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ORIGINAL ARTICLE

Esophageal squamous papilloma: Literature review and case–control retrospective study with histopathological exam of human papillomavirus

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Abstract

Background and Aim: Esophageal squamous papilloma (ESP) is a benign growth in the esophagus with unknown malignant potential. The mechanism underlying ESP formation is unknown, but human papillomavirus (HPV) infection has been proposed as a potential etiology. We sought to investigate the clinical characteristic of ESP in our population, review the current literature, and highlight the role of HPV.
Methods: This is a retrospective case–control study conducted at two referral centers. We selected the ESP population by free-text search in the pathology department database and selected controls randomly from the general endoscopy population. Immunostains were used to evaluate ESP tissue for HPV.
Results: Between January 2016 and December 2021, we identified 66 patients with ESP, with a prevalence of 0.72%. ESP patients were younger, with a median age of 52 years ($P = 0.021$), and more likely African American (34.4 *vs* 7.5%, $P < 0.001$) compared to controls. On endoscopy images, the growth was predominantly solitary (92.5%) in the middle of the esophagus (39.4%), with sizes ranging from 0.2 to 2.3 cm. A total of 62 patients had available tissue for HPV immune staining, and none tested positive for HPV. Eighteen patients had a follow-up endoscopy with an average of 504.5 days follow-up period. One patient developed esophageal squamous cell carcinoma during follow-up.
Conclusions: We observed a higher prevalence of ESP compared to previous studies. The formation of ESP is multifactorial and partially explained by HPV infection in selected populations. The malignant potential of ESP is low but not negligible.

Introduction

Squamous cell papillomas (SCPs) are benign growths at various locations in the body. Structurally, papillomas would be either exophytic or endophytic lesions, with the epithelium surrounding a fibrovascular core on histology.[1] Esophageal squamous papilloma (ESP) is a subtype of SCP seen in the esophagus. In comparison with other forms of SCP, ESP is an asymptomatic lesion diagnosed incidentally by esophagogastroduodenoscopy (EGD), where it appears as an exophytic growth with crossing surface vessels on narrow-band imaging.[2,3] Its rarity can be partially due to its internal location and asymptomatic nature.

ESP was first described anatomically in 1927[4] and histologically in 1959.[5] Since then, our knowledge of ESP has expanded from case reports and series. The proposed mechanisms for ESP formation include mechanical trauma, or chemical injury as in gastroesophageal reflux disease (GERD). Infection with human papillomavirus (HPV) is an alternative explanation, while other infections such as Epstein–Barr virus (EBV) have been cited. Lastly, ESP can be a part of a genetic disorder, as seen in Goltz–Gorlin syndrome and Cowden syndrome.[1,6]

ESP is commonly approached as a benign lesion and treated with complete resection. The long-term prognosis and outcomes for recurrence and potential malignancy of ESP are lacking in order to develop optimal management of ESP. The aim of our study is to identify the clinical risk factors of ESP in comparison with a control population and examine the role of HPV in ESP formation.

Methods

The present study is a retrospective case–control study of electronic medical records (EMRs) as well as human tissue sample staining and reviewing. The study was conducted at Medstar Washington Hospital Center and MedStar Georgetown University Hospital, both tertiary referral centers in Washington,

DC. The Institutional Review Boards (IRBs) at Georgetown University and MedStar Health reviewed and approved the study.

The ESP population was extracted from the pathology department database through a free-text search of pathology reports. We included patients from January 2016 to December 2021. Patients were included in the study if they had a previous pathological diagnosis of ESP after EGD with available tissue samples. Patients were excluded from the study if younger than 18 years of age or if endoscopic information was not available.

The control population was selected randomly from the pool of patients who underwent EGD using the International Classification of Diseases 10th Revision (ICD-10) codes during the same time period as the cases. Controls were included in the study if EGD data were available and excluded if they were younger than 18 years of age. Controls were matched to the cases using propensity matching based on the site where EGD was performed, the year of EGD, and the setting as inpatient or ambulatory. We matched ESP to control with a 1:5 ratio.

EMRs of both cases and controls were reviewed systematically. We gathered the patient's demographics, medical comorbidities, pre-endoscopic symptom profile, and medication use. We reviewed EGD report regarding ESP location, size, morphological description, and recurrence on subsequent EGDs. Pathology reports were reviewed by the investigator, and, independently, the tissue samples were evaluated by a pathologist to confirm the diagnosis.

To investigate ESP tissue samples for HPV virus involvement, 3-μm-thick sections from formalin-fixed, paraffin-embedded tissue blocks were obtained. The samples were stained with HE and HPV stain (clone K1H8; ready-to-use, Dako, CA, USA), which has been validated to detect HPV 6, 11, 16, 18, 31, 33, 42, 51, 52, 56, and 58, based on the manufacturer's specification. Staining was performed according to the manufacturer's instructions with adequate positive controls. HE and immunostains were reviewed by a single pathologist.

For data analysis, the D'Agostino–Pearson test was used to test normality. Categorical variables were presented as the frequency with percentages (%), and associations were examined using the Fisher exact test. On the other hand, for non-normal continuous variables, we used the Kruskal–Wallis rank sum test and presented the data with the median and interquartile range (IQR). Analysis was done with R software, and significance was set at a P-value of <0.05.

Results

Population summary. During the study period from January 2016 to December 2021, 9406 patients underwent EGDs and 68 patients had ESP, corresponding to a prevalence of 0.7% of EGD cases. We excluded two ESP patients: one younger than 18 years of age, and the other missing a detailed EGD report. The control group was randomly selected from those patients who had an EGD taken during the study period with a ratio of five controls per case, and thus a total of 340 control patients were selected. Among the selected control group patients, 333 were included for further analysis after excluding 7 due to the unavailability of a detailed EGD report. Of the total study population, 92.5% had their EGD done in an outpatient setting, 58.2% in MedStar Georgetown University Hospital, and 41.8% in MedStar Washington Hospital Center.

The ESP population was younger, with a median age of 52 years ($P = 0.021$) compared to 59 in the control population. Females represented 57.6% of the ESP study group, and a similar proportion was observed in the non-ESP control patients ($P = 1$). In the ESP group, there were 31 Caucasians (48.4%) and 22 African Americans (34.4%), in comparison to 296 (88.9%) and 25 (7.5%), respectively, in the control group ($P < 0.001$). None of the patients in the ESP cohort was Hispanic, while the control group had 12 Hispanic patients (3.6%) (Table 1).

Clinical characteristics. Upon reviewing the clinical characteristics, patients with papilloma infection had similar rates of active smoking (40.9 *vs* 42.0%, $P = 0.892$), heavy alcohol consumption (46.2 *vs* 45.2%, $P = 1$), diabetes (16.7 *vs* 22.2%, $P = 0.41$), hypertension (40.9 *vs* 51.7%, $P = 0.138$), hyperlipidemia (27.3 *vs* 31.5%, $P = 0.56$), and GERD (31.8 *vs* 43.5%, $P = 0.1$) when compared with controls. On the other hand, the rate of cirrhosis (6.1 *vs* 19.2%, $P = 0.007$) and use of proton pump inhibitors (PPIs; 33.3 *vs* 47.7%, $P = 0.042$) were higher in the control population. ESP patients showed a similar basic laboratory profile as that in controls (Table 2). The median hemoglobin concentration, platelets count, white cells count, glomerular filtration rate, and electrolyte level were comparable between the study groups. On the other hand, aspartate transaminase ($P = 0.002$), alanine transaminase ($P = 0.012$) were higher and albumin ($P = 0.021$) concentrations were lower in controls.

Patients' presentation. The indication for endoscopic evaluation in ESP patients fell under three categories: presenting some gastrointestinal (GI) symptoms (34 patients), surveillance of known gastrointestinal illness (28 patients), and abnormal imaging findings on radiography (4 patients). The most frequent symptoms before endoscopy in ESP patients were epigastric pain in 24 patients (36.4%), followed by dysphagia in 12 (18.2%). In contrast, heartburn and epigastric pain were the most frequent symptoms in the controls, with 85 patients (25.5%) in each category. The symptom profile is shown in Figure 1. There was no statistical difference in symptoms between ESP patients and controls, except for heartburn, which was significantly more common in controls ($P = 0.021$).

ESP on endoscopy. ESP was found at various locations, with various numbers and size ranges in different patients. ESP was located in the upper esophagus in 20 patients (30.3%), in the middle esophagus in 26 patients (39.4%), in the lower esophagus in 14 patients (21.2%), and near or at the *Z*-line in 4 patients (6.1%). Only two patients (3.0%) had ESP in more than one location. Regarding the number of lesions, 61 patients (92.4%) had a solitary ESP, 5 patients (7.5%) had multiple ESPs but less than five lesions, and none had more than five lesions. Lastly, the size of ESP ranged from 0.2 to 2.3 cm at the largest diameter. All ESP patients underwent complete resection of the lesions.

Biopsy and tissue findings. For further histopathological examination, we identified 62 ESP patients (93.9%) with

Table 1 Demographics, clinical characteristics, and endoscopy findings of esophageal squamous papilloma and control population

	Overall	Case	Control	*P*-value
n	399	66	333	
Age (median [IQR])	58.0 [46.0, 67.0]	52.0 [38.5, 67.0]	59.0 [49.0, 68.0]	**0.021**
Female (%)	228 (57.1)	38 (57.6)	190 (57.1)	1
Ethnicity/race (%)				**<0.001**
White	327 (82.4)	31 (48.4)	296 (88.9)	
African American	47 (11.8)	22 (34.4)	25 (7.5)	
Hispanic	12 (3.0)	0 (0.0)	12 (3.6)	
Others	11 (2.8)	11 (17.2)	0 (0.0)	
BMI (median [IQR])	26.6 [23.0, 32.0]	27.0 [23.2, 32.6]	26.6 [22.8, 32.0]	0.438
Smoking (%)	167 (41.9)	27 (40.9)	140 (42.0)	0.892
Alcohol drinking (%)	181 (45.5)	30 (46.2)	151 (45.3)	1
Hypertension (%)	199 (49.9)	27 (40.9)	172 (51.7)	0.138
Diabetes (%)	85 (21.3)	11 (16.7)	74 (22.2)	0.41
Hyperlipidemia (%)	123 (30.8)	18 (27.3)	105 (31.5)	0.561
GERD (%)	166 (41.6)	21 (31.8)	145 (43.5)	0.1
Cirrhosis (%)	68 (17.0)	4 (6.1)	64 (19.2)	**0.007**
Proton pump inhibitor (%)	181 (45.4)	22 (33.3)	159 (47.7)	**0.042**
H2 blocker (%)	46 (11.5)	7 (10.6)	39 (11.7)	1
NSAIDs (%)	65 (16.3)	15 (22.7)	50 (15.0)	0.14
Metformin (%)	33 (8.3)	5 (7.6)	28 (8.4)	1
Hiatal hernia (%)	54 (13.5)	3 (4.5)	51 (15.3)	**0.017**
Helicobacter pylori (%)	10 (2.5)	4 (6.0)	6 (1.8)	0.065
History of GI cancers (%)	41 (10.3)	5 (7.6)	36 (10.8)	0.513
History of laryngeal cancer (%)	5 (1.3)	2 (3.0)	3 (0.9)	0.193

Significance was set at a *P*-value of <0.05.

BMI, body mass index; GERD, gastroesophageal reflex disease; GI, gastrointestinal; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

available tissue blocks for HPV immune staining. Our investigation results were negative for HPV 6, 11, 16, 18, 31, 33, 42, 51, 52, 56, and 58 in all ESP patients. We had gastric biopsy results for 27 ESP patients (40.9%). Of those, 4 (6%) had *Helicobacter pylori*, and 1 (1.5%) had a benign gastric ulcer. In contrast, 201 patients in the control group had gastric biopsy, 6 (1.8%) had *H. pylori* ($P = 0.06$), and 21 (6.3%) had a gastric ulcer ($P = 0.14$).

Cancer and recurrence. All the lesions of ESP patients were completely removed, and 18 patients underwent subsequent EGDs for various indications after ESP diagnosis, with an average follow-up duration of 504.5 days. Of those, 17 showed no signs of recurrence, while one patient developed esophageal squamous cell carcinoma (ESCC). In our ESP group, two patients were identified with having ESCC. One patient had simultaneous ESP and ESCC diagnosis, while the other had in situ ESCC originating from ESP tissue, which progressed to ESCC at an adjacent site during follow-up. Neither patient showed dysphagia, and both had nonspecific symptoms such as epigastric pain, nausea, vomiting, bloating, and heartburn. Neither patient reported a history of smoking, GERD, or a family history of ESCC, but one had a history of alcohol abuse. During EGD, both patients had papillomas larger than 1 cm and nodular esophageal mucosa with ulceration. Additionally, one ESP patient was coincidentally diagnosed with gastric carcinoid.

Discussion

Demographics and prevalence. ESP is a relatively rare finding in endoscopy. The reported prevalence of ESP found on endoscopy in the literature has ranged from 0.01 to 0.45%[7–10] as seen in Table 3. Pediatric population has a prevalence comparable to adults at 0.08%.[2] Our findings suggested a prevalence rate of 0.7% in our study population during our 6-year study period. The high prevalence can be explained by the significantly uptrending ESP incidence rate from 0.13 to 0.57% between 2000 and 2013 in the United States.[21] The observed increase in ESP can be related to increasing EGD availability, recent improvements in ESP detection with new high-definition endoscopes, and the awareness of gastroenterologists of the condition. An old autopsy-based study found a prevalence of 0.04% in 7549 autopsies.[22]

The typical demographics of ESP patients are not clearly known because of the rarity of the disease. Studies have shown a median age between 49 and 50 years.[9,10,18] Recent studies have shown a higher proportion of female ESP patients,[10,18] although old literature shows male predominance.[13,23] Few studies have reported the race of ESP patients, but predominantly more White patients had ESP.[23] In our study, we found that ESP patients are younger, are more African Americans, and have the same male-to-female ratio, compared to the control group. These findings are similar to those of a study on the Italian population, which showed that the ESP population is younger compared to the general endoscopy population with similar male-to-female ratio.[15]

Table 2 Laboratory finding for esophageal squamous papilloma and control population

	Overall	Esophageal squamous papilloma	Control	*P*-value
n	399	66	333	
Blood type (%)				0.776
A+	48 (24.6)	6 (25.0)	42 (24.6)	
A–	5 (2.6)	0 (0.0)	5 (2.9)	
B+	35 (17.9)	4 (16.7)	31 (18.1)	
B–	2 (1.0)	0 (0.0)	2 (1.2)	
O+	87 (44.6)	11 (45.8)	76 (44.4)	
O–	10 (5.1)	3 (12.5)	7 (4.1)	
AB+	6 (3.1)	0 (0.0)	6 (3.5)	
AB–	2 (1.0)	0 (0.0)	2 (1.2)	
White blood count (median [IQR])	6.6 [5.0, 9.1]	7.3 [5.4, 8.7]	6.3 [4.9, 9.2]	0.568
Absolute lymphocyte count (median [IQR])	1.5 [1.1, 2.2]	1.8 [1.4, 2.7]	1.5 [1.0, 2.1]	0.074
Absolute neutrophil count (median [IQR])	4.0 [2.5, 6.1]	4.6 [2.5, 5.4]	3.9 [2.5, 6.1]	0.901
Absolute eosinophil count (median [IQR])	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	0.657
Hematocrit (median [IQR])	37.7 [32.3, 41.2]	39.8 [36.4, 41.0]	37.1 [31.2, 41.3]	0.064
Hemoglobin (median [IQR])	12.4 [10.3, 13.6]	12.9 [11.6, 13.7]	12.2 [10.2, 13.6]	0.104
Platelets (median [IQR])	232.0 [162.0, 302.0]	262.5 [216.2, 310.2]	222.0 [158.0, 300.0]	0.056
Sodium (median [IQR])	140.0 [138.0, 142.0]	140.0 [138.0, 142.0]	140.0 [138.0, 142.0]	0.539
Potassium (median [IQR])	4.2 [3.8, 4.5]	4.1 [3.7, 4.5]	4.2 [3.9, 4.5]	0.345
Chloride (median [IQR])	104.0 [101.5, 107.0]	103.0 [101.0, 106.0]	104.0 [102.0, 107.0]	0.336
HCO_3 (mean [SD])	25.2 (3.3)	26.0 (3.2)	25.1 (3.3)	0.162
Calcium (median [IQR])	9.1 [8.6, 9.5]	9.2 [8.7, 9.4]	9.1 [8.6, 9.5]	0.935
Glucose (median [IQR])	100.0 [88.0, 125.2]	96.5 [88.2, 135.0]	101.0 [88.0, 125.0]	0.741
BUN (median [IQR])	14.0 [11.0, 19.0]	13.0 [10.0, 18.0]	14.0 [11.0, 19.0]	0.373
Creatinine (median [IQR])	0.8 [0.7, 1.1]	0.8 [0.7, 1.1]	0.8 [0.7, 1.1]	0.166
Glomerular filtration rate (median [IQR])	60.0 [60.0, 75.0]	60.0 [60.0, 81.8]	60.0 [60.0, 63.5]	0.331
Aspartate transaminase (median [IQR])	25.0 [18.0, 41.0]	18.0 [16.0, 25.0]	26.0 [19.0, 43.0]	**0.002**
Alanine transaminase (median [IQR])	25.0 [17.2, 38.0]	19.0 [13.0, 25.0]	26.0 [18.0, 40.0]	**0.012**
Albumin (median [IQR])	3.7 [3.0, 4.3]	4.2 [3.5, 4.5]	3.7 [3.0, 4.2]	**0.021**

Significance was set at a *P*-value of <0.05.
BUN, blood urea nitrogen; IQR, interquartile range.

Symptoms, laboratory results, and endoscopic features. The pre-endoscopic symptomatology profiles for the ESP patients and control patients are shown in Figure 1. Epigastric pain was the most common symptom and was seen in more than one-third of the ESP patients, but it is unclear whether ESP is a contributor to the reported pain. Previous studies have shown higher rates of epigastric pain than our population, ranging from 47.6 to 62.5%.[15,18] As for dysphagia, the ESP and control groups had similar rates: 18.2 *versus* 14.4%, which are significantly higher than those from earlier studies that showed 0–4.3%[15,18] of ESP patients had dysphagia. The low rate of dysphagia in other studies is likely due to the small size of ESP on endoscopy. Heartburn, a surrogate for GERD, was seen only in 12.1% of ESP patients, compared to 25.5% in the control population, thus suggesting that GERD may not be a major pathogenic mechanism for ESP formation.

The control population in the study showed a 19.2% liver cirrhosis rate. The observed high rate of cirrhosis is related to the nature of the study hospital, which is a referral center for liver transplants. In light of that, controls showed higher liver enzyme levels and lower albumin levels. The previous investigation of ESP patients did not include laboratory evaluation for comparison. Our study did not show any difference between the general endoscopy population and ESP patients except for the liver profile.

On endoscopy, ESP is usually seen as a single exophytic lesion less than 5 mm on the largest diameter.[8,15,18,24] Multiple lesions and larger diameters are reported, as seen in our study, in a small number of cases but are not typical.[9,18,25] ESP can be seen in any part of the esophagus. Earlier studies have shown lower esophageal ESP as predominant, while our study and many recent studies show that ESP is predominantly found in the middle esophagus (Table 3).

Etiology and pathogenesis mechanisms. The mechanism for ESP formation is an active field of investigation. HPV infections have been proposed as a possible etiology or a contributor since HPV has been observed in the papillomas in other parts of the body, such as oral and nasopharyngeal papillomas.[1] HPV is a DNA virus and a member of the Papillomaviridae family.[26] There are more than 100 types of HPV, which are divided into high-risk and low-risk groups based on their oncological potential.[26] As shown in Table 3, the rate of HPV detection in ESP varies drastically between different studies, ranging from 0 to 87.5%. The geographical region where the study was conducted cannot explain this difference in HPV detection. Our results showed no HPV detection on immunohistochemistry (IHC) of the ESP pathology specimens from ESP patients, in contrast to the study done in the United States in 1994, which showed a rate of

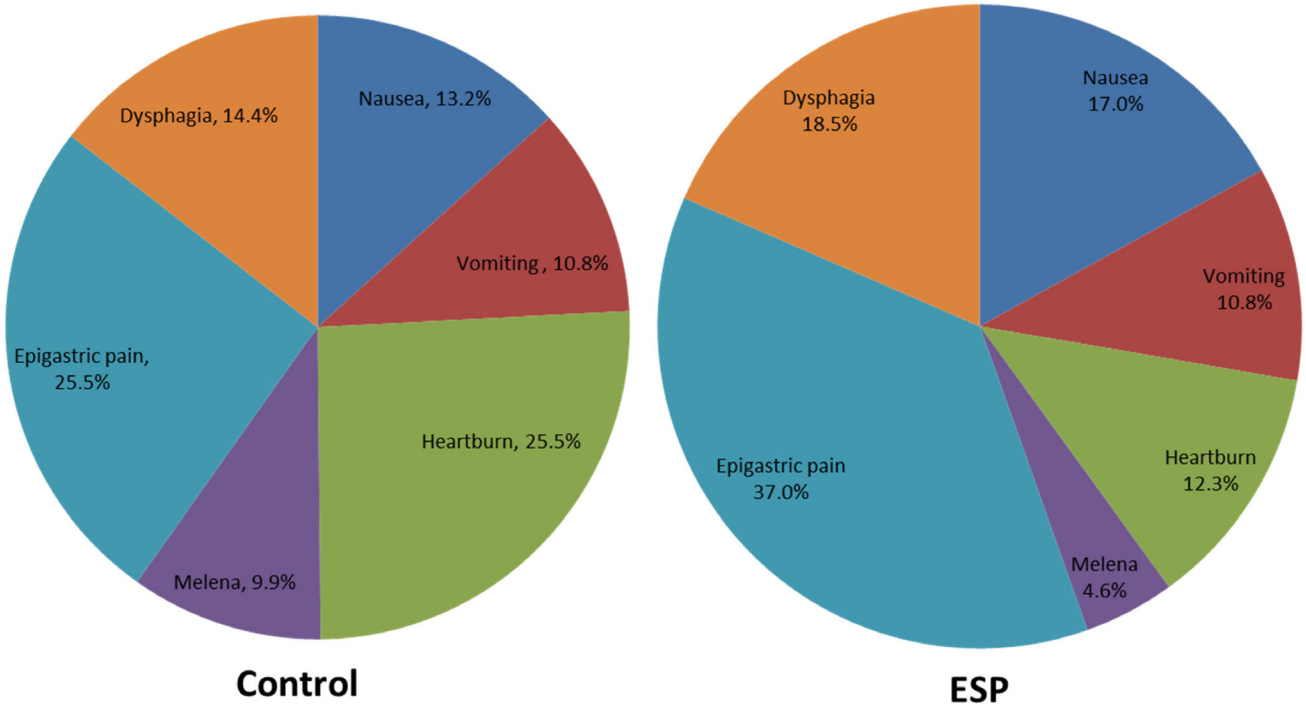

Figure 1 Pre-endoscopy symptoms of esophageal squamous papilloma (ESP) and controls.

4.7% using polymerase chain reaction (PCR).[14] A similar finding was seen in Italy, with contradicting results from the same regions.[7,15] The results also did not show any consistent trend over time, and HPV was detected at various rates in earlier and recent studies (Table 3). Thus, these findings indicate that HPV detection rates in ESP are not related to recent HPV vaccination or changes in the HPV prevalence over time. Moreover, different HPV testing modalities cannot explain this wide variation. Although different HPV detecting methods have different sensitivities,[27,28] a similar detection rate was seen in studies comparing and using multiple HPV detection modalities.[17,29] This is consistent with the conclusion of a meta-analysis conducted in 2012.[30]

Low-risk HPV 6 and 11 are the most commonly seen variants in ESP-HPV-positive patients, which is consistent with the observed pattern in the upper aerodigestive track.[1] High-risk HPV 16 was observed in some ESP patients too.[13] Transmission of HPV to esophageal mucosa is not clearly understood. Vertical transmission is a potential method that requires further

Table 3 Esophageal squamous papilloma (ESP) literature summary

Year	Country	ESP number	Prevalence	Predominant location (%)	HPV detection method	HPV positive rate	HPV predominate subtype	Cancer rate	Recurrence rate
1983[11]	Italy	15	0.075%	Lower (66.67%)	NA	NA	NA	NA	NA
1988[8]	Italy	35	0.45%	Middle (46%)	NA	NA	NA	None	None
1991[12]	Finland	12	0.077%	NA	ISH\PCR	None	NA	NA	NA
1993[13]	Canada	33	NA	Lower (70%)	PCR	50%	16	NA	NA
1994[14]	USA	17	NA	Lower (64%)	ISH\PCR	4.3%	6/11	NA	NA
2000[15]	Italy	42	0.35%	Middle (54.76%)	PCR	4.76%	NA	None	None
2001[7]	Italy	9	0.01%	Middle (78%)	ISH	None	None	None	None
2005[16]	Hungary	172	0.26%	Middle	PCR	46.2%	High risk	None	0.65%
2006[10]	Japan	38	0.20%	Middle (52.6%)	PCR	10.5%	6	NA	NA
2008[17]	Mexico	19	NA	Upper (57.89%)	IHC\PCR	87.5%	6/11	NA	NA
2015[9]	France	78	0.01%	NA	IHC	None	NA	1.3%	3.8%
2016[18]	Taiwan	24	0.42%	Middle (57.5%)	NA	NA	NA	NA	NA
2017[19]	Turkey	38	NA	Middle (68%)	PCR	19%	6	NA	NA
2021[20]	Turkey	52	0.44%	Middle (51%)	NA	NA	NA	NA	NA

HPV, human papilloma virus; IHC, immunohistochemistry; ISH, in situ hybridization; NA, not reported; PCR, polymerase chain reaction.

investigation. The pediatric ESP rate is similar to that in adults, and most of the pediatric cases were HPV-negative, reducing the likelihood of vertical transmission being the primary method.[2] Direct transition from the oral mucosa is less plausible, as HPV-positive ESP was seen all over the esophagus and commonly in distal esophagus (Table 3). HPV transmission through blood might explain the observed findings.[31]

As HPV does not explain most of the observed ESP, alternative mechanisms have been suggested. The proposed pathogenesis of ESP includes chronic irritation, inflammation, and regeneration.[14,23] Several factors, such as GERD, direct trauma, smoking, and alcohol intake, have been investigated as possible causes. GERD was hypothesized in earlier studies because ESP patients had high rates of reflux esophagitis, and ESP was located predominantly in the lower esophagus in those studies[13,23] (Table 3). A study in Japan suggested that HPV-negative ESP has a higher rate of neutrophil infiltrate, with increased neutrophils toward the lower esophagus.[10] This finding suggests that inflammation plays an integral role in HPV-negative ESP and that reflux esophagitis might be a driving factor for lower esophagus ESP. Our population was HPV-negative, with a comparable but slightly lower rate of GERD and lower heartburns in ESP cases compared to controls. Furthermore, ESP in our study was predominantly located in the middle esophagus. Our findings are consistent with most recent literature, which show a low rate of reflux esophagitis and predominant location of ESP as the middle esophagus[10,15,19,20] (Table 3). The increasing use of PPIs in recent times might explain some of this shift, although our result shows higher rates of PPI use in controls.

Alcohol and smoking are well-known irritants to the esophagus, and both have been associated with ESCC.[32,33] Their role in ESP is suggested but not supported by evidence. The rate of smoking and alcohol use was similar in our study between ESP cases and controls. In an Italian study comparing the rate of smoking and alcohol consumption between patients with ESP or ESCC with the general endoscopy population, ESP patients had a similar rate of alcohol consumption as the general endoscopy population.[15] ESP patients had a higher rate of smoking compared to the general population in the Italian study, but it did not reach statistical significance.[15] Lastly, minor esophageal trauma has been reported to precede ESP formation, as noted in an esophageal cancer case symptomatically managed with a stent, which then became complicated by dysphagia due to ESP.[34] A theory combining all the previously mentioned factors may explain some ESP lesions, but many patients do not have any of the suggested mechanisms or risk factors. Future studies are needed to investigate alternative etiologies.

Recurrence, cancer risk, and follow-up. Many studies, including ours, reported follow-ups of ESP cases.[7–9,16] In most studies, there was no recurrence after the removal of benign, non-dysplastic ESP. A French study showed a recurrence rate of 3.4% after the first ESP removal and 0% after the second one.[9] In the study, they did not remove many ESPs on the first EGD, and records were used to judge which ESPs reoccurred and which were not removed in the first place.[9] The follow-up rate varies, but none of the studies reported a follow-up rate higher than 50%. The low follow-up rate, as well as low recurrence rate of ESP, limits the efforts to understand ESP recurrence, but based on our findings and current evidence, the recurrence rate ranged from zero to very low.

The concern on potential esophageal cancer in ESP came from case reports that showed a malignant transformation in what is known to be benign lesions.[25,35–37] Although the majority of the studies did not show malignant transformation during the follow-up period, our study and a few others showed a malignant transformation during the follow-up period. Moreover, squamous cell papilloma in other regions of the body, under special circumstances, can have malignant potential.[1] The characteristics of the ESP that showed malignant transformation are large, multiple, circumferential, and confluent.[9,25,35,37] On biopsy, they observed dysplastic changes and atypia.[9,25,35,37] HPV testing from most patients was negative,[25,35,36] and most of the patients had a presentation of dysphagia.[9,25,35,36]

The high rate of smoking and drinking in patients with malignant transformation is a major confounding factor in concluding the malignant potential of ESP. Field carcinogenesis theory can be applied to this condition, especially with observed synchronous malignancy cases[9,16] with high concurrent Barrett's and reflux esophagitis in some studies.[13] While HPV is common and implicated in poor outcomes in ESCC[29,38] and malignant transformation of papillomas in other parts of the body,[1] ESP cases with malignant transformations were negative for HPV.

Esophageal cancer is the sixth leading cause of cancer death and tends to affect males more than females.[39] On the other hand, ESP affects both genders, with slight female predominance in the newer studies as ours.[10,18] A study comparing ESP and ESCC population found that ESP patients are younger by more than 10 years on average and have no dysphagia on presentation, which is present in 82% of ESCC patients.[15] These vast differences in population demographics decrease the possibility that ESP is a direct precursor of ESCC, but it can act as an indirect precursor with selective progression into ESCC in some populations.

Considering the relatively low rates of recurrence and malignant transformation in patients with ESP, it is necessary to establish criteria to determine which patients require close monitoring and the appropriate intervals. Our recommendation is to closely monitor patients with multiple confluent ESPs, those larger than 0.5 cm, and those with atypia or dysplasia detected through histological analysis. Special consideration should be given to patients with other risk factors such as smoking and alcohol use. Additionally, dysphagia in a patient with ESP should be viewed as a warning sign. However, owing to the scarcity of data and limited evidence to support a specific follow-up interval, the decision on the duration of monitoring of ESP should be made jointly by the patient and physician.

Our study is the largest clinical study on ESP in the US population, with matched controls representing the general endoscopy population. However, the relatively small number of ESP cases due to its rarity has limited detailed subgroup analyses. In addition, our results were subject to limitations of the retrospective observational study design and referral bias due to being done in tertiary medical centers.

In conclusion, ESP is a rare esophageal lesion diagnosed on EGD with a nonspecific symptom profile. The pathogenesis of ESP is not well known but likely multifactorial. HPV and GERD may explain the subgroup of ESP formation, but other

unknown etiologies and pathogenic mechanisms will need further investigations in the future. The malignant potential of ESP is very low, but large or multiple ESPs with dysplasia on histology carries a definitely high malignancy potential and therefore should be resected. The role of longer term follow-up of patients with small, low-risk ESP is unclear, but closer follow-up of those with large or high-risk ESP is prudent. However, an appropriate follow-up interval for those ESP patients is uncertain because of the limited data on longer term follow-up of ESP patients.

References

1 Syrjänen S, Syrjänen K. HPV-associated benign squamous cell papillomas in the upper aero-digestive tract and their malignant potential. *Viruses*. 2021; **13**: 1624.
2 Tou AM, Al-Nimr AO. Esophageal squamous papilloma in children: a single-center case series. *J. Pediatr. Gastroenterol. Nutr.* 2021; **72**: 690–2.
3 Cho JY, Cheung DY, Kim TJ, Kim JK. A case of esophageal squamous cell carcinoma in situ arising from esophageal squamous papilloma. *Clin. Endosc.* 2019; **52**: 72–5.
4 Patterson EJ. Multiple papillomata of the esophagus report of a case. *Ann. Otol. Rhinol. Laryngol.* 1927; **36**: 1169.
5 Adler RH, Carberry DM, Ross CA. Papilloma of the esophagus. *J. Thorac. Surg.* 1959; **37**: 625–35.
6 Brinson RR, Schuman BM, Mills LR, Thigpen S, Freedman S. Multiple squamous papillomas of the esophagus associated with Goltz syndrome. *Am. J. Gastroenterol.* 1987; **82**: 1177–9.
7 Mosca S, Manes G, Monaco R, Bellomo PF, Bottino V, Balzano A. Squamous papilloma of the esophagus: long-term follow up. *J. Gastroenterol. Hepatol.* 2001; **16**: 857–61.
8 Sablich R, Benedetti G, Bignucolo S, Serraino D. Squamous cell papilloma of the esophagus. Report on 35 endoscopic cases. *Endoscopy*. 1988; **20**: 5–7.
9 d'Huart M-C, Chevaux J, Bressenot A *et al*. Prevalence of esophageal squamous papilloma (ESP) and associated cancer in northeastern France. *Endosc. Int. Open*. 2015; **3**: E101–6.
10 Takeshita K, Murata SI, Mitsufuji S *et al*. Clinicopathological characteristics of esophageal squamous papillomas in Japanese patients – With comparison of findings from western countries. *Acta Histochem. Cytochem.* 2006; **39**: 23–30.
11 Franzin G, Musola R, Zamboni G, Nicolis A, Manfrini C, Fratton A. Squamous papillomas of the esophagus. *Gastrointest. Endosc.* 1983; **29**: 104–6.
12 Chang F, Janatuinen E, Pikkarainen P, Syrjänen S, Syrjänen K. Esophageal squamous cell papillomas failure to detect human papillomavirus DNA by in situ hybridization and polymerase chain reaction. *Scand. J. Gastroenterol.* 1991; **26**: 535–43.
13 Odze R, Antonioli D, Shocket D, Noble-Topham S, Goldman H, Upton M. Esophageal squamous papillomas: a clinicopathologic study of 38 lesions and analysis for human papillomavirus by the polymerase chain reaction. *Am. J. Surg. Pathol.* 1993; **17**: 803–12.
14 Carr NJ, Bratthauer GL, Lichy JH, Taubenberger JK, Monihan JM, Sobin LH. Squamous cell papillomas of the esophagus: a study of 23 lesions for human papillomavirus by in situ hybridization and the polymerase chain reaction. *Hum. Pathol.* 1994; **25**: 536–40.
15 Talamini G, Capelli P, Zamboni G *et al*. Alcohol, smoking and papillomavirus infection as risk factors for esophageal squamous-cell papilloma and esophageal squamous-cell carcinoma in Italy. *Int. J. Cancer*. 2000; **86**: 874–8.
16 Szántó I, Szentirmay Z, Banai J *et al*. Squamous papilloma of the oesophagus. Clinical and pathological observations based on 172 papillomas in 155 patients. *Orv. Hetil.* 2005; **146**: 547–52.
17 Bohn OL, Navarro L, Saldivar J, Sanchez-Sosa S. Identification of human papillomavirus in esophageal squamous papillomas. *World J. Gastroenterol.* 2008; **14**: 7107–11.
18 Wong MW, Bair MJ, Shih SC *et al*. Using typical endoscopic features to diagnose esophageal squamous papilloma. *World J. Gastroenterol.* 2016; **22**: 2349–56.
19 Tiftikci A, Kutsal E, Altiok E *et al*. Analyzing esophageal squamous cell papillomas for the presence of human papilloma virus. *Turk. J. Gastroenterol.* 2017; **28**: 176–8.
20 Ekin N, Bestas R, Cetin A. Clinicopathological characteristics of patients with oesophageal squamous papilloma in Turkey and comparison with the literature data: the largest case series ever reported from Turkey. *Int. J. Clin. Pract.* 2021; **75**: e14420.
21 Pantham G, Ganesan S, Einstadter D, Jin G, Weinberg A, Fass R. Assessment of the incidence of squamous cell papilloma of the esophagus and the presence of high-risk human papilloma virus. *Dis. Esophagus*. 2017; **30**: 1–5.
22 Plachta A. Benign tumors of the esophagus: review of literature and report of 99 cases. *Am. J. Gastroenterol*. 1962; **38**: 639–52.
23 Carr NJ, Monihan JM, Sobin LH. Squamous cell papilloma of the esophagus: a clinicopathologic and follow-up study of 25 cases. *Am. J. Gastroenterol.* 1994; **89**: 245–8.
24 Jideh B, Weltman M, Wu Y, Chan CHY. Esophageal squamous papilloma lacks clear clinicopathological associations. *World J. Clin. Cases*. 2017; **5**: 134–9.
25 Reynoso J, Davis RE, Daniels WW, Awad ZT, Gatalica Z, Filipi CJ. Esophageal papillomatosis complicated by squamous cell carcinoma in situ. *Dis. Esophagus*. 2004; **17**: 345–7.
26 Bansal A, Singh M, Rai B. Human papillomavirus-associated cancers: a growing global problem. *Int. J. Appl. Basic Med. Res.* 2016; **6**: 84–9.
27 Lee HS, Lee JH, Choo JY, Byun HJ, Jun JH, Lee JY. Immunohistochemistry and polymerase chain reaction for detection human papilloma virus in warts: a comparative study. *Ann. Dermatol.* 2016; **28**: 479–85.
28 Nakamura Y, Mashima Y, Kameyama K, Mukai M, Oguchi Y. Detection of human papillomavirus infection in squamous tumours of the conjunctiva and lacrimal sac by immunohistochemistry, in situ hybridisation, and polymerase chain reaction. *Br. J. Ophthalmol.* 1997; **81**: 308–13.
29 Petrick JL, Wyss AB, Butler AM *et al*. Prevalence of human papillomavirus among oesophageal squamous cell carcinoma cases: systematic review and meta-analysis. *Br. J. Cancer*. 2014; **110**: 2369–77.
30 Syrjänen K, Syrjänen S. Detection of human papillomavirus in esophageal papillomas: systematic review and meta-analysis. *APMIS*. 2013; **121**: 363–74.
31 Cladel NM, Jiang P, Li JJ *et al*. Papillomavirus can be transmitted through the blood and produce infections in blood recipients: evidence from two animal models. *Emerg. Microbes Infect.* 2019; **8**: 1108–21.
32 Yang X, Chen X, Zhuang M *et al*. Smoking and alcohol drinking in relation to the risk of esophageal squamous cell carcinoma: a population-based case-control study in China. *Sci. Rep.* 2017; **7**: 17249.
33 Freedman ND, Abnet CC, Leitzmann MF *et al*. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am. J. Epidemiol.* 2007; **165**: 1424–33.
34 Karras PJ, Barawi M, Webb B, Michalos A. Squamous cell papillomatosis of esophagus following placement of a self-expanding metal stent. *Dig. Dis. Sci.* 1999; **44**: 457–61.
35 Attila T, Fu A, Gopinath N, Streutker CJ, Marcon NE. Esophageal papillomatosis complicated by squamous cell carcinoma. *Can. J. Gastroenterol.* 2009; **23**: 415–9.
36 Bronswijk M, Christiaens P, Moons V. Diffuse esophageal papillomatosis complicated by squamous cell carcinoma. *Dig. Liver Dis.* 2019; **51**: 1197.

37 Donnellan F, Walker B, Enns R. Esophageal papillomatosis complicated by squamous cell carcinoma. *Endoscopy*. 2012; **44**: E110–1.
38 Bognár L, Hegedus I, Bellyei S *et al*. Prognostic role of HPV infection in esophageal squamous cell carcinoma. *Infect. Agent. Cancer*. 2018; **13**: 38.
39 Morgan E, Soerjomataram I, Rumgay H *et al*. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. *Gastroenterology*. 2022; **163**: 649–658.e2.