RESEARCH ARTICLE

Joint Effects of Smoking and Alcohol Drinking on Esophageal Cancer Mortality in Japanese Men: Findings from the Japan Collaborative Cohort Study

Yumi Yaegashi[1]*, Toshiyuki Onoda[1], Seiji Morioka[2], Tsutomu Hashimoto[2], Tatsuya Takeshita[2], Kiyomi Sakata[1], Akiko Tamakoshi[3]

Abstract

Background: The purpose of our study was to elucidate the joint effects of combined smoking and alcohol intake on esophageal cancer mortality in Japanese men through a large cohort study with a 20-year follow-up period. Materials and Methods: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in the late 1980s, including 46,395 men and 64,190 women aged 40 years and older and younger than 80. Follow-up of these participants was conducted until 2009. We used the Cox proportional hazards model to analyze data for 42,408 people excluding female participants, 411 people with histories of malignant neoplasms, and 3,576 with unclear smoking and drinking data. Results: The joint effects of age at start of smoking and amount of alcohol consumed per day were compared with non-smokers and non-drinkers or those consuming less than one unit of alcohol per day. The mortality risk was 9.33 (95% confidence interval, 2.55-34.2) for those who started smoking between ages 10 and 19 years and drinking at least three units of alcohol per day. Regarding the joint effects of cumulative amount of smoking and alcohol intake, the risk was high when both smoking and alcohol intake were above a certain level. Conclusions: In this Japanese cohort study, increased cancer mortality risks were observed, especially for people who both started smoking early and drank alcohol. Quitting smoking or not starting to smoke at any age and reducing alcohol consumption are important for preventing esophageal cancer in Japan.

Keywords: Esophageal cancer - smoking - alcohol drinking - joint effects - cohort study

Asian Pac J Cancer Prev, **15 (2)**, 1023-1029

Introduction

Esophageal cancer is the eighth most common cancer worldwide, with about 407,000 deaths (5.4% of all cancer deaths) every year (International Agency for Research on Cancer, 2010). For men, esophageal cancer is the fifth leading cause of death behind lung, liver, gastric and colon cancers. In Japan, according to estimates from recent cancer statistics, 10,141 men and 1,829 women died of esophageal cancer in 2011. Comparing with numbers in the past several years, 9,992 men and 1,875 women in 2010, 9,908 and 1,805 in 2009, 9,997 and 1,749 in 2008, and 9,900 and 1,769 in 2007, the number of deaths in men has been increasing with some variation; however, the number of deaths in women has leveled off (Foundation for Promotion of Cancer Research, 2009; 2010; 2011; 2012). The number of deaths from cancer is largest between the ages of 55 and 79 years in both men and women (Foundation for Promotion of Cancer Research, 2012). The five-year survival rate in the period from 2000 to 2002 for men with esophageal cancer was about 33%, indicating that this cancer has a poorer prognosis than that for gastric cancer or colon cancer, 5-year survival rates in the same period being about 70% (Center for Cancer Control and Information Services, National Cancer Center, 2011).

Esophageal cancer has two main histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). Each type has its own associated risk factors and the main type of esophageal cancer differs according to areas and races. Excessive use of alcohol, tobacco use, low intake of fresh fruits and vegetables, low socioeconomic status, and drinking *mate* (especially hot *mate*) increase the risk of ESCC. On the other hand, important risk factors of EA are gastroesophageal acid reflux, obesity, smoking, and absence of *H pylori* (Kamangar et al., 2009). As for regional differences in the two types, ESCC is the dominant type of esophageal cancer in East Asian countries including Japan, China, and Korea. In contrast,

*[1]Department of Hygiene and Preventive Medicine, Iwate Medical University, Iwate, [2]Department of Public Health, Wakayama Medical University, Wakayama, [3]Hokkaido University Graduate School of Medicine, Hokkaido, Japan *For correspondence: yumiyae@iwate-med.ac.jp*

EA has been increasing in Western countries, especially in Caucasian men (Hongo et al., 2009).

Public health reports in Japan, based on reviews of four cohort studies including our ten-year follow-up Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) and nine case-control studies, indicated that alcohol drinking increases the risk of esophageal cancer in the Japanese population. In addition, a review of four cohort studies including our JACC study and eight case-control studies showed a strong positive association between esophageal cancer and cigarette smoking (Oze et al., 2011; 2012). Our JACC study on the associations of smoking and alcohol drinking with esophageal cancer, a follow-up study for about ten years, showed joint effects of smoking and alcohol drinking in some combinations; however, the results were not conclusive because of the small number of deaths from esophageal cancer (Sakata et al., 2005). In this study, we verified 196 deaths from esophageal cancer during a 20-year follow-up period.

The objectives of this study were to examine which characteristics of smoking and alcohol intake contribute to esophageal cancer mortality and to elucidate more specific joint effects of smoking and alcohol intake through a follow-up of about 20 years, using data from the JACC Study.

Materials and Methods

Study subjects

Details of the cohort and follow-up procedures have been described elsewhere (Tamakoshi et al., 2005; 2007; 2013). JACC study sponsored by the Ministry of Education, Science, Sports and Culture (Monbusho) was a multicenter collaborative study in which 24 centers voluntarily participated. Recruitment of study subjects living in 45 areas was managed by individual investigators whose responsibility was to construct the cohort in that area. Data were collected from 1988-1990. 110,585 participants (46,395 men and 64,190 women) aged 40-79 years were ultimately deemed eligible as subjects for the JACC Study.

We excluded women from the analysis because of the small number of women who had smoked and drunk alcohol. For this study, 411 men were eliminated because they had a history of cancer, and 3,576 men were excluded because they did not give information about their smoking or drinking status. Data for the remaining 42,408 men were used for analysis. The protocol was approved by the Ethical Boards of Nagoya University School of Medicine and Wakayama Medical University.

Baseline data collection

Baseline data were collected with a self-administered questionnaire including information about alcohol consumption, smoking status, dietary habits, demographic characteristics, histories of hypertension, diabetes mellitus, and other chronic diseases, healthy habits, exercise, occupation, educational background, and subjective view of life. Smoking habit was established by asking the subjects whether they were a non-smoker, ex-smoker, or current smoker. Those who were current smokers were asked about the amount of cigarettes consumed per day and age at which smoking started. Packs were calculated by the number of cigarettes smoked divided by 20, and pack-years were calculated as the product of packs per day and duration of smoking. Alcohol intake was based on the usual yearly intake of *sake* (Japanese rice wine), *shochu* (Japanese spirits), beer, whisky, and wine among current drinkers. The daily amount of alcohol consumption was assessed in terms of the conventional alcohol unit (*go*) of Japanese sake, one unit of which is equivalent to about 22 grams of alcohol. In terms of intake of vegetables and fruit, each food had a five-level answer: 'rarely eat'; 'once or twice per month'; 'once or twice per week'; 'three or four times per week'; 'almost daily'.

Follow-up procedure

As follow-up information, dates and causes of death were annually or biannually confirmed, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) and/or the Ministry of Health, Labour and Welfare, Japan. The date of move-out of cohort members from the study area was also annually or biannually verified by the investigator in each area by reviewing population-register sheets of the cohort members. Death from esophageal cancer was determined by the coding 15.0 through C15.9 for ICD-10. In most areas, follow-up was completed at the end of 2009; however, it was stopped at the end of 1999 in 4 areas, at the end of 2003 in another 4 areas, and at the end of 2008 in 2 areas.

Statistical analysis

The Cox proportional hazards model was used to estimate the relative risk due to cigarette smoking or alcohol intake or combinations of cigarette smoking and alcohol intake adjusted for age, study centers, and intake of vegetables and fruits. People who took at least one of five kinds of vegetables (spinach, carrot, tomato, cabbage, and Chinese cabbage) three times per week were defined as vegetable intake. Likewise, people who took at least one of three kinds of fruits (orange, juice, and other fruits) three times per week were defined as fruits intake. All calculations were performed with SPSS 16.0.

Results

The baseline characteristics of the study participants are shown in Table 1. Subjects in their 40s, 50s, and 60s accounted for about 30% of the total subjects, with about 14% of the subjects being in their 70s. As for smoking, more than half of the subjects were smokers and about 26% were ex-smokers. Those who started smoking between the ages of 20 and 24 years accounted for almost 60% of the total subjects, while almost 17% of the subjects started smoking at 25 years of age or older. About 20% of the subjects started smoking between the ages of 10 and 19 years, illegal ages for smoking in Japan. Subjects who smoked 11 to 20 cigarettes daily accounted for almost 56% of the total subjects, while about 17% of the subjects smoked 21 to 30 cigarettes daily and almost 16%

smoked 1 to 10 cigarettes daily. Subjects who smoked 31 or more cigarettes per day accounted for only about 9% of the total subjects. As for drinking, 75% of the subjects were current alcohol drinkers and just over 6% were ex-drinkers. Men who drank 1.0 to 1.9 units per day made up the largest group (about 32% of the total subjects), with those drinking 2.0 to 2.9 units per day making up the next largest group (almost 27%). Those who drank 3.0 units or more per day accounted for almost 13% of the total subjects, and those drinking less than 1.0 unit per day accounted for only 7% of the total subjects. With respect to type of alcohol, those drinking *sake* comprised the largest group (56%), with the next largest group being those drinking beer (almost 41%), followed by *shochu* (about 15%), and then whisky (about 14%). Wine drinkers accounted for only about 5% of the total subjects.

Table 2 shows the breakdown of age group and intake of vegetables and fruit by smoking status (non-smokers, ex-smokers, and smokers). Among non-smokers, subjects in their 50s accounted for almost 35%, and about 27% were in their 40s. Among ex-smokers, subjects in their 60s accounted for almost 36%, and about 26% were in their 50s. Among smokers, subjects in their 40s, 50s, and 60s each accounted for about 30%. Almost 69% of non-smokers consumed vegetables more than three times per week, while about 64% of smokers had vegetables more than three times per week. As for intake of fruit, almost 58% of non-smokers consumed fruits more than three times per week, while just over 51% of smokers had fruits. Vegetable and fruit intake of ex-smokers was similar to that of non-smokers.

Table 3 shows the breakdown of age group and intake of vegetables and fruit by drinking status (non-drinkers, ex-drinkers, and drinkers). Among non-drinkers, subjects in their 60s accounted for almost 32%, and almost 27% of the subjects were in their 50s. Among ex-drinkers, subjects in their 60s accounted for almost 40%, and just over 26% of the subjects were in their 70s. Among drinkers, subjects in their 40s, 50s, and 60s each accounted for about 30%. Almost 70% of ex-drinkers consumed vegetables more than three times per week, while about 66% of non-drinkers and drinkers had vegetables more than three times per week. As for intake of fruit, almost 59% of non-drinkers consumed fruits more than three times per week, compared with just over 52% of drinkers.

Table 4 shows hazard ratios of esophageal cancer by smoking status, after adjusting for age, study centers, and intake of vegetables and fruits. Using non-smokers as the standard, current smokers and ex-smokers had significantly higher mortality risks (3.30 and 2.03, respectively). Considering age at the start of smoking, in all categories, the risk increased about 2.6 to 4.6 times, and a dose-response relationship was observed (p for trend=0.01). Although a dose-response association was not found in either number of cigarettes smoked per day or number of smoking years, cumulative amount smoking showed a dose-response relationship (p for trend=0.05).

Table 5 shows hazard ratios of esophageal cancer by alcohol intake status. Using non-drinkers as the standard, current drinkers had a significantly increased risk (2.28) compared with non-drinkers. Ex-drinkers had a 2.10-times

Table 1. Baseline Chracteristics of Study Participants (Men)

Factors	Categories	No.	(%)
Total		42,408	100.0
Age at baseline (year)	40-49	11,228	26.5
	50-59	12,900	30.4
	60-69	12,551	29.6
	70-79	5,729	13.5
Smoking	Non-smokers	8,698	20.5
	Ex-smokers	11,096	26.2
	Smokers	22,614	53.3
Age at start of smoking (year)	25+	3,762	16.6
	20-24	13,463	59.5
	10-19	4,239	18.7
	Unknown	1,150	5.1
Cigarettes smoked per day	1-10 cigaretts/day	3,605	15.9
	11-20	12,645	55.9
	21-30	3,926	17.4
	31+	2,135	9.4
	Unknown	303	1.3
Alcohol drinking	Non-drinkers	7,977	18.8
	Ex-drinkers	2,616	6.2
	Drinkers	31,815	75.0
Alcohol units* consumed per day	<1.0 units/day	2,263	7.1
	1.0-1.9	10,320	32.4
	2.0-2.9	8,552	26.9
	3.0+	4,037	12.7
	Unknown	6,643	20.9
Type of alcohol (multiple answer)	Sake	17,819	56.0
	Shochu†	4,868	15.3
	Beer	12,888	40.5
	Whisky	4,500	14.1
	Wine	1,475	4.6

*One unit contains about 22 g of alcohol; †Japanese spirits

Table 2. Smoking Status and Intake of Vegetables and Fruit (Men)

Categories		Non-smokers n (%)	Ex-smokers n (%)	Smokers n (%)
Total		n=8,698	n=11,096	n=22,614
Age group	40-49	2,356 (27.1)	2,109 (19.0)	6,763 (29.9)
	50-59	3,000 (34.5)	2,894 (26.1)	7,006 (31.0)
	60-69	2,090 (24.0)	3,936 (35.5)	6,525 (28.9)
	70-79	1,252 (14.4)	2,157 (19.4)	2,320 (10.3)
Vegetable intake				
	Intake	5,995 (68.9)	7,538 (67.9)	14,500 (64.1)
	Low/no intake	2,703 (31.1)	3,558 (32.1)	8,114 (35.9)
Fruit intake	Intake	5,004 (57.5)	6,199 (55.9)	11,553 (51.1)
	Low/no intake	3,694 (42.5)	4,897 (44.1)	11,061 (48.9)

*Intake: Consuming vegetables and fruits more than three times per week; **Low or no intake: Less than twice per week, or unknown

Table 3. Drinking Status and Intake of Vegetables and Fruit (Men)

Categories		Non-drinkers n (%)	Ex-drinkers n (%)	Drinkers n (%)
Total		n=7,977	n=2,616	n=31,815
Age group	40-49	1,732 (21.7)	282 (10.8)	9,214 (29.0)
	50-59	2,149 (26.9)	604 (23.1)	10,147 (31.9)
	60-69	2,527 (31.7)	1,043 (39.9)	8,981 (28.2)
	70-79	1,569 (19.7)	687 (26.3)	3,473 (10.9)
Vegetable intake				
	Intake	5,344 (67.0)	1,822 (69.6)	20,867 (65.6)
	Low/no intake	2,633 (33.0)	794 (30.4)	10,948 (34.4)
Fruit intake	Intake	4,673 (58.6)	1,473 (56.3)	16,610 (52.2)
	Low/no intake	3,304 (41.4)	1,143 (43.7)	15,205 (47.8)

*Intake: Consuming vegetables and fruits more than three times per week; **Low or no intake: Less than twice per week, or unknown

higher risk, but the risk was not considered significant. In terms of amount of alcohol consumed per day, esophageal cancer risk rose with increased alcohol intake, especially more than 2.0 units per day, and it showed a dose-response relationship (p for trend=0.02). In subjects drinking 3.0 units per day, the risk was 4.62-times higher. However, as for number of years of alcohol intake, no dose-response relationship was observed. By unit-year, the group of subjects with 40.0 unit-years or greater showed the highest risk (3.34). According to type of alcohol consumed, the highest risk was with whisky (2.99), followed by *shochu* (2.75), and *sake* (2.45). For beer and wine, no significant increase in risk was observed.

Table 6 shows joint effects of smoking and alcohol consumption on risk of esophageal cancer death. We divided smokers into three categories (non-smokers, ex-smokers and smokers) and we also divided drinkers into three categories (non-drinkers, ex-drinkers and drinkers). First, comparing the combination of non-smokers and non-drinkers as the standard with other combinations of smoking and drinking status, the hazard ratio increased to 2.54 in only the combination of current smoking and current drinking. Second, in terms of joint effects based on number of cigarettes and amount of alcohol consumed per day, comparing non-smokers and non-drinkers or those drinking less than one unit per day with those smoking less than 20 cigarettes per day and drinking one or more units of alcohol but less than three, the hazard ratio was 3.57, which increased to 4.29 for those smoking less than 20 cigarettes and drinking three units or more per day. Likewise, comparing non-smokers and non-drinkers or those drinking less than one unit per day with those smoking 21 cigarettes or more and drinking one or more units of alcohol but less than three, the hazard ratio was 3.64, which increased to 6.05 for those smoking 21 cigarettes or more and drinking three units or more per day. These results indicated a synergistic increase in risk for combined smoking and drinking. Third, regarding joint effects based on age at start of smoking and amount of alcohol consumed per day, comparing non-smokers and non-drinkers or those drinking less than one unit per day with those who started smoking at 25 years of age or older and drinking three units or more per day, the hazard ratio was 3.77. Comparing non-smokers and non-drinkers or those drinking less than one unit per day with those who started smoking between the ages of 20 and 24 years and drinking one or more units of alcohol but less than three, the hazard ratio was 3.66, which increased to 4.21 for those who started smoking between the ages of 20 and 24 years and drinking three units or more per day. Moreover, comparing non-smokers and non-drinkers or those drinking less than one unit per day with those who started smoking between the ages of 10 and 19 years and drinking one or more units of alcohol but less than three, the hazard ratio was 6.50, which increased to 9.33 for those who started smoking between the ages of 10 and 19 years and drinking three units or more per day. Last, with respect to the joint effects of smoking and drinking, using the group of non-smokers and non-drinkers or those with less 30.0 unit-years as a standard, the hazard ratio was 5.61 for smokers with less than 40.0 pack-years and drinkers with 40.0 unit-years or more. For smokers with 40.0 pack-years or more and alcohol drinkers with 30.0-39.9 unit-years, an increased risk of 7.71 was observed. For smokers with 40.0 pack-years or more and alcohol

Table 4. Hazard Ratios (HRs) of Death from Esophageal Cancer according to Smoking Status at Baseline (Men)

Variables	Person-years	No. of deaths	HR* (95% CI)	p for trend
Non-smokers	143,182	18	1.00 (reference)	
Ex-smokers	169,235	45	2.03 (1.16-3.55)	
Smokers	356,556	133	3.30 (2.01-5.42)	
Age at start of smoking				
Non-smokers	143,182	18	1.00 (reference)	
25+	57,914	22	2.61 (1.39-4.90)	
20-24	213,377	80	3.28 (1.96-5.50)	
10-19	67,918	27	4.57 (2.43-8.60)	0.01
Cigarettes smoked per day				
Non-smokers	143,182	18	1.00 (reference)	
1-10 cigaretts/day	53,299	21	2.78 (1.47-5.25)	
11-20	197,824	79	3.44 (2.05-5.76)	
21-30	65,266	20	3.01 (1.55-5.86)	
31+	35,442	11	3.45 (1.53-7.76)	0.10
Duration of smoking (years)				
Non-smokers	143,182	18	1.00 (reference)	
-25	87,292	12	2.58 (0.98-6.77)	
25.1-35.0	107,137	34	3.46 (1.84-6.52)	
35.1-45.0	109,467	61	4.00 (2.33-6.87)	
45.1+	35,505	22	2.92 (1.34-6.39)	0.16
Cumulative amount of smoking				
Non-smokers	143,182	18	1.00 (reference)	
1-19.9 pack-years	52,494	11	2.14 (0.99-4.62)	
20.0-29.9	88,864	32	3.59 (1.99-6.49)	
30.0-39.9	83,344	33	3.57 (1.99-6.41)	
40.0+	111,599	52	3.56 (2.07-6.13)	0.05

*Hazard ratio adjusted for age, centers, and intake of vegetables and fruits

Table 5. Hazard Ratios (HRs) of Death from Esophageal Cancer according to Alcohol Intake Status at Baseline (Men)

Variables	Person-years	No. of deaths	HR* (95% CI)	p for trend
Non-drinkers	121,019	18	1.00 (reference)	
Ex-drinkers	33,350	12	2.10 (0.99-4.42)	
Drinkers	514,604	166	2.28 (1.40-3.72)	
Alcohol units† consumed per day				
Non-drinkers	121,019	18	1.00 (reference)	
<1.0 units/day	34,675	6	1.16 (0.41-3.24)	
1.0-1.9	164,815	36	1.48 (0.82-2.69)	
2.0-2.9	139,335	64	3.34 (1.90-5.87)	
3.0+	64,333	34	4.62 (2.46-8.68)	0.02
Duration of alcohol drinking (years)				
Non-drinkers	121,019	18	1.00 (reference)	
-25.0	193, 353	39	1.91 (1.02-3.57)	
25.1-35.0	109,475	47	3.09 (1.73-5.54)	
35.1-45.0	67,277	34	2.58 (1.41-4.74)	
45.1+	20,793	12	2.34 (0.99-5.57)	0.21
Cumulative amount of alcohol intake (unit-years)				
Non-drinkers	121,019	18	1.00 (reference)	
1-29.9	124,384	20	1.25 (0.63-2.50)	
30.0-39.9	49,313	12	1.83 (0.85-3.93)	
40.0+	184,442	96	3.34 (1.96-5.70)	0.07
Type of alcohol (multiple answer)				
Non-drinkers	121,019	18	1.00 (reference)	
Sake	285,027	103	2.45 (1.44-4.18)	
Shochu‡	77,942	32	2.75 (1.47-5.15)	
Beer	210,143	47	1.72 (0.96-3.08)	
Whisky	75,366	25	2.99 (1.53-5.84)	
Wine	25,047	7	2.61 (0.86-7.94)	

*Hazard ratio adjusted for age,centers, and intake of vegetables and fruits; †One unit contains about 22 g of alcohol; ‡Japanese spirits

Table 6. Joint Effects of Smoking and Alcohol Drinking on Risk of Esophageal Cancer Death (Men)

Smoking	Alcohol drinking	No. of deaths	HR* (95% CI)
By smoking and drinking status			
Non-smokers	Non-drinkers	7	1.00 (reference)
	Ex-drinkers	2	1.35 (0.27-6.65)
	Drinkers	9	0.52 (0.19-1.43)
Ex-smokers	Non-drinkers	4	0.75 (0.22-2.63)
	Ex-drinkers	3	0.96 (0.23-3.93)
	Drinkers	38	1.50 (0.66-3.41)
Smokers	Non-drinkers	7	0.74 (0.25-2.16)
	Ex-drinkers	7	2.55 (0.85-7.66)
	Drinkers	119	2.54 (1.18-5.48)
By smoked cigarettes and consumed alcohol in units† per day			
Non-smokers	Non- or <1.0**	7	1.00 (reference)
	1.0-2.9	5	0.63 (0.19-2.13)
	3.0+	1	0.64 (0.07-5.96)
1-20	Non- or <1.0	7	0.88 (0.30-2.57)
(cigarettes/day)	1.0-2.9	63	3.57 (1.53-8.30)
	3.0+	15	4.29 (1.57-11.7)
21+	Non- or <1.0	2	0.80 (0.15-4.15)
	1.0-2.9	13	3.64 (1.26-10.5)
	3.0+	10	6.05 (1.87-19.6)
By age at start of smoking and consumed alcohol in units† per day			
Non-smokers	Non- or <1.0**	7	1.00 (reference)
25+	Non- or <1.0	10	1.17 (0.30-4.61)
	1.0-2.9	20	2.62 (0.98-7.00)
	3.0+	11	3.77 (1.01-14.1)
20-24	Non- or <1.0	11	0.64 (0.18-2.32)
	1.0-2.9	57	3.66 (1.55-8.66)
	3.0+	21	4.21 (1.51-11.7)
10-19	Non- or <1.0	8	0.83 (0.09-7.56)
	1.0-2.9	19	6.50 (2.25-18.8)
	3.0+	14	9.33 (2.55-34.2)
By cumulative amount of smoking and alcohol intake			
Non-smokers	Non- or <30.0**	8	1.00 (reference)
	30.0-39.9	0	-
	40.0+	5	1.47 (0.46-4.73)
1-39.9	Non- or <30.0	17	1.66 (0.70-3.95)
(pack-years)	30.0-39.9	4	2.39 (0.67-8.53)
	40.0+	45	5.61 (2.51-12.5)
40.0+	Non- or <30.0	7	1.49 (0.53-4.18)
	30.0-39.9	5	7.71 (2.30-25.8)
	40.0+	26	5.45 (2.33-12.7)

*Hazard ratio adjusted for age,centers, and intake of vegetables and fruits; **units/day drinkers; †One unit contains about 22 g of alcohol

drinkers with 40.0 unit-years or more, the risk was 5.45. In non-smokers, however, even with increased cumulative alcohol intake, no increased esophageal cancer mortality risk was observed. In addition, in non-drinkers or those with less than 30.0 unit-years, even with increased cumulative amount of smoking, there was no increased esophageal cancer mortality risk.

Discussion

We evaluated the association between smoking and esophageal cancer and also the association between alcohol drinking and esophageal cancer through a prospective Japanese cohort with a follow-up of about 20 years. Furthermore, we elucidated joint effects of smoking and alcohol drinking on esophageal cancer in Japanese men. In our previous study using data for 42,578 Japanese men with a follow-up of period about 10 years, the number of deaths from esophageal cancer was 100 (Sakata et al., 2005). In the present study with a follow-up period of about 20 years, we verified 196 deaths from esophageal cancer.

Regarding smoking, we confirmed that the earlier a person starts smoking, the higher is the risk of esophageal cancer death in the future. Although smoking is prohibited for teenagers in Japan, about 20% of the subjects in this study started smoking as teenagers. This is a critical issue in our society, and paying attention to the starting age for smoking will be a key for preventing esophageal cancer in the future. In terms of cumulative amount of smoking, the groups with more than 20.0 pack-years showed about 3.6 times higher risk than that for non-smokers.

Concerning alcohol drinking, the risk of esophageal cancer increased in the groups consuming more than 2.0 units per day, but no significant risk in those consuming less than 2.0 units per day was shown. With respect to the duration of alcohol drinking, groups with drinking for more than 25 years and less than 45 years had increased risk for esophageal cancer; however, in the group with over 45 years of drinking, no significant risk was shown. That might mean other health problems have occurred or that people have changed their habit of drinking for some reason. Looking at types of alcohol beverage, whisky showed the highest risk (2.99), followed by *shochu* (2.75), and *sake* (2.45), but there was no significant risk in beer and wine. We confirmed that both alcohol content and amount of alcohol intake, but not duration of drinking, contributed to the risk for esophageal cancer. According to a case-control study in Spain having in which it was examined whether susceptibility to esophageal cancer differed depending on type of alcohol, it was found that the consumption of any combination of hard liquors seemed to be harmful, whereas a low consumption of only wine might not be harmful (Vioque et al., 2008). Another case-control study in France suggested that alcohol consumption and tobacco consumption influenced the risk of esophageal cancer in different ways. In the case of alcohol, the risk depended only on mean intake; however, with regard to smoking, the risk depended mainly on duration of consumption (Launoy et al., 1997). These results were almost in accordance with the results of our study for a prospective cohort.

Regarding joint effects of various combinations of smoking and alcohol drinking status, we first affirmed that the hazard ratio increased to 2.54 for the combination of current smoking and current drinking compared with the combination of non-smokers and non-drinkers as the standard. In addition, for those smoking less than 20 cigarettes and drinking three units or more per day, the hazard ratio was 4.29. The risk increased to 6.05 for those smoking 21 cigarettes or more and drinking three units or more per day. Moreover, for those who started smoking between ages of 10 and 19 years and drinking one or more units of alcohol but less than three, the hazard ratio was 6.50. The risk increased to 9.33 for those who started smoking between ages of 10 and 19 years and drinking three units or more per day.

According to a 14-year large-scale prospective cohort study in Korean men in which the combination of no alcohol intake or intake of <25 g/day and never having smoked as the standard was compared with various combinations, combined HRs of mortality were 2.5 for

the combination of alcohol consumption (<25 g/day) and having smoked, 2.3 for the combination of alcohol consumption (≥25 g/day) and never having smoked, and 5.4 for the combination of alcohol consumption (≥25 g/day) and having smoked (Kimm et al., 2010). The Shanghai Cohort Study revealed combined effects of number of years of smoking and number of drinks per day on risk of esophageal cancer. The highest risk was found among subjects with longest duration of smoking (more than 40 years) and largest alcohol intake (more than 4 drinks per day), and the hazard ratio was 8.00. Although hazard ratios of other combinations of number of years of smoking (< 40, ≥ 40 years) and non-drinkers and also those of number of drinks per day (< 4, ≥ 4 drinks) and non-smokers were not statistically significant, the risk tended to increase (Fan et al., 2008).

In our study, it became possible to observe joint effects by cumulative amounts of smoking and alcohol intake. The combination of cumulative number of cigarettes (1-39.9 pack-years) and cumulative amount of alcohol drinking (≥ 40.0 unit-years) increased the risk by 5.6 times. Furthermore, the combination of cumulative number of cigarettes (≥ 40.0 pack-years) and cumulative amount of alcohol drinking (30.0-39.9 unit-years) increased the risk by 7.7 times.

Along with important risk factors of esophageal cancer such as smoking and alcohol drinking, we need to take account of some other factors. According to a prospective cohort study in Japan, a dose-dependent decrease in the risk of ESCC was associated with a higher intake of total fruit and vegetables. That study indicated the beneficial effect of a high intake of fruits and vegetables for protection against the occurrence of ESCC, but also suggested that smoking and drinking cessation should be the primary strategy to prevent ESCC (Yamaji et al., 2008). Another cohort study in the USA showed that the association between total fruit and vegetable intake and risk of esophageal cancer differed by histological type: total fruit and vegetable intake was significantly associated with decreased risk of ESCC but not with decreased risk of EA (Freedman et al., 2007). Increased consumption of fruits (including oranges/tangerines), seafood and milk were found to be protective against the development of esophageal caner by the Shanghai cohort study (Fan et al., 2008). A case control study in Taiwanese men found that intake of preserved foods, overheated soups and drinks might be positively associated with risk of esophageal cancer but that increasing the intake of fruits, vegetables, and tea could reduce the risk of esophageal cancer (Hung et al., 2004). Regarding associations between three main dietary nutrients, carbohydrates, fat and protein, and the risk of developing esophageal cancer, a population-based case-control study in Sweden showed that a diet with a low proportion of carbohydrates and a high proportion of fat might increase the risk of EA (Lagergren et al., 2013).

On the basis of results of our study and previous studies, we need to devise specific preventive strategies for esophageal cancer. Recent data of the National Health and Nutrition Survey in Japan show that the percentage of male smokers has been decreasing from about 47% in 2003 to 32% in 2011. On the other hand, the percentage of men who drink alcohol has remained constant (about 35%) (Ministry of Health, Labour and Welfare, 2011). Considering that the annual number of deaths due to esophageal cancer has been increasing despite a decrease in the percentage of smokers, people's habits of both prolonged smoking and large amount of alcohol drinking might have strongly affected esophageal cancer in Japanese men.

Therefore, what we can do to prevent esophageal cancer is to disseminate accurate information regarding joint effects of smoking and alcohol drinking on esophageal cancer not only at a regional level but also in the workplace, adding some information about good effects of fruit and vegetable intake, and eventually to encourage people to change their bad habits. Quitting smoking as quickly as possible or not starting to smoke at any age, especially in teens, and also reducing alcohol intake will be very important. For teenagers, it is very critical for them to receive health education including education on smoking and alcohol drinking and also to learn through life skill training at school for maintenance of health and thus prevention of cancers including esophageal cancer in the future. Moreover, adults must take responsibility for providing an environment to keep children from smoking.

Our study has some limitations. First, there was a high percentage of unknown categories among drinkers in baseline data, which might cause an information bias. Second, we analyzed the risk for both ESCC and EA together because we could not obtain histological data. Third, as our analysis was based on baseline data from 1988 through to 1990, habits of smoking and drinking alcohol at the time might have changed during the follow-up period of 20 years. That could be a reason for the group with heavy smoking and heavy drinking showing a slightly lower risk.

Despite these limitations, our study has several strengths. The strengths include that this study being a population-based study design with a long follow-up period of about 20 years and the elucidation of joint effects of smoking and alcohol drinking as well as each risk of smoking and alcohol drinking.

In conclusion, the combination of smoking and alcohol drinking increases the risk of cancer mortality. Quitting smoking or not starting to smoke at any age, especially in teens and reducing alcohol consumption are very important for preventing esophageal cancer, especially ESCC, in Japan.

Member List of the JACC Study Group

The present members of the JACC Study Group who coauthored this paper are: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Drs. Mitsuru Mori & Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical University; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer

Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr.Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School Medicine; Dr.Yasuhiko Wada, Faculty of Nutrition, University of Kochi; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr.Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, School of Human Science and Environment, University of Hyogo; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Drs. Takesumi Yoshimura & Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Moriyama Municipal Hospital.

Acknowledgements

We wish to express our sincere thanks to Drs. Kunio Aoki and Yoshiyuki Ohno, Professors Emeritus of the Nagoya University School of Medicine and former chairpersons of the JACC Study. For their encouragement and support during this study, we are also greatly indebted to Dr. Haruo Sugano, former Director of the Cancer Institute, Tokyo, who contributed greatly to the initiation of the JACC Study, to Dr. Tomoyuki Kitagawa, Director Emeritus of the Cancer Institute of the Japanese Foundation for Cancer Research and former project leader of the Grant-in-Aid for Scientific Research on Priority Area 'Caner', and to Dr. Kazuo Tajima, Aichi Cancer Center, who was the previous project leader of the Grant-in-Aid for Scientific Research on Priority Area of Cancer Epidemiology.

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), and Grants-in-Aid for Scientific Research on Priority Areas of Cancer, as well as Grants-in-Scientific Research on Priority Areas of Cancer Epidemiology from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Monbu-Kagaku-sho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026 and 20390156).

References

Center for Cancer Control and Information Services, National Cancer Center (2011). Monitoring of Cancer Incidence in Japan - Survival 2000-2002 Report.

Fan Y, Yuan JM, Wang R, Gao YT, Yu MC (2008). Alcohol, tobacco, and diet in relation to esophageal cancer: the Shanghai cohort study. *Nutr Cancer*, **60**, 354-63.

Foundation for Promotion of Cancer Reserach. Cancer Statistics in Japan (2009), Tokyo.

Foundation for Promotion of Cancer Reserach. Cancer Statistics in Japan (2010), Tokyo.

Foundation for Promotion of Cancer Reserach. Cancer Statistics in Japan (2011), Tokyo.

Foundation for Promotion of Cancer Reserach. Cancer Statistics in Japan (2012), Tokyo.

Freedman ND, Park Y, Subar AF, et al (2007). Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer*, **121**, 2753-60.

Hongo M, Nagasaki Y, Shoji T (2009). Epidemiology of esophageal cancer: orient to occident. Effects of chronology, geography and ethnicity. *J Gastroenterol Hepatol*, **24**, 729-35.

Hung HC, Huang MC, Lee JM, et al (2004). Association between diet and esophageal cancer in Taiwan. *J Gastroenterol Hepatol*, **19**, 632-7.

International Agency for Research on Cancer (2010). GLOBOCAN 2008. IARC Press, Lyon.

Kamangar F, Chow WH, Abnet CC, Dawsey SM (2009). Environmental causes of esophageal cancer. *Gastroenterol Clin North Am*, **38**, 27-57.

Kimm H, Kim S, Jee SH (2010). The independent effects of cigarette smoking, alcohol consumption, and serum aspartate aminotransferase on the alanine aminotransferase ratio in korean men for the risk for esophageal cancer. *Yonsei Med J*, **51**, 310-7.

Lagergren K, Lindam A, Lagergren J (2013). Dietary proportions of carbohydrates, fat, and protein and risk of oesophageal cancer by histological type. *PLoS One*, **8**, 54913.

Launoy G, Milan CH, Faivre J, et al (1997). Alcohol, tobacco and oesophageal cancer: effects of the duration of consumption, mean intake and current and former consumption. *Br J Cancer*, **75**, 1389-96.

Ministry of Health, Labour and Welfare (2011). National Health and Nutrition Examination Survey 2011, Tokyo.

Oze I, Matsuo K, Wakai K, et al (2011). Alcohol drinking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, **41**, 677-92.

Oze I, Matsuo K, Ito H, et al (2012). Cigarette smoking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol*, **42**, 63-73.

Sakata K, Hoshiyama Y, Morioka S, et al (2005). Smoking, alcohol drinking and esophageal cancer: findings from the JACC Study. *J Epidemiol*, **15**, 212-9.

Tamakoshi A, Yoshimura T, Inaba Y, et al (2005). Profile of the JACC study. *J Epidemiol*, **15**, 4-8.

Tamakoshi A (2007). Overview of the Japan collaborative cohort study for evaluation of cancer (JACC). *Asian Pac J Cancer Prev*, **8**, 1-8.

Tamakoshi A, Ozasa K, Fujino Y, et al (2013). Cohort profile of the japan collaborative cohort study at final follow-up. *J Epidemiol*, **23**, 227-32.

Vioque J, Barber X, Bolumar F, et al (2008). Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer*, **8**, 221.

Yamaji T, Inoue M, Sasazuki S, et al (2008). Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: the JPHC study. *Int J Cancer*, **123**, 1935-40.