco and betel nut chewing, both independent risk factors for oral cancer. The increasing prevalence in recent years reflects not just the addictive and stimulatory properties of tobacco, but also the lack of social stigma associated with betel nut use among Pakistan's lower and middle socioeconomic classes.[19] The results of this study lay a foundation for devising improved diagnostic strategies, effective treatment modalities, and advanced screening programs to mitigate the future burden of HPV-driven HNC in Pakistan.

CONCLUSION

This study underscores the significant, yet complex, relationship between HPV and head and neck cancer, particularly highlighting the demographic, behavioral, and gender differences. The findings provide valuable insights for healthcare providers to tailor preventive strategies, diagnostic procedures, and treatment modalities. They also stress the importance of developing comprehensive HPV screening programs and targeted vaccinations, particularly in regions with lower socioeconomic status. Further research is warranted to delve deeper into the multifaceted role of HPV in head and neck cancers and to further elucidate the factors impacting its prevalence and progression.

CONFLICT OF INTEREST

Authors declare no conflict of interest

AUTHOR CONTRIBUTIONS

Nargis Aalam Abro: Study design and concept and data acquisition.

Ghulam Haider: Supervision and critical appraisal

Aamera Shah and Tooba Sarim
: Literature review
Reeta Kumari: Result interpretation
Sorath Bhutto and Sana Hashmat: Data acquisition and draft writing

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