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Original Article

Demographic and lifestyle factors and survival among patients with esophageal and gastric cancer: The Biobank Japan Project

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ABSTRACT

Background: Several studies have evaluated associations between the characteristics of patients with esophageal and gastric cancer and survival, but these associations remain unclear. We described the distribution of demographic and lifestyle factors among patients with esophageal and gastric cancer in Japan, and investigated their potential effects on survival.

Methods: Between 2003 and 2007, 24- to 95-year-old Japanese patients with esophageal and gastric cancer were enrolled in the BioBank Japan Project. The analysis included 365 patients with esophageal squamous cell carcinoma (ESCC) and 1574 patients with gastric cancer. Hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality were estimated using medical institution-stratified Cox proportional hazards models.

Results: During follow-up, 213 patients with ESCC (median follow-up, 4.4 years) and 603 patients with gastric cancer (median follow-up, 6.1 years) died. Among patients with ESCC, the mortality risk was higher in ever drinkers versus never drinkers (multivariable HR = 2.37, 95% CI: 1.24, 4.53). Among patients with gastric cancer, the mortality risk was higher in underweight patients versus patients of normal weight (multivariable HR = 1.66, 95% CI: 1.34, 2.05). Compared to patients with gastric cancer with no physical exercise habit, those who exercised ≥3 times/week had a lower mortality risk (multivariate HR = 0.75, 95% CI = 0.61, 0.93). However, lack of stage in many cases was a limitation.

Conclusions: Among patients with ESCC, alcohol drinkers have a poor prognosis. Patients with gastric cancer who are underweight also have a poor prognosis, whereas patients with physical exercise habits have a good prognosis.

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Introduction

Esophageal cancer is the seventh most common type of cancer and the sixth most common cause of death from cancer worldwide.[1] Esophageal cancer is classified into two main histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). The incidence of each type differs depending on race and geographical region. EA is increasing in Western countries, whereas ESCC is the dominant type of esophageal cancer in East Asian countries such as China, Korea, and Japan.[2] Gastric cancer is the fifth most common type of cancer and the third most common cause of death from cancer worldwide.[1] Established risk factors for esophageal cancer include tobacco smoking, heavy alcohol drinking, and frequent consumption of high-temperature beverages.[3] Risk factors for gastric cancer include smoking,[4] high salt intake,[5] and infection by *Helicobacter pylori*.[6,7] In addition, gastroesophageal reflux disease and the reflux-related condition Barrett's esophagus are known risk factors for esophageal cancer, because the esophagus is connected to the cardia of the stomach.[8,9] Thus, esophageal and gastric cancer should be investigated together.

Some studies have reported that male sex, increased age, weight loss, smoking and alcohol drinking decrease survival in patients with esophageal cancer,[10,11] but other studies revealed no significant association between smoking and alcohol drinking and esophageal cancer.[12,13] In patients with gastric cancer, smoking has been shown to decrease survival,[14] but other studies revealed no significant association.[12,13,15] Tobacco smoking remains a popular lifestyle choice among many East Asian males,[16] despite it being an established risk factor for multiple cancers in the general population. Moreover, evidence for associations between demographic and lifestyle factors and the prognosis of esophageal and gastric cancer in Japan is scarce.

The objective of this study was to describe the distribution of demographic and lifestyle factors among patients with esophageal and gastric cancer registered in the BioBank Japan (BBJ) project. In addition, we investigated the potential effect of demographic and lifestyle factors on survival in patients with esophageal and gastric cancer.

Material and methods

Study population

Between 2003 and 2007, patients with any of 47 target common diseases were enrolled in the BBJ at 66 hospitals, which comprised 12 cooperating medical institutions, located throughout Japan. Details of the study design have been described elsewhere.[17–19] We included participants whose disease duration could be calculated from the date of diagnosis of esophageal and/or gastric cancer and the date of registration for this study. In the present study, 1258 patients with esophageal cancer and 5597 patients with gastric cancer were included at baseline. Of these patients, 1162 patients with esophageal cancer and 5103 patients with gastric cancer completed follow-up. When we performed the analysis for prognosis, new patients who entered the study ≤90 days after diagnosis were included. Among patients with esophageal cancer, patients who entered this study >90 days after diagnosis (n = 702), patients with a histology other than ESCC (n = 93), and patients whose smoking history and/or alcohol drinking history were missing (n = 2) were excluded from the survival analysis. Because ESCC is the major histologic type of esophageal cancer in Asian countries, including Japan,[2] we focused on ESCC herein. Among patients with gastric cancer, patients for whom >90 days passed between diagnosis and study entrance (n = 3513) and patients for whom smoking and alcohol drinking histories were missing (n = 16) were excluded from the survival analysis. Patients whose smoking and alcohol drinking histories were missing were excluded because these are significant risk factors for ESCC and gastric cancer in the general population. A total of 365 patients with ESCC and 1574 patients with gastric cancer were included in the survival analysis. The study design was reviewed and approved by the Ethics Committees of all participating institutions. Written informed consent was obtained from all participants.

Data collection

Baseline clinical information was collected through medical records and interviews using a standardized questionnaire. Interview items included smoking and alcohol drinking habits, height, weight, and frequency of physical exercise. Information collected from medical records included birth year and sex. In this study, esophageal and gastric cancer histology was determined from excised tissue specimens, and missing histological data were complemented by biopsy or cytological specimens. Esophageal and gastric cancer stages were classified according to the Japanese Classification of Esophageal Cancer, ninth edition (1999) and the Japanese Classification of Gastric Carcinoma, twelfth edition (1993).

Follow-up surveys

A survival follow-up survey was implemented from 2010 to 2014 for patient vital statistics. Information about death using the 10th revision of the International Classification of Disease codes was collected from the Vital Statistics of the Statistics and Information Department of the Ministry of Health, Labour and Welfare, Japan.[20]

Statistical analysis

To calculate expected survival rates, a survival rate table of a Japanese reference cohort was obtained from the Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan.[21] The survival rate table was based on sex- and age-specific mortality rates and Gompertz-Makeham's law in Abridged Life Tables, which is annually published by the Statistics and Information Department of the Ministry of Health, Labour and Welfare, Japan.[22] Relative survival rates were calculated by dividing cumulative survival rates by expected sex- and age-adjusted survival rates. Patients ≥100 years old were excluded due to a lack of data in the reference life table. We compared the 5-year relative survival rates of esophageal and gastric cancer patients in this study to data from the Japanese Association of Clinical Cancer Centers (cases diagnosed from 2004 to 2007).[23]

Univariate and multivariate hazard ratios (HRs) and 95% confidence intervals (CI) of demographic and lifestyle factor variables for mortality risk were evaluated using medical institution-stratified Cox proportional hazards model. The following variables were included in the multivariate models: sex, age (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, or ≥80 years), year of diagnosis (2003, 2004, 2005, 2006, 2007, or 2008), body mass index (BMI) (<18.5, 18.5–24.9, 25–29.9, ≥30.0 kg/m^2, or unknown), smoking history (never or ever smoker), alcohol drinking history (never or ever drinker), physical exercise (no habit, 1–2 times/week, ≥3 times/week, or unknown), and stage (0, I, II, III, IVa, IVb, or unknown for ESCC, and Ia, Ib, II, IIIa, IIIb, IVa, IVb, or unknown for gastric cancer). All statistical analyses were performed using the SAS statistical package for Windows (version 9.4, SAS). Differences were considered statistically significant at $p < 0.05$.

Results

The proportions of patients by age group according to the BBJ, the Japanese Association of Cancer Registries,[24] and the Patient Survey[25] are shown in Fig. 1 for esophageal cancer and Fig. 2 for gastric cancer. Compared to the Japanese Association of Cancer Registries and the Patient Survey, which were performed in Japan, the proportion of patients with esophageal and gastric cancer age 55–69 years in the BBJ was about 4% higher within each 5-year age group, whereas the proportion of patients ≥75 years was about 5% lower.

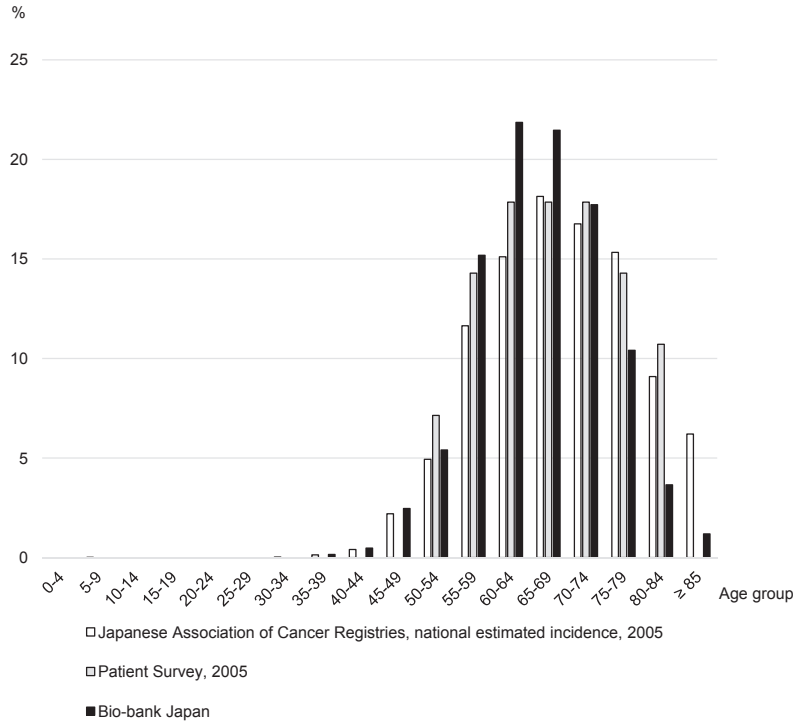

Fig. 1. Proportion of patients with esophageal cancer by age group.

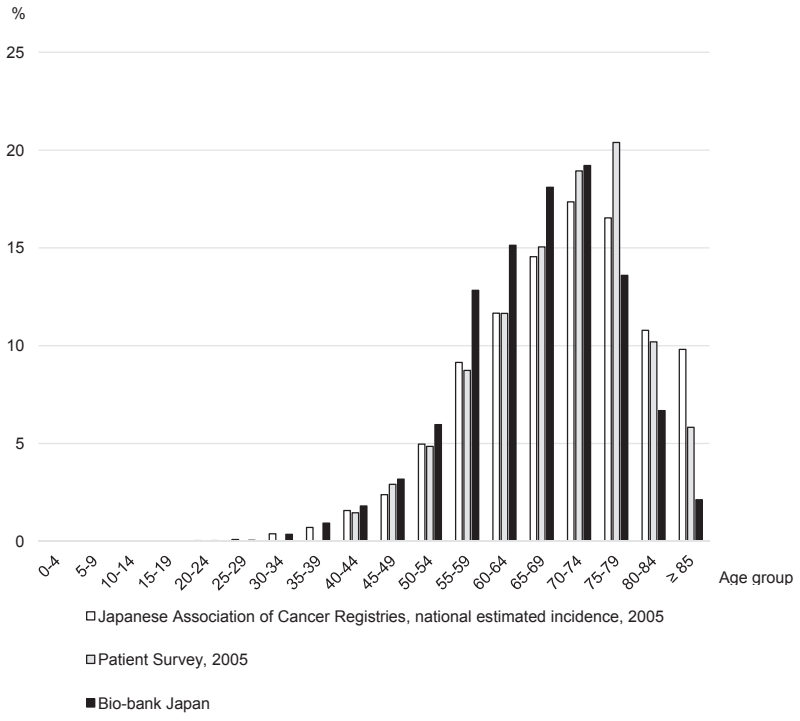

Fig. 2. Proportion of patients with gastric cancer by age group.

Table 1
Demographic and lifestyle factors of patients with esophageal and gastric cancer at baseline in the Biobank Japan Project.

	Esophageal cancer (n = 1258)		Gastric cancer (*n* = 5597)	
	No.	(%)	No.	(%)
Sex				
Male	1088	(86.5)	4095	(73.2)
Female	170	(13.5)	1502	(26.8)
Age range, y				
20–29	0	(0.0)	5	(0.1)
30–39	2	(0.2)	72	(1.3)
40–49	37	(2.9)	279	(5.0)
50–59	259	(20.6)	1052	(18.8)
60–69	545	(43.3)	1860	(33.2)
70–79	354	(28.1)	1836	(32.8)
≥80	61	(4.9)	493	(8.8)
BMI range, kg/m^2				
<18.5	347	(28.4)	1124	(21.0)
18.5–24.9	786	(64.3)	3694	(69.1)
25–29.9	85	(7.0)	486	(9.1)
≥30	4	(0.3)	41	(0.8)
Unknown	36	–	252	–
Smoking history				
Never smoker	214	(17.2)	1861	(33.7)
Ever smoker	1027	(82.8)	3659	(66.3)
Unknown	17	–	77	–
Alcohol drinking history				
Never drinker	166	(13.4)	2048	(37.2)
Ever drinker	1074	(86.6)	3453	(62.8)
Unknown	18	–	96	–
Physical exercise				
No habit	822	(73.9)	3639	(72.7)
1–2 times/week	41	(3.7)	238	(4.8)
≥3 times/week	249	(22.4)	1129	(22.6)
Unknown	146	–	591	–
Year of diagnosis				
–2000	232	(18.4)	1463	(26.1)
2001	65	(5.2)	323	(5.8)
2002	85	(6.8)	437	(7.8)
2003	128	(10.2)	669	(12.0)
2004	183	(14.6)	767	(13.7)
2005	172	(13.7)	737	(13.2)
2006	184	(14.6)	697	(12.5)
2007	199	(15.8)	483	(8.6)
2008	10	(0.8)	21	(0.4)
Histology of esophageal cancer				
Squamous cell carcinoma	971	(89.9)		
Adenocarcinoma	73	(6.8)		
Adenosquamous carcinoma	13	(1.2)		
Adenoid cystic carcinoma	1	(0.1)		
Basaloid cell carcinoma	2	(0.2)		
Anaplastic carcinoma	6	(0.6)		
Other cancers	14	(1.3)		
Unknown	178	–		
Histology of gastric cancer				
Papillary adenocarcinoma			93	(1.9)
Tubular adenocarcinoma			2988	(61.5)
Poorly differentiated adenocarcinoma			884	(18.2)
Signet-ring cell carcinoma			620	(12.8)
Mucinous adenocarcinoma			80	(1.6)
Special type			18	(0.4)
Other cancers			179	(3.7)
Unknown			735	–
Stage of esophageal cancer				
0	40	(10.1)		
I	70	(17.7)		
II	118	(29.9)		
III	102	(25.8)		
IVa	40	(10.1)		
IVb	25	(6.3)		
Unknown	863	–		
Stage of gastric cancer				
Ia			689	(48.0)
Ib			227	(15.8)
II			168	(11.7)
IIIa			142	(9.9)
IIIb			65	(4.5)
IVa			66	(4.6)
IVb			77	(5.4)
Unknown			4163	–

Baseline demographic and lifestyle factors of patients with esophageal and gastric cancer are shown in Table 1. Among patients with esophageal and gastric cancer, patients were more likely to be male (esophageal cancer: 86.5%; gastric cancer: 73.2%), age 60–69 or 70–79 years (esophageal cancer: 43.3% and 28.1%, respectively; gastric cancer: 33.2% and 32.8%, respectively), have a BMI of 18.5–24.9 kg/m^2 (esophageal cancer: 64.3%; gastric cancer: 69.1%), be ever smokers (esophageal cancer: 82.8%; gastric cancer: 66.3%), be ever drinkers (esophageal cancer: 86.6%; gastric cancer: 62.8%), and have no physical exercise habit (esophageal cancer: 73.9%; gastric cancer: 72.7%). For patients with esophageal cancer, almost all had ESCC histology (89.9%), and among cases for which the stage was known, stage II (29.9%) and III (25.8%) disease was most common. For patients with gastric cancer, tubular adenocarcinoma was the most common histology (61.5%), and among patients for whom the stage was known, stage Ia disease was most common (48.0%).

Table 2 shows the 5-year relative survival rate of patients with esophageal and gastric cancer. Relative survival rates of all patients and patients who participated in the study for ≤90 days after diagnosis are shown. The 5-year relative survival rate of patients for whom ≤90 days passed from diagnosis to study enrollment was 49.6% and 75.7% for esophageal and gastric cancer, respectively.

For patients with ESCC who participated in the study for ≤90 days after diagnosis, the median follow-up period was 4.4 years. During 1605 person-years, there were 213 deaths. The HRs and 95% CIs for mortality according to demographic and lifestyle factors among patients with ESCC are shown in Table 3. Compared to patients aged 50–59 years, patients ≥80 years had an increased risk of mortality after adjusting for other variables (multivariate HR = 2.79, 95% CI = 1.34, 5.80). With respect to alcohol drinking, the multivariate HR for mortality in ever drinkers was 2.37 (95% CI = 1.24, 4.53) compared to that of never drinkers. No significant association was observed for smoking history.

In gastric cancer patients who participated in the study for ≤90 days after diagnosis, the median follow-up period was 6.1 years. During 9620 person-years, there were 603 deaths. The HRs and 95% CIs for mortality according to demographic and lifestyle factors among patients with gastric cancer are shown in Table 4. For males, the multivariate HR for mortality was 1.42 (95% CI = 1.11, 1.81) compared to females. Compared to patients aged 50–59 years, younger patients had a decreased risk of mortality (40–49 years: multivariate HR = 0.55, 95% CI = 0.34, 0.90), and older patients had an increased risk of mortality (70–79 years: multivariate HR = 1.94, 95% CI = 1.53, 2.46; ≥80 years: multivariate HR = 3.50, 95% CI = 2.52, 4.87). Multivariate HR for mortality in patients with a BMI <18.5 kg/m^2 was 1.66 (95% CI = 1.34, 2.05) compared to patients with a BMI 18.5–24.9. Compared to patients who had no physical exercise habit, patients who exercised ≥3 times/week had a decreased risk of mortality (multivariate HR = 0.75, 95% CI = 0.61, 0.93).

Table 2
Five-year relative survival rate of patients with esophageal and gastric cancer.

		No. of patients	Follow-up rate (%)	Relative survival rate (%)
Esophageal cancer	Biobank Japan (total)	1158	97.5	59.3
	Biobank Japan[a]	460	96.7	49.6
	Japanese Association of Clinical Cancer Centers	6109	95.1	42.4
Gastric cancer	Biobank Japan (total)	5094	97.6	82.1
	Biobank Japan[a]	1590	97.4	75.7
	Japanese Association of Clinical Cancer Centers	23,690	93.5	73.0

[a] Patients who entered the study ≤90 days after diagnosis.

Table 3
HRs and 95% CIs for mortality according to demographic and lifestyle factors among patients with ESCC in the Biobank Japan Project (n = 365).

	Person-years	No. of deaths	Univariate model		Multivariate model[a]	
			HR	(95% CI)	HR	(95% CI)
Sex						
Male	1344	181	1.05	(0.71,1.55)	0.70	(0.42,1.17)
Female	260	32	1.00		1.00	
Age range, years						
30–39	19	0	NA		NA	
40–49	56	10	1.53	(0.77,3.04)	1.56	(0.77,3.15)
50–59	408	51	1.00		1.00	
60–69	784	91	0.96	(0.68,1.36)	0.84	(0.58,1.20)
70–79	307	50	1.14	(0.76,1.70)	1.19	(0.78,1.81)
≥80	31	11	2.18	(1.11,4.29)*	2.79	(1.34,5.80)**
Year of diagnosis						
2003	101	17	1.00		1.00	
2004	266	46	1.03	(0.57,1.85)	1.44	(0.76,2.70)
2005	331	33	0.63	(0.34,1.20)	0.94	(0.47,1.86)
2006	365	50	0.83	(0.45,1.52)	1.23	(0.64,2.38)
2007	495	65	0.75	(0.42,1.34)	1.15	(0.61,2.17)
2008	45	2	0.27	(0.06,1.19)	0.41	(0.09,1.86)
BMI range, kg/m^2						
<18.5	343	52	1.17	(0.85,1.61)	0.90	(0.63,1.28)
18.5–24.9	1107	145	1.00		1.00	
25–29.9	133	14	0.84	(0.48,1.47)	0.93	(0.52,1.67)
≥30	10	0	NA		NA	
Unknown	12	2	1.00	(0.24,4.15)	0.92	(0.20,4.23)
Smoking history						
Never smoker	274	36	1.00		1.00	
Ever smoker	1330	177	0.97	(0.67,1.40)	0.97	(0.62,1.50)
Alcohol drinking history						
Never drinker	183	17	1.00		1.00	
Ever drinker	1422	196	1.43	(0.86,2.36)	2.37	(1.24,4.53)**
Physical exercise						
No habit	1053	144	1.00		1.00	
1–2 times/week	102	6	0.46	(0.20,1.06)	0.36	(0.15,0.86)
≥3 times/week	338	44	0.93	(0.66,1.32)	0.96	(0.67,1.39)
Unknown	111	19	1.21	(0.74,1.97)	1.26	(0.76,2.11)

All analyses were stratified by medical institution.
* $p < 0.05$, ** $p < 0.01$.
[a] Multivariate HRs were adjusted for sex, age, year of diagnosis, BMI, smoking history, alcohol drinking history, physical exercise and stage.

Discussion

We have described the distribution of demographic and lifestyle factors among patients with esophageal and gastric cancer in Japan. Patients with ESCC experienced shorter survival due to aging and alcohol drinking. Among patients with gastric cancer, those who were older and/or underweight experienced shorter survival, while those with a physical exercise habit lived longer.

The results of the present study demonstrated a relatively similar age distribution compared to other surveys performed in Japan, although slight differences existed. The 5-year relative survival rate of all patients in this study was higher than that of patients in the Japanese Association of Clinical Cancer Centers. However, patients for whom ≤90 days passed from diagnosis to study entry showed a similar 5-year relative survival rate to that of patients in the Japanese Association of Clinical Cancer Centers (42.4% and 73.0% for esophageal and gastric cancer, respectively).[23] It was possible to reduce the bias for the number of years of study registration by including only patients who participated in the study for ≤90 days after diagnosis.

The present survival results for patients with ESCC were consistent with those of previous studies.[10,11,26] Among ESCC patients in a cohort study in China, alcohol drinkers were more likely to experience poor survival compared to nondrinkers (HR = 1.372, 95% CI = 1.2, 1.6).[11] In another Chinese cohort study, patents with esophageal cancer (ESCC or EA) who were ever drinkers also experienced poor survival (HR = 1.22, 95% CI = 1.06, 1.41), and the study demonstrated a dose-response relationship between alcohol consumption and survival.[26] However, studies conducted in Western countries showed no significant association between alcohol drinking and mortality in ESCC and EA patients.[12,13,15] The frequencies of EA and ESCC are similar in Western countries,

Table 4
HRs and 95% CIs for mortality according to demographic and lifestyle factors among patients with gastric cancer in the Biobank Japan Project (n = 1574).

	Person-years	No. of deaths	Univariate model		Multivariate model[a]	
			HR	(95% CI)	HR	(95% CI)
Sex						
Male	6910	481	1.48	(1.21,1.81)***	1.42	(1.11,1.81)**
Female	2710	122	1.00		1.00	
Age range, years						
20–29	18	1	1.35	(0.19,9.73)	1.55	(0.21,11.50)
30–39	204	5	0.64	(0.26,1.57)	0.72	(0.29,1.78)
40–49	946	20	0.53	(0.33,0.86)**	0.55	(0.34,0.90)*
50–59	2474	109	1.00		1.00	
60–69	3235	175	1.19	(0.94,1.51)	1.16	(0.91,1.48)
70–79	2394	233	2.00	(1.59,2.52)***	1.94	(1.53,2.46)***
≥80	348	60	3.33	(2.42,4.58)***	3.50	(2.52,4.87)***
Year of diagnosis						
2003	998	60	1.00		1.00	
2004	1918	131	1.04	(0.77,1.42)	0.93	(0.68,1.28)
2005	2415	147	0.89	(0.66,1.21)	0.89	(0.64,1.22)
2006	2346	136	0.89	(0.65,1.21)	0.80	(0.58,1.12)
2007	1858	121	0.95	(0.69,1.30)	0.89	(0.64,1.25)
2008	85	8	1.36	(0.64,2.87)	1.13	(0.53,2.41)
BMI range, kg/m^2						
<18.5	1145	121	1.65	(1.34,2.02)***	1.66	(1.34,2.05)***
18.5–24.9	6885	398	1.00		1.00	
25–29.9	1280	62	0.82	(0.63,1.08)	0.86	(0.65,1.13)
≥30	115	3	0.43	(0.14,1.33)	0.59	(0.19,1.87)
Unknown	195	19	1.47	(0.92,2.35)	1.21	(0.75,1.95)
Smoking history						
Never smoker	3215	184	1.00		1.00	
Ever smoker	6405	419	1.14	(0.96,1.36)	0.96	(0.78,1.18)
Alcohol drinking history						
Never drinker	3563	224	1.00		1.00	
Ever drinker	6057	379	1.06	(0.90,1.25)	1.11	(0.92,1.34)
Physical exercise						
No habit	6392	430	1.00		1.00	
1–2 times/week	516	17	0.56	(0.35,0.92)*	0.70	(0.43,1.15)
≥3 times/week	2105	113	0.82	(0.66,1.01)	0.75	(0.61,0.93)**
Unknown	607	43	1.09	(0.78,1.52)	1.08	(0.77,1.53)

All analyses were stratified by medical institution.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] Multivariate HRs were adjusted for sex, age, year of diagnosis, BMI, smoking history, alcohol drinking history, physical exercise and stage.

whereas ESCC is the dominant type of esophageal cancer in East Asian countries.[2] Differences in the relative proportions in esophageal cancer types between Asian and Western populations likely contribute to the difference in factors associated with survival.

The present observation that underweight gastric cancer patients experience poor survival is similar to that of several other studies.[27,28] In the Japanese population, lower BMI has been observed to be associated with an increased risk of mortality among gastric cancer patients, with a linear inverse association.[27] Some studies have reported that being overweight has no effect on long-term survival among patients with gastric cancer,[29,30] while another study in Japan indicated better prognoses in overweight patients.[31] Given these observations, the present findings remain inconsistent. Further studies are required to investigate the association between BMI and long-term survival in gastric cancer. In the present study, gastric cancer patients who had physical exercise habits experienced better survival. However, the results of a previous study conducted in Sweden indicated no significant association between physical exercise and long-term survival in gastric cancer.[12] A meta-analysis of seven cohort and nine case-control studies demonstrated that physical exercise is associated with a reduced risk of gastric cancer in the general population.[32] As few previous reports have examined physical exercise habits, it is necessary to further assess the association between physical exercise and gastric cancer prognosis.

We observed no significant difference in survival of ESCC and gastric cancer patients between never and ever smokers. Some studies have reported that smoking decreases survival in patients with ESCC[10,11] and gastric cancer,[14] but other studies revealed no significant association.[26,33] Although smoking is an established risk factor for both esophageal and gastric cancer in the general population,[3,4] whether or not it influences patient prognosis remains unclear.

A strength of the present cohort study is that it involved prospective observation of a large number of patients who were recruited nationwide in Japan. However, the lack of stage information for many patients might have affected the multivariate analyses.

In conclusion, we found that among Japanese patients with esophageal and gastric cancer, patients were more likely to be male, older, of normal weight, be ever smokers, be ever drinkers, and have no physical exercise habit. The present findings suggest that patients with ESCC experience decreased survival due to alcohol consumption. Gastric cancer patients who are underweight also have a poor prognosis, whereas patients with physical exercise habits have a good prognosis. Further studies are required to clarify the impact of demographic and lifestyle factors on long-term survival for esophageal and gastric cancer in different populations and to confirm the underlying mechanisms of these findings.

Conflicts of interest

All authors declare that there are no conflicts of interest.

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