

Original Article

Assessment of the incidence of squamous cell papilloma of the esophagus and the presence of high-risk human papilloma virus

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SUMMARY. *Background and Aims:* There has been a recent increase in the incidence of oropharyngeal cancer (OPC) associated with high-risk human papilloma virus (HPV) infection. We investigated the incidence of esophageal papilloma and the presence of high-risk HPV infection. *Methods:* This is a cross-sectional study conducted at a County teaching hospital. Patients with esophageal papilloma between January 2000 and December 2013 were identified. Patients with sufficient specimens were tested for the HPV virus. *Results:* Sixty patients with esophageal papilloma lesions were identified from 2000 to 2013. (31 males, age 51 ± 13 years). The incidence was 0.13% in 2000 and increased to 0.57% in 2013 ($P < 0.0001$). Twenty-nine patients (48.3%) had a papilloma that was more than 5 mm in size, and 20% had multiple lesions. The papilloma was located in the distal esophagus in 35 (58.3%) patients, mid esophagus in 17 (28.3%) patients, and proximal in 8 (13.3%) patients. Three (5%) patients had associated OPC, and 9 (47.4%) of the 19 patients tested were positive for high-risk HPV serotype 16. *Conclusions:* The incidence of esophageal papilloma has increased by fourfolds over the past 14 years. About half of the tested patients demonstrated high risk HPV. This may suggest a potential growing risk for esophageal squamous cell cancer in the future.

KEY WORDS: esophageal papilloma, esophageal squamous cell carcinoma, human papilloma virus.

ABBREVIATIONS: EGD: esophagogastroduodenoscopy; HPV: human papilloma virus; OPC: oropharyngeal cancers

INTRODUCTION

Squamous cell papilloma of the esophagus is a benign lesion that is seen incidentally during esophagogastroduodenoscopy (EGD). The clinical relevance, possible association with other pathological conditions, and role as a premalignant lesion remain to be further elucidated. The prevalence of squamous papilloma during EGD has been reported to vary from 0.01 to 0.43%.^{1–3}

There are no previous studies estimating the annual detection rates and the secular trend of the disease over time. However, there are several studies that have described the prevalence of esophageal papilloma. There are also limited data regarding esophageal papilloma and its association with the human papilloma virus (HPV) infection in the United States.^{4,5} Clinical observation in our endoscopy unit showed an apparent increase in the detection rate of esophageal papilloma during routine EGD over the past several years.

The incidence of HPV related oropharyngeal cancers (OPCs) worldwide, including in the United States, is on the rise.^{6–8} Presently, HPV associated OPC is more common than OPC due to smoking, chewing tobacco, or alcohol consumption. The squamous cell surface epithelium of the esophagus is contiguous with the oropharynx. Thus an oropharyngeal HPV infection may migrate beyond the upper esophageal sphincter and infect the esophagus. Because HPV

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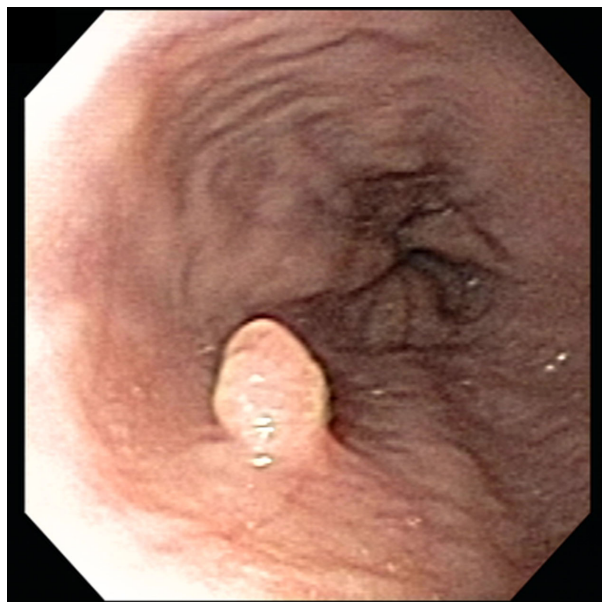


Fig. 1 Esophageal papilloma from a study participant. [Color figure can be viewed in the online issue, which is available at [wiley-onlinelibrary.com](https://onlinelibrary.com).]

has been shown to be associated with OPC, as well as esophageal cancer,^{9–11} the growing prevalence of HPV-associated OPC raises concerns about a future similar trend in the esophagus because both anatomical structures are covered with the same type of epithelium and are in close proximity to each other. Thus, the aims of this study were to determine the annual detection rate of esophageal papilloma, to evaluate whether the detection rate has increased over the past several years, and to determine the relationship between esophageal papilloma and high-risk HPV infection. Based on our clinical observations, we hypothesize that the incidence and prevalence of esophageal papilloma has been increasing over the last decade and thus may have an important future implication for esophageal cancer.

MATERIALS AND METHODS

Patients

The electronic medical record database at MetroHealth Medical Center, a Case Western Reserve University-affiliated teaching hospital, was searched for all patients who had undergone an upper endoscopy between January 2000 and December 2013. It is a standard practice here to biopsy any raised abnormal mucosal lesions in the esophagus (Fig. 1). Patients with a diagnosis of esophageal papilloma lesions were identified from the pathology reports. A standardized data collection process was used to obtain the information directly from the patient's electronic health records. The study protocol was

approved by the MetroHealth Medical Center institutional review board.

Data collected

Information obtained from medical records included demographics, size, and location of the lesion in the esophagus (distance from incisor teeth). The location was categorized as proximal (less than 24 centimeters [cm] from incisors), mid (24–32 cm from incisors), and distal portion of the esophagus (greater than 32 cm from incisors). The indication for upper endoscopy and the histopathological findings in the esophagus were also noted. The electronic medical record was searched for any history of oropharyngeal, gastrointestinal, or other malignancies. Any subsequent upper endoscopy for recurrence of these lesions was noted. Pathology reports were abstracted to obtain histological diagnoses, evidence of inflammation, dysplasia, and malignancy.

HPV serotype testing

All patients with sufficient available samples were tested for high-risk HPV serotypes 16 and 18. For genomic DNA extraction and polymerase chain reaction (PCR), formalin-fixed, paraffin-embedded (FFPE) blocks were sectioned at 5–10 μ m thickness. Five to 10 sections were subjected to genomic DNA extraction using Qiagen's QIAamp DNA FFPE Tissue Kit (Germantown, MD) following the manufacturer's protocol. Genomic DNA was eluted in 100 μ L of TE buffer and quantified using a nanodrop 2000c spectrophotometer (Thermo Fisher Scientific, Waltham, MA). For PCR analyses, 100 μ g of total DNA were used in 25 μ L of PCR mix with primers 5'-atgcacaaaagagaactgcaa and 5'-tcacatacagcatatggattcccatc for HPV-16 E6, 5'-gcatggagatacatgcatg and 5'-tgtgtcttgtacgcacaaccgaag for HPV-16 E7, as well as 5-atggacctaaggcaacattgcaagaca and 5'-tcggctcgtcgggctggtaa for HPV-18 E6. PCR was conducted using the profile: 95°C, 3 minutes for 1 cycle; 94°C, 20 seconds (sec)/60°C, 20 seconds/72°C, 30 seconds for 46 cycles, and 72°C for 5 minutes for 1 cycle. PCR products were run on a 2% agarose (Thermo Fisher) gel along with the 100 bp ladder and stained with 1% ethidium bromide (Thermo Fisher). Gel images were documented using the ChemiDoc XRS imaging system (Bio-Rad, Hercules, CA).

Statistical analysis

Patients' characteristics were summarized using means and standard deviations. The change in rate of papilloma over time was assessed using the Cochran–Armitage trend test. A *P* value of less than 0.05 was

Table 1 Yearly detection rate of esophageal papilloma

Year	Number of EGDs	Number of cases with esophageal papilloma	Percentage per year (95% CI)
2000	1551	2	0.13 (0.02–0.47)
2001	1672	0	0 (0–0.2)
2002	1820	0	0 (0–0.2)
2003	2062	1	0.05 (0–0.27)
2004	2125	1	0.05 (0–0.26)
2005	2200	3	0.14 (0.03–0.34)
2006	1960	3	0.15 (0.03–0.45)
2007	2007	5	0.25 (0.08–0.58)
2008	2194	4	0.18 (0.04–0.47)
2009	2131	7	0.33 (0.13–0.68)
2010	2061	7	0.34 (0.14–0.70)
2011	2091	8	0.38 (0.17–0.75)
2012	2251	5	0.22 (0.07–0.52)
2013	2476	14	0.57 (0.31–0.95)
Total	28,601	60	0.21 (0.16–0.27)

CI, confidence interval.

considered statistically significant. All analyses were done using SAS version 9.4.

RESULTS

Between 2000 and 2013, we identified a total of 60 patients with a histologically confirmed diagnosis of esophageal papilloma. A total of 28,601 EGDs were performed during the study period. The number of EGDs per year, number of lesions identified each year, and yearly detection rate in percentage are shown in Table 1. The data were analyzed with the Cochran–Armitage trend test, which showed a statistically significant ($P < 0.0001$) rise in the detection of esophageal papilloma over a period of 14 years (Fig. 2).

The study population had an average age of 51 ± 13 years (range: 26–79 y); of those, 31 (52%)

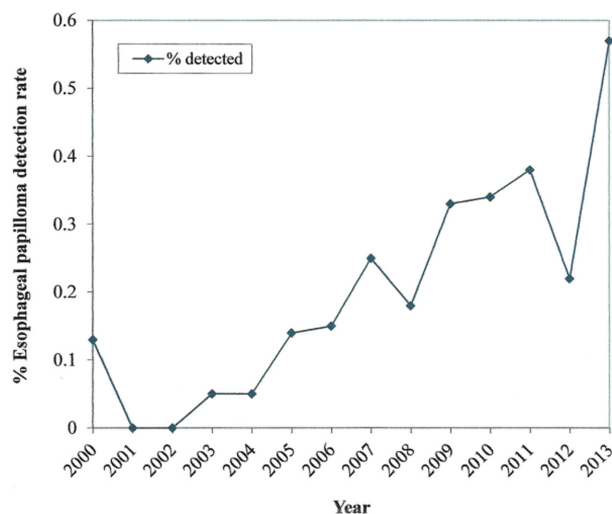


Fig. 2 The percent of esophageal papilloma detection trend over 14 years. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

patients were male, and the average BMI was 29 ± 7 kg/m² (range: 16–45 kg/m²) (Table 2). The size of the papilloma lesions varied from less than 5 mm to about 3 cm, and 29 patients (48.3%) had lesions of more than 5 mm in size. The lesions were found in the distal esophagus in 35 patients (58.3%), mid esophagus in 17 subjects (28.3%), and proximal esophagus in 8 (13.3%) patients. The average distance of these lesions from the incisors was 30.8 ± 7.5 cm (range: 15–42 cm). Twelve patients (20%) had more than one papilloma lesion in the esophagus. Histology of these lesions apart from papillomatous changes showed acute inflammatory cells in 10 patients (16.7%), chronic inflammation in 10 patients (16.7%), reactive atypia in 5 patients (8.3%), and mild dysplasia in 2 patients (3.3%). None of the lesions showed evidence of malignancy. Follow-up upper endoscopy was done in 10 subjects (16.7%) after 2–24 months; none showed recurrence of the papilloma lesions.

Among the study patients, the indication for upper endoscopy was evaluation of gastroesophageal reflux disease in 25 (42.6%) patients, perioperative surveillance for OPC in 4 (6.7%) patients, and epigastric pain, variceal screening, persistent nausea, and hematemesis in the remainder. The upper endoscopy findings showed changes of reflux esophagitis in 18 (30%) patients, Barrett's mucosa in 3 (5%) patients, and adenocarcinoma of the lower end of the esophagus in 1 patient. Three of the 60 patients had squamous cell carcinoma of the oropharynx, one patient had pyriform sinus cancer of the larynx, one had large cell cancer of the lung, and one had adenocarcinoma of the colon.

The papilloma lesion samples of 19 patients (seven male, average age: 51 ± 11.5 years) who had upper endoscopy between January 2010 and December 2013 were available to be tested for HPV serotypes. Of those, nine (47.4%) patients (two males, average age: 55 ± 7.5 years) were tested positive for HPV serotype 16. Two patients had proximal esophageal lesions (one in the mid esophagus), and the remaining six patients had distal lesions. The average distance of these lesions was 28.8 ± 9.3 cm (range: 15–40 cm) from the incisors. There were no statistically significant differences between the HPV-positive and HPV-negative patients (Table 2). HPV testing could not be done in other patient samples due to a lack of adequate specimens. None of the participants were tested positive for human immunodeficiency virus (HIV) antibodies.

DISCUSSION

Our single center study demonstrated a significant increase in the annual detection rate of squamous cell papilloma of the esophagus over the last 14 years, reaching 0.57% of the total number of endoscopies in 2013. The majority of patients tested were positive

Table 2 Patient demographics and findings

	Total patients	Subjects analyzed for high-risk HPV	HPV-positive patients	P value*
Number of patients	60	19	9	
Mean age (years) (1SD)	51 ± 13	51 ± 11.5	55 ± 7.5	0.15
Male	31 (51.7%)	7 (36.8%)	2 (22.2%)	0.35
Size > 5 mm	29 (48.3%)	9 (47.4%)	3 (33.3%)	0.37
Proximal esophageal lesions	8 (13.3%)	2 (10.5%)	2 (22.2%)	0.47
Mid esophageal lesions	17 (28.3%)	3 (15.8%)	1 (11.1%)	
Distal esophageal lesions	35 (58.3%)	14 (73.7%)	6 (66.7%)	

*For comparison of HPV-positive with HPV-negative patients.

for high-risk HPV serotype 16 from the lesions found in different sites of the esophagus (Table 2). Among all 60 patients, 5% had squamous cell carcinoma of the oropharynx (one tonsillar and two base of the tongue).

It is postulated that the etiology of esophageal papilloma is due to injury and inflammation resulting from events such as reflux esophagitis, mucosal irritation from nasogastric tubes, and bougie-assisted mechanical esophageal dilatation followed by regeneration.^{4,12} Several other studies have described the prevalence and association of HPV infection with papilloma lesions.^{5,13–15} Bohn *et al.* reported that 85.7% of papilloma lesions were associated with mostly low-risk HPV.¹³ In our study, high-risk HPV serotype 16 was detected in 9 of 19 (47.4%) patients tested. Our study results are comparable to the previous study by Odze *et al.*, who found approximately 57% of esophageal papilloma lesions positive for mostly HPV serotype 16 by viral PCR from a North American patient population.⁵

Among the patients in the current study, three (5%) had squamous cell cancer of the oropharynx, which is associated with high-risk HPV, further raising the possibility that esophageal papilloma in these individuals may be caused by HPV infection. Among these three patients, only one tissue sample was tested for HPV (others were not tested), and it was positive for high-risk HPV with the *in situ* hybridization test. The proximal esophageal lesions in two of the patients who tested positive for high-risk HPV may be due to migration of the virus from the oral cavity to the esophagus.

The etiology for the increased detection rate of esophageal papilloma that we found in our study is unclear. Possibly, it is due to rising incidence of HPV infection in the community as a result of oral sexual transmission. This hypothesis is supported by Dunne *et al.* who demonstrated a higher burden of HPV infection in the United States compared with earlier studies.¹⁶

Among all study participants, a majority of the lesions (35/60) were located in the distal esophagus, similar to previous studies^{4,5} suggesting that mucosal injury by acid reflux apart from HPV infection may also play an etiologic role in esophageal papilloma formation.

The observed increase in the detection rate of esophageal papilloma is concerning due to the recent global trend of increasing incidence of OPC associated with high-risk HPV.^{7,25} High-risk HPV is known to be associated with cervical, anal, vaginal, vulvar, penile, oropharyngeal, and esophageal cancers due to its preference for infecting the differentiating squamous cell epithelium.^{17–21} Head and neck malignancies were mostly caused by tobacco and alcohol prior to last decade; however, recent studies have shown that about 70% of cancers of the oropharynx may be linked to high-risk HPV infection.^{22–25} Additionally, recent studies have shown an increase in the incidence of HPV-associated OPC in the United States.^{26,27} Because the squamous cell lining of the oropharyngeal mucosa is in direct continuity with the esophagus, HPV can potentially migrate and infect the adjacent esophagus. Increased infection with HPV of the esophageal squamous epithelium may result in an increase of esophageal cancer, especially if the mucosa is also affected by the acid reflux. Previous studies have suggested a causal role for HPV in esophageal squamous cell cancer,^{9–11} even though some other studies have shown a low detection rate of HPV viral DNA in malignant tissue samples.²⁸

Among the 60 patients in the current study, none demonstrated evidence of esophageal squamous cell malignancy. Papilloma samples from two (3.3%) patients showed evidence of mild dysplasia, which rarely progresses to malignancy; no follow-up upper endoscopy was done. There was no recurrence of lesions in 10 (16.7%) patients who underwent upper endoscopy from 2 to 24 months later. However, a recent study published by d'Huart *et al.* showed that 1 of 78 study patients (1.3%) was diagnosed with squamous cell carcinoma of the esophagus at the previous papilloma resection site during a follow-up endoscopy 2 years later.²⁹ Currently, there are no guidelines for surveillance of these patients. However, long-term follow-ups are needed to determine the malignant potential of these lesions.

None of the study patients tested positive for HIV, which can increase the risk of HPV infection.^{30,31} However, our study demonstrates the presence of HPV infection in half of the papilloma's tested, which is independent of co-infection with HIV.

There are several limitations to our study. This was a single-center, population-based project that focused on a population from one hospital. Consequently, the results may not be generalizable to other sites or regions. We were unable to test all study patients for high-risk HPV due to lack of adequate specimens. The rate of high-risk HPV in the tested sample set may not be representative of the rest of the patients in the study group.

Despite the above-mentioned limitations, our study is the first to report the rising incidence of esophageal papilloma in a community hospital-based study.

In summary, our study demonstrates a dramatic rise in the detection rate of esophageal papilloma in the last decade. In addition we demonstrated the presence of high risk HPV in about half of the tested papillomas. While there was no evidence in our study that these findings were also associated with increased incidence of esophageal squamous cell carcinoma, the study may suggest that we should be vigilant in the future because the trend may continue to rise. Routine assessment of all papilloma lesions for high-risk HPV, testing saliva samples of these people for high-risk HPV and possibly initiation of a surveillance program for those with HPV-related papilloma should be considered. Further research is also needed to substantiate our findings in other patient populations.

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