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ORIGINAL ARTICLE

#### **Retrospective Study**

# Esophageal squamous papilloma lacks clear clinicopathological associations

Bilel Jideh, Martin Weltman, Yang Wu, Calvin H Y Chan

Bilel Jideh, Martin Weltman, Yang Wu, Calvin H Y Chan, Department of Gastroenterology and Hepatology, Nepean Hospital, Sydney, NSW 2747, Australia

Author contributions: Chan CHY designed the study and supervised manuscript preparation; Wu Y acquired study data; Weltman M supervised manuscript preparation; Jideh B acquired study data, reviewed the literature and wrote the paper.

Institutional review board statement: Nepean Hospital institutional review board gave ethics approval of study design and protocol.

Informed consent statement: This was a retrospective study; some of the patients had deceased. Patient consent was not obtained but the presented data are anonymized and the risk of identification is low/nil. The study design was approved by Nepean Hospital institutional review board.

Conflict-of-interest statement: None of the authors have any conflict of interest to declare.

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Correspondence to: Bilel Jideh, Gastroenterology Trainee, Department of Gastroenterology and Hepatology, Nepean Hospital, Derby Street, Kingswood, Sydney, NSW 2747, Australia. bjid7747@uni.sydney.edu.au Telephone: +61-413-724433 Fax: +61-247-341313

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## Abstract

#### AIM

To determine the prevalence of esophageal squamous papillomas (ESPs) in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

#### **METHODS**

Data from a total of 6962 upper gastrointestinal endoscopies over a five year period were retrospectively obtained and analysed.

#### RESULTS

ESP was found in sixteen patients (0.23%). Eight (50%) patients had a high body mass index, seven (44%) had history of cigarette smoking. Reflux esophagitis was found in four (25%) patients. All ESPs were solitary with a mean endoscopic size of 3.8 mm and located in the mid to lower esophagus. Human papilloma virus (HPV) was tested in three (19%) patients and was negative. Esophageal SCC was found in seven patients (0.10%) during the same period. None of the specimens were tested for HPV, and none had associated papillomatous changes.

#### **CONCLUSION**

ESP is an uncommon tumour with unclear clinical associations and malignant potential.

Key words: Esophagus; Papilloma; Gastroesophageal reflux disease; Human papilloma virus; Squamous cell



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#### Jideh B et al. Esophageal squamous papilloma

#### carcinoma

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**Core tip:** Esophageal squamous papilloma is a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. A high body mass index and a history of cigarette smoking, both risk factors for gastroesophageal reflux disease, were the most prevalent patient characteristic in our cohort with esophageal squamous papillomas (ESPs), however no definite associations can be established. None of the esophageal squamous cell carcinomas during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

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#### INTRODUCTION

Esophageal squamous papilloma (ESP) is a rare tumour of the esophagus with a reported prevalence of 0.01% to 0.45%<sup>[1-5]</sup>. Lesions rarely cause symptoms, and are usually an incidental finding on endoscopy. Typical endoscopic appearance is that of a small, less than 5mm sessile wart-like fleshy nodule (Figure 1) located predominantly in the middle to lower esophagus<sup>[1,2]</sup>. Larger lesions with a more raised, erythematous appearance have also been described<sup>[6]</sup>. The aetiology has not yet been established; proposed factors include chronic gastroesophageal reflux disease (GERD), human papilloma virus (HPV) and mucosal trauma<sup>[5,7-13]</sup>. The clinical associations and malignant potential of these lesions is unknown. Currently, there is no consensus on appropriate management and surveillance strategies for ESPs. In this study we aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations. We also attempted to assess its association with esophageal squamous cell carcinoma (SCC).

#### MATERIALS AND METHODS

All patients between June 2010 and March 2015 with ESP and esophageal SCC at a tertiary teaching hospital (Nepean Hospital) were retrospectively identified using the electronic pathology department database. Over this period a total of 6962 upper gastrointestinal endoscopies were performed. Patients were identified and their



Figure 1 Esophageal squamous papilloma on upper endoscopy. A well demarcated soft wart-like sessile nodule with an estimated endoscopic size of 3 mm.

medical records and endoscopic reports were reviewed and analysed. The clinical information assessed included age, gender, body mass index (BMI), cigarette smoking history and use of acid suppression therapy [proton pump inhibitor (PPI)]. The endoscopic findings comprised the location, size and number of lesions; presence of a hiatus hernia, and presence of reflux esophagitis. Results of HPV testing were noted when performed; histology reports for patients with esophageal SCC during the same period were carefully perused for any papillomatous changes.

#### RESULTS

Among the 6962 upper gastrointestinal endoscopies performed over the study period, sixteen patients were found to have ESPs giving a prevalence of 0.23%. Patient characteristics are summarised in Table 1. The patients with ESPs comprised of ten (62.5%) females with mean age of 52  $\pm$  16 (SD) years (range 33-83 years). Eight (50%) patients were overweight or obese having BMIs between 25-39; seven (44%) patients were cigarette smokers; three (19%) patients were using regular acid suppression therapy (PPIs). The indications for the endoscopic procedure varied with two of the sixteen patients having the procedure for investigation of GERD and one patient for dysphagia. One patient had evidence of a hiatus hernia, which was small. Reflux esophagitis was found in four (25%) of the sixteen patients. All patients had solitary papillomas; mean endoscopic size of lesions was  $3.8 \pm 3.2$  (SD) mm (range 1-12 mm) and the mean size of histological specimens was 2.9  $\pm$ 1.5 (SD) mm (range 1-7 mm). All the papillomas were found in the middle to lower esophagus. Seven (44%) of them were biopsied; seven (44%) were removed with a polypectomy snare and details of the remaining two were not documented. Patients that had lesions biopsied did not have a repeat gastroscopy within the same study period for definitive resection of the lesion. Two (13%) patients had repeat endoscopies following endoscopic snare resection within the same study period and there was no evidence of papilloma recurrence. Helicobacter



Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI	PPI use (Y/N)	Indication for endoscopy	Location of P ESP from incisors E	No. Endoscopic of size of ESP ESPs (mm)	copic Histological f ESP size of ESP n) specimen (mm)	Hiatus hernia (Y/N)	Reflux esophagitis (Y/N)	<i>Helicobacter</i> <i>pylori</i> (positive/ negative)	HPV test (positive/ negative)	Method of ESP resection/sampling
-	57	ц	γ	20	z	Upper GI bleed	Distal	1 Small	all 2	z	z	Negative	n/a	n/a
2	83	щ	Z	19	γ	Dvshpagia	20	1 3	£	Z	Y	Negative	n/a	Snare polypectomy
ю	<del>6</del> 6	Μ	Z	24	Z	Abdominal pain	32	1 Small	all 4	Z	Z	Negative	n/a	Snare polypectomy
4	74	Μ	Z	36	Z	Abdominal pain	39	1 Small		Z	Z	n/a	n/a	Hot biopsy
ß	60	ц	Z	34	Υ	GERD	33	1 4	3	Y (3 cm)	Υ	Negative	n/a	Snare polypectomy
9	39	Μ	Z	30	Z	GERD	38	1 3		Z	Y	Negative	Negative	Snare polypectomy
7	39	ц	Z	24	Z	Bloating	28	1 3		Z	Z	Negative	n/a	Biopsy
8	33	ц	Z	21	Z	Anaemia	27	1 Small		Z	Y	Negative	n/a	Snare polypectomy
6	49	Μ	Υ	30	Z	Abdominal pain, family history CRC	Distal	1 Small	all 3	Z	Z	Negative	n/a	n/a
10	37	ц	Z	24	Z	Family history of gastric cancer	32	1 1		Z	Z	Negative	Negative	Biopsv
11	54	ц	γ	23	Z	Variceal screen	35	1 2	4	Z	Z	n/a	n/a	Biopsy
12	39	Μ	Υ	34	Z	Abdominal pain	39	1 4		Z	Z	Negative	n/a	Biopsv
13	81	ц	Υ	28	Z	Diarrhoea	25	1 Small		Z	Z	Negative	n/a	Biopsv
14	45	Μ	Υ	31	Υ	Abdominal pain	Upper third	1 2		Z	Z	Negative	n/a	Snare polypectomy
15	38	щ	Υ	n/a	Z	Bloating, abdominal pain	25	1 n/a		n/a	n/a	Negative	n/a	Biopsv
Ţ	Į	F		L C			L		l			0		· · · · · · · · · · · · · · · · · · ·
16	41	Ľ.	Z	27	Z	Abdominal pain	35	1 12	2	Z	Z	Negative	Negative	Snare polypectomy
BMI: Body Yes; N: No	y mass ii o.	ndex;  PPI:	Proton pur	ihni qn	lbitor; CRC	BMI: Body mass index; PPI: Proton pump inhibitor; CRC: Colorectal cancer; GERD: Gastroesophageal reflux disease; HPV: Human papilloma virus; n/a: Not available; ESP: Esophageal squamous papilloma; M: Male; F: Female; Y: Yes, N: No.	ıgeal reflux dise	ase; HPV: F	luman papilloma viru	ıs; n/a: Not a	vailable; ESP:	Esophageal squan	nous papillon	na; M: Male; F: Female; Y
	•						ų	-	:	:	:			
<i>pylori</i> v Sev	vas not en nat	t eviden ients w	it on mici ere obse	oscor rved t	oy in any to have	<i>pylor</i> was not evident on microscopy in any of the patients. HPV testing was performed on only three patient and all were negative. Seven natients were observed to have esonhageal SCC in the same period, giving a prevalence of 0.10%. Patient characteri	as pertorme period. givin	d on only a a prev	r three patient ar alence of 0.10%	nd all were . Patient (	e negative. characteris	tics are summ	harised in	sting was performed on only three patient and all were negative. Same period. giving a prevalence of 0.10%. Patient characteristics are summarised in Table 2. The group
compri	sed of	five (71	¦%) femĕ	ales a	nd with		ars (range 5	0-92 yea	Irs). Two (29%)	patients v	vere overw	reight, one (1 <sup>2</sup>	4%) patier	SD) years (range 50-92 years). Two (29%) patients were overweight, one (14%) patient was underweight
with a specim	BMI of ens. ∏	f 18, an 1ere we	id the rei ire no rep	mainii orted	ng four ( I papillon	with a BMI of 18, and the remaining four (57%) patients had BMIs within healthy rar specimens. There were no reported papillomatous changes on histological examination.	in healthy т examination	ange. Th '.	ree (43%) patie	nts were (	cigarette sı	mokers. HPV 1	was not te	IIs within healthy range. Three (43%) patients were cigarette smokers. HPV was not tested on any of the ological examination.
DISCUSSION	USSI	NO												
In our nrevioi	study is stud	the pre ies in H	svalence he literat	of ES	SPs was The fem;	In our study the prevalence of ESPs was 0.23% which is consistent with previously published studies <sup>[1-5]</sup> . The majority of the patients were middle-aged also similar to previous studies in the literature. The female predominance in our cohort is an inconsistent observation compared to previous reports on ESPs <sup>[1,7,8,14]</sup> . Althouch GERD has	th previousl rt is an inco	y publist	hed studies <sup>[1-5]</sup> .	The major mared to	rity of the	patients were	e middle-a	stent with previously published studies <sup>[1-5]</sup> . The majority of the patients were middle-aged also similar to ur cohort is an inconsistent observation compared to previous reports on FSPs <sup>[1,7,8,14]</sup> . Although GFRD has
been p	ostulat	ed to b	ie a facto	in t	the aetio	been postulated to be a factor in the aetiology of $ESP^{(5,9,15)}$ , only two (1)	2.5%) of ou	r study p	atients underwe	ant upper	endoscopy	/ for GERD. H	lowever, w	two (12.5%) of our study patients underwent upper endoscopy for GERD. However, we cannot ascertain
with ar	iy certi	ainty th	lat the ot	her p	atients (		sported by t	he findir	ig of reflux esop	hagitis in	two (12.5 <sup>4</sup>	%) patients w	ho had th	is is supported by the finding of reflux esophagitis in two (12.5%) patients who had the procedure for an
indicati	on oth	er than	GERD (c	ne fo	or the inv	indication other than GERD (one for the investigation of anaemia and the	and the other for dysphagia, Table 1)	vsphagia	, Table 1).	I				
ΥP.	igh BM	I was ti	high BMI was the most	preva	alent of t	A high BMI was the most prevalent of the assessed patient characteristics in our study with 50% of patients having a BMI in the overweight-obese range. An association	istics in our :	study wit	eristics in our study with 50% of patients	its having	a BMI in th	having a BMI in the overweight-obese rang	-obese rai	nge. An association

characteristic in the studied patients was a history of cigarette smoking found in seven (44%) patients. Cigarette smoking was not found to be associated with ESP in a previous study<sup>[14]</sup>, but similar to a high BMI, cigarette smoking is a risk factor for the development of GERD<sup>[12]</sup>. Hiatus hernia is another risk factor for GERD which was between BMI and ESPs has not been previously demonstrated. However, an elevated BMI is an established risk factor for GERD<sup>116</sup>. The second most prevalent clinical observed in one (6.25%) patient in our cohort and it was small-sized.

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Patient No.	Age (yr)	Sex (M/F)	Cigarette smoking (Y/N)	BMI	Indication for endoscopy	Location of SCC from incisors (cm)	HPV test (positive/ negative)	Papillomatous changes on histopathology	Management of SCC
1	50	М	Y	21	Dysphagia, B/G achalasia	40	n/a	No	Ivor-Lewis esophagectomy
2	92	F	Ν	29	Dysphagia	32	n/a	No	Palliation
3	62	F	Y	25	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy
4	86	F	Ν	20	Dysphagia	15	n/a	No	Radiation therapy, Palliation
5	76	F	Ν	20	n/a	Middle	n/a	No	Neoadjuvant Chemo-Radiation, Ivor Lewis esophagectomy
5	59	F	Ν	18	n/a	Middle	n/a	No	Ivor-Lewis esophagectomy, Chemotherapy, Palliation
7	72	М	Y	20	Dyspnoea. B/G achalasia	Distal	n/a	No	Radiation therapy, PEG tube feeding Palliation

BMI: Body mass index; HPV: Human papilloma virus; SCC: Squamous cell carcinoma; n/a: Not available; M: Male; F: Female; Y: Yes; N: No.

The mean size and location of ESPs were consistent with previous observations<sup>[1,2]</sup>. They were all solitary and appeared as rounded well delineated sessile wart-like lesions (Figure 1) as traditionally described. Multiple lesions have been observed in some studies<sup>[18-20]</sup>.

ESPs were not all removed with therapeutic intent, which is the general recommendation, despite the ambiguity about their malignant potential<sup>[21]</sup>. Histological diagnosis remains important due to the endoscopic resemblance to other pathologies including alvcogenic acanthosis, verrucoid border of SCC, and verrucous carcinoma<sup>[2,21]</sup>. Case reports of alternative ablative techniques including radiofrequency ablation have been described<sup>[22]</sup>. Recurrence after definitive endoscopic removal is thought to be low<sup>[2]</sup>. This was true for the two patients in our series that had repeat gastroscopies within the same study period and no evidence of papilloma recurrent was found. It is unclear whether other lesions not endoscopically removed were not followed due to lack of well-established management and surveillance guidelines.

Three patients in our cohort had testing for HPV (serotype 16) in the ESP specimen and the results were all negative. Although HPV infection is a proposed aetiological factor since the demonstration of HPV antigens in ESPs<sup>[23]</sup>, the extent of the contribution is controversial and most reported lesions, similar to our study, are found in the absence of HPV<sup>[2,13,14,24,25]</sup>. *Helicobacter pylori* has not been proposed to have any association in any of the previous ESP studies, and in our cohort the bacterium was not detected on microscopy in any of the patients.

The prevalence of esophageal SCC in this study was 0.10%. Most patients (71%) were females and generally older than the cohort with ESPs years. The risk of esophageal SCC, unlike esophageal adenocarcinomas, is not generally increased with obesity<sup>[26]</sup> and this was true in our cohort with five (71%) patients having BMIs within healthy range. Cigarette smoking is an established risk factor for esophageal SCC and in our group three (43%) patients had a history of cigarette smoking.

HPV was not tested in any of the esophageal SCC specimens in our cohort, neither were any papillomatous changes reported. Whilst HPV infection and papilloma

formation are considered a precursor in cervical and oropharyngeal squamous carcinoma<sup>[27,28]</sup>, the relation between HPV and esophageal SCC is controversial with conflicting results across multiple studies. Several systematic reviews and meta-analyses have addressed this relation, two of the most recent by Li *et al*<sup>[29]</sup> and who Petrick *et al*<sup>[30]</sup> concluded that further studies are needed to clarify the association.

This study has several limitations. The study is a retrospective assessment of results which can lead to the possibility of inaccurate and incomplete data. It was performed in a single, tertiary-care institution which can introduce a selection bias. Most patients with ESP did not have follow-up gastroscopies to assess for ESP clearance or recurrence. Finally, the analysis of results is largely descriptive given the low prevalence and small absolute numbers of patients with ESPs making it difficult to draw conclusions on any clinical associations.

In summary, ESPs remains a rare endoscopic finding with uncertain clinicopathological associations. They are usually asymptomatic and their aetiology is unknown. Whilst a high BMI and a history of cigarette smoking, both risk factors for GERD, were the most prevalent patient characteristic in our cohort with ESP, no definite associations can be established. None of the esophageal SCCs during the same study period progressed from ESP. Long-term longitudinal studies would be valuable to clarify clinical associations and the malignant potential of ESPs in order to establish appropriate management and surveillance strategies.

### COMMENTS

#### Background

Esophageal squamous papilloma (ESP) is a rare tumour with a reported prevalence of 0.01% to 0.45%. It is usually asymptomatic and discovered incidentally on upper endoscopy. The aetiology, clinical associations along with its malignant potential are unknown. The aim of this study was to determine the prevalence of ESPs in a tertiary teaching hospital and to assess for any clinical associations, including relations with esophageal squamous cell carcinomas (SCCs).

#### Research frontiers

There are limited studies on ESPs. Gastroesophageal reflux disease (GERD),

human papilloma virus (HPV) and mucosal trauma are proposed aetiological factors. No studies have assessed associations between ESPs and SCCs.

#### Innovations and breakthroughs

This study identified certain clinical features to be prevalent in patients with ESP including high body mass index and cigarette smoking, which have not been previously described. Also, the SCCs in the study period did not seem to progress from ESPs which may suggest ESP are benign.

#### Applications

This study contributes to the body of hypotheses surrounding ESP. Large longitudinal studies are required to help clarity clinicopathological associations of ESPs and their malignancy potential in order to establish appropriate management and surveillance strategies.

#### Peer-review

The authors aimed to identify the prevalence of ESPs in an Australian tertiary hospital cohort and to assess for possible clinical associations and to assess its association with esophageal SCC whose large data from a total of 6962 upper gastrointestinal endoscopies. Well written, well balanced.

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