Received: 14 September 2020 | Revised: 25 November 2020 | Accepted: 25 November 2020

DOI: 10.1111/cas.14753

ORIGINAL ARTICLE

Cancer Science WILEY

Risk factors for esophageal iodine-unstained lesions and changing trends among Japanese alcohol-dependent men (2003-2018)

Akira Yokoyama[1] | Tai Omori[2] | Tetsuji Yokoyama[3]

[1]National Hospital Organization Kurihama Medical and Addiction Center, Kanagawa, Japan

[2]Endoscopy Center, Kawasaki Municipal Ida Hospital, Kanagawa, Japan

[3]Department of Health Promotion, National Institute of Public Health, Saitama, Japan

Correspondence
Akira Yokoyama, National Hospital Organization Kurihama Medical and Addiction Center, 5-3-1 Nobi, Yokosuka, Kanagawa 239-0841, Japan.
Email: a-yoko@ab.auone-net.jp

Abstract

Globally, a decreasing incidence of male esophageal squamous cell carcinoma (ESCC) has been observed in recent decades. We evaluated the determinants of esophageal distinct iodine-unstained lesions (DIULs), high-cancer-risk lesions and ESCC, among 3858 Japanese alcohol-dependent men (40-79 years) who underwent chromoendoscopic screening between 2003 and 2018. The initial screening detected DIULs ≥ 5 mm in 541 patients (dysplasia in 319 and SCC in 129) and multiple DIULs in 640. The detection rates for DIULs and chronic atrophic gastritis (CAG), pack-years, and the mean corpuscular volume (MCV) decreased over the course of the study period, while the detection of hiatal hernia and/or columnar-lined esophagus (HH/CLE) and the carriers of inactive heterozygous *aldehyde dehydrogenase-2* (*ALDH2*, rs671) increased. Multiple logistic regression analyses showed that an older age, larger number of pack-years, smaller body mass index, larger MCV, presence of a slow-metabolizing *alcohol dehydrogenase-1B* genotype (rs1229984), presence of an inactive heterozygous *ALDH2* genotype, and more advanced degree of CAG increased the odds ratios (ORs) for DIULs, while the 2008-2013 and 2014-2018 screening periods had lower ORs for DIULs than the 2003-2007 screening period. The presence of HH/CLE decreased the OR for multiple DIULs and was associated with a more proximal location of ESCC. In conclusion, the detection of DIULs in an alcohol-dependent population decreased between 2003 and 2018. In addition to reported determinants of ESCC, CAG and HH/CLE were associated with the risk of DIULs. Enigmatically, however, the decline in the detection of DIULs was not adequately explained by these factors and warrants further research.

KEYWORDS

alcohol dependence, chronic atrophic gastritis, esophageal cancer, esophageal dysplasia, hiatal hernia

1 | INTRODUCTION

Squamous cell dysplasia and carcinoma in the upper aerodigestive tract as well as chronic atrophic gastritis (CAG) and gastric adenocarcinoma are frequently detected by chromoendoscopic screening using esophageal iodine staining in Japanese alcohol-dependent men.[1-4] Esophageal dysplasia and esophageal squamous cell carcinoma (ESCC) were histologically diagnosed in 88% of mucosal biopsy specimens of distinct iodine-unstained lesions (DIULs) with a greatest dimension of 5 mm or more.[3] The presence of multiple esophageal DIULs is also frequently found in this population.[3] The presence of DIULs ≥ 5 mm[5] and multiple DIULs[6-9] indicate a high risk of multicentric cancerization in the upper aerodigestive tract among Japanese drinkers.

Inactive aldehyde dehydrogenase-2 encoded by the *ALDH2*1/*2* genotype (rs671) and slow-metabolizing alcohol dehydrogenase-1B encoded by the *ADH1B*1/*1* genotype (rs1229984) are strong risk factors for ESCC,[1-6,10-12] DIULs ≥ 5 mm,[3,13] and multiple DIULs[3,6,13,14] among East Asian drinkers.

We recently reported that the detection rate of ESCC as well as that of CAG and gastric adenocarcinoma decreased markedly between 2003 and 2018 in an alcohol-dependent population.[4] The reduction in *Helicobacter pylori* (*H. pylori*) infection is the main reason for the reductions in CAG and gastric cancer.[15] Growing evidence has shown that the presence of CAG increases the risk of ESCC.[16-24] A meta-analysis of seven studies has shown a 1.94-fold higher relative risk of ESCC among people with CAG.[20] We have also demonstrated a high risk of ESCC among Japanese alcohol-dependent men with CAG.[4,25] The reduction in ESCC in this population might also be linked to global trends toward a decreasing incidence of male ESCC during recent decades.[26]

The aims of this study were to evaluate the trends in the detection of large DIULs and multiple DIULs, which are regarded as high-cancer-risk lesions, between 2003 and 2018 and to clarify the factors associated with DIULs among Japanese alcohol-dependent men.

2 | MATERIALS AND METHODS

2.1 | Subjects

The subjects were 3858 Japanese alcohol-dependent men aged 40-79 years old who (a) visited the Kurihama Medical and Addiction Center for the treatment of alcohol dependence, (b) did not have any history of upper aerodigestive tract or gastric cancer treatment or a gastrectomy, and (c) underwent endoscopic screening with esophageal iodine staining between 2003 and 2018. We used only the initial screening results, and there was no overlap among the subjects.

All the subjects met the DSM-IIIR, DSM-IV, or ICD-10 criteria for alcohol dependence.[27-29] Each subject was asked about his usual alcohol consumption during the preceding year and smoking habits using a structured questionnaire, as previously reported.[1,3] The proposal for this study was approved by the ethics committee of the Kurihama Medical and Addiction Center. The ethics committee determined that the requirement for additional informed consent to participate in the present study was waived because of its retrospective design, and patients were able to exclude themselves using the opt-out method on the Center's website.

2.2 | Endoscopic screening

The examinations were performed using Olympus endoscopes (models XQ230, Q240, Q240Z, Q260, and Q260Z in chronological order of use; Olympus Optical Co. Ltd.). Almost all the screening examinations were performed by a single endoscopist (A. Yokoyama) or were performed under his supervision. The screening program and diagnostic procedure have been described in previous reports.[1,3] A 3% iodine solution was consistently used for esophageal iodine staining during the study period. Mucosal biopsy specimens were collected from DIULs whose greatest diameter was 5 mm or more (Figure 1A). Multiple DIULs were recorded when 10 or more DIULs of any size were observed in at least one endoscopic field of view (Figure 1B). The center of each ESCC lesion was defined as "the distance from the incisor to the proximal end of the DIUL" plus "half of the axial diameter of the DIUL." Using digitalized images stored within a medical imaging communication system, a single endoscopist (A. Yokoyama) reviewed the endoscopic findings for the hiatal hernia and/or columnar-lined esophagus (HH/CLE) and CAG. When the axial length between the diaphragmatic pinch and the border between the white squamous epithelium and the red epithelium was ≥10 mm for the entire circumference (Figure 1C), the subject was diagnosed as having an HH/CLE ≥ 10 mm, which was regarded as evidence of long-term gastroesophageal reflux. A digitalized record of the area around the esophagogastric junction was absent in 37 subjects. According to the Kimura-Takemoto classification system for CAG (Figure 1D),[30] no atrophy was classified as C0. Atrophic mucosa limited to the antrum, the gastric angle or the lower corpus, the upper corpus, or the gastric cardia surroundings with maintained folds in the greater curvature was classified as C1, C2, C3, or O1, respectively. Atrophy in the entire stomach with a lack of folds in the greater curvature was classified as O3, while O2 represented an intermediate designation between O1 and O3. The patients were classified into three categories (C0 to C2, C3 to O1, and O2-O3) because the gastric cancer detection rate reportedly increase in a stepwise manner according to these categories.[31]

2.3 | Evaluation of *H. pylori* infection

In February 2013, the Japanese universal health insurance plan was expanded to include coverage for *H. pylori* eradication therapy for

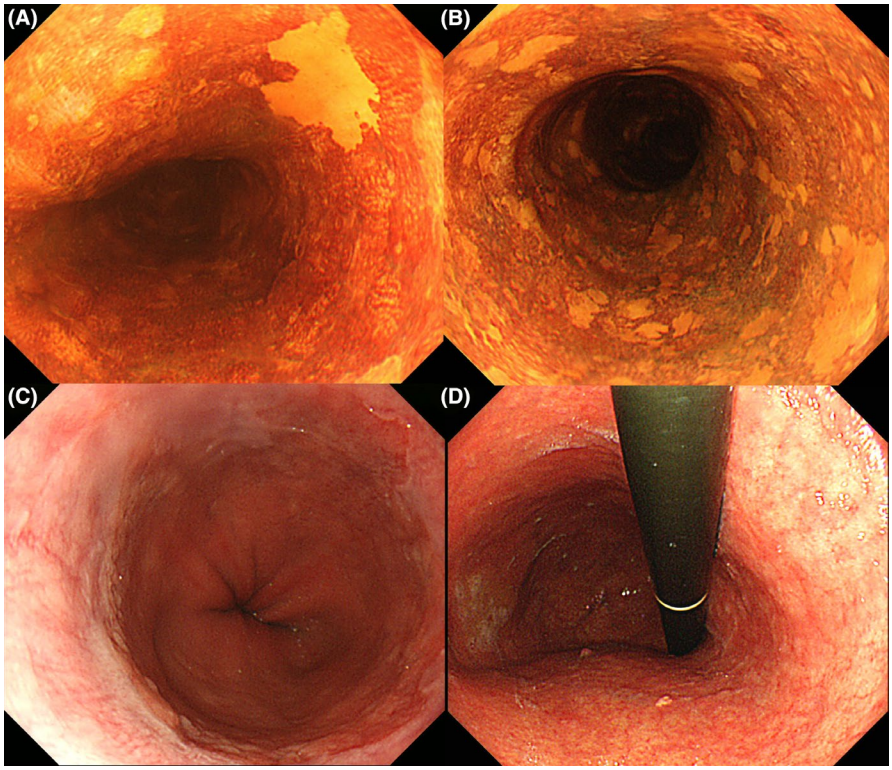

FIGURE 1 A distinct iodine-unstained lesion (DIUL) ≥ 5 mm was diagnosed as dysplasia (A). "Multiple DIULs" was defined as the presence of 10 or more DIULs of any size in at least one endoscopic field of view (B). "The hiatal hernia and/or columnar-lined esophagus (HH/CLE) ≥10 mm" was diagnosed when the axial length between the diaphragmatic pinch and the border between the white squamous epithelium and the red epithelium was ≥10 mm for the entire circumference (C). The degree of chronic atrophic gastritis was diagnosed according to the Kimura-Takemoto classification system (D)

H. pylori–associated gastritis.[32] Since then, the presence of *H. pylori* infection has been examined using the stool antigen test (Testmate Rapid Pylori Antigen; Wakamoto Pharmaceutical) and the (13)C-urea breath test (BML, Ltd.) in patients who did not have a history of *H. pylori* eradication and wished to undergo testing.

2.4 | Mean corpuscular volume

During each patient's initial visit to the Center for the treatment of alcohol dependence, we measured the mean corpuscular volume (MCV) using the electrical impedance method with an autoanalyzer (CELL-DYN 3500; Abbott). We dichotomized the results into an MCV < 106 fl group and an MCV ≥ 106 fl group because macrocytosis with an MCV value ≥ 106 fl was found to be associated with an increased risk of ESCC in our previous studies of alcohol-dependent men[5,33] and men who had undergone an endoscopic mucosectomy for early ESCC.[34]

2.5 | *ALDH2* and *ADH1B* genotyping

We had previously determined the *ALDH2* and *ADH1B* genotypes of 3335 subjects from whom written informed consent had been obtained for the study of *ALDH2* and *ADH1B* genotype–associated phenotypes and comorbidities, which had been approved by the ethics committee of the Center. PCR-restriction fragment length polymorphism methods were used to genotype *ALDH2* and *ADH1B* in DNA obtained from blood samples.[1]

2.6 | Statistical analysis

Values were expressed as the mean and standard deviation (SD) or the percentage. Age was compared using the χ^2 test or the *t* test between two groups, and trends were tested using a linear regression model. Age-adjusted *P*-values for other variables were calculated using an analysis of the covariance, a multiple linear regression model, or the Cochran-Mantel-Haenszel test, as appropriate. The multivariate odds ratios (ORs) and the 95% confidence intervals (CIs) were calculated using multiple logistic models. We combined the *ADH1B*1/*2* genotype carriers and the *ADH1B*2/*2* genotype carriers into a single group because of the semidominant nature of the *ADH1B*2* allele.[35,36] Statistical significance was defined as a *P*-value of <0.05. All the statistical analyses were performed using SAS software (version 9.4; SAS Institute).

3 | RESULTS

DIULs ≥ 5 mm and multiple DIULs were diagnosed in 541 (14.0%) and 640 (16.6%) subjects, respectively. A targeted biopsy of DIULs ≥ 5 mm was performed in 471 subjects, and esophageal squamous cell dysplasia and ESCC were diagnosed in 319 and 129 subjects, respectively. The main reasons for not performing a biopsy were the presence of a bleeding tendency and/or liver cirrhosis.

Table 1 shows the background factors according to whether the DIULs were ≥5 mm (all), whether the DIULs were ≥5 mm (dysplasia), whether the DIULs were ≥5 mm (SCC), and whether multiple

TABLE 1 Background characteristics of Japanese alcohol-dependent men according to the results of esophageal iodine staining

	DIULs ≥ 5 mm						Multiple DIULs		
	Absent	Present		Dysplasia		SCC	Absent	Present	
	N = 3317	N = 541	*P*	N = 319	*P*	N = 129	*P*	N = 3218	N = 640	*P*
Age (years old) (n, %)										
40-49	1107 (33.4)	69 (12.8)	‡	42 (13.2)	‡	15 (11.6)	‡	1080 (33.6)	96 (15)	‡
50-59	1153 (34.8)	207 (38.3)		121 (37.9)		47 (36.4)		1133 (35.2)	227 (35.5)	
60-69	755 (22.8)	198 (36.6)		120 (37.6)		48 (37.2)		726 (22.6)	227 (35.5)	
70-79	302 (9.1)	67 (12.4)		36 (11.3)		19 (14.7)		279 (8.7)	90 (14.1)	
Mean ± SD	55.1 ± 9.6	59.4 ± 8.3	‡	59.3 ± 8.3	‡	60.1 ± 8.6	‡	54.9 ± 9.6	59.4 ± 8.7	‡
Alcohol intake (g ethanol/d)	N = 3310	N = 541		N = 319		N = 129		N = 3212	N = 639	
Mean ± SD	119.1 ± 74.6	111.4 ± 62.7		109.1 ± 58.9		107.4 ± 49.9		119.8 ± 75.7	109.0 ± 57.7	
Pack-years	N = 3310	N = 541		N = 319		N = 129		N = 3211	N = 640	
Mean ± SD	30.8 ± 23.1	36.3 ± 24.9	*	37.0 ± 25.3	*	35.7 ± 24.0		30.8 ± 22.9	35.5 ± 25.8	*
Body mass index (kg/m^2)	N = 3239	N = 526		N = 310		N = 123		N = 3145	N = 620	
Mean ± SD	22.0 ± 3.5	21.1 ± 3.2	‡	20.8 ± 3.1	‡	21.2 ± 3.1		21.9 ± 3.6	21.4 ± 3.3	*
MCV	N = 3275	N = 534		N = 316		N = 128		N = 3173	N = 636	
Mean ± SD	99.9 ± 8.0	102.9 ± 8.5	‡	102.9 ± 8.2	‡	103.8 ± 8.7	‡	99.8 ± 7.9	103.3 ± 8.6	‡
MCV ≥ 106 fl	706 (21.6)	178 (33.3)	‡	102 (32.3)	‡	49 (38.3)	‡	665 (21)	219 (34.4)	‡
ALDH2 genotype (n, %)										
**1/*1* (active)	2496 (87.3)	319 (67.0)	‡	201 (74.4)	‡	54 (42.2)	‡	2447 (88.5)	368 (64.6)	‡
**1/*2* (inactive)	363 (12.7)	157 (33.0)		69 (25.6)		74 (57.8)		318 (11.5)	202 (35.4)	
ADH1B genotype (n, %)										
**1/*1* (slow)	760 (26.6)	191 (40.1)	‡	101 (37.4)	‡	60 (46.9)	‡	699 (25.3)	252 (44.2)	‡
**1/*2* or **2/*2* (fast)	2099 (73.4)	285 (59.9)		169 (62.6)		68 (53.1)		2066 (74.7)	318 (55.8)	
HH/CLE ≥ 10 mm										
Absent	2308 (70.3)	413 (76.8)	*	246 (77.6)	*	93 (72.7)		2220 (69.6)	501 (79.1)	†
Present	975 (29.7)	125 (23.2)		71 (22.4)		35 (27.3)		968 (30.4)	132 (20.9)	
Chronic atrophic gastritis (n, %)										
C0-C2	2266 (68.3)	275 (50.8)	‡	162 (50.8)	‡	63 (48.8)	†	2194 (68.2)	347 (54.2)	†
C3-O1	754 (22.7)	172 (31.8)		105 (32.9)		37 (28.7)		738 (22.9)	188 (29.4)	
O2-O3	297 (9.0)	94 (17.4)		52 (16.3)		29 (22.5)		286 (8.9)	105 (16.4)	

Note: P values were tested between the DIUL-absent and -present groups. *Note:* Age was compared by χ^2 test or *t* test between groups. For other variables, *P*-values were adjusted for age by analysis of covariance for mean values and by Cochran-Mantel-Haenszel test for categorical data (for trend for chronic atrophic gastritis).

Abbreviations: ADH1B, alcohol dehydrogenase-1B; ALDH2, aldehyde dehydrogenase-2; DIULs, distinct iodine-unstained lesions; HH/CLE, hiatal hernia and/or columnar-lined esophagus; MCV, mean corpuscular volume; SCC squamous cell carcinoma.

*<0.05.

†<0.0005.

‡<0.0001.

DIULs were present. As a significantly older age was observed in the DIULs-present groups, compared with the DIULs-absent groups, all the subsequent statistical analyses were performed with age adjustments. An MCV ≥ 106 fl, the inactive heterozygous *ALDH2*1/*2* genotype, the slow-metabolizing *ADH1B*1/*1* genotype, and advanced degrees of CAG were more frequently found in all the DIULs-present groups. A larger number of pack-years, a smaller body mass index (BMI), and a lower frequency of HH/CLE ≥ 10 mm were observed in all the DIULs-present groups except for the ESCC group.

For the 2003-2007 period, the 2008-2012 period, and the 2013-2018 period, the respective detection rates of DIULs ≥ 5 mm (all:

20.6%, 12.4%, and 8.6%; dysplasia: 11.7%, 7.9%, and 4.8%; SCC: 4.4%, 3.1%, and 2.4%) and multiple DIULs (20.0%, 14.9%, and 14.9%) decreased (Table 2). The incidence of advanced CAG also decreased, while that of HH/CLE ≥ 10 mm increased, during the study period. No significant differences in age, daily alcohol consumption, BMI, or genotype distribution of *ADH1B* were seen during the study period. The number of pack-years, mean MCV, and the frequency of macrocytosis with an MCV ≥ 106 fl all decreased. The frequency of inactive *ALDH2*1/*2* increased from 13.9% to 15.1% and 17.8% for the respective time periods.

The distance of the ESCC lesion from the incisors, the ESCC depth, and the intraesophageal multiplicity of ESCCs were compared according to whether an HH/CLE ≥ 10 mm was present or according to the degree of CAG (Table 3). ESCC lesions were located in more proximal sites of the esophagus in subjects with an HH/CLE ≥ 10 mm. An HH/CLE ≥ 10 mm was more frequently accompanied by a milder degree of CAG.

Table 4 shows the associations of the *H. pylori* status with CAG and HH/CLE during the 2013-2018 period. CAG classification was strongly associated with *H. pylori* infection. A high rate

TABLE 2 Changes in detection of esophageal DIULs and background factors during 2003 and 2018 in Japanese alcohol-dependent men

Year of endoscopic screening	2003-2007 N = 1274	2008-2012 N = 1473	2013-2018 N = 1111	*P*
Age (y), mean ± SD	55.2 ± 9.0	56.1 ± 9.9	55.7 ± 9.7	.20
Alcohol intake (g ethanol/d)	N = 1270	N = 1470	N = 1111	
Mean ± SD	117.0 ± 71.3	119.0 ± 72.8	117.8 ± 75.7	.57
Pack-years	N = 1271	N = 1469	N = 1111	
Mean ± SD	33.3 ± 23.8	32.3 ± 22.9	28.5 ± 23.6	<.0001
Body mass index (kg/m^2)	N = 1250	N = 1423	N = 1092	
Mean ± SD	21.8 ± 3.4	21.8 ± 3.6	22.0 ± 3.5	.055
MCV	N = 1234	N = 1470	N = 1105	
Mean ± SD	101.3 ± 7.8	101.0 ± 8.1	98.4 ± 8.2	<.0001
MCV ≥ 106 fl	26.8%	25.2%	16.6%	<.0001
ALDH2 genotype	N = 922	N = 1366	N = 1047	
**1/*1* (active)	86.1%	84.9%	82.2%	.016
**1/*2* (inactive)	13.9%	15.1%	17.8%	
ADH1B genotype	N = 922	N = 1366	N = 1047	
**1/*1* (slow)	28.3%	29.0%	28.1%	.99
**1/*2* or **2/*2* (fast)	71.7%	71.0%	71.9%	
DIULs	N = 1274	N = 1473	N = 1111	
DIULs ≥ 5 mm (all)	20.6%	12.4%	8.6%	<.0001
DIULs ≥ 5 mm (dysplasia)	11.7%	7.9%	4.8%	<.0001
DIULs ≥ 5 mm (SCC)	4.4%	3.1%	2.4%	.007
Multiple DIULs	20.0%	14.9%	14.9%	.0004
HH/CLE	N = 1250	N = 1466	N = 1105	
≥10 cm	23.7%	27.9%	35.7%	<.0001
Chronic atrophic gastritis	N = 1274	N = 1473	N = 1111	
C0-C2	60.0%	63.8%	75.2%	<.0001
C3-O1	27.5%	25.7%	17.8%	
O2-O3	12.5%	10.5%	6.9%	

Note: P-values were for trend by a linear regression model for age. For other variables, *P*-values were for trend adjusted for age by a multiple linear regression model for mean values and by Cochran-Mantel-Haenszel test for categorical data.

Abbreviations: ADH1B, alcohol dehydrogenase-1B; ALDH2, aldehyde dehydrogenase-2; DIULs, distinct iodine-unstained lesions; HH/CLE, hiatal hernia and/or columnar-lined esophagus; MCV, mean corpuscular volume; SCC, squamous cell carcinoma.

TABLE 3 Esophageal SCC, HH/CLE, and chronic atrophic gastritis in Japanese alcohol-dependent men

	HH/CLE ≥ 10 mm			Chronic atrophic gastritis			
	Absent	Present	*P*	C0-C2	C3-O1	O2-O3	*P*
Most proximal SCC lesion							
<30.4 cm from incisor	25 (58.1)	18 (41.9)	.010	23 (52.3)	15 (34.1)	6 (13.6)	.054
30.4-34.5 cm from incisor	33 (76.7)	10 (23.3)		24 (55.8)	9 (20.9)	10 (23.3)	
>34.5 cm from incisor	35 (83.3)	7 (16.7)		16 (38.1)	13 (31.0)	13 (31.0)	
Mean ± SD (cm)	32.7 ± 5.7	30.4 ± 5.8	.041	31.7 ± 5.3	31.3 ± 7.1	33.6 ± 4.7	.17
Most distal SCC lesion							
<31.0 cm from incisor	27 (62.8)	16 (37.2)	.061	27 (61.4)	11 (25.0)	6 (13.6)	.11
31.0-36.0 cm from incisor	32 (74.4)	11 (25.6)		16 (37.2)	16 (37.2)	11 (25.6)	
>36.0 cm from incisor	34 (81.0)	8 (19.0)		20 (47.6)	10 (23.8)	12 (28.6)	
Mean ± SD (cm)	34.0 ± 5.5	31.7 ± 5.9	.036	33.1 ± 5.5	32.8 ± 6.5	34.5 ± 4.8	.28
SCC depth							
Intraepithelium	43 (72.9)	16 (27.1)	.56	28 (47.5)	17 (28.8)	14 (23.7)	.56
Proper mucosal layer	16 (66.7)	8 (33.3)		16 (66.7)	6 (25.0)	2 (8.3)	
Muscularis mucosa	11 (68.8)	5 (31.3)		7 (43.8)	6 (37.5)	3 (18.8)	
Submucosa	11 (73.3)	4 (26.7)		8 (50.0)	2 (12.5)	6 (37.5)	
Beyond proper muscle layer	12 (85.7)	2 (14.3)		4 (28.6)	6 (42.9)	4 (28.6)	
Multiple intraesophageal SCCs							
Absence	72 (74.2)	25 (25.8)	.48	44 (44.9)	30 (30.6)	24 (24.5)	.13
Presence	21 (67.7)	10 (32.3)		19 (61.3)	7 (22.6)	5 (16.1)	
Chronic atrophic gastritis (n, %)							
C0-C2	1635 (65.0)	882 (35.0)					
C3-O1	744 (81.3)	171 (18.7)					
O2-O3	342 (87.9)	47 (12.1)					

Note: P-values were for the trend for chronic atrophic gastritis and for the homogeneity for HH/CLE, where age was adjusted using a multiple linear regression model for continuous variables and by the Cochran-Mantel-Haenszel test for categorical variables.

Abbreviations: ADH1B, alcohol dehydrogenase-1B; ALDH2, aldehyde dehydrogenase-2; HH/CLE, hiatal hernia and/or columnar-lined esophagus; SCC, squamous cell carcinoma.

of *H. pylori*–negative results was observed with the C0-C1 classification, while a low rate was observed with the C2-O1 classification. The rate was intermediate for the O2-O3 classification. HH/CLE ≥ 10 mm was found more frequently among *H. pylori*–negative patients.

Multiple logistic regression analyses showed that the C3-O1 category and the O2-O3 category of CAG increased the ORs (95% CI) for DIULs ≥ 5 mm (all: 1.52 [1.18-1.90] and 1.76 [1.27-2.44], respectively; dysplasia: 1.57 [1.15-2.15] and 1.72 [1.15-2.58], respectively; SCC: 1.56 [0.96-2.54] and 2.27 [1.29-3.99]) and multiple DIULs (1.40 [1.10-1.79] and 1.67 [1.22-2.30], respectively), compared with the C0-C2 category (Table 5). The presence of HH/CLE ≥ 10 mm decreased the OR for multiple DIULs (0.71 [0.56-0.91]). Screening during the 2008-2012 period and the 20013-2018 period showed a decrease in the ORs in all the DIULs-present groups, compared with the 2003-2007 period. An older age and the presence of the *ALDH2*1/*2* and *ADH1B*1/*1* genotypes increased the ORs in all the DIULs-present groups, while a larger BMI decreased the ORs. An MCV ≥ 106 fl increased the ORs in the DIULs-present groups except for the ESCC group, while a smaller number of pack-years decreased the ORs for DIULs ≥ 5 mm (dysplasia) and multiple DIULs.

After excluding the 129 ESCC patients, 234 patients had DIULs ≥ 5 mm and multiple DIULs simultaneously. The abovementioned backgrounds of these 234 patients were compared with those of 178 patients with DIULs ≥ 5 mm alone and 303 patients with multiple DIULs alone. A multiple linear regression analysis using a stepwise procedure and $P < 0.05$ as the criterion for entry and removal showed that a 10-year increment of age, an *ALDH2*1/*2* genotype, and an *ADH1B*1/*1* genotype increased the ORs (95% CI) for the simultaneous presence of DIULs ≥ 5 mm and multiple DIULs (1.78 [1.31-2.40], 4.43 [2.38-8.25], and 2.29 [1.39-3.77], respectively), compared with the presence of DIULs ≥ 5 mm alone. A comparison of the simultaneous presence of DIULs ≥ 5 mm and multiple DIULs with the presence of multiple DIULs alone did not select any significant background factors.

4 | DISCUSSION

The detection rates of DIULs ≥ 5 mm (all), DIULs ≥ 5 mm (dysplasia), and multiple DIULs, which are regarded as high-ESCC-risk lesions, and of ESCC were relatively high during the chromoendoscopic screening of alcohol-dependent men. The rates of all DIULs and advanced CAG decreased, and the rate of HH/CLE ≥ 10 mm increased during the study period. The CAG classification was strongly associated with the status of *H. pylori* infection. The relatively high rate of negative results for *H. pylori* infection with O2-O3 atrophy probably reflects previous *H. pylori* infection including the spontaneous disappearance of *H. pylori* because of severe atrophy.[37] The reduction in *H. pylori* infection in Japan is the main reason for the decrease in the detection of advanced CAG over time.[15,32] Advanced CAG increased the ORs of all the DIULs, and the presence of HH/CLE ≥ 10 mm decreased the OR of the multiple DIULs. Other factors associated with the DIULs were an older age, a larger number of pack-years, a smaller BMI, a larger MCV, the presence of a slow-metabolizing *ADH1B* genotype, and the presence of an inactive heterozygous *ALDH2* genotype.

There is growing evidence of a positive association between CAG and the risk of ESCC.[4,16-25] Oral microflora form acetaldehyde, a carcinogen for ESCC, from ethanol and contribute to the high acetaldehyde levels in saliva after ethanol ingestion.[38,39] An overgrowth of oral microflora and high acetaldehyde production in the saliva is observed in alcohol-dependent patients.[39,40] Saliva containing microflora are transported from the mouth to the esophagus and stomach. The oral bacterial overgrowth in the esophagus and hypochlorhydric stomach with CAG may increase local acetaldehyde production.[41]

TABLE 4 Association of *H. pylori* infection status with chronic atrophic gastritis and HH/CLE in Japanese alcohol-dependent men (2013-2018)

		H. pylori infection		
	N	Negative	Positive or after eradication	*P*
Chronic atrophic gastritis				
C0-C1	330	293 (88.8%)	37 (11.2%)	<.0001
C2	114	24 (21.1%)	90 (78.9%)	
C3	93	10 (10.8%)	83 (89.2%)	
O1	55	7 (12.7%)	48 (87.3%)	
O2	40	14 (35.0%)	26 (65.0%)	
O3	16	6 (37.5%)	10 (62.5%)	
HH/CLE ≥ 10 mm				
Absent	437	226 (51.7%)	211 (48.3%)	.022
Present	208	128 (61.5%)	80 (38.5%)	

Note: H. pylori infection status was examined using the stool antigen test and the (13)C-urea breath test in the patients without a history of *H. pylori* eradication. *P*-values were examined by χ^2 test.

Abbreviation: HH/CLE, hiatal hernia and/or columnar-lined esophagus.

TABLE 5 Multiple logistic analyses for identifying determinants of esophageal DIULs in Japanese alcohol-dependent men

	DIULs ≥ 5 mm (all)	DIULs ≥ 5 mm (dysplasia)	DIULs ≥ 5 mm (SCC)	Multiple DIULs
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (per +10 y)	1.67 (1.47-1.90)	1.52 (1.29-1.78)	1.81 (1.43-2.29)	1.70 (1.50-1.92)
Alcohol intake (per +22 g ethanol/day)	0.99 (0.96-1.03)	0.97 (0.93-1.02)	0.98 (0.91-1.05)	0.97 (0.94-1.01)
Pack-years (per −10 pack-years)	0.96 (0.92-1.004)	0.95 (0.90-0.998)	0.96 (0.89-1.05)	0.95 (0.92-0.99)
Body mass index (per +1 kg/m^2)	0.92 (0.89-0.95)	0.89 (0.85-0.93)	0.93 (0.87-0.99)	0.94 (0.91-0.97)
MCV ≥ 106 fl vs <106 fl	1.50 (1.18-1.90)	1.59 (1.18-2.14)	1.20 (0.77-1.88)	1.72 (1.37-2.17)
*ALDH2*1/*2* carriers vs. **1/*1* carriers	3.44 (2.67-4.43)	2.28 (1.65-3.16)	10.1 (6.65-15.5)	4.30 (3.39-5.46)
*ADH1B*1/*1* carriers vs **2* carriers	2.68 (2.12-3.39)	2.45 (1.83-3.28)	3.50 (2.29-5.35)	3.47 (2.78-4.34)
HH/CLE ≥ 10 mm	0.94 (0.73-1.21)	0.88 (0.64-1.21)	1.13 (0.72-1.78)	0.71 (0.56-0.91)
Chronic atrophic gastritis				
C0-C2	1 (referent)	1 (referent)	1 (referent)	1 (referent)
C3-O1	1.52 (1.18-1.96)	1.57 (1.15-2.15)	1.56 (0.96-2.54)	1.40 (1.10-1.79)
O2-O3	1.76 (1.27-2.44)	1.72 (1.15-2.58)	2.27 (1.29-3.99)	1.67 (1.22-2.30)
Year of endoscopic screening				
2003-2007	1 (referent)	1 (referent)	1 (referent)	1 (referent)
2008-2012	0.45 (0.35-0.57)	0.58 (0.43-0.79)	0.37 (0.23-0.59)	0.60 (0.47-0.76)
2013-2018	0.32 (0.24-0.42)	0.37 (0.25-0.53)	0.27 (0.16-0.46)	0.68 (0.52-0.89)

Note: Multivariate odds ratios were estimated using a logistic regression model with all the variables entered.

Abbreviations: ADH1B, alcohol dehydrogenase-1B; ALDH2, aldehyde dehydrogenase-2; CI, confidence interval; DIULs, distinct iodine-unstained lesions; HH/CLE, hiatal hernia and/or columnar-lined esophagus; MCV, mean corpuscular volume; OR, odds ratio; SCC, squamous cell carcinoma.

On the other hand, the incidences of HH and CLE, which are indicators of gastroesophageal reflux, are increased by excessive drinking,[42,43] the increment of gastric juice acidity,[44] and the absence of *H. pylori* infection.[45] In the present population, the presence of HH/CLE ≥ 10 mm was also positively associated with a milder degree of CAG and the absence of *H. pylori* infection. Antiseptic acid reflux with an HH/CLE ≥ 10 mm and milder or no CAG reduces and alters the esophageal microflora[46] and might reduce the risk of DIULs. These changes are more likely to occur in the distal esophagus, which may partly explain why ESCC lesions were less frequent in the distal esophagus in subjects with an HH/CLE ≥ 10 mm in this study.

The number of pack-years decreased by 4.8 pack-years during the study period. This reduction yielded only a modest decrease in the ORs for the DIULs. An increment in BMI has been reported to reduce the risk of ESCC,[4,5,47] and we observed a lower risk of the DIULs with an increment in the BMI. However, the increment in BMI was modest and nonsignificant during the study period. Macrocytosis with an MCV ≥ 106 fl increased the ORs for the DIULs, consistent with the results of earlier studies.[5,13,33,34] MCV is increased by excessive drinking, drinking in subjects with an ALDH2 deficiency, smoking, a low BMI, and folate deficiency.[33,48] The reduction in alcohol-dependent patients with an MCV ≥ 106 fl may reflect less smoking and improvements in nutrition during the study period. The genotype distributions of the *ALDH2* and *ADH1B* genotypes were previously reported to be strong determinants of DIULs.[3,6,13,14] The reduction in DIUL detection is thus all the more puzzling, considering the increase in patients with inactive ALDH2 during the study period. The multivariate ORs for all the DIULs according to the screening periods markedly decreased during the study period after the addition of all the adjusted variables, suggesting that unidentified strong confounders have caused a reduction in DIUL detection during the study period. The possible causes of the present reductions in the incidences of DIULs and ESCC in the alcohol-dependent population warrants future research.

Globally, a decreasing incidence of male ESCC has been observed in recent decades.[26] The age-adjusted mortality rate for esophageal cancer in Japan, where most cases of esophageal cancer were SCC, was 10.3 per 100 000 men in 2003, but this rate has been gradually decreasing, reaching 7.0 per 100 000 men in 2018.[49] The reduction in the detection of DIULs might be partly linked to global trends suggesting a decreasing incidence of ESCC among men. However, caution is needed when extrapolating the results to public health in general. This study was performed in a selected cohort of alcohol-dependent men with a mean age of middle-fifties. Any generalization of the present results will require confirmation among various populations of drinkers, including subjects with mild alcoholism and drinkers without alcohol dependence.

Follow-up studies have demonstrated that the presence of DIULs ≥ 5 mm predicted the future development of ESCC in cancer-free, alcohol-dependent men,[5] while the presence of multiple DIULs predicted the metachronous development of ESCC in men after an endoscopic mucosectomy for ESCC.[7-9] We showed that the simultaneous presence of both types of DIULs was more strongly associated with the ESCC-susceptible genetic backgrounds of the *ALDH2*1/*2* and *ADH1B*1/*1* genotypes, compared with the presence of DIULs ≥ 5 mm alone. Follow-up data for these DIULs in combination or alone are required to clarify the difference between DIULs ≥ 5 mm and multiple DIULs as cancer biomarkers and to assess the importance of trends in risk indicators of ESCC.

We did not observe any effects of recent alcohol consumption on the detection of DIULs. This result might be related to the homogeneity of the study population, with regard to alcohol dependence. Nationwide surveys conducted in 2003, 2008, and 2013 showed that the percentage of alcohol dependence did not change among Japanese men, but declining trends in the percentage of daily drinkers and the amount of alcohol consumed per week were reported for Japanese men.[50] Changes in the drinking culture of Japan during this period may have affected the long-term drinking profiles of alcohol-dependent patients. A study examining the effects of alcohol consumption for a longer period of time could provide useful information. We cannot rule out the possibility that changes in endoscope models and the diagnostic skills of endoscopists might have influenced the reduction in the detection of DIULs. However, the detection rates of early ESCC, as well as DIULs, have markedly decreased without any changes in cancer depth during the same period,[4] while endoscopic images have been improved by new models of endoscopes. Almost all the screening examinations were performed by a single endoscopist or were performed under his supervision. Another limitation was that factors such as *H. pylori* infection during the entire study period, actual gastroesophageal reflux, oral-esophageal-gastric microbiota, oral hygiene, and dietary habits (including the intake of fruit and vegetables and high-temperature beverages) were not examined, and all these factors might have had considerable impacts on carcinogenesis in the esophagus.[51-53]

In conclusion, the detection of DIULs and ESCC decreased between 2003 and 2018 in an alcohol-dependent population. In addition to reported determinants of ESCC, CAG and HH/CLE were associated with the risk of DIULs. Enigmatically, however, the declining trend in DIULs was not adequately explained by these factors and warrants further research.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ORCID


Akira Yokoyama https://orcid.org/0000-0003-1869-1359

REFERENCES

1. Yokoyama A, Muramatsu T, Omori T, et al. Alcohol and aldehyde dehydrogenase gene polymorphisms and oropharyngolaryngeal, esophageal and stomach cancers in Japanese alcoholics. *Carcinogenesis*. 2001;22:433-439.

2. Yokoyama A, Yokoyama T, Omori T, et al. Helicobacter pylori, chronic atrophic gastritis, inactive aldehyde dehydrogenase-2, macrocytosis and multiple upper aerodigestive tract cancers and the risk for gastric cancer in alcoholic Japanese men. *J Gastroenterol Hepatol*. 2007;22:210-217.
3. Yokoyama A, Hirota T, Omori T, et al. Development of squamous neoplasia in esophageal iodine-unstained lesions and the alcohol and aldehyde dehydrogenase genotypes of Japanese alcoholic men. *Int J Cancer*. 2012;130:2949-2960.
4. Yokoyama A, Omori T, Yokoyama T. Changing trends in cancer incidence of upper aerodigestive tract and stomach in Japanese alcohol-dependent men (1993–2018). *Cancer Med*. 2020;9:837-846.
5. Yokoyama A, Omori T, Yokoyama T, et al. Risk of squamous cell carcinoma of the upper aerodigestive tract in cancer-free alcoholic Japanese men: an endoscopic follow-up study. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2209-2215.
6. Muto M, Hitomi Y, Ohtsu A, Ebihara S, Yoshida S, Esumi H. Association of aldehyde dehydrogenase 2 gene polymorphism with multiple oesophageal dysplasia in head and neck cancer patients. *Gut*. 2000;47:256-261.
7. Shimizu Y, Tsukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Metachronous squamous cell carcinoma of the esophagus arising after endoscopic mucosal resection. *Gastrointest Endosc*. 2001;54:190-194.
8. Urabe Y, Hiyama T, Tanaka S, et al. Metachronous multiple esophageal squamous cell carcinomas and Lugol-voiding lesions after endoscopic mucosal resection. *Endoscopy*. 2009;41:304-309.
9. Katada C, Yokoyama T, Yano T, et al. Alcohol consumption and multiple dysplastic lesions increase risk of squamous cell carcinoma in the esophagus, head, and neck. *Gastroenterology*. 2016;15:860 e7–869 e7.
10. Cui R, Kamatani Y, Takahashi A, et al. Functional variants in ADH1B and ALDH2 coupled with alcohol and smoking synergistically enhance esophageal cancer risk. *Gastroenterology*. 2009;137:1768-1775.
11. Yang SJ, Yokoyama A, Yokoyama T, et al. Relationship between genetic polymorphisms of ALDH2 and ADH1B and esophageal cancer risk: a meta-analysis. *World J Gastroenterol*. 2010;16:4210-4220.
12. Zhao T, Wang C, Shen L, et al. Clinical significance of ALDH2 rs671 polymorphism in esophageal cancer: evidence from 31 case-control studies. *Onco Targets Ther*. 2015;8:649-659.
13. Yokoyama A, Yokoyama T, Omori T, et al. Endoscopic screening using esophageal iodine staining and genotypes of ADH1B and ALDH2 in Japanese alcohol-dependent women. *PLoS ONE*. 2019;14:e0210546.
14. Katada C, Muto M, Tanabe S, et al. Factors associated with the presence of multiple Lugol-voiding lesions in patients with esophageal squamous-cell carcinoma. *Dis Esophagus*. 2014;27:457-462.
15. Wang C, Nishiyama T, Kikuchi S, et al. Changing trends in the prevalence of H. pylori infection in Japan (1908–2003): a systematic review and meta-regression analysis of 170,752 individuals. *Sci Rep*. 2017;7:15491.
16. Ye W, Nyren O. Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia. *Gut*. 2003;52:938-941.
17. 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*. 2004;96:388-396.
18. 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*. 2007;102:1603-1609.
19. 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*. 2009;9:34.
20. Islami F, Sheikhattari P, Ren JS, Kamangar F. Gastric atrophy and risk of oesophageal cancer and gastric cardia adenocarcinoma–a systematic review and meta-analysis. *Ann Oncol*. 2011;22:754-760.
21. Nasrollahzadeh D, Malekzadeh R, Aghcheli K, et al. Gastric atrophy and oesophageal squamous cell carcinoma: possible interaction with dental health and oral hygiene habit. *Br J Cancer*. 2012;107:888-894.
22. Almodova Ede C, de Oliveira WK, Machado LF, et al. Atrophic gastritis: risk factor for esophageal squamous cell carcinoma in a Latin-American population. *World J Gastroenterol*. 2013;19:2060-2064.
23. Ekheden I, Yang X, Chen H, et al. Associations between gastric atrophy and its interaction with poor oral health elevate the risk for esophageal squamous cell carcinoma in a high-risk region of China: a population-based case-control study. *Am J Epidemiol*. 2020;189:931-941.
24. Kamangar F, Diaw L, Wei WQ, et al. Serum pepsinogens and risk of esophageal squamous dysplasia. *Int J Cancer*. 2009;124:456-460.
25. Yokoyama A, Yokoyama T, Omori T, et al. Chronic atrophic gastritis and metachronous gastric cancer in Japanese alcoholic men with esophageal squamous cell carcinoma. *Alcohol Clin Exp Res*. 2009;33:898-905.
26. Wang QL, Xie SH, Wahlin K, Lagergren J. Global time trends in the incidence of esophageal squamous cell carcinoma. *Clin Epidemiol*. 2018;10:717-728.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. rev. Washington, DC: American Psychiatric Association; 1987.
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association; 1994.
29. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*, 10th edn. rev. (ICD-10). Geneva: World Health Organization; 1992.
30. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy*. 1969;1:87-97.
31. Masuyama H, Yoshitake N, Sasai T, et al. Relationship between the degree of endoscopic atrophy of the gastric mucosa and carcinogenic risk. *Digestion*. 2015;91:30-36.
32. Hiroi S, Sugano K, Tanaka S, Kawakami K. Impact of health insurance coverage for Helicobacter pylori gastritis on the trends in eradication therapy in Japan: retrospective observational study and simulation study based on real-world data. *BMJ Open*. 2017;7:e015855.
33. Yokoyama A, Yokoyama T, Muramatsu T, et al. Macrocytosis, a new predictor for esophageal squamous cell carcinoma in Japanese alcoholic men. *Carcinogenesis*. 2003;24:1773-1778.
34. Katada C, Yokoyama T, Yano T, et al. Association between macrocytosis and metachronous squamous cell carcinoma of the esophagus after endoscopic resection in men with early esophageal squamous cell carcinoma. *Esophagus*. 2020;17:149-158.
35. Yin SJ, Bosron WF, Magnes LJ, Li TK. Human liver alcohol dehydrogenase: purification and kinetic characterization of the $\beta_2\beta_2$, $\beta_2\beta_1$, $\alpha\beta_2$ and $\beta_2\gamma_1$ 'oriental' isozymes. *Biochemistry*. 1984;23:5847-5853.
36. Chiang CP, Lai CL, Lee SP, et al. Ethanol-metabolizing activities and isozyme protein contents of alcohol and aldehyde dehydrogenases in human liver: phenotypic traits of the ADH1B*2 and ALDH2*2 variant gene alleles. *Pharmacogenet Genomics*. 2016;26:184-195.
37. Kishikawa H, Ojiro K, Nakamura K, et al. Previous Helicobacter pylori infection-induced atrophic gastritis: a distinct disease entity in an understudied population without a history of eradication. *Helicobacter*. 2020;25:e12669.
38. Homann N, Tillonen J, Meurman JH, et al. Increased salivary acetaldehyde levels in heavy drinkers and smokers: a microbiological approach to oral cavity cancer. *Carcinogenesis*. 2000;21:663-668.

39. Yokoyama A, Tsutsumi E, Imazeki H, Suwa Y, Nakamura C, Yokoyama T. Contribution of the alcohol dehydrogenase-1B genotype and oral microorganisms to high salivary acetaldehyde concentrations in Japanese alcoholic men. *Int J Cancer*. 2007;121:1047-1054.
40. Hauge T, Persson J, Danielsson D. Mucosal bacterial growth in the upper gastrointestinal tract in alcoholics (heavy drinkers). *Digestion*. 1997;58:591-595.
41. Maejima R, Iijima K, Kaihovaara P, et al. Effects of ALDH2 genotype, PPI treatment and L-cysteine on carcinogenic acetaldehyde in gastric juice and saliva after intragastric alcohol administration. *PLoS ONE*. 2015;10:e0120397.
42. Matsuzaki J, Suzuki H, Kobayakawa M, et al. Association of visceral fat area, smoking, and alcohol consumption with reflux esophagitis and Barrett's esophagus in Japan. *PLoS ONE*. 2015;10:e0133865.
43. Yokoyama A, Hirata K, Nakamura R, et al. Presence of columnar-lined esophagus is negatively associated with the presence of esophageal varices in Japanese alcoholic men. *World J Gastroenterol*. 2017;23:7150-7159.
44. Kishikawa H, Kimura K, Ito A, et al. Association between increased gastric juice acidity and sliding hiatal hernia development in humans. *PLoS ONE*. 2017;12:e0170416.
45. Erőss B, Farkas N, Vincze Á, et al. *Helicobacter pylori* infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. *Helicobacter*. 2018;23:e12504.
46. Baba Y, Iwatsuki M, Yoshida N, Watanabe M, Baba H. Review of the gut microbiome and esophageal cancer: Pathogenesis and potential clinical implications. *Ann Gastroenterol Surg*. 2017;1:99-104.
47. Song H, Saito E, Sawada N, et al. Body mass index change during adulthood and risk of oesophageal squamous-cell carcinoma in a Japanese population: the Japan Public Health (JPHC)-based prospective study. *Br J Cancer*. 2017;117:1715-1722.
48. Yokoyama A, Yokoyama T, Brooks PJ, et al. Macrocytosis, macrocytic anemia, and genetic polymorphisms of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 in Japanese alcoholic men. *Alcohol Clin Exp Res*. 2014;38:1237-1246.
49. Ministry of Health, Labour and Welfare. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan). https://ganjoho.jp/reg_stat/statistics/dl/index.html#mortality, Accessed 16 June 2020 (in Japanese).
50. Osaki Y, Kinjo A, Higuchi S, et al. Prevalence and trends in alcohol dependence and alcohol use disorders in Japanese adults; Results from periodical nationwide surveys. *Alcohol Alcohol*. 2016;51:465-473.
51. Ahrens W, Pohlabeln H, Foraita R, et al. Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: the ARCAGE study. *Oral Oncol*. 2014;50:616-625.
52. Liu J, Wang J, Leng Y, Lv C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. *Int J Cancer*. 2013;133:473-485.
53. Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk–a systematic review. *Int J Cancer*. 2009;125:491-524.

How to cite this article: Yokoyama A, Omori T, Yokoyama T. Risk factors for esophageal iodine-unstained lesions and changing trends among Japanese alcohol-dependent men (2003-2018). *Cancer Sci*. 2021;112:734–743. https://doi.org/10.1111/cas.14753