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The incidence of esophageal second primary cancer in head and neck cancer patients

Tz-Wei Chiou, MD[a], Chi-Kuang Young, MD[b,c], Ken-Hao Hsu, MD[b,c], Chun-Ta Liao, MD[b,c], Yu-Feng Hu, MD[b,c], Chung-Jan Kang, MD, PhD[b,c], Shiang-Fu Huang, MD, PhD[b,d,*]

Abstract

This study aims to investigate the correlation between esophageal second primary neoplasm (ESPN) in head and neck cancers. Panendoscopy findings of ESPN can guide clinicians in timely interventions and improve patients' outcomes. We performed a retrospective cohort study in Linkou Chang Gung Memorial Hospital, and 365 patients who met the criteria from 2015 to 2021 were enrolled. We collected the lifestyle habits and panendoscopy report after the HNC was diagnosed. Of 365 HNC patients, 37 (10.1%) had ESPNs, which included low dysplasia, high dysplasia, squamous cell carcinoma in situ and squamous cell carcinoma. We found that alcohol ($P = .004$) and areca-quids (AQs) consumption ($P = .003$) had significant differences in different HNC subsites. Oral cavity cancers had the highest association with alcohol and AQs consumption. Hypopharyngeal cancer has the highest ESPN incidence with highest odds ratio (OR = 13.3, $P < .001$), followed by oropharynx, larynx, and oral cavity. In addition, we found that alcohol ($P = .002$) and cigarette consumption ($P = .040$) were associated with the ESPN development. Other panendoscopy findings such as gastroesophageal reflux disease, esophageal mucosa break, gastritis ulceration, and gastritis showed insignificant correlations with the occurrence of ESPN. Half of the ESPN were found within 24 months after the diagnosis of HNC, especially for hypopharyngeal cancer, in which ESPN even occurs within 12 months of the diagnosis of primary tumor. Routine panendoscopy for patients with HNC is highly advised, and our study suggests having intensive surveys in the first 24 months after the diagnosis of primary HNC; especially for hypopharyngeal cancer. This study was reported in strict compliance with the strengthening the reporting of observational studies in epidemiology (STROBE) guideline.

Abbreviations: AQ = areca quid, CI = confidence interval, EGD = esophagogastroduodenoscopy, ER = endoscopic resection, ESD. = eendoscopic submucosal dissection, ESPNs = esophageal second primary neoplasms, HNC = head and neck cancer, NBI-M = barrow-band imaging with magnification, ORs = odds ratios, WLE = white-light endoscopy.

Keywords: esophageal cancer, head and neck cancer, panendoscopy, secondary primary cancer

1. Introduction

Head and neck cancer (HNC), which includes cancers from the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx, and esophageal cancer are both increasing worldwide in recent years.[1,2] Patients with HNC are also at increased risk of developing second primary tumor, which including the esophageal cancer.[3] This risk of having esophageal cancer after HNC treatments is an 8-fold to 22-fold higher than the general population.[4–6] The second primary tumor development now can be explained by the "field cancerization theory": Premalignant epithelial changes are caused by repeated exposure to common carcinogens, such as alcohol, tobacco and areca quid (AQ), which contributes to the development of synchronous or metachronous second primary tumors.[7]

In south Asia, such as Taiwan, the risk factors of HNC with esophageal second primary cancer not only have alcohol and tobacco, but also have AQ chewing.[8] Due to the increased consumption of these carcinogens in recent years, the prevalence of HNC and esophageal cancer gets higher.

Esophageal carcinomas are often diagnosed in advanced stages because they can be asymptomatic at the early development.[9] Generally, esophageal cancer at the early stage only can be screened by esophagogastroduodenoscopy (EGD), and

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was performed in compliance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital [IRB no. 202400276B0].

[a] Department of Medical Education, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan (ROC), [b] Department of Otorhinolaryngology, Chang Gung Memorial Hospital at LinKou, Taoyuan City, Taiwan (ROC), [c] College of Medicine, Chang Gung University, Taoyuan City, Taiwan (ROC), [d] Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan City, Taiwan (ROC).

** Correspondence: Shiang-Fu Huang, Department of Otorhinolaryngology, Chang Gung Memorial Hospital at LinKou, No.5, Fu-Shing St., Kwei-Shan Dist. Taoyuan City 333, Taiwan (ROC) (e-mail: shiangfu.huang@gmail.com).*

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can be treated by invasive ER.[10] EGD, also known as upper endoscopy or panendoscopy, is a procedure to inspect the upper gastrointestinal tract, including the esophagus, stomach, the first and the second portion of the duodenum. In addition to these, the esophageal second primary cancers will affect the survival of patients who have HNC.[11,12] If an esophageal second primary cancer can be detected and treated early, it can improve the overall outcome of patients with HNC.[12–14]

Second primary esophageal tumors are often diagnosed when the stage is esophageal squamous cell carcinoma or high-grade dysplasia of squamous intraepithelial lesion. But the low-grade dysplasia is also a precursor of squamous cell carcinoma,[15] the secondary primary esophageal tumors in our study would include low-grade dysplasia, high-grade dysplasia, squamous cell carcinoma in situ and squamous cell carcinoma, in case we would not miss any condition which would evolve into the esophageal cancer.

In view of different etiological factors from other places in the worldwide, we want to investigate both the incidence and the relationship of HNC with second primary esophageal cancer. In addition to above, we also want to study the correlation between the results of EGD, the head and cancers or the second primary esophageal cancers. The aims are to find the specific findings on EGD before the diagnosis of second primary esophageal cancer and the best timing to do the EGD follow-up for preventing the occurrence.

2. Materials and methods

2.1. Data source

We performed a retrospective study in Chang Gung Memorial Hospital (Linkou, Taiwan. All the staging of esophageal cancers and head and neck cancers (HNCs) are according to AJCC Cancer Staging Manual, 8th edition.[16] This study was approved by the Institutional Review Board of Linkou Chang Gung Memorial Hospital (No. 202400276B0), Taiwan.

2.2. Study population

The retrospective study was from 2015 to 2021, retrieved 592 newly diagnosed HNC, including oral cancer, oropharynx cancer, hypopharyngeal cancer, and laryngeal cancer. Primary HNC was diagnosed by otolaryngologists by clinical examination and imaging studies (Fig. 1). Pathological confirmation and histological grading of HNC were confirmed by experienced pathologists.[17] These medical records include information about patients' sex, age at diagnosis, histological type of cancer, tumor status, nodal metastasis, and distant metastasis classification, and cancer sites.

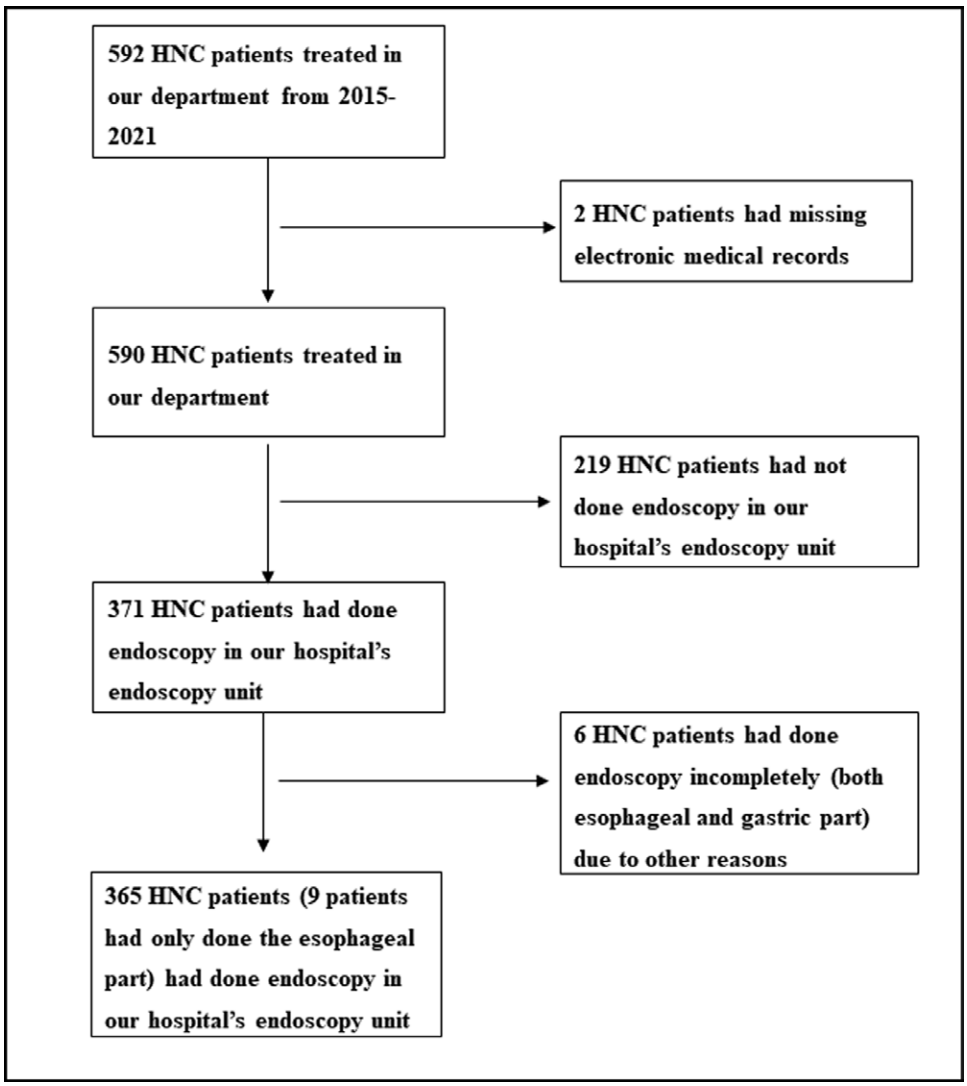

Figure 1. Flow chart for the recruitment of patients and inclusion/exclusion criteria.

Endoscopic examinations were performed by the trained, experienced endoscopists at Linkou CGMH. Treatment at our hospital's endoscopy center involves the use of high-resolution zoom endoscopy and narrow-band imaging with the Evis Lucera CV-290 Endoscopy Processor System (GIF-H290Z, GIF-HQ290, or GIF-Q260J; Olympus Medical System Corp, Tokyo, Japan). To achieve optimal imaging with up to 80x magnification, a soft black hood (MAJ-1989, Olympus Medical System Corp) is attached to the tip of the endoscope. For patients with trismus, a 5.5mm diameter endoscope (XP-260N or XP-290N, Olympus Medical System Corp; Evis Lucera CLV-290) is used for examination. Initial endoscopic evaluation for detecting any suspicious mucosal lesions in the upper gastrointestinal tract is performed using white-light endoscopy and narrow-band imaging with magnification (NBI-M). Then Lugol chromoendoscopy was performed on suspicious lesions or exminer's decisions. The scope first examined the whole esophagus, then enter the stomach, and finally reached the second portion of the duodenum. All of the upper gastrointestinal tract was completely screened, and the endoscopic biopsies were performed on suspicious neoplastic lesions and sent for pathological analysis.[17] Esophageal second primary neoplasms (ESPNs) in this study included low-grade dysplasia, high-grade dysplasia, squamous cell carcinoma in situ, and squamous cell carcinoma.

All patients received a standard work-up, and EGD at the time HNC was diagnosed. Patients underwent follow-up every month during the 1st year, every 2 months in the second year, every 3 months in the third year, and every 6 months thereafter. Follow-up EGD was arranged in the follow-up: abnormal findings in the screening EGD such gastroesophageal reflux disease (GERD), ulcerations or leukoplakia etc; patients had symptoms of dysphagia; abnormal findings in follow-up imaging studies (computed tomography or magnetic resonance imaging).

2.3. Statistical analysis

Continuous data were presented as the mean, standard deviation and range. Categorical data were expressed as frequencies and percentages. Differences between the categories were assessed using the chi-square tests, and the independent *T*-test was used to analyze the continuous variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for the occurrence of ESPN according to the subsite of the HNC lesion were determined and assessed using univariate modeling. Cumulative incidence rates of ESPN were calculated Kaplan–Meier method. Probability values for statistical tests were 2-tailed and $P < .05$ was considered significant. All analyses were performed with SPSS Statistics (Version 26, IBM, SPSS, Inc., New York).

3. Result

3.1. Patient characteristics

Of the 592 cases diagnosed with HNC as the first malignancy, 2 cases had missing electronic medical records, 219 patients did not undergo EGD screening in our hospital's endoscopy unit, and 6 patients underwent EGD but with incomplete study. Those with incomplete study are examine undergoing the esophageal part or gastric part due to reasons such as EGD only for nasogastric tube insertion or the endoscope could not pass through the esophagus due to the HNC invasion. The remaining 365 patients were included in this final analysis. Patients and HNC characteristics are present in Table 1.

The mean age of patients was 57.36 years (range: 25 to 94 years), and 341 (93.4%) were male. Alcohol, AQ, and cigarette consumption were divided into 3 categories: no consumption, occasionally consumption, and heavy consumption until now or had quit; 99 (27.1%), 78 (21.4%), and 50 (13.7%) of patients did not have habitual use of alcohol, AQ and cigarette respectively; 107 (29.3%), 232 (63.6%), and 247 (67.7%) are the cases of occasionally consumption of alcohol, AQ and cigarette respectively; 159 (43.6%), 55 (15.1%), and 68 (18.6%) are the cases of heavy consumption of alcohol, AQ and cigarette respectively. The most common HNC location was oral cavity (n = 233, 63.8%), followed by hypopharynx (n = 65, 17.8%), oropharynx (n = 52, 14.2%), and larynx (n = 15, 4.1%). Most HNCs' tumor type was squamous cell carcinoma (95.6%).

3.2. Habitual carcinogen exposure and the HNC development

We classified habitual carcinogen exposures into never used and ever used which included occasionally consumption and heavy consumption (Table 2). The analysis showed that alcohol ($P = .004$) and AQ consumption ($P = .003$) had significant difference on HNC subsites, especially the oral cavity cancers. In addition to above, cigarette consumption didn't show significant differences between 4 HNC subsites.

3.3. ESPNs

ESPNs were pathologically confirmed in 37 patients (10.1%). 3 were low-grade dysplasia (0.8%), 7 high-grade dysplasia (1.9%), 3 squamous cell carcinoma in situ (0.8%), and 24 squamous cell carcinoma (6.6%). The prevalence of ESPNs based on the HNC location is hypopharynx (29.2%), oropharynx (19.2%), larynx (6.7%), and oral cavity (3.0%).

3.4. Association between HNC subsites and ESPNs development

χ^2 tests showed that there was a significant difference between the HNC location and the ESPN ($P < .001$, Table 3). Regardless of the ESPN grading (low, high, SCC in situ, SCC), hypopharyngeal cancer patients had the highest incidence to have the ESPN, and the following subsites were oropharynx, larynx and oral cavity. Compared with the oral cavity cancers, hypopharyngeal cancers had the highest odds ratio (OR = 13.335, $P < .001$), and oropharyngeal cancer had the second highest OR with significant difference (OR = 7.687, $P < .001$). HNC at the larynx showed odds ratio without statistical significance (OR = 2.306, $P = .436$).

Alcohol ($P = .002$) and cigarette consumption ($P = .040$) were associated with the ESPNs development; AQs consumption was not related with the development of ESPNs in head and cancer patients.

3.5. Primary cancer sites versus EGD finding

The relationship between ESPN and primary tumor subsites were summarized in Table 4. We found that in all HNC tumor subsites, taking oral cavity as reference, hypopharynx has the highest risk (OR: 13.335, 95% CI: 5.3–33.555) to develop ESPN compared with oropharynx (OR: 7.687, 95% CI: 2.771–21.328) and larynx (OR: 2.306, 95% CI: 0.265–20.071). We found that the HNC subsites had significant difference with the esophageal glycogen acanthosis ($P = .046$), showing that compared with oral cavity cancer, oropharynx cancer (OR = 4.851, $P = .008$), and hypopharynx cancer (OR = 3.800, $P = .028$), larynx cancer (OR = 3.257, $P = .269$) had higher probabilities to find the esophageal glycogen acanthosis when the EGD screening follow-up, although the overall incidence of esophageal glycogen acanthosis in HNC patients is 4.4% in our study. In 356 cases (excluded 9 cases due to incomplete surveys of the gastric part), gastric erosion was found to have higher possibility in patients who had oral cavity cancers, and less chance to find it in patients who had oropharyngeal cancers (OR = 0.466,

Table 1

Patients' characteristics (n = 365).

	N (%)
Sex	
Male	341 (93.4)
Female	24 (6.6)
Age, mean (range)	57.36 (25–94)
<65	284 (77.8)
≥65	81 (22.2)
Alcohol consumption	
No	99 (27.1)
Occasionally	107 (29.3)
Heavy	159 (43.6)
Betel nut consumption	
No	78 (21.4)
Occasionally	232 (63.6)
Heavy	55 (15.1)
Cigarette consumption	
No	50 (13.7)
Occasionally	247 (67.7)
Heavy	68 (18.6)
Tumor type*	
Squamous cell carcinoma	349 (95.6)
Verrucous carcinoma	4 (1.1)
Sarcomatoid carcinoma	1 (0.3)
Mucoepidermoid carcinoma	1 (0.3)
Poorly differentiated carcinoma	2 (0.5)
Tumor location	
Oral cavity	233 (63.8)
Oropharynx	52 (14.2)
Hypopharynx	65 (17.8)
Larynx	15 (4.1)
T stage*	
T1	71 (19.5)
T2	97 (26.6)
T3	56 (15.3)
T4a/T4b	113 (31.0)/ 21 (5.8)
Tis	1 (0.3)
N stage*	
0	182 (49.9)
1	31 (8.5)
2a/2b/2c	14 (3.8)/ 63 (17.3)/ 24 (6.6)
3a/3b	1 (0.3)/ 44 (12.1)
M stage*	
0	348 (95.4)
1	11 (3.0)
TNM stage†	
I	52 (14.2)
II	57 (15.6)
III	35 (9.6)
Iva/IVb/IVc	181 (49.6)/23 (6.3)/11 (3.0)

TNM = tumor status, nodal metastasis, and distant metastasis.

* Four patients who had pre-malignancy, 1 with hematologic malignancy and 1 with lymphoepithelial carcinoma were not able to have tumor stage.

P = .042), hypopharyngeal cancers (OR = 0.417, P = .010), or laryngeal cancers (OR = 0.644, P = .460). Other endoscopic findings such as esophageal erosion, esophageal mucosal breaks, gastric ulceration, gastric polyps, gastritis, et al was not significantly different between each HNC subsite.

In 356 cases that completed all panendoscopy surveys, GERD, esophageal mucosal breaks, gastric ulceration, and gastritis (including all types of gastritis such as erosive gastritis, erythematous gastritis, superficial gastritis, atrophic gastritis, or chronic gastritis) had significant relationships (all P < .05) with ESPNs (Table 5).

The tumor stage and treatment modalities were listed in Table 6. Ten of the ESPN cases were low-grade to high-grade dysplasia. Six of the dysplasia lesions were small and regularly followed up by PES. One carcinoma-in situ lesion was also regularly followed. In all 33 esophageal lesion, 5 patients received either upfront surgery (endoscopic submucosal dissection, ESD), 1 with ESD and concurrent chemoradiation therapy, 1 minimal invasive esophagectomy and 1 with neoadjuvant chemotherapy and esophagectomy. All the surgeries were R0 resection.

3.6. Cumulative incidence rates of ESPNs

The overall cumulative incidence rates were represented in Figure 2. It indicated that in patients with hypopharyngeal cancer would develop ESPN, more than 50% of the ESPN would occur within 12 months after diagnosis of hypopharyngeal cancer. In addition to patients with hypopharyngeal cancer, if patients with oropharyngeal cancer, laryngeal cancer, or oral cavity cancer would develop ESPN, more than 50% of possibility that ESPN would occur within 24 months after diagnosis of primary cancers. The cumulative incidence curve was statistically different (P < .001).

4. Discussion

In terms of the primary HNC locations, our study's distribution corresponded to other Asian-related studies, showing that laryngeal cancer had the least incidence,[8,18] and oral cavity cancer had the highest incidence compared to Western population. Many studies found that it was more related to AQs consumption in Asia than in Western countries.[10] Male (93.4%) was the majority in HNCs of this study; squamous cell carcinoma also accounted for the majority of the tumor type (95.6%). Both of the above were consistent with the worldwide epidemiology of HNC.

Due to previous several studies' results, the effect of alcohol, AQs, and cigarette consumption on the development of HNCs was known. Our study showed that alcohol and AQs consumption had different influences on different HNC locations. Interestingly, cigarette consumption didn't influence the HNC subsites in our study.

The incidence of developing ESPNs in our study was 10.1%. Compared to other studies, our study's incidence was in the usual range. In Table 4, ESPNs were most frequently seen in hypopharyngeal cancer (OR = 13.335, 95% CI: 5.3–33.555), followed by oropharyngeal cancer (OR = 7.687, 95% CI: 2.771–21.328), and there was no difference between laryngeal cancer and oral cavity cancer. This results were similar to the studies published by Lee et al,[19] Tseng et al,[20] Gong et al,[21] and Wang et al.[22] Therefore, hypopharyngeal cancer and oropharyngeal cancer were categorized into the high-risk groups of developing ESPNs, and compared with them, oral cavity cancer and laryngeal cancer were categorized as the low-risk group. Due to the above findings, we suggested that if patients were diagnosed with the high-risk group, they should be followed up on PES much more frequently to detect possible esophageal neoplasms early. In addition, the surgical treatments of all the ESPNs as the second primary cancer in our cohort was less than esophageal cancers as primary cancer. The treatments of primary HNC distort the anatomic structures of oral cavity, oropharynx and esophageal inlet. They add difficulties in surgical planning in these ESPNs as second cancer patients. The importance of early detection of ESPNs in HNC patients is mandatory in these patients.

Based on previous studies, "field cancerization theory" is the concept that HNC patients will develop second primary tumors due to repeated epithelial damage caused by common carcinogens exposure. It is thus important to investigate whether those 3 carcinogens in Taiwan are truly related with the occurrence of ESPNs. Similar with previous studies,[17,22–25] we found alcohol consumption was highly associated with the development of ESPNs (P = .002). Furthermore, cigarette consumption appeared to be a significant risk factor for the ESPNs development in our study, some studies indicated that[17,22–26] alcohol

Table 2

Relationship between cigarette, alcohol and areca quid consumptions and different head and neck cancers subsites and esophageal second primary neoplasms.

Habit	Alcohol [n (%)]			Areca quid [n (%)]			Cigarette [n (%)]		
	Yes*	No	*P*-value	Yes*	No	*P*-value	Yes*	No	*P*-value
HNC subsites			**.004**			**.003**			.185
Oral cavity	159 (59.8)	74 (74.7)		195 (67.9)	38 (48.7)		196 (62.2)	37 (74.0)	
Oropharynx	37 (13.9)	15 (15.2)		35 (12.2)	17 (21.8)		44 (14.0)	8 (16.0)	
Hypopharynx	59 (22.2)	6 (6.1)		49 (17.1)	16 (20.5)		61 (19.4)	4 (8.0)	
Larynx	11 (4.1)	4 (4.0)		8 (2.8)	7 (9.0)		14 (4.4)	1 (2.0)	
Total	266 (100)	99 (100)		287 (100)	78 (100)		315 (100)	50 (100)	
ESPN			**.002**			.420			**.040**
Yes	35 (13.2)	2 (2.0)		31 (10.8)	6 (7.7)		36 (11.4)	1 (2.0)	
No	231 (86.8)	97 (98.0)		256 (89.2)	72 (92.3)		279 (88.6)	49 (98.0)	
Total	266 (100)	99 (100)		287 (100)	78 (100)		315 (100)	50 (100)	

Bold values indicate *P* value < .05.

* Yes: including occasional, heavy and quit; No: never had this habit; HNC: head and neck cancer; ESPN: esophageal second primary neoplasms, including low-grade dysplasia, high-grade dysplasia, SCC in situ, and SCC.

Table 3

Relationship between primary cancer sites and endoscopic findings.

	Oral cavity [n (%)]	Oropharynx [n (%)]	Hypopharynx [n (%)]	Larynx [n (%)]	*P*-value
Esophageal neoplasms, grade					
No neoplasm	226 (97.0)	42 (80.8)	46 (70.8)	14 (93.3)	**.010**
Low-grade dysplasia	0 (0.0)	1 (1.9)	2 (3.1)	0 (0.0)	
High-grade dysplasia	1 (0.4)	0 (0.0)	5 (7.7)	1 (6.7)	
SCC in situ	1 (0.4)	0 (0.0)	2 (3.1)	0 (0.0)	
SCC	5 (2.1)	9 (17.3)	10 (15.4)	0 (0.0)	
Total	233 (100)	52 (100)	65 (100)	15 (100)	
Esophageal neoplasms					
Yes	7 (3.0)	10 (19.2)	19 (29.2)	1 (6.7)	**.010**
No	226 (97.0)	42 (80.8)	46 (70.8)	14 (93.3)	
Total	233 (100)	43 (100)	65 (100)	15 (100)	
Glycogen acanthosis					
Yes	5 (2.1)	5 (9.6)	5 (7.7)	1 (6.7)	**.045**
No	228 (97.9)	47 (90.4)	60 (92.3)	14 (93.3)	
Total	233 (100)	52 (100)	65 (100)	15 (100)	
Gastric erosion (n = 356*)					
Yes	83 (36.1)	10 (20.8)	12 (19.0)	4 (26.7)	**.024**
No	147 (63.9)	38 (79.2)	51 (81.0)	11 (73.3)	
Total	230 (100)	48 (100)	63 (100)	15 (100)	

Only list the result which had significant difference above.

Bold values indicate *P* value < .05.

* Nine cases did not complete the endoscopy survey of gastric part.

Table 4

Risks of endoscopic findings in different tumor subsites.

	ESPN	
	Odds ratios (95% CI)	*P*-value
Oral cavity	1 [Reference]	–
Oropharynx	7.687 (2.771–21.328)	**<.001**
Hypopharynx	13.335 (5.3–33.555)	**<.001**
Larynx	2.306 (0.265–20.071)	.436

Bold values indicate *P* value < .05.

ESPN = Esophageal second primary neoplasms, including low-grade dysplasia, high-grade dysplasia, SCC in situ, and SCC.

consumption is the only significant risk factor. However, Kim et al[24] also found current smoking is a risk factor (OR = 10.181, 95% CI: 1.293–80.140, *P* = .015). Instead, there was no association between alcohol drinking and ESPNs development in the study of Kim et al.[24] After referring to other related studies, all studies presented AQs consumption was not related to ESPN development. There were some explanations: first, alcohol consumption was highly linked with the field cancerization theory due to the upper digestive tract was passed through by alcohol when people drink. Cigarette consumption was also correlated with the theory due to the smoke may go through the upper aerodigestive tract just like the air. However, AQ consumption was different from the above 2 factors. Usually, consumers chewed to taste the smell of AQs and others added ingredients without swallowing. We considered that AQs consumption was less like to develop ESPNs compared with alcohol and cigarette consumption. Second, populations of the 3 habits are highly overlapped. It is difficult to analyze their effects individually.

For HNCs, we listed the findings which had statistical significance including esophageal glycogen acanthosis and gastric erosion. Esophageal glycogen acanthosis had the most possibility to be seen in oropharyngeal cancer (OR = 4.851, 95% CI: 1.350–17.425, *P* = .008). Esophageal glycogen acanthosis is related to long-term alcohol, cigarette consumption and/or spicy/hot food. Adding on this already-known knowledge, we

Table 5

Relationship between ESPN and endoscopic findings.

	With ESPN [n (%)]	Without ESPN [n (%)]	OR [±95% CI]	*P*-value
GERD				
Yes	7 (21.2)	136 (42.1)	0.370 [0.156–0.878]	**.020**
No	26 (78.8)	187 (57.9)	1	
Total	33 (100)	323 (100)		
Esophageal mucosa break				
Yes	6 (18.2)	131 (40.6)	0326 [0.131–0.811]	**.012**
No	27 (81.8)	192 (59.4)	1	
Total	33 (100)	323 (100)		
Gastric ulceration				
Yes	3 (9.1)	87 (26.9)	0.271 [0.081–0.912]	**.025**
No	30 (90.9)	236 (73.1)	1	
Total	33 (100)	323 (100)		
Gastritis				
Yes	23 (69.7)	275 (85.1)	0.401 [0.180–0.896]	**.022**
No	10 (30.3)	48 (14.9)	1	
Total	33 (100)	323 (100)		

Only list the results which had significant difference.

Bold values indicate *P* value < .05.

ESPN = esophageal secondary primary neoplasms including low-grade, high-grade dysplasia, SCC in situ, and SCC, GERD = gastroesophageal reflux disease.

Table 6

Esophageal second primary neoplasm staging and treatment.

No.	ESPN grade	TNM Stage	Treatment
1	SCC	T3N0M0	CCRT
2	SCC	T2N3M1	Chemotherapy
3	SCC	T3N2M1	Chemotherapy
4	SCC	T3N3M0	CCRT
5	SCC	T1N1M0	CCRT
6	SCC	T1bN0M0	MIE
7	SCC	T3N1M0	CCRT
8	SCC	T3N2M0	CCRT
9	SCC in situ	T1bN0M0	ESD
10	SCC	T4N3M1	Chemotherapy
11	High-grade dysplasia	T1aN0M0	ESD
12	SCC	T1bN2M0	CCRT
13	SCC	T4N3M0	Chemotherapy
14	SCC	T3N3M0	CCRT
15	SCC	T3N0M0	CCRT
16*	SCC	–	Escape
17	SCC	T3N2M0	CCRT
18	Low-grade dysplasia	TisN0M0	Biopsy
19	SCC	T2N0M1	CCRT
20	High-grade dysplasia	T1bN1M0	Radiotherapy
21	SCC in situ	TisN0M0	ESD
22	SCC	T1bN0M0	ESD
23	Low-grade dysplasia	TisN0M0	RFA
24	SCC	T3N2M0	CCRT
25	SCC	T1bN0M0	CCRT
26	Low-grade dysplasia	TisN0M0	Biopsy
27	SCC	T3N0M0	NACT + MIE
28	High-grade dysplasia	TisN0M0	Biopsy
29	SCC in situ	TisN0M0	Biopsy
30	Low-grade dysplasia	TisN0M0	Biopsy
31	SCC	T3N2M1	CCRT
32	SCC	T2N2M0	CCRT
33	SCC	T2N1M0	CCRT
34	High-grade dysplasia	TisN0M0	Biopsy
35	SCC	T1bN0M0	ESD + CCRT
36	High-grade dysplasia	TisN0M0	Biopsy
37	High-grade dysplasia	TisN0M0	ESD

CCRT = concurrent chemoradiotherapy, ESD = endoscopic submucosal dissection, ESPN = esophageal second primary neoplasm, MIE = minimally invasive esophagectomy, NACT = neoadjuvant chemotherapy, RFA = radiofrequency ablation, SCC = squamous cell carcinoma, TNM = tumor status, nodal metastasis, and distant metastasis.

*No treatment due to the terminal stage of head and neck primary cancer.

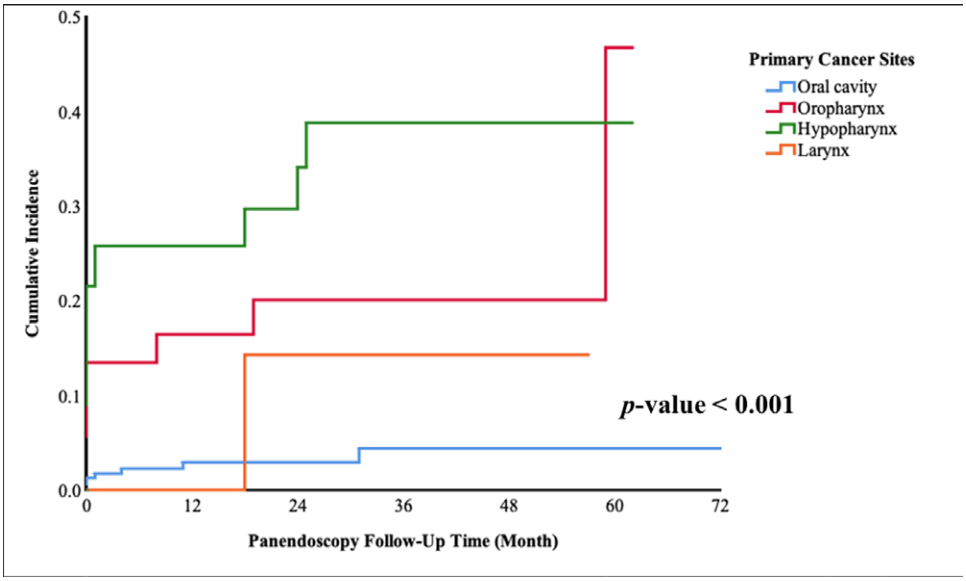

Figure 2. Cumulative incidence of esophageal second primary neoplasms according to different tumor subsites.

can summarize that patients with oropharyngeal or hypopharyngeal cancer and having habits of smoking or drinking have a higher chance to find esophageal glycogen acanthosis compared to patients with laryngeal or oral cavity cancer. There was a completely different result from gastric erosion within 4 different sites of HNC. Compared to oral cavity cancer, oropharyngeal and hypopharyngeal cancer had less possibility to find gastric erosion (OR = 0.466, 95% CI: 0.221–0.983, P = .042/ OR = 0.417, 95% CI: 0.210–0.826, P = .01), and laryngeal cancer still had the same possibility as oral cavity cancer.

In addition to the esophageal neoplasms, PES findings include GERD, esophageal mucosa break, gastritis ulceration, and gastritis. All these 4 findings showed negative correlations with the occurrence of ESPNs. Patients with ESPNs seemed less likely to have GERD, esophageal mucosa break, gastric ulceration, and gastritis. GERD was related with esophageal adenocarcinoma than esophageal squamous cell carcinoma.

Alcohol, from our study, was closely related with primary hypopharynx cancer. And it is also increased ESPN in HNC especially in hypopharyngeal cancer (OR: 13.335, 95% C.I: 5.3–33.555). The phenomenon was evident in Taiwan because of the alcohol metabolism in Asian is slower than the Western. It was often referred as "alcohol flush syndrome" and Asians are thus more susceptible to the carcinogens or metabolites from the alcohol.[27,28] In the literature, alcohol was reported to increase the risks of esophageal cancer. Our study proved that alcohol also played important roles in hypopharyngeal cancer.

Cumulative incidence of ESPNs from the Kaplan–Meier method indicated that half of the esophageal neoplasms occurred within about 24 months after diagnosis of primary HNCs. For the esophageal neoplasms in hypopharyngeal cancer, half of them occurred within 12 months after the diagnosis of hypopharyngeal cancer. Due to the important finding, we recommend that HNC patients undergo regular PES within the first 24 months after diagnosis of primary HNC. Specifically, for patients with hypopharyngeal cancer, we advise more frequent panendoscopy during the first 12 months followed by regular checkups in the second 12 months, consistent with other HNC patients.

5. Limitation

Our study has some limitations. First, this study was conducted in 1 single center, and we are expecting to collect multi-center data in the future to increase statistical power. Second, our patients were reviewed retrospectively, and some variables were not recorded in a comprehensive way. It increased the difficulty of collecting data and having missing data. For a retrospective analysis, the overall incidence of ESPNs could be underestimated. Finally, some risk factors affected the occurrence of HNCs or ESPNs were not investigated in our studies such as HPV infection.

6. Conclusion

Our study showed the association between the 3 most common carcinogens in Taiwan and the development of ESPNs, and also found some other gastrointestinal diseases related to HNCs and ESPNs. Most importantly, we suggest patients who are newly diagnosed with HNC have a routine PES survey. A high-resolution endoscopy with NBI or chromoendoscopy would be recommended. For hypopharyngeal cancers, they would require a more frequent survey, especially in the first 24 months after diagnosis of HNC.

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Author contributions

Conceptualization: Tz-Wei Chiou, Shiang-Fu Huang.
Data curation: Tz-Wei Chiou, Yu-Feng Hu, Chung-Jan Kang.
Formal analysis: Tz-Wei Chiou, Chi-Kuang Young.
Investigation: Tz-Wei Chiou, Chi-Kuang Young, Yu-Feng Hu, Chung-Jan Kang, Shiang-Fu Huang.
Methodology: Tz-Wei Chiou, Chi-Kuang Young, Ken-Hao Hsu, Chun-Ta Liao, Chung-Jan Kang, Shiang-Fu Huang.
Project administration: Shiang-Fu Huang.
Resources: Chun-Ta Liao.
Supervision: Shiang-Fu Huang.
Validation: Ken-Hao Hsu, Chun-Ta Liao, Yu-Feng Hu, Shiang-Fu Huang.
Visualization: Tz-Wei Chiou, Chi-Kuang Young.
Writing – original draft: Tz-Wei Chiou, Shiang-Fu Huang.
Writing – review & editing: Chi-Kuang Young, Chun-Ta Liao, Yu-Feng Hu, Chung-Jan Kang, Shiang-Fu Huang.

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