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Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: The Miyagi Cohort Study

Munira Akhter^{a,*}, Shinichi Kuriyama^a, Naoki Nakaya^a, Taichi Shimazu^a, Kaori Ohmori^a, Yoshikazu Nishino^b, Yoshitaka Tsubono^c, Akira Fukao^d, Ichiro Tsuji^a

^aDivision of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, 2-1 Seiryomachi, Aoba-ku, Sendai-shi, Miyagi-ken 980-8575, Japan

^bDivision of Epidemiology, Miyagi Cancer Centre Research Institute, Natori, Japan

^cDivision of Health Policy, Tohoku University School of Public Policy, Sendai, Japan

^dDepartment of Public Health, Yamagata University School of Medicine, Yamagata, Japan

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ABSTRACT

The association between alcohol consumption and the risk of cancer of the proximal or distal colon or rectum remains controversial. We examined this association in a large population-based cohort of Japanese men. In 1990, a self-administered questionnaire on alcohol drinking and other health habits was delivered to 25,279 Japanese men aged 40 to 64 years of age. After exclusion of subjects who gave incomplete responses on alcohol drinking or prevalent cancer cases at the baseline, a total of 21,199 men remained. Of these, 307 men were diagnosed as having colorectal cancer after 11 years of follow-up. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with adjustments made for potential confounders. Compared with never drinkers, past and current drinkers had multivariate HRs of 1.1 (95% CI, 0.6–1.9) and 1.6 (95% CI, 1.1–2.2) for colorectal cancer, respectively. A dose-response relationship with current volume of alcohol drinkers was observed for cancer of the distal colon and rectum, but not for proximal colon. The multivariate HRs for distal colon and rectal cancer among current heavy drinkers (45.6 g or more ethanol per day) as compared with never drinkers were 4.2 (1.6–10.7; p for trend = 0.0002) and 1.8 (1.1–3.2; p for trend = 0.04), respectively. In contrast, no significant linear association was found for proximal colon cancer (p for trend = 0.2). These data indicate that alcohol consumption in Japanese men is associated with a statistically significant increased risk of cancer of the distal colon and rectum, but not cancer of the proximal colon.

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1. Introduction

Colorectal cancer is a major cause of cancer death not only in Western Europe and North America¹ but also among the Jap-

anese population. In 2003, colorectal cancer was the fourth most common cause of cancer death in Japanese men (21,026 deaths, 11.2% of all cancer deaths) and the most common cause of cancer death in Japanese women (17,883 deaths,

* Corresponding author. Tel.: +81 22 717 8123; fax: +81 22 717 8125.

E-mail address: munira@mail.tains.tohoku.ac.jp (M. Akhter).

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14.6% of all cancer deaths). Furthermore, mortality due to colorectal cancer has been increasing rapidly in the Japanese population during the last 50 years from 1950 to 2003. The age-adjusted death rates per 100,000 population increased 4.9 fold (from 2.9 to 13.8) for colon cancer and 1.6 fold (from 5.6 to 9.0) for rectal cancer in men, and 2.9 fold (from 3.3 to 9.5) for colon cancer in women, but remained stable for rectal cancer in women (from 4.2 to 4.0).²

Although a panel of experts commissioned by the World Cancer Research Fund and the American Institute for Cancer Research in 1997 concluded that there was 'probable' evidence that alcohol drinking increased the risk of colon and rectal cancer,³ it remains to be clarified whether the carcinogenic effects of alcohol drinking differ among anatomical subsites in the colon and rectum. Data from previous prospective epidemiological studies^{4–28} on alcohol consumption and the risk for cancer of the proximal and distal colon or rectum are limited,^{6,9,26} and the association remain controversial. Two prospective^{6,9} studies and one pooled analysis²⁶ of eight cohort studies of anatomical subsites have been conducted. Of these studies, one⁶ found an increased risk of cancer in the proximal colon and another⁹ found an increased risk in the sigmoid colon and rectum. The remaining study²⁶ found that alcohol drinking carried risk of cancer in all of these subsites.

It is relevant to consider that these studies^{6,9,26} had some methodological limitations, including the use of mortality rather than incidence as an end point,⁹ not separating the rectum from the distal colon as a cancer site,⁶ no information about the dose of alcohol consumed,⁹ and lack of confirmation of the validity^{6,9} and reproducibility^{6,9,26} of questionnaire assessment of alcohol consumption. Thus, there is still no unequivocal evidence that alcohol consumption may be associated with an increased risk of cancer at specific subsites in the colon and rectum.

The aim of the present study was to further address the hypothesis that alcohol drinking is associated with an increased risk of colon and rectal cancer by separating anatomical subsites. Our subjects were all men living in a rural area of northern Japan, where dietary habits and genetic backgrounds differ considerably from those in previous cohort studies performed in western countries.^{6,26}

2. Patients and methods

2.1. Miyagi cohort study

We have reported the design of this prospective cohort study in detail elsewhere.²⁹ Briefly, we delivered a self-administered questionnaire on various health habits to 51,921 subjects (25,279 men and 26,642 women) aged 40 to 64 years living in 14 municipalities of Miyagi Prefecture in rural northern Japan from June through to August 1990. The questionnaires were delivered to, and collected at, the subjects' residences by members of health promotion committees appointed by the municipal governments. Usable questionnaires were returned from 47,605 subjects (22,836 men and 24,769 women), yielding a response rate of 91.7% (90.3% for men and 93.0% for women). The study protocol was approved by the institutional review board of Tohoku University Graduate School of Medicine. We

considered the return of the questionnaires signed by the subjects to imply their consent to participate in the study.

2.2. Baseline survey

For assessment of drinking status, the questionnaire inquired firstly if subjects were current or past drinkers or had never drunk alcohol. Current and past drinkers were further asked about the age at which they started to drink alcohol. Current drinkers were then asked about their frequency of drinking (less than once per week, once or twice per week, three or four times per week, or five times or more per week), the amount (1 go = 22.8 g ethanol) drunk on one occasion, and the types of beverage usually consumed (sake, shochu, beer, whisky, wine, or others). From these data, we calculated the amount of ethanol (in grams) consumed per day, and classified the current drinkers into three categories: light drinkers, moderate drinkers, and heavy drinkers (less than 22.8, 22.8 to 45.5, and 45.6 g ethanol or more per day, respectively).

2.3. Follow-up

We followed up the vital and residential status of the subjects from June 1, 1990, through to March 31, 2001 by use of the population registries of the 14 municipalities. We also ascertained incident cases of cancer by computerised record linkage with the Miyagi Prefectural Cancer Registry, which covers the study areas. Cancer cases were registered from medical records like clinics and hospitals (inpatients and outpatients) which were confirmed by radiology, and pathology departments, autopsy records, mass screening records and death certificates. About 40% of cases were reported from hospitals and clinics, and 60% of cases were collected by the registry personnel.³⁰ Multiple primary cancers for the same persons were registered according to the IARC/IACR criteria³¹ with exception that colon cancers with different four digit codes of the International Classification of Diseases, 9th revision (ICD-9),³² were regarded as multiple primaries and registered separately. The site and histology of each cancer were coded according to the International Classification of Diseases for Oncology, Second Edition (ICD-O2).³³ In this cancer registry, the proportion of colorectal cancer cases for which information was available only from death certificates was 9% for men and 14% for women.³⁴

Since the number of current drinkers was small among women ($n = 4995$), we limited the analysis to men. Of the 22,836 men in this cohort who responded to the questionnaire, we excluded 427 who already had cancer at the baseline. We further excluded 1210 subjects who did not fully answer the questions on the frequency or amount of alcohol consumed and on alcohol drinking status. Consequently, 21,199 subjects with a total of 307 cases of colorectal cancer incident (179 colon, 131 rectum and three with both colon and rectal cancer) remained for this analysis. Cases were identified by the International Classification of Diseases Code (Second Ed: ICD-O-2): colon (C18.0, C18.2–C18.9) and rectosigmoid junction or rectum (C19.0–C20.9).³³ When colon stratified separately, 78 proximal colon (cecum to splenic flexure, C18.0, C18.2–C18.5) and 78 distal colon cases (descending colon to sigmoid colon, C18.6, 18.7) were found. Tumours with

overlapping (C18.8) or unspecified (C18.9) points of origin were (23 cases) excluded from the subsite specific analyses, but were included in the combined analyses.

Among the subjects, 2976 men (14% of the analysed cohort) attended a health check-up provided by the municipalities in 1990, and we compared the self-reported alcohol consumption at the baseline survey with the data from liver function tests obtained at the health check-up. To compare the mean levels of liver function tests for different volumes of alcohol consumption among current drinkers, we employed analysis of variance. We found a significant linear relationship with the mean levels of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and serum γ -glutamyltransferase (GGT) among the self-reported alcohol consumption levels (p for trend < 0.0001). The Pearson correlation coefficients between the volume of alcohol consumed and the serum AST, ALT, GGT levels were 0.2, 0.1, and 0.4, respectively (p for trend < 0.0001).

In the study population 113 subjects also responded to the questionnaire twice, one year apart, and provided four 3-day diet records within a year. Spearman's coefficient for the correlation between the amounts of alcohol consumed according to the questionnaire and the amounts consumed according to the diet records was 0.9, and the correlation between consumption measured by the two questionnaires over one year was 0.8.³⁵ These findings suggest that the data for self reported drinking dose at the baseline survey were sufficiently valid and accurate.

2.4. Statistical analysis

We counted the person-years of follow-up for each subject from June 1, 1990, until the date of diagnosis of colorectal cancer, date of emigration outside the study district, date of death, or the end of the follow-up period (March 31, 2001), whichever occurred first. The total number of person-years was accrued to 216,494. There were 976 subjects (4.6% of the analysed cohort) who emigrated from the study municipalities, and we discontinued follow-up in these subjects because of logistic limitations.

We used Cox proportional-hazards regression analysis to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of colorectal cancer according to drinking status, with adjustment for potentially confounding variables, using the SAS version 9.1 statistical software package 2004 (by SAS, Institute Inc., Cary, NC, USA). As the primary outcome, we examined the association between alcohol consumption and the risk of colorectal cancer incidence. Hazard ratios were computed as the incidence rate among subjects for each status of alcohol consumption divided by the rate among those who had never drunk alcohol. The subjects who had never drunk alcohol were treated as a reference group. We adjusted for the following variables as potential confounders: age, family history of colorectal cancer, education level, body mass index; time spent walking per day, cigarette smoking status, and consumption frequencies of meat, green-yellow vegetables, and fruits. The p – values for the analysis of linear trends were also calculated by treating the volume of alcohol drunk per day by assigning ordinal exposure variables as continuous terms (never drink-

ers were coded zero, and past drinkers were excluded). All p – values were two-tailed, and p for trend < 0.05 was considered statistically significant. Tests for interaction between alcohol consumption and all confounders were tested through the addition of cross-product terms to the regression model. No statistically significant effect modifications were found, except for consumption of green-yellow vegetables.

3. Results

Table 1 compares the baseline characteristics and hazard ratios of the subjects according to alcohol drinking status. At the baseline, the proportions of never, past, and current drinkers were 15.8%, 7.5%, and 76.7%, respectively. In Japan, alcohol consumption is socio-culturally acceptable, with alcohol being widely consumed as the most popular beverage among adults, with only a few people actually avoiding drinking alcohol. As a result, the percentage of never drinkers was found to be smaller than that of current drinkers in this study population. Compared to subjects who had never drunk alcohol, current drinkers were younger, more likely to be current smokers, and less likely to consume fruits daily, whereas past drinkers were also older, and less likely to be current smokers, and more likely to consume green-yellow vegetables every day. The age-adjusted HRs (95% CIs) for the lifestyle factors like medium and higher education level, medium and higher walking time, and past smokers were found statistically significant when compared with the corresponding reference group.

Table 2 presents the HRs and 95% CIs of cancer of the colorectum, colon, proximal colon, distal colon and rectum according to alcohol drinking status. Compared with never drinkers, we found a significant increase in both age-adjusted and multivariate-adjusted risk for colorectal cancer among current drinkers. These results remained unchanged for colon cancer, and then for distal colon cancer after further stratification according to anatomical subsites, but not for proximal colon and rectal cancer. The multivariate-adjusted HRs (95% CIs) for current drinkers were 1.6 (1.1–2.2), 1.7 (1.0–2.6), and 3.2 (1.3–7.9) for colorectum, colon, and distal colon cancer, respectively.

The volume of alcohol drunk per day among current drinkers showed a significant linear association with increased risk of colorectal cancer incidence (Table 3). The multivariate-adjusted HRs (95% CIs) for colorectal cancer in current drinkers who drank less than 22.8, 22.8 to 45.5, and 45.6 g ethanol or more per day in comparison to those who had never drunk alcohol were 1.2 (0.8–1.9), 1.3 (0.9–2.1), and 1.9 (1.3–2.8), respectively (p for trend = 0.0001). When colon cancer and rectal cancer were analysed separately, significant linear increases in the risks of association were observed for both. After stratification of colon cancer, only the distal colon showed a dose-dependent significant linear association for current alcohol drinkers. The multivariate-adjusted HRs (95% CIs) for distal colon cancer in subjects who had been drinking for less than 22.8, 22.8 to 45.5, and 45.6 g ethanol or more per day were 1.7 (0.6–4.9), 3.3 (1.2–8.9) and 4.2 (1.6–10.7), respectively (p for trend 0.0002). The corresponding multivariate-adjusted HRs (95% CIs) for rectal cancer were

Table 1 – Characteristics and hazard ratios (95% confidence intervals) of subjects according to alcohol drinking status^a

Characteristics	Alcohol drinking status			Crude or age-adjusted HRs (95% CIs)
	Never	Past	Current	
Number of subjects	3349	1595	16,255	
Mean age, y (SD) ^b	52.5 (7.7)	54.8 (7.2)	51.1 (7.5)	1.09 (1.07–1.10)
Family history of colorectal cancer (%)				
Yes	1.1	1.6	1.5	1.00 (Referent)
No	98.9	98.4	98.5	0.77 (0.34–1.73)
Education level, age (%)				
≤15 years	44.0	50.2	38.9	1.00 (Referent)
16–18 years	42.9	38.4	46.4	1.58 (1.23–2.03)
≥19 years	13.1	11.5	14.8	1.50 (1.05–2.15)
Body mass index (%)				
<18.5 kg/m ²	2.5	3.4	1.8	1.00 (Referent)
18.5–24.9 kg/m ²	70.7	68.5	70.6	1.68 (0.62–4.52)
≥25.0 kg/m ²	26.8	28.1	27.7	1.61 (0.59–4.40)
Walking time (%)				
<30 min/day	32.8	32.9	30.5	1.00 (Referent)
30 min/day–1 h/day	21.7	23.3	24.2	1.66 (1.26–2.18)
>1 h/day	45.5	43.7	45.3	1.35 (1.02–1.79)
Cigarette smoking status (%)				
Never	27.4	13.1	17.4	1.00 (Referent)
Past	15.3	31.6	19.6	1.47 (1.01–2.12)
Current	57.4	55.2	63.0	1.34 (0.97–1.86)
Food habits Meat consumption (%) ^c				
≤1–2 times/month	22.6	27.6	21.3	1.00 (Referent)
1–2 times/week	52.3	48.1	53.1	0.94 (0.68–1.31)
3–4 times/week	20.8	22.0	22.2	1.04 (0.71–1.53)
Everyday	4.2	2.4	3.5	1.26 (0.64–2.48)
Green-yellow vegetables consumption (%) ^d				
≤1–2 times/month	8.2	7.6	7.4	1.00 (Referent)
1–2 times/week	29.1	23.5	28.4	0.86 (0.51–1.45)
3–4 times/week	32.9	35.7	35.2	0.91 (0.55–1.51)
Everyday	29.8	33.2	28.9	0.83 (0.50–1.40)
Fruits consumption (%) ^e				
≤1–2 times/month	11.3	12.5	17.2	1.00 (Referent)
1–2 times/week	25.8	25.0	27.9	1.29 (0.86–1.95)
3–4 times/week	27.7	29.8	28.8	1.04 (0.68–1.57)
Everyday	35.3	32.7	26.1	1.06 (0.70–1.61)

Because of rounding, not all percentages add to 100.

a N = 21,199 men.

b SD denotes standard deviation.

c The maximum intake of beef, pork, or chicken.

d The maximum intake of spinach, carrot or pumpkin, or tomato.

e The maximum intake of orange, or other fruits.

1.4 (0.8–2.6), 1.00 (0.5–1.1) and 1.8 (1.1–3.2), respectively (p for trend = 0.04). We also further evaluated and found statistically significant risk of association for multivariate HRs (95% CIs) of colorectum 1.2 (1.1–1.4), colon 1.3 (1.1–1.5), distal colon 1.5 (1.2–1.8), and rectal cancer 1.2 (1.0–1.4) except for proximal colon 1.2 (1.0–1.5) by using alcohol consumption as a continuous variable instead of only dividing into groups.

Table 4 shows the combined effect of age, education level, body mass index, walking time, cigarette smoking, and alcohol consumption on the risk of colorectal cancer. The comparison showed that the HRs were very high among heavy

drinkers when older age, low BMI, medium walking time, and past smokers present simultaneously.

We also conducted stratified analyses according to anatomical subsites between duration of alcohol consumption and risk of colorectal cancer. Significant linear trends were found for cancer of the colorectum (p for trend = 0.005), colon (p for trend = 0.02) and distal colon (p for trend = 0.002) in current drinkers compared with subjects who had never drunk alcohol. For rectal cancer, a marginal linear association was found (p for trend = 0.06), but no positive association was found for cancer of the proximal colon.

Table 2 – Hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer according to alcohol drinking status

Cancer site	Alcohol drinking status		
	Never	Past	Current
Colorectum			
Person-years	34,553	15,719	166,222
Number of incident cases	36	22	249
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.15 (0.68–1.95)	1.61 (1.14–2.29)
Multivariate HRs (95% CIs) ^a	1.00 (Referent)	1.08 (0.64–1.85)	1.56 (1.10–2.22)
Colon			
Person-years	34,605	15,743	166,501
Number of incident cases	20	15	144
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.39 (0.71–2.71)	1.70 (1.06–2.71)
Multivariate HRs (95% CIs) ^a	1.00 (Referent)	1.30 (0.66–2.55)	1.65 (1.03–2.64)
Proximal Colon			
Person-years	34,644	15,773	166,843
Number of incident cases	12	8	58
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.28 (0.52–3.12)	1.11 (0.60–2.07)
Multivariate HRs (95% CIs) ^a	1.00 (Referent)	1.22 (0.49–3.03)	1.09 (0.58–2.04)
Distal Colon			
Person-years	34,656	15,776	166,763
Number of incident cases	5	5	68
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.78 (0.51–6.14)	3.30 (1.33–8.19)
Multivariate HRs (95% CIs) ^a	1.00 (Referent)	1.70 (0.49–5.91)	3.19 (1.28–7.94)
Rectum			
Person-years	34,620	15,769	166,734
Number of incident cases	16	7	108
Age-adjusted HRs (95% CIs)	1.00 (Referent)	0.84 (0.35–2.04)	1.54 (0.91–2.61)
Multivariate HRs (95% CIs) ^a	1.00 (Referent)	0.79 (0.32–1.94)	1.49 (0.88–2.53)

a Adjusted for age in years; family history of colorectal cancer; education level (15 years or less, 16 to 18 years, 19 years or more); body mass index (less than 18.5 kg/m², 18.5 to 24.9 kg/m², 25.0 kg/m² or more); walking time (less than 30 min/day, 30 min/day to 1 h/day, more than 1 h/day); cigarette smoking status (never, past, and current smokers); consumption frequencies of meat, green-yellow vegetables, and fruits (1 to 2 times/month or less, 1 to 2 times/week, 3 to 4 times/week, everyday).

4. Discussion

In this population-based prospective cohort study of Japanese men, we found a significant linear dose-response association between the volume of alcohol consumed per day and the risk of colorectal cancer in current drinkers in comparison with subjects who had never drunk alcohol. With regard to anatomical subsites, we observed a significant linear increase in risk with the volume of alcohol consumed for cancer of the distal colon and rectum, but not for cancer of the proximal colon.

Few prospective cohort studies have examined the risk of colorectal cancer at anatomic subsites due to alcohol consumption, particularly in men. Wu and colleagues⁶ found a statistically significant increase in the risk of proximal colon cancer with higher alcohol consumption. As that study included few cases of rectal cancer, combination with distal colon cancer showed no clear association. In a Japanese study,⁹ Hirayama grouped the cancers into those of the caecum, proximal colon (upper and transverse colon), descending colon, sigmoid colon, and rectum and observed a trend for increasing risk of both sigmoid colon and rectal cancer associated with a higher frequency of alcohol consumption. The remaining study involved a pooled analysis²⁶ of eight cohort studies from different western countries, which demonstrated a significant linear increase in the association of prox-

imal colon, distal colon and rectal cancer for different volumes of daily alcohol consumption among men and women combined.

There are many possible reasons for the apparently inconsistent findings among these previous studies.^{6,9,26} Different investigators^{6,9} used different grouping of subsites within the colon. Two studies^{6,9} presented gender-specific results and the other²⁶ used combined data for both sexes. In addition, studies carried out in different geographic locations may be characterised by different patterns of exposure, for example ethnicity and genotypes. Most Japanese studies have reported a positive association between aldehyde dehydrogenase among alcohol drinkers and colorectal cancer, as acetaldehyde levels in Japanese individuals are generally higher than in Caucasians.³⁶ However, the results of the present study suggested that Japanese male current drinkers are more susceptible to cancer of the distal part of the large bowel than to cancer in the proximal part.

Our study had several strengths over previous studies examining the association between alcohol consumption and risk of colorectal cancer. First, we recruited our subjects from the general population and identified a large number of cases of colorectal cancer. Second, a low degree of selection bias was possible because the rate of response of participants to the questionnaire was high (90.3%). Third, cancer incidence rather than mortality was used as an endpoint, making it

Table 3 – Hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer according to different alcohol consumption level

Cancer site	Alcohol consumption (g/day)				P for trend ^a
	Never drinkers	Current drinkers			
		Light	Moderate	Heavy	
		< 22.8	22.8–45.5	≥ 45.6	
Colorectum					
Person-years	34,553	50,398	39,854	75,969	
Number of incident cases	36	57	54	138	
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.24 (0.82–1.89)	1.40 (0.92–2.14)	1.97 (1.37–2.85)	< 0.0001
Multivariate HRs (95% CIs) ^b	1.00 (Referent)	1.24 (0.81–1.88)	1.34 (0.88–2.05)	1.91 (1.32–2.78)	0.0001
Colon					
Person-years	34,605	50,464	39,916	76,121	
Number of incident cases	20	29	36	79	
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.15 (0.65–2.04)	1.69 (0.98–2.92)	2.06 (1.26–3.36)	0.0005
Multivariate HRs (95% CIs) ^b	1.00 (Referent)	1.15 (0.65–2.03)	1.61 (0.93–2.80)	2.03 (1.23–3.33)	0.0008
Proximal Colon					
Person-years	34,644	50,522	40,027	76,293	
Number of incident cases	12	13	12	33	
Age-adjusted HRs (95% CIs)	1.00 (Referent)	0.84 (0.38–1.84)	0.92 (0.42–2.06)	1.39 (0.72–2.70)	0.17
Multivariate HRs (95% CIs) ^b	1.00 (Referent)	0.82 (0.37–1.80)	0.89 (0.40–1.99)	1.40 (0.72–2.75)	0.16
Distal Colon					
Person-years	34,656	50,516	39,992	76,254	
Number of incident cases	5	10	18	40	
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.64 (0.56–4.81)	3.44 (1.28–9.28)	4.32 (1.70–10.95)	< 0.0001
Multivariate HRs (95% CIs) ^b	1.00 (Referent)	1.68 (0.57–4.92)	3.30 (1.22–8.91)	4.17 (1.63–10.66)	0.0002
Rectum					
Person-years	34,620	50,480	40,010	76,242	
Number of incident cases	16	29	18	61	
Age-adjusted HRs (95% CIs)	1.00 (Referent)	1.40 (0.76–2.58)	1.04 (0.53–2.03)	1.92 (1.11–3.33)	0.02
Multivariate HRs (95% CIs) ^b	1.00 (Referent)	1.40 (0.76–2.59)	0.996 (0.51–1.96)	1.84 (1.05–3.21)	0.04

a *P* for trend excludes past alcohol drinkers.

b Adjusted for age in years; family history of colorectal cancer; education level (15 years or less, 16 to 18 years, 19 years or more); body mass index (less than 18.5 kg/m², 18.5 to 24.9 kg/m², 25.0 kg/m² or more); walking time (less than 30 min/day, 30 min/day to 1 h/day, more than 1 h/day); cigarette smoking status (never, past, and current smokers); consumption frequencies of meat, green-yellow vegetables, and fruits (1 to 2 times/month or less, 1 to 2 times/week, 3 to 4 times/week, everyday).

possible to distinguish whether alcohol consumption was related to cancer incidence, cancer survival, or both. Finally, we controlled extensively for potentially confounding variables, such as age, body mass index, daily walking time, cigarette smoking, and diet (consumption of meat, green-yellow vegetables, and fruits).

Our study also had several limitations that may need to be considered. First, information on alcohol drinking and other variables was based on self-administered questionnaires; some misclassification of subjects was inevitable. Nevertheless, because this information was collected before the subjects developed colorectal cancer or other serious diseases, any misclassification of drinking status would likely have been nondifferential and resulted in conservative estimates of the association between alcohol drinking and the risk of colorectal cancer. Second, the different volume of specific beverage types was not identified at the beginning of follow-up, and we were unable to conduct a separate analysis for these subgroups. Some previous prospective studies have shown that higher intake of beer was associated with a stronger risk of colorectal cancer.^{4,9,12,16,20,26} Finally, we did not check whether some nutrients such as folate, methionine, calcium or non-steroidal

anti-inflammatory drugs³⁷ affected the association between alcohol consumption and colorectal cancer risk.

In summary, our data clearly shows that alcohol consumption plays an important role in the aetiology of distal colon cancer and rectal cancer in Japanese men. These findings indicate that the effect of alcohol-drinking on the proximal part of large bowel differs from that on the distal part. From a public health perspective, further studies are needed to clarify the role of alcohol consumption in the aetiology of cancer of specific subsites in the colon and rectum. Such information would be useful in education programs about alcohol use when discussing the possible harmful effects of alcohol consumption.

Conflict of interest statement

None declared.

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All the authors of this article have directly participated in the planning, execution or analysis of this study. This study was

Table 4 – Hazard ratios (HRs) and 95% confidence intervals (CIs) of colorectal cancer according to combined effect of different alcohol consumption level and the selected lifestyle factors

Characteristics	Alcohol consumption (g/day)				
	Never drinkers	Past drinkers	Current drinkers		
			Light	Moderate	Heavy
			< 22.8	22.8–45.5	≥ 45.6
Age					
40–54 years	1.00 (Referent)	1.40 (0.48–4.10)	1.42 (0.68–2.96)	1.54 (0.72–3.29)	1.86 (0.94–3.68)
Multivariate HRs (95% CIs) ^a					
55–64 years	3.41 (1.63–7.92)	3.59 (1.63–7.92)	3.68 (1.80–7.52)	4.11 (2.02–8.37)	6.40 (3.31–12.40)
Multivariate HRs (95% CIs) ^a					
Education level (years of age)					
≤15	1.00 (Referent)	0.79 (0.29–2.15)	0.75 (0.30–1.88)	0.79 (0.31–2.01)	0.95 (0.40–2.26)
Multivariate HRs (95% CIs) ^a					
16–18	0.56 (0.21–1.48)	0.88 (0.30–2.54)	0.91 (0.37–2.24)	1.12 (0.46–2.71)	1.76 (0.76–4.06)
Multivariate HRs (95% CIs) ^a					
≥19	0.76 (0.29–1.98)	1.04 (0.26–4.19)	1.04 (0.38–2.86)	1.02 (0.34–3.03)	1.35 (0.53–3.47)
Multivariate HRs (95% CIs) ^a					
Body Mass Index (kg/m ²)					
<18.5 kg/m ²	NA	1.99 (0.27–14.79)	NA	NA	2.23 (0.67–7.45)
Multivariate HRs (95% CIs) ^a					
18.5–24.9 kg/m ²	1.00 (Referent)	1.27 (0.66–2.44)	1.21 (0.72–2.05)	1.43 (0.85–2.40)	2.05 (1.29–3.24)
Multivariate HRs (95% CIs) ^a					
≥25.0 kg/m ²	1.46 (0.74–2.89)	0.83 (0.29–2.41)	1.46 (0.79–2.71)	1.20 (0.59–2.41)	1.67 (0.97–2.88)
Multivariate HRs (95% CIs) ^a					
Walking time					
>1 h/day	1.00 (Referent)	1.55 (0.68–3.54)	0.83 (0.39–1.77)	1.02 (0.49–2.15)	2.08 (1.14–3.82)
Multivariate HRs (95% CIs) ^a					
30 min/day – 1 h/day	1.55 (0.66–3.63)	1.40 (0.50–3.96)	2.47 (1.24–4.93)	2.35 (1.14–4.81)	2.65 (1.39–5.04)
Multivariate HRs (95% CIs) ^a					
<30 min/day	1.47 (0.67–3.23)	0.91 (0.30–2.79)	1.66 (0.81–3.41)	1.60 (0.75–3.42)	2.36 (1.24–4.48)
Multivariate HRs (95% CIs) ^a					
Cigarette smoking status					
Never	1.00 (Referent)	1.14 (0.24–5.52)	1.72 (0.70–4.22)	1.60 (0.58–4.41)	1.81 (0.70–4.68)
Multivariate HRs (95% CIs) ^a					
Past	1.77 (0.64–4.89)	1.56 (0.55–4.45)	1.81 (0.73–4.49)	2.71 (1.13–6.50)	2.83 (1.23–6.48)
Multivariate HRs (95% CIs) ^a					
Current	1.48 (0.63–3.48)	1.86 (0.74–4.66)	1.56 (0.68–3.60)	1.64 (0.72–3.76)	2.79 (1.29–6.03)
Multivariate HRs (95% CIs) ^a					

^bP for trend excludes past alcohol drinkers.

^a Adjusted for age in years; family history of colorectal cancer; education level (15 years or less, 16 to 18 years, and 19 years or more); body mass index (less than 18.5 kg/m², 18.5 to 24.9 kg/m², 25.0 kg/m² or more); walking time/day (less than 30 min, 30 min to 1 h, and more than 1 h); cigarette smoking status (never, past, current smokers); consumption frequencies of meat, green yellow-vegetables, and fruits (rarely, 1 to 2 times/month, 1 to 2 times/week, 3 to 4 times/week, and everyday). Each model is stratified by age, education level, BMI, walking time per day, and cigarette smoking did not include variables for each stratum, respectively.

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