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Effectiveness of screening endoscopy for esophageal squamous cell carcinoma in Japanese males

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Abstract

Background: Esophageal squamous cell carcinoma (ESCC) has a poor prognosis; therefore, early detection is essential. In Japan, more than 90% of esophageal cancers are ESCC. Endoscopy is effective to detect ESCC in the early stage, but there is a limited number of reports examining its efficacy and effectiveness.

Objective: This study aimed to evaluate the efficacy of screening endoscopy for detecting ESCC.

Methods: This retrospective study analyzed the prevalence of ESCC, annual transition of prevalence, and the stage of each ESCC among 128,520 medical check-up patients who underwent esophagogastroduodenoscopy from April 2015 to March 2020 at Yamanashi Koseiren Health Care Center. Furthermore, a case-control study utilized the multivariate logistic regression analysis was performed to assess the risk factor of ESCC.

Results: Among a total of 128,520 subjects, 42 ESCC patients were detected, with 95.2% being diagnosed at early stages. Annual prevalence in males was 0.015% (2/13,122) in 2015, 0.044% (6/13,562) in 2016, 0.044% (6/13,676) in 2017, 0.074% (10/13,488) in 2018%, and 0.11% (16/14,386) in 2019. ESCC prevalence has been increasing each year. A significant increase was observed between 2015 and 2018 ($p = 0.039$). ESCC prevalence was 0.102% (25/24,272) when focusing on males aged over 50 years with a history of smoking and drinking. Regarding the case-control study, the multivariate logistic regression analysis revealed smoking ($p = 0.044$), mean corpuscular volume (MCV) ($p = 0.0018$), and severe gastric atrophy ($p = 0.048$) as positively correlated with ESCC.

Conclusion: In conclusion, ESCC has been increasing in our center from 2015 to 2019, and the prevalence has been approaching that of gastric cancer in 2019 in male subjects. ESCC can be detected efficiently by targeting males with high MCV who have a history of drinking and smoking.

KEYWORDS

erythrocyte indices, esophageal neoplasms, esophageal squamous cell carcinoma, prevalence, retrospective studies, stomach neoplasms

INTRODUCTION

Esophageal carcinoma (EC) is the seventh most common cancer worldwide, with more than 570,000 cases diagnosed annually. Also, it ranks as the sixth most aggressive cancer, with mortality exceeding 500,000 deaths worldwide.[1] There are two major types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). In Western countries, the incidence of EA has been increasing, whereas that of ESCC has been decreasing.[2] However, in Japan, according to the graph of national estimates of age-adjusted morbidity of esophageal cancer, the age-adjusted morbidity of esophageal cancer is gradually increasing, especially for men. More than 90% of esophageal cancer in Japan is ESCC. The Japanese National Cancer Center has recently demonstrated that 9571 males and 2048 females (11,619 in total) died of ESCC in 2019 and that the 5 year survival rate was 41.5% (male 40.6%, female 45.9%) among newly diagnosed cases from 2009 to 2011.[3] The poor prognosis of ESCC is attributed to late detection of most lesions, that is, in their advanced stages; therefore, early detection is essential to treat and cure ESCC.

Thus, we examined the annual changes in ESCC prevalence at our health care center by age group and evaluated the efficacy and effectiveness of screening endoscopy for detecting early esophageal cancer. Then, we conducted a multivariate logistic regression analysis to assess the following risk factors: male sex, alcohol consumption, cigarette smoking, MCV, body mass index (BMI), and gastric atrophy.

Key summary

Summarise the established knowledge on this subject

- Esophageal squamous cell carcinoma (ESCC) has a poor prognosis and more than 90% of esophageal cancers are ESCC in Japan.
- Endoscopy is effective to detect ESCC in the early stage, but there is a limited number of reports examining its efficacy and effectiveness.

What are the significant and/or new findings of this study?

- The prevalence of ESCC has been increasing in our center from 2015 to 2019, and the prevalence has been approaching that of gastric cancer in 2019 for male subjects.
- ESCC can be detected efficiently by identifying males with high mean corpuscular volume (MCV) who have a history of drinking and smoking.

MATERIALS AND METHODS

This retrospective study included medical check-up patients aged over 50 who underwent esophagogastroduodenoscopy (EGD) from April 2015 to March 2020 at Yamanashi Koseiren Health Care Center to analyze ESCC prevalence, annual prevalence transition, and the stage of each ESCC. Screening endoscopy was intended for the early detection of gastric cancer. All cases were only among health checkup protocol and they did not have symptoms that required EGD diagnosis.

The endoscopes used were OLYMPUS® GIF-Q260, GIF-H290, GIF-XP260N, GIF-XP290N, or FUJIFILM® EG-L580NW7. We used white light and Narrow Band Imaging for the OLYMPUS® endoscope and white light and Blue Laser Imaging for the FUJIFILM® endoscope. We did not use lugol staining systematically; it was only used when we suspected cancer. EC prevalence was analyzed by age group and year. Additionally, we performed a case-control study to investigate risk factors, specifically alcohol drinking, cigarette smoking, MCV, and gastric atrophy. We defined habitual alcohol drinking as the consumption of >20 g of pure alcohol per day. Gastric atrophy was measured by endoscopy using Kimura-Takemoto classification: atrophy was defined as C-II, C-III, or Open type, while severe atrophy was defined as O-II, III. The degree of atrophic gastritis is classified using the Kimura-Takemoto classification based on endoscopic findings and is based on the grading of the atrophic boundary extending from the gastric angle to the gastric body.[4]

With regard to the case-control study, the controls were those who underwent the medical check-up in our center from 2015 to 2019 and had no localized lesions in the upper gastrointestinal tract that matched gender and age. There were no patients and control people who were suffering from liver cirrhosis. We conducted univariate and multivariate logistic regression analyses. Statistical analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[5] Comparisons were performed by using the Mann–Whitney *U* test or the Fisher's exact test. Differences were considered to be significant when p was <0.05. The Koseiren Health Care Center Ethics Committee approved the present study (No. 3–2 on 13 September 2021 and No. 2–8 on 4 January 2021).

RESULTS

This study included 128,520 subjects, among whom a total of 45 patients with EC was detected: 42 cases were ESCC, and 3 cases were adenocarcinoma. Summaries of clinical profiles of 42 patients are shown in Table 1. The average age was 65.1 ± 9.9 years, and the male: female ratio was 40:2. Of the 42 cases, 40 (95.2%) cases had superficial esophageal cancers, while only 1 case had an advanced stage. The actual stages of all cases are shown in Table 2. The average pack-years of smoking was 29.3 ± 25.4. The average amount of pure alcohol consumed was 39.0 ± 23.6 g/day. In males, 32 of 40 had a

TABLE 1 Characteristics of the cases

Patients; n	42
Age, years (mean ± SE)	65.1 ± 9.9
Sex, women, n (%)	2 (4.8%)
Classification, superficial versus advanced, n (%)	40 (95.2%) versus 2 (4.8%)
Alcohol intake (g/day) (mean ± SE)	39.0 ± 23.6
Pack-years of smoking (mean ± SE)	29.3 ± 25.4
History of habitual drinking; n	32
History of habitual smoking; n	32
Average MCV (fl)	97.1 ± 6.5
Average BMI	22.0 ± 4.1

Abbreviations: BMI, body mass index; MCV, mean corpuscular volume; SE, standard error.

TABLE 2 Staging of all cases

Stage	Cases (n)	Treatment	
Dysplasia	3	ESD	Observation
T1a-EP	15	ESD	Observation
T1a-LPM	12	ESD	Observation
T1a-MM	2	ESD	Observation
T1a	2	ESD	Observation
T1b-SM1	2	ESD	Resection
		ESD	CRT
T1b-SM2	2	ESD	Resection
		ESD	Resection (N1)
T1b-SM2 more	1	ESD	CRT
T1b-SM3	0		
cT1b	1	Chemotherapy	
T2N1M0	1	Neoadjuvant chemoradiation therapy	Resection
T3 more NXM1	1	Chemotherapy	

Abbreviations: CRT, chemoradiation therapy; ESD, endoscopic submucosal dissection.

history of habitual drinking (80.0%), and 32 of 40 had a smoking (80.0%) habit (including formerly and currently). In females, 1 of 2 had a history of drinking habit (50.0%), and 1 of 2 had a smoking habit (50.0%). The average MCV in blood was 97.1 ± 6.5 fl (reference range 83.8–103.4fl), and the mean BMI was 22.0 ± 4.1. Of the 42 cases, 13 cases (30.1%) met or exceeded 100 fl.

Figure 1 shows an age-specific analysis. There were three patients in their 40s, nine patients in their 50s, 15 patients in their 60s, 11 patients in their 70s, and four patients in their 80s. ESCC prevalence by age group from 2015 to 2019 was 0.011% in their 40s (3/27,545), 0.029% in their 50s (9/30,841), 0.041% in their 60s (15/36,144), 0.050% in their 70s (11/21,851), 0.13% in their 80s (4/3081), and 0.033% (42/128,520) in total.

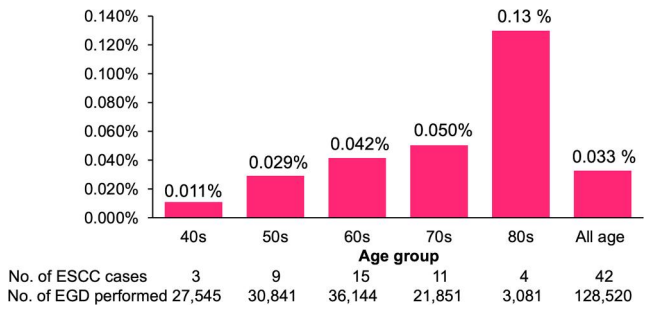

FIGURE 1 Prevalence of patients with esophageal carcinoma (EC) by age group in our center from April 2015 to March 2020. ESCC, esophagus squamous cell carcinoma; EGD, esophagogastroduodenoscopy

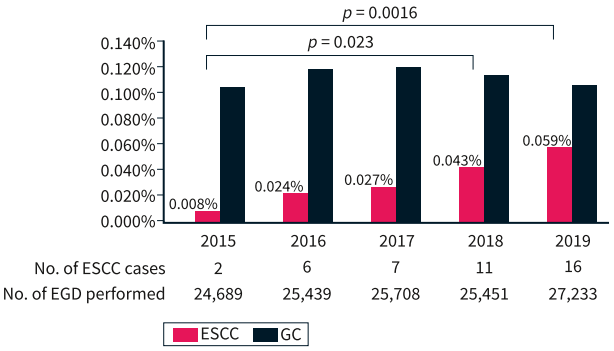

FIGURE 2 Prevalence of patients with esophageal carcinoma and gastric carcinoma (GC) by year in our center (2015–2019). The detection rate of ESCC has been increasing by the years. ESCC, esophagus squamous cell carcinoma; GC, gastric carcinoma; EGD, esophagogastroduodenoscopy

Figure 2 shows the prevalence in each year, which was 0.008% in 2015 (2/24,689), 0.024% in 2016 (6/25,439), 0.027% in 2017 (7/25,708), 0.043% in 2018 (11/25,451), and 0.059% in 2019 (16/27,233). ESCC detection rate has been increasing year by year and plateaued for the last 2 years. A significant increase was observed between 2015 and 2018 (p = 0.023) (Fisher's exact test). In contrast, gastric carcinoma (GC) detection rates at our center were 0.11% (2015), 0.12% (2016), 0.12% (2017), 0.11% (2018), and 0.11% (2019), showing no significant difference during this period.

The following studies were conducted only on males, as 40 of the 42 cases were male. Figure 3 shows the change in cases by age group in male subjects. There were 3 cases in their 40s, 8 cases in their 50s, 14 cases in their 60s, 11 cases in their 70s, and 4 cases in their 80s.

ESCC prevalence by age in male subjects was 0.026% in their 40s (3/15,496), 0.048% in their 50s (8/16,563), 0.079% in their 60s (14/17,778), 0.10% in their 70s (11/10,984), and 0.22% in their 80s (4/1789). The detection rate increased with age.

ESCC prevalence in each year in male subjects was 0.015% (2/13,122) in 2015, 0.044% (6/13,562) in 2016, 0.044% (6/13,676) in 2017, 0.074% (10/13,488) in 2018%, and 0.11% (16/14,386) in 2019 (Figure 4). ESCC detection rate has also been increasing year by year. A significant increase was observed when comparing between 2015 and 2018 (p = 0.0039) or between 2015 and 2019 (p = 0.0016) (Fisher's exact test). On the other hand, GC detection rates in male subjects at our center were 0.14% (2015), 0.18% (2016), 0.15% (2017), 0.16% (2018), and 0.10% (2019), showing no significant change.

With regard to female subjects, there were only 1 case in their 50 and 60s each, and ESCC prevalence by age was 0.0070% in their 50s (1/14,278) and 0.0054% in their 60s (1/18,366). ESCC prevalence in each year in female subjects was 0% (0/11,567) in 2015, 0% (0/11,877) in 2016, 0.0083% (1/12,032) in 2017, 0.0084% (1/11,963) in 2018%, and 0% (0/12,847) in 2019.

The results of the univariate and multivariate logistic regression analyses are shown in Table 3. Thirty-seven cases were included in this study, whereas 74 people were included as controls. The univariate analysis demonstrated that alcohol consumption (p = 0.0069), smoking

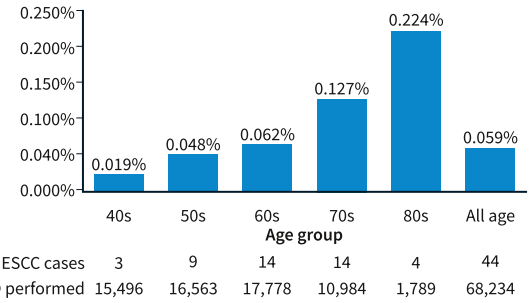

FIGURE 3 Prevalence of ESCC in male subjects by age group from April 2015 to March 2020. ESCC, esophagus squamous cell carcinoma; EGD, esophagogastroduodenoscopy

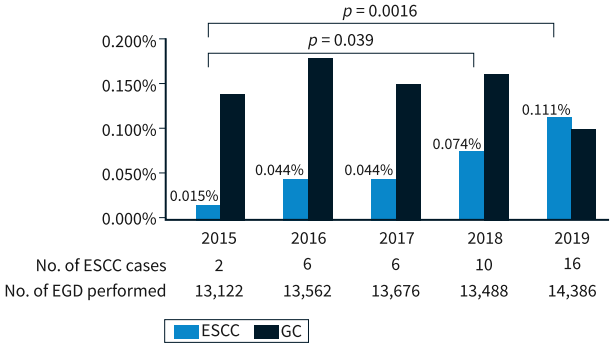

FIGURE 4 Prevalence of ESCC and gastric carcinoma in male subjects by year (2015–2019). The detection rate of ESCC has been increasing every year and has risen to 0.11% in 2019, approaching the detection rate of gastric cancer. ESCC, esophagus squamous cell carcinoma; GC, gastric carcinoma; EGD, esophagogastroduodenoscopy

(p = 0.0047), MCV (p = 0.0000005), and severe gastric atrophy (p = 0.043) were significantly correlated with ESCC development.

The multivariate logistic regression models were calculated on the basis of dichotomous variables (alcohol consumption of more than or equal to 20 g of ethanol/day or less than 20 g of ethanol/day, cigarette smoking of more than or equal to pack-years 20 or less than pack-years 20, MCV of more than or equal to 100 fl or less than 100 fl, and severe gastric atrophy or no severe gastric atrophy), which revealed that smoking (odds ratio [OR], 2.86; 95% confidence interval [CI], 1.03–7.93; p = 0.044), MCV (OR, 34.8; 95% CI, 3.77 smoking 321; p = 0.0018), and severe atrophy (OR, 2.72; 95% CI, 1.01 smoking 7.31; p = 0.048) were positively correlated with ESCC.

DISCUSSION

This study revealed an essential finding: the number of ESCC cases at our health care center significantly increased during the studied period. ESCC prevalence in male subjects has risen to 0.10% in 2018 and 0.11% in 2019.

From the results of the medical check-up data targeting the general public at our center, ESCC prevalence has been increasing

TABLE 3 Case-control study

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Alcohol intake	3.25	1.27–8.95	0.0069	1.93	0.67–5.56	0.22
Smoking	3.23	1.32–8.21	0.0047	2.86	1.03–7.93	0.044
Mean corpuscular volume	38.2	5.24–1686	0.0000005	34.8	3.77–321	0.0018
Severe atrophy: No severe atrophy	2.47	1.02–6.09	0.043	2.72	1.01–7.31	0.048
Atrophy: No atrophy	1	0.41–2.47	1			
BMI	0.6	0.18–1.81	0.33			

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

annually. Particularly, a significant increase was observed both in all and male subjects between 2015 and 2018 or between 2015 and 2019. On the other hand, the gastric cancer detection rate tended to be flat or declining, which may be associated with the widespread use of *Helicobacter pylori* eradication therapy prescription and the decrease of *H. pylori* prevalence in Japanese people.[6,7]

Screening endoscopy must be an effective measure to detect ESCC in the early stage. With regard to male subjects, the prevalence rose to 0.11% in 2019, approaching the detection rate for gastric cancer. More importantly, 97.5% of the male subjects had superficial esophageal cancers, which enabled us to treat them in the early stage. These facts mean that screening endoscopy should be considered for early detection of ESCC and detection of GC. There has been image-enhanced observation constantly improving in the area of endoscopy, which might contribute to the finding of ESCC in the early stage.[8] Further, we hold regular clinical conferences and are investigating lesions discovered, including ESCC. Therefore, it is possible that the learning curve could be influenced by these conferences and be involved in finding lesions.

Most of the subjects were men with a history of alcohol drinking or cigarette smoking, both of which are the two major risk factors for ESCC.[9] When focused on males aged over 50 years with a history of smoking and drinking, ESCC prevalence was as high as 0.103% (25/24,272). This tendency in the patients' history might be related to the fact that those who worked during the period of high economic growth, when there was a large number of heavy drinkers and smokers, have reached the age prone to ESCC.

Regarding the multivariate logistic regression, it showed that there was a significant correlation between ESCC and smoking, MCV, and severe atrophy.

Cigarette smoking is one of the essential risk factors, especially in developed countries. Our results showed that the OR of ESCC for former and current smokers was 2.86, which is consistent with previous reports.[10-12] MCV is a traditional marker of alcoholism, and high MCV is associated with inactive heterozygous aldehyde dehydrogenase-2 (ALDH2), which is encoded by *ALDH2*1/2*2*. MCV alone could be used as a predictor of ESCC.[13] As of this moment, our result suggests that MCV remained a stronger risk factor than the amount of alcohol in Japanese individuals. According to Yokoyama, heavy alcohol intake in persons with ALDH2 deficiency in Japan markedly increases MCV, and MCV ≥100 fl can be used as a biomarker for suspecting drinkers with the inactive heterozygous *ALDH2*1/2*2* genotype who drink moderate to heavy alcohol, suggesting that they are at high risk of esophageal cancer.[14] Therefore, MCV is likely to be a convenient indicator for selecting those who are at high risk of ESCC. With reference to severe gastric atrophy, Islami says that there is an association between ESCC and atrophic gastritis,[15] and our results showed that there is an association between severe gastric atrophy and ESCC (OR 2.72, 95% CI 1.01–7.31). In this study, we targeted a group of people who underwent medical examination with high smoking and drinking rates, and in such a group, atrophic gastritis can be promoted, and the risk of ESCC is also increased.[16] Atrophic gastritis is a condition in which the mucous membrane of the stomach is chronically inflamed, inducing the loss of parietal cells. Most atrophic gastritis is caused by *H.pylori* infection in Japan,[17] and parietal cell destruction in atrophic gastritis leads to gastric hyposecretion. Particularly, profound hypochlorhydria is a cause of non-cardiac gastric cancer,[18] which causes bacterial overgrowth in the stomach, resulting in the formation of carcinogens, such as nitrosamines[19,20] and acetaldehyde.[21,22] These carcinogens also form DNA adducts.[20,23] Therefore, it is highly probable that carcinogens and DNA adducts produced in the stomach reach the esophagus through reflux and venous plexus, which further induces the formation of ESCC.

In conclusion, ESCC has been increasing, and its prevalence has been approaching that of GC in 2019 in male subjects. Therefore, screening endoscopy should be considered to be an effective measure for early detection of ESCC. Hence, ESCC can be detected efficiently by targeting males with high MCV who have a history of drinking and smoking.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The dataset generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

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