Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2950-23
Intern Med 63: 3019-3024, 2024
http://internmed.jp

【 ORIGINAL ARTICLE 】

A Study of the Risk Factors for 402 Patients with Esophageal Squamous Cell Carcinoma - A Retrospective Comparison with Health Checkup Participants

Jun Nakamura[1], Ken Haruma[2], Noriaki Manabe[1], Tomoki Yamatsuji[3], Yoshinori Fujiwara[4], Takahisa Murao[5], Minoru Fujita[1], Akiko Shiotani[6], Mitsuhiko Suehiro[2], Hirofumi Kawamoto[2], Minoru Haisa[3], Tomio Ueno[4], Tomoari Kamada[5], Toshihiro Takao[5], Yasumasa Monobe[7], Takashi Akiyama[8], Yoshio Naomoto[3] and Jiro Hata[9]

Abstract:

Objective Esophageal cancer is a gastrointestinal cancer with a poor prognosis. However, it is curable and can be treated endoscopically if it is detected at an early stage. The objective of this study was to identify the factors that contribute to early detection.

Methods From April 2011 to December 2019, we retrospectively investigated consecutive patients diagnosed with esophageal squamous cell carcinoma (ESCC) through upper gastrointestinal endoscopy at two hospitals of Kawasaki Medical University based on medical records. The factors contributing to the early detection of ESCC were investigated by comparing patients with ESCC with those undergoing health checkups in whom no organic lesions were found in the upper gastrointestinal tract on endoscopy (controls).

Patients Factors contributing to early detection were examined in 402 ESCC cases and 391 sex- and age-matched controls, and early and advanced cancers were compared along with the risk factors for ESCC.

Results A multivariate analysis showed that alcohol consumption and smoking, concomitant cancer of other organs, and a low body mass index (BMI) were factors associated with ESCC (odds ratio [OR], 4.65; 95% confidence interval [CI], 2.880-7.520, OR, 3.63; 95% CI, 2.380-5.540, OR, 2.09; 95% CI, 1.330-3.270, OR, 6.38; 95% CI, 3.780-10.800), whereas dyslipidemia was significantly less common in patients with ESCC (OR, 0.545; 95% CI, 0.348-0.853). Comparing early and advanced cancers, a history of endoscopic screening was the only factor involved in early detection (OR, 7.93; 95% CI, 4.480-14.000).

Conclusion The factors associated with ESCC include alcohol consumption, smoking, concomitant cancer of other organs, and a low BMI. Endoscopy in subjects with these factors may therefore be recommended for the early detection of ESCC.

Key words: esophageal squamous cell carcinoma, risk factors, early detection

(Intern Med 63: 3019-3024, 2024)
(DOI: 10.2169/internalmedicine.2950-23)

[1]Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Japan, [2]Department of General Internal Medicine 2, Kawasaki Medical School, Japan, [3]Department of General Surgery, Kawasaki Medical School, Japan, [4]Department of Digestive Surgery, Kawasaki Medical School, Japan, [5]Department of Health Care Medicine, Kawasaki Medical School, Japan, [6]Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Japan, [7]Department of Pathology, Okayama Medical Laboratories Co., Ltd., Japan, [8]Department of Pathology, Kawasaki Medical School, Japan and [9]Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Japan
Received: September 21, 2023; Accepted: February 12, 2024; Advance Publication by J-STAGE: April 2, 2024
Correspondence to Dr. Ken Haruma, kharuma@med.kawasaki-m.ac.jp

Introduction

Esophageal cancer is the eighth most commonly diagnosed cancer and sixth most common cause of cancer-related deaths worldwide. Globally, there were approximately 604,000 new cases and 544,000 deaths from esophageal cancer in 2020 (1), and the incidence is predicted to increase further (2). As in Western countries, esophageal cancer is a male-dominated cancer in Japan. However, in contrast to Western countries, where esophageal adenocarcinoma is more common than esophageal squamous cell carcinoma (ESCC), ESCC accounts for 86.7% of esophageal cancer cases and it is the eighth most common cancer in men (3). In 2019, 26,382 new cases of ESCC were diagnosed in Japan (21,719 men), and in 2020, 19,981 deaths were attributed to ESCC (8,978 men) (4). Furthermore, the number of ESCC cases in Japan continues to increase. Recent epidemiological reports on ESCC in Japan showed no downward trend in men and an increase in women (5).

Although the association between gastric mucosal atrophy and gastric cancer is well known, there are conflicting reports on the association between gastric mucosal atrophy and ESCC (6-10). Lifestyle-related diseases, such as hypertension, diabetes, dyslipidemia, and obesity (i.e., metabolic syndrome) are increasing worldwide (11-13), and are of concern because they are risk factors for cardiovascular diseases. Furthermore, although metabolic syndrome is a risk factor for some cancers (14-16), it remains unclear whether it is also a risk factor for ESCC.

Previously, we analyzed 469 cases of ESCC at our institution and reported that in the group without subjective symptoms, such as dysphagia, cancer was detected early in the disease stage, and life expectancy was significantly better than in the group diagnosed with subjective symptoms (17). The main objective of this study was to identify the risk factors for ESCC by first comparing ESCC cases with those undergoing health check-ups as healthy subjects. We then compared early and advanced cancers and the factors contributing to early detection.

Materials and Methods

From April 2011 to December 2019, we retrospectively investigated patients diagnosed with ESCC using upper gastrointestinal endoscopy at Kawasaki Medical University General Medical Center and University Hospital, Okayama, Japan, based on medical records. Patients with previous treatment or lesions other than squamous cell carcinoma were excluded if there were insufficient data. We also excluded cases with an unconfirmed disease course of more than one year, but included patients who died within one year. We excluded patients older than 80 years of age because few patients in this age group underwent regular health checkups. To examine the risk factors, sex and age were matched to control groups of cases that underwent endoscopy within the same period in which no organic lesions were found in the upper gastrointestinal tract. We collected medical records and examined the presence or absence of alcohol consumption, smoking, body mass index (BMI), presence or absence of cancer in other organs, gastric mucosal atrophy, diabetes, hypertension, and dyslipidemia. Data on gastric mucosal atrophy did not include any postoperative gastric cancer cases.

The diagnosis of metabolic syndrome was made after a thorough medical history was taken, medical records were examined, and the presence or absence of therapeutic drugs was recorded.

Gastric mucosal atrophy was determined in six stages based on the Kimura-Takemoto classification by three endoscopy specialists using endoscopic images (closed groups: C 1, C2, and C3; open groups: O1, O2, and O3) (18). In this study, only C1 was determined to have no atrophy, all others were judged to be atrophied, and O2 and O3 showed high atrophy. Furthermore, because advanced cancer includes cases in which dietary intake is difficult, we also examined superficial cancers. Superficial cancer was defined as a lesion that penetrated the wall of the submucosal layer.

This study followed procedures in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution (No. 3806-1).

Statistical analyses

Statistical analyses were performed using the EZR software program (Version 1.54) (19). Clinical characteristics were assessed using the chi-square test or Fisher's exact test. Univariate and multivariate analyses were performed using the Cox regression analysis to estimate hazard ratios and calculate 95% confidence intervals. Statistical significance was set at a two-sided p value <0.05.

Results

This study enrolled 402 patients with ESCC and 391 controls. The patient background characteristics are shown in Table 1. The majority of cases were male (83.6%) with a mean (SD) age of 66.27±7.64 years. BMI was 21.26±3.28 in the ESCC group was 23.67±3.62 control group ($p<0.001$). The proportion of patients with a BMI <20 was significantly higher in the ESCC group than in the control group (36.6% vs. 11.0%; $p<0.001$). A history of alcohol consumption and smoking was more common in the ESCC group than in the control group (87.9% vs. 56.8% and 83.9% vs. 47.6%, respectively), and a history of cancer other than ESCC was more common in the ESCC group (31.9% vs. 15.4%) ($p<0.001$ for all comparisons). Head and neck cancer was the most common (54 cases), followed by gastric cancer (52 cases), colorectal cancer (23 cases), lung cancer (12 cases), and liver cancer (11 cases). There was no significant between-group difference in gastric mucosal atrophy of C2 or higher (64.2% in the ESCC group and 60.8% in the control group) or in severe atrophy of O2 or higher

Table 1. Comparison of Characteristics between ESCC Cases and Controls.

	ESCC cases (n=402)	Controls (n=391)	p value
Age, years (mean±SD)	66.27 (±7.64)	65.97 (±7.53)	0.579
Male/Female	336/66	326/65	1
BMI, kg/m^2 (mean±SD)	21.26 (±3.28)	23.67 (±3.62)	<0.001
BMI <20kg/m^2 , n (%)	147 (36.6)	41 (11.0)	<0.001
History of alcohol consumption, n (%)	349 (87.9)	222 (56.8)	<0.001
History of smoking consumption, n (%)	334 (83.9)	186 (47.6)	<0.001
History of cancer other than ESCC, n (%)	128 (31.9)	60 (15.4)	<0.001
History of gastric surgery, n (%)	26 (6.5)	11 (2.8)	0.018
Gastric mucosal atrophy (C2 or higher) , n (%)*	226 (64.2)	216 (60.8)	0.393
Gastric mucosal atrophy (O2 or higher) , n (%)*	48 (13.0)	46 (13.6)	0.825
DM, n (%)	67 (16.7)	65 (16.6)	1
HT, n (%)	164 (41.0)	166 (42.6)	0.666
DL, n (%)	67 (16.7)	132 (33.8)	<0.001

*Excluding history of gastric surgery

ESCC: Esophageal squamous cell carcinoma, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia

Table 2. Multivariate Analysis of Clinical Factors Associated with ESCC (Excluding History of Gastric Surgery).

	Odds ratio	95% CI	p value
BMI <20kg/m^2	6.38	3.780-10.800	<0.001
History of alcohol consumption	4.65	2.880-7.520	<0.001
History of smoking consumption	3.63	2.380-5.540	<0.001
History of cancer other than ESCC	2.09	1.330-3.270	0.00129
Gastric mucosal atrophy (C2 or higher)	1.04	0.716-1.510	0.832
DM	1.08	0.658–1.790	0.753
HT	0.944	0.639–1.390	0.772
DL	0.545	0.348–0.853	0.00799

ESCC: Esophageal squamous cell carcinoma, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia, CI: confidence interval

(13.0% vs. 13.6%). The mean ESCC size was 40.58±30.17 mm, and the tumor was located in the mid-thoracic esophagus in 132 (54.5%) patients and in the upper and lower thoracic areas in 46 (19.0%) and 55 (22.7%) patients, respectively. The tumor was moderately differentiated in 214 (61.0%) patients, well-differentiated in 75 (21.4%), and poorly differentiated in 62 (17.7%). TNM stages were 0, I, II, III, and IV in 58 (17.6%), 60 (18.2%), 43 (13.1%), 82 (24.9%), and 86 (26.1%) patients, respectively.

Diabetes, hypertension, and dyslipidemia were found in 16.7% vs. 16.6%, 41.0% vs. 42.6%, and 16.7% vs. 33.8% of the ESCC and control groups, respectively. A multivariate analysis showed that alcohol consumption, smoking, and multi-organ cancer were significantly more common in the ESCC group; conversely, dyslipidemia was significantly less common in the ESCC group (Table 2). Notably, there was no significant association between ESCC and gastric mucosal atrophy in the present study.

A univariate analysis showed that patients with advanced cancer had a low BMI, whereas patients with superficial cancer were more likely to have metabolic syndrome, a history of multiple organ cancers, and many superficial cancers after gastric surgery (Table 3). Therefore, patients with a history of hospital visits were more likely to have superficial cancer (Table 3). Regarding the trigger for the diagnosis of superficial ESCC, the proportion of patients with symptoms was small, and thus, ESCC was often detected on endoscopy conducted during a health checkup. According to a multivariate analysis, patients with superficial cancer had a higher rate of health checkup detection than those with advanced cancer (odds ratio 7.93, 95% confidence interval 4.480-14.00) (Table 4).

Discussion

The results of the analysis of risk factors for ESCC were analyzed by comparing ESCC patients with subjects who had undergone health check-ups, in addition to alcohol consumption and smoking history, which are conventionally known to be associated with a risk of ESCC (20-22), Concomitant cancer of other organs and low BMI were associated with a risk of ESCC, whereas dyslipidemia was significantly less common in patients with ESCC. The only factor contributing to early disease detection is a history of endo-

Table 3. Univariate Analysis of the Backgrounds of the Patients in between Early Stage ESCC and Advanced ESCC.

	Superficial (n=181)	Advanced (n=221)	p value
Age, years (mean±SD)	66.38 (±7.57)	66.19 (±7.72)	0.809
Male/Female	157/24	179/42	0.137
BMI, kg/m^2 (mean±SD)	21.80 (±3.07)	20.81 (±3.38)	0.003
BMI <20kg/m^2 , n (%)	54 (29.8)	93 (42.1)	0.013
History of alcohol consumption, n (%)	161 (90.4)	188 (85.8)	0.168
History of smoking consumption, n (%)	150 (83.8)	184 (84.0)	1
History of cancer other than ESCC, n (%)	69 (38.3)	59 (26.7)	0.014
History of gastric surgery, n (%)	18 (9.9)	8 (3.6)	0.014
Gastric mucosal atrophy (C2 or higher) , n (%)*	104 (66.7)	122 (61.8)	0.434
Gastric mucosal atrophy (O2 or higher) , n (%)*	17 (10.9)	31 (15.8)	0.212
DM, n (%)	38 (21.0)	29 (13.1)	0.043
HT, n (%)	93 (51.4)	71 (32.4)	<0.001
DL, n (%)	42 (23.2)	25 (11.4)	0.002
History of hospital visit, n (%)	161 (89.0)	169 (76.8)	0.002
Diagnosis by health check up, n (%)	86 (61.0)	28 (13.7)	<0.001

*Excluding history of gastric surgery

ESCC: Esophageal squamous cell carcinoma, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia

Table 4. Multivariate Analysis of the Backgrounds of the Patients in between Early Stage ESCC and Advanced ESCC (Excluding History of Gastric Surgery).

	Odds ratio	95% CI	p value
Male	0.891	0.365-2.18	0.8
BMI <20kg/m^2	1.23	0.676-2.23	0.501
History of alcohol consumption	0.645	0.238-1.75	0.388
History of smoking consumption	1.09	0.471-2.54	0.833
History of cancer other than ESCC	1.04	0.545-1.99	0.901
Gastric mucosal atrophy （C2 or higher)	0.92	0.524-1.62	0.771
DM	0.854	0.403-1.81	0.68
HT	0.758	0.414-1.39	0.371
DL	0.624	0.289-1.35	0.229
History of hospital visit (%)	0.646	0.289-1.44	0.286
Diagnosis by health check up (%)	7.93	4.480-14.00	<0.001

ESCC: Esophageal squamous cell carcinoma, BMI: body mass index, DM: diabetes mellitus, HT: hypertension, DL: dyslipidemia, CI: confidence interval

scopic screening. In a univariate analysis, attending a hospital for the treatment of an underlying disease was a factor contributing to early detection. This may be because patients are more likely to undergo endoscopic examinations if they attend a medical institution, either because of mild subjective symptoms or as part of cancer screening endoscopy. In total, 169 (76.8%) of 221 patients with advanced cancer who visited the hospital for treatment had a history of diabetes, hypertension, or dyslipidemia. It is important for outpatient physicians to ask patients visiting a hospital for treatment, whether they have undergone cancer screening, and to actively recommend upper gastrointestinal endoscopy to patients with a history of cancer of other organs or a history of alcohol consumption or smoking. Practitioners should consider this when treating patients. Alcohol consumption, smoking (20-22) and a history of cancer in other organs (23, 24) are known risk factors for ESCC. In the present study, 18 of 402 ESCC cases (4.48%) had no history of alcohol consumption or smoking and no history of cancer in other organs, and only two of them were male; it was observed in only 0.6%. Thus, ESCC can be easily targeted for endoscopy.

Known risk factors for ESCC include male sex, alcohol consumption, smoking (20-22), complications of other organ cancers (23, 24), a low BMI (25-27), achalasia (28, 29), hypertension (30), and atrophic gastritis and infection with its causative organism, *Helicobacter pylori* (6-8). However, our multivariate analysis results showed a correlation with a history of alcohol consumption and smoking, complications of other organ cancers, and low BMI, but not with hyperten-

sion or atrophic gastritis. Several studies on ESCC and atrophic gastritis have reported conflicting results, with some reports showing a relationship (6-8) and others showing no association (5, 9, 10). In the present study, the diagnosis of atrophic gastritis was determined by endoscopy using the Kimura-Takemoto classification system and it was found to be 13.5% in patients with ESCC and 12.1% in controls, with no association between ESCC and atrophic gastritis. In 2007, Iijima et al. (7) evaluated 73 patients with superficial esophageal cancer and sex- and age-matched controls. They examined atrophic gastritis through histological examination of gastric biopsies and measured the serum pepsinogen I levels. A multivariate analysis showed that atrophic gastritis of the fundus is a risk factor for superficial esophageal cancer. In 2009, Akiyama et al. diagnosed atrophic gastritis based on endoscopic findings and conducted a similar study, concluding that there was a correlation between atrophic gastritis and ESCC (8); however, in their study, the number of cases with severe atrophy was high (50.2%) in the control group. Their study results may be the product of an era in which there were many *H. pylori*-infected patients; therefore, atrophic gastritis was more frequent and advanced. In recent years, *H. pylori* infection rates have decreased; consequently, the frequency and extent of atrophic gastritis have also decreased (31). Our study found no association between atrophic gastritis and ESCC. If such an association exists, it should be possible to detect ESCC and gastric cancer using the ABC method (32), a popular risk screening method for gastric cancer. However, in the present study, 35.8% of ESCC cases had a non-atrophic mucosa that could not be detected by the ABC method. As the main cause of atrophic gastritis is *H. pylori* infection, its relationship with *H. pylori* infection must be considered when discussing atrophic gastritis. This was a retrospective study based on a chart search of cases diagnosed with ESCC, and the presence or absence of *H. pylori* infection and history of eradication therapy were not included in the present study due to insufficient information.

There have been many reports on the relationship between ESCC and a low BMI (25-28) and it is thought that one of the reasons for this is the inability to ingest food due to symptoms, such as dysphagia, in advanced cancer. In the present study, we compared BMI <20 in two groups: superficial cancer patients with no or minimal subjective symptoms, with cancer mainly detected by medical examination, and advanced cancer patients with subjective symptoms such as dysphagia, and found that there was a significant difference between the two groups according to a univariate analysis (p=0.013), but the significant difference disappeared in a multivariate analysis (p=0.501).

These results suggest that there is an association between a poor nutritional status and ESCC. In the present study, concomitant dyslipidemia was associated with a significant reduction in the incidence of ESCC. Although medications for the treatment of dyslipidemia were not investigated in the present study, statins are the first-line treatment for dyslipidemia (33) and it is likely that statins were also used in the present study. Among patients diagnosed with dyslipidemia and subsequently treated for ESCC, those who adhere to statin therapy have a better prognosis than those who do not (34). Cancer incidence is significantly lower among adherents, including those with esophageal adenocarcinoma (35). A recent multicenter retrospective study from Japan by Arai et al. also reported a significantly lower incidence of ESCC and esophageal adenocarcinoma in statin users (36).

According to the Ministry of Health, Labour, and Welfare guidelines, endoscopy for gastric cancer screening is recommended once every 2 years (37). Recent data from Nezu et al. on endoscopic screening at health screening centers have shown that the detection rate of gastric cancer has decreased, whereas the detection rate of ESCC has increased (38). Because of the rapid growth rate of ESCC (39), annual endoscopy is therefore considered to be necessary for patients with a history of alcohol consumption, smoking, and complications involving cancers of other organs.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Carmen Innes, BSc for editing the draft of this manuscript. We are grateful to Prof. Satoshi Morita, PhD, of the Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Japan, for his helpful advice and guidance on the statistical analysis.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin **71**: 209-249, 2021.
2. Morgan E, Soerjomataram I, Rumgay H, et al. The global landscape of esophageal squamous cell and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. Gastroenterology **163**: 649-658, 2022.
3. Watanabe M, Toh Y, Ishihara R, et al; Registration Committee for Esophageal Cancer of the Japan Esophageal Society. Comprehensive registry of esophageal cancer in Japan, 2015. Esophagus **20**: 1-28, 2023.
4. ganjoho.jp [Internet]. [cited 2024 Jan 15]. Available from: https://ganjoho.jp/public/index.html
5. Wang QL, Xie SH, Wahlin K, Lagergren J. Global time trends in the incidence of esophageal squamous cell carcinoma. Clin Epidemiol **10**: 717-728, 2018.
6. Ye W, Held M, Lagergren J, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Cancer Inst **96**: 388-396, 2004.
7. Iijima K, Koike T, Abe Y, et al. Extensive gastric atrophy: an increased risk factor for superficial esophageal squamous cell carcinoma in Japan. Am J Gastroenterol **102**: 1603-1609, 2007.
8. Akiyama T, Inamori M, Iida H, et al. Macroscopic extent of gastric mucosal atrophy: increased risk factor for esophageal squamous cell carcinoma in Japan. BMC Gastroenterol **9**: 34,

2009.
9. Venerito M, Kohrs S, Wex T. *Helicobacter pylori* infection and fundic gastric atrophy are not associated with esophageal squamous cell carcinoma: a case-control study. Eur J Gastroenterol Hepatol **23**: 859-864, 2011.
10. Ekheden I, Yang X, Chen H, et al. Associations between gastric atrophy and its interaction with poor oral health and the risk for esophageal squamous cell carcinoma in a high-risk region of China: A population-based case-control study. Am J Epidemiol **189**: 931-941, 2020.
11. Yoshiike N, Seino F, Tajima S, et al. Twenty-year changes in the prevalence of overweight in Japanese adults: the National Nutrition Survey 1976-95. Obes Rev **3**: 183-190, 2002.
12. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care **34**: 216-219, 2011.
13. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab **93**: S9-S30, 2008.
14. Shen X, Wang Y. Metabolic syndrome and the risk of colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis **36**: 2215-2225, 2021.
15. Li Y, Shi J, Liu X, Deng Q, Huang Y, Yang Z. Metabolic syndrome relates to high risk in hepatocellular carcinoma: a meta-analysis. Discov Med **26**: 185-196, 2018.
16. Zhao P, Xia N, Zhang H, Deng T. The metabolic syndrome is a risk factor for breast cancer: a systematic review and meta-analysis. Obes Facts **13**: 384-396, 2020.
17. Nakamura J, Manabe N, Yamatsuji T, et al. Subjective factors affecting prognosis of 469 patients with esophageal squamous cell carcinoma: a retrospective cohort study of endoscopic screening. BMC Gastroenterol **22**: 319, 2022.
18. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy **1**: 87-97, 1969.
19. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplantation **48**: 452-458, 2013.
20. Domper Arnal MJ, Ferrández Arenas Á, Lanas Arbeloa Á. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol **21**: 7933-7943, 2015.
21. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology **154**: 360-373, 2018.
22. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clin J Gastroenterol **13**: 1010-1021, 2020.
23. Onochi K, Shiga H, Takahashi S, et al. Risk factors linking esophageal squamous cell carcinoma with head and neck cancer or gastric cancer. J Clin Gastroenterol **53**: e164-e170, 2019.
24. Mitani S, Kato K, Daiko H, et al. Second primary malignancies in patients with clinical T1bN0 esophageal squamous cell carcinoma after definitive therapies: supplementary analysis of the JCOG trial: JCOG0502. J Gastroenterol **57**: 455-463, 2022.
25. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol **41**: 1706-1718, 2012.
26. Lindkvist B, Johansen D, Stocks T, et al. Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580,000 subjects within the Me-Can project. BMC Cancer **14**: 103, 2014.
27. Koyanagi YN, Matsuo K, Ito H, et al. Body mass index and esophageal and gastric cancer: a pooled analysis of ten population-based cohort studies in Japan. Cancer Sci **114**: 2961-2972, 2023.
28. Torres-Aguilera M, Remes Troche JM. Achalasia and esophageal cancer: risks and links. Clin Exp Gastroenterol **11**: 309-316, 2018.
29. Sato H, Terai S, Shimamura Y, et al. Achalasia and esophageal cancer: a large database analysis in Japan. J Gastroenterol **56**: 360-370, 2021.
30. Seo JH, Kim YD, Park CS, Han KD, Joo YH. Hypertension is associated with oral, laryngeal, and esophageal cancer: a nationwide population-based study. Sci Rep **10**: 10291, 2020.
31. Kamada T, Haruma K, Ito M, et al. Time trends in *Helicobacter pylori* infection and atrophic gastritis over 40 years in Japan. Helicobacter **20**: 192-198, 2015.
32. Miki K. Gastric cancer screening by combined assay for serum anti-*Helicobacter pylori* IgG antibody and serum pepsinogen levels - "ABC method". Proc Jpn Acad Ser B Phys Biol Sci **87**: 405-414, 2011.
33. Dayar E, Pechanova O. Targeted strategy in lipid-lowering therapy. Biomedicines **10**: 1090, 2022.
34. Lv J, Chen P, Wu J, Wen Z, Zhao C. The association between statin use and prognosis in esophageal cancer patients: a meta-analysis. Medicine (Baltimore) **102**: e33359, 2023.
35. Alexandre L, Clark AB, Bhutta HY, Holt S, Lewis MP, Hart AR. Statin use is associated with reduced risk of histologic subtypes of esophageal cancer: a nested case-control analysis. Gastroenterology **146**: 661-668, 2014.
36. Arai J, Niikura R, Hayakawa Y, et al. Chemoprevention of oesophageal squamous-cell carcinoma and adenocarcinoma: a multicentre retrospective cohort study. Digestion **103**: 192-204, 2022.
37. Ministry of Health, Labour, and Welfare. Cancer screening [Internet]. [cited 2024 Jan 15]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000059490.html
38. Nezu Y, Manabe N, Yoda Y, Haruma K. Effectiveness of screening endoscopy for esophageal squamous cell carcinoma in Japanese males. United European Gastroenterol J **10**: 868-873, 2022.
39. Haruma K, Tokutomi T, Yoshihara M, Sumii K, Kajiyama G. Rapid growth of untreated esophageal squamous-cell carcinoma in 10 patients. J Clin Gastroenterol **13**: 129-134, 1991.