Frequency of Human Papilloma Virus in Patients With Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background: Human Papilloma Viruses (HPVs) are said to be implicated in a variety of human squamous cell carcinomas, including carcinoma of cervix, anogenital region, skin, upper respiratory tract, and digestive tract. Human papilloma virus (HPV) is found frequently in esophageal squamous cell carcinoma (ESCC) from high incidence areas.The study will provide us data about Human Papilloma Virus involvement in ESCC and will draw attention of professionals dealing with gastroenterology ultimately making certain suggestions regarding HPV vaccination, screening and eradication of HPV in high risk groups for ESCC.

Objective: To find frequency of human Papilloma Virus in patients with esophageal squamous cell carcinoma.

Material & Method: This cross sectional descriptive study was carried out in department of Pathology, Khyber Medical College and Blood bank Khyber Teaching Hospital Peshawar from January 2017 to January 2018. A total 121 patients were subjected to this study, using 27.7%[5] proportion of HPV in ESCC, 95% confidence interval and 8% margin of error under WHO sample size calculations. All patients were diagnosed with esophageal squamous cell carcinoma, in the age range of 30-60 years .Both gender were included. All the biopsy specimens used for diagnosis of ESCC were processed in Pathology department, Khyber Medical College for the detection of human Papilloma virus, using Dako Monoclonal Mouse Anti Human Papilloma Virus clone K1H8 code M3528 on formalin fixed paraffin embedded tissues. Positive and negative control was provided in the Dako kit for comparison. Antigen antibody complex formation imparting color to the nuclei of neoplastic cells was taken as positive.

Results: Mean age distribution was 50 years ± 1.72. Fifty five percent (55%)patients were male and 45%, female. The frequency of human Papilloma virus was 3%.

Conclusion: This study shows involvement of Human Papilloma Virus in 3% patients with esophageal squamous cell carcinoma.

Key Words: *Human Papilloma Virus, Esophageal Squamous Cell Carcinoma*

This article may be cited as: Naz S, Nadeem S.
Frequency of Human Papilloma Virus in Patients With Esophageal Squamous Cell Carcinoma JSMC 2018.8;2:62-65.

INTRODUCTION:

The incidence of esophageal cancer varies more than that of any other cancer around the globe. It is endemic in the Transkei region of South Africa and in Asian. Esophageal cancer belt that extends across middle of Asia from the Caspian Sea (In the north of Iran) to china including northern areas of Pakistan. The highest incidence in the world is in Linxian in Henan province of China, where it is most common single cause of death, with more than 100 cases per 100,000 population per annum. Incidence rates varies from less than 5:100,000 in white people in USA to 26.5:100,000 in some regions of France[1,2,3]. The pathogenesis of esophageal cancer remains unclear[4]. Data from studies suggests the oxidative damage from factors such as smoking or gastro-esophageal reflux, which causes inflammation, increase cell turnover and may initiate a carcinogenic process[.5,6]

Human papilloma viruses (HPVs) have been considered as a causal agent in a variety of human squamous cell carcinomas, including those of the cervix, anogenital region, skin, upper respiratory tract, and digestive tract[7,8]

Human papilloma virus with more than 200 genotypes is implicated in the genesis of several cancers, particularly squamous cell carcinoma of the cervix, and anogenital, oral and laryngeal regions[9,10,11.]

There is a huge geographical variation in the rate of HPV in squamous cell carcinoma of esophagus even within countries (Iran and China). Our present study is designed in order to determine the frequency of HPV in newly diagnosed patients of esophageal squamous cell carcinoma. The rationale behind doing this study is that no local study is done to determine the frequency of HPV in ESCC which as evident from above has a huge geographical variation. The results of this study will provide us with local statistics of the magnitude of HPV in ESCC and this will open window for further research. If its frequency is proven high in our setup, it will draw attention of

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Received: June 20th 2018, Accepted July 07th 2018

general surgeons and gastroenterologists for making certain suggestions regarding HPV vaccination, screening and eradication of HPV in high risk groups for ESCC.

MATERIAL AND METHOD:

The current study was conducted at department of Pathology and Blood bank of Khyber Medical College and Khyber Teaching Hospital Peshawar. Study design was cross sectional descriptive study and duration of the study was one year starting from January 2017 to January 2018 in which a total of 121 patients were observed by using 27.7%[5] proportion of HPV in ESCC, 95% confidence interval and 8% margin of error under WHO sample size calculations. More over consecutive non probability sampling. All patients ranging from 30-60 years of age were diagnosed with esophageal squamous cell carcinoma. Both male and female diagnosed with ESCC or HPV infection based on history and medical records were included. Women with diagnosed cervical cancer were also included because of possible relationship between HPV and esophageal cancer. Endoscopic biopsies of all the patients with esophageal squamous cell carcinoma were taken from both indoor and outdoor patients meeting the inclusion criteria and presented to the laboratory of the hospital. A written informed consent was obtained. All the biopsy specimens used for diagnosis of ESCC were processed in Khyber Medical College for the detection of human papilloma virus using Dako Monoclonal Mouse Anti Human papilloma virus clone K1H8 code M3528 on formalin fixed parafin embedded tissues. Positive and negative control were provided in the Dako kit for comparison. Antigen antibody complex formation impart color to the nuclei of neoplastic cells was taken as positive. Data was analyzed using SPSS version 10.0. For quantitative variables like age, mean and standard deviation were calculated and for qualitative variables like gender and Human papilloma virus, frequencies and percentages were calculated. HPV was stratified among age and gender to see the effect modification.

RESULTS:

In this study age distribution among 121 patients was analyzed as 14(12%) patients were in the age range of 31-40 years, 40(33%) patients were in the age range of 41-50 years, and 67(55%) patients were more than 50 years of age. Mean age was 50 years with SD ± 1.72. (Table No 1). Sixty seven (55%) patients were male and 45% patients were female. (Table No 2).About four(3%) patients had Human Papilloma Virus while 117(97%) patients were not having Human Papilloma Virus. (Table No 3). Stratification of Human Papilloma Virus with age and gender distribution is given in Table No 4,5.

TABLE NO 1. AGE DISTRIBUTION (n=121)

AGE	FREQUENCY	PERCENTAGE
31-40 years	14	12%
41-50 years	40	33%
>50 years	67	55%
Total	**121**	**100%**

Mean age was 50 years with SD ± 1.72

TABLE NO 2. GENDER DISTRIBUTION (n=121)

GENDER	FREQUENCY	PERCENTAGE
Male	67	55%
Female	54	45%
Total	**121**	**100%**

TABLE NO 3. HUMAN PAPILLOMA VIRUS (n=121)

HUMAN PAPILLOMA VIRUS	FREQUENCY	PERCENTAGE
Yes	4	3%
No	117	97%
Total	**121**	**100%**

TABLE NO 4. STRATIFICATION OF HUMAN PAPILLOMA VIRUS WITH AGE (n=121)

HUMAN PAPILLOMA VIRUS	31-40 years	41-50 years	>50 years	Total	P Value
Yes	0	1	3	4	0.6545
No	14	39	64	117	
Total	**14**	**40**	**67**	**121**	

TABLE NO 5. STRATIFICATION OF HUMAN PAPILLOMA VIRUS WITH GENDER (n=121)

HUMAN PAPILLOMA VIRUS	Male	Female	Total	P value
Yes	3	1	4	0.4219
No	64	53	117	
Total	**67**	**54**	**121**	

DISCUSSION:

Esophageal cancer, usually esophageal squamous cell carcinoma (SCC) and esophageal adenocarcinoma (AC), is one of the most common malignant tumors in the world[12] Esophageal cancer is the sixth leading cause of cancer death in the world. Esophageal squamous-cell carcinoma and esophageal adenocarcinoma represent the core histological subtypes of esophageal cancer.[13]Esophageal carcinoma represents a poor prognosis among gastrointestinal cancers. While esophageal squamous cell carcinoma predominates worldwide, Western nations have seen a marked rise in the incidence of esophageal adenocarcinoma that parallels the obesity epidemic. Efforts directed toward early detection have been difficult, assumed that the dysplasia and early cancer is generally asymptomatic. However, significant developments have been made in the past 10 to 15 years that permit for endoscopic management and often cure in the early stage of esophageal malignancy.[14]

Our study shows that mean age was 50 years with SD ± 1.72. Fifty five percent patients were male and 45% patients were female. The frequency of human papilloma virus in our setup was 3%.

In study conducted by Far AE et al[15] 140 patients were enrolled 50.7% were female and 49.3% were male, aged between 20 and 81 years. 33 tumor specimens (23.6%) and 12 (8.6%) non-involved tumor margins were HPV positive. From HPV positive tumor cases 36% were positive in tumor margins. The HPV positive cases were 21.7% male and 25.3% female. There is no correlation between presence and types of HPV with patients' gender and age. The frequency of HPV subtypes was as follows: HPV-16, 60.6%; HPV-18, 30.3%; HPV-33, 6.1%; and HPV-31, 3%. We found only HPV-16 in tumor margins. The incidence of HPV infection in ESCC patients was significantly higher in comparison to controls having normal esophageal mucosa.

DreilichM et al[16] had reported that the incidence of HPV type 16 was detected in 16% of ESCC patients in Uppsala, Sweden. Xu et al[17] reported that the detection rate of infection with all HPV types (16, 18 and 58) in ESCC tissue in Chinese patients was 50%. When investigated by nested polymerase chain reaction, HPV DNA was identified in all ESCC tumor tissue in German patients[18]. Yousaf S et al[19] had reported that the frequency of HPV was detected in nine (18%) out of fifty paraffin embedded tissues of squamous cell carcinoma of cervix. Out of the 9 cases that were positive, five (55.6%) were infected with HPV16, while in the rest of the positive samples, the genotype could not be identified in four (44.4%). HPV was not determined in majority (82%) of the samples. Pastrez PRA et al[20] had reported that high-risk HPV (hr-HPV) was found in the same frequency (13.8%) in esophageal squamous cell carcinoma (ESCC) and in healthy individuals. The p53 expression was positive in 67.5% of tumor tissue, 20.0% of adjacent non-tumorous tissue and 1.8% of normal esophageal tissue. p16 was positive in 11.6% of esophageal cancer cases and 4.7% of adjacent non-tumor tissue. p16 was undetectable among control group samples. P53 and p16 levels were not

significantly associated with the HPV status. Hardefeldt HA[11] had reported that the prevalence of HPV in esophageal SCC was found to be 248%.Petrick JL et al[21] had reported that the average HPV prevalence (95% confidence interval) among OSCC cases was 0.277 (0.234, 0.320) by polymerase chain reaction; 0.243 (0.159, 0.326) by in situ hybridisation; 0.304 (0.185, 0.423) by immunohistochemistry; 0.322 (0.154, 0.490) by L1 serology; and 0.176 (0.061, 0.292) by Southern/slot/dot blot. The highest HPV prevalence was found in Africa and Asia, notably among Chinese studies from provinces with high OSCC incidence rates.

CONCLUSION

In conclusion we in this small prospective and well conducted study concluded that although the incidence of human papilloma virus in KPK is very low, about 3% but even though the low risk HPV phenotypes could be one of the co-activators and co-carcinogens in complex, that leads to progressive, multifactorial and multistep esophageal carcinogenesis.

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