Alcohol Consumption, Smoking, and Subsequent Risk of Colorectal Cancer in Middle-Aged and Elderly Japanese Men and Women: Japan Public Health Center-based Prospective Study

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Abstract

Few studies have examined the association of alcohol consumption and cigarette smoking with colorectal cancer in Asian populations whose genetic susceptibility to these factors are different from Western populations. We investigated this association and the joint effect of these factors, and estimated the population-attributable fraction to clarify the public health impact on a Japanese population, based on a prospective study. We analyzed the 10-year (cohort I) and 7-year (cohort II) follow-up data of the Japan Public Health Center-based prospective study on cancer and cardiovascular disease, derived from 90,004 (42,540 male and 47,464 female) middle-aged and elderly Japanese. We identified 716 (457 in men and 259 in women) newly diagnosed cases of colorectal cancer. Both alcohol consumption and smoking were clearly associated with colorectal cancer in men, after adjusting for age, family history of colorectal cancer, body mass index, and physical exercise. Regular heavy drinking of 150 g/week or more of ethanol showed a statistically significant increased risk compared with nondrinkers: relative risks (RRs) were 1.4 [95% confidence interval (CI), 1.1–1.9] for 150–299 g/week and 2.1 (95% CI, 1.6–2.7) for 300 g/week or more. On the contrary, regular ethanol consumption was not associated with colorectal cancer (RR, 0.7; 95% CI, 0.4–1.1) in women. In terms of smoking, the RRs were 1.4 (95% CI, 1.1–1.8) for current smokers and 1.3 (95% CI, 0.98–1.7) for ex-smokers compared with never-smokers in men. The risk of smoking in women was similar to that in men, although not statistically significant. The colorectal cancer risk with 300 g/week or more of ethanol in current smokers was estimated at 3.0 (95% CI, 1.8–5.1) compared with nondrinkers among nonsmokers in men. Colorectal cancer attributable to alcohol consumption or smoking was estimated to be 46%. In conclusion, approximately half of the colorectal cancer cases may be preventable by tobacco and alcohol controls in middle-aged and elderly Japanese men.

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Introduction

Colorectal cancer is one of the most common cancers in Western countries, and its incidence rate has increased recently in Asian countries, especially in Japan (1), as Japan has been westernized over the past few decades. In fact, the high incidence in Japanese migrants to Hawaii may suggest that a change of environmental factors, including the westernization of dietary habits and lifestyle, may contribute to this increase (1, 2).

Many epidemiological studies have reported the association of alcohol consumption with colorectal cancer (3) and adenoma. Recent prospective studies using incidence data have consistently supported this association (4–11). However, most of such studies of the incidence data have targeted Western populations; an Asian population has been investigated in only

one study (11). Alcohol consumption has increased in Asian populations, especially Japanese, so as to now reach the levels of Western populations (12). At the same time, half of all Japanese people have an atypical allele of the aldehyde dehydrogenase 2 gene (*ALDH2*; Ref. 13), which catalyzes the acetaldehyde metabolism less (14), resulting in a high blood level of acetaldehyde after drinking (15). Because of this genetic polymorphism, Japanese may have a susceptibility to alcohol consumption different from that in Western populations. Therefore, a study using a Japanese population would be expected to detect a stronger effect of alcohol consumption in relation to colorectal cancer than in Western populations.

Studies over the past decade have consistently reported a positive association between smoking and colorectal cancer (16–20). In addition, it has been revealed that smoking requires a long induction period to lead to colorectal carcinogenesis (19, 20). However, evidences of the association and the public health impact of smoking are only available for Western populations (19, 21). It is important to clarify the public health impact of smoking in populations with a high prevalence of smoking like Japanese men (53.5% of males ≥20 years of age in 2000; Ref. 22).

Therefore, we investigated the association of alcohol consumption, smoking, and their joint effect with colorectal cancer and estimated the population-attributable fraction (PAF) to clarify their public health impact, based on a population-based prospective cohort study.

Materials and Methods

Study Population. The Japan Public Health Center-based prospective study on cancer and cardiovascular disease (JPHC study) started in 1990 for the first group (cohort I) and in 1993 for the second group (cohort II). Cohort I covered 5 areas administered by the Public Health Centers (PHC) in 5 prefectures (Iwate, Akita, Nagano, Okinawa, and Tokyo). Cohort II included 6 PHC areas in 6 prefectures (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). Cohort I comprised all residents aged 40–59 as of January 1, 1990 except for Tokyo, and cohort II comprised all residents aged 40–69 as of January 1, 1993 except for Osaka. The study subjects were identified by population registries maintained by local municipalities. When analyzing the present data, we excluded the subjects in Tokyo whose incidence data were not available, and those in Osaka who were not all within the specific age range. Thus, we defined a population-based cohort of 57,714 men (27,063 in cohort I and 30,651 in cohort II) and 59,182 women (27,435 in cohort I and 31,747 in cohort II). Those deemed ineligible during this study period were excluded, such as non-Japanese (29 men and 20 women), those who had already moved away at baseline (94 men and 57 women), and those outside of the 40–59 age parameters in cohort I (2 women). This left 57,591 men and 59,103 women eligible subjects. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The study design is described in detail elsewhere (23).

Baseline Survey. A self-administered questionnaire was distributed mostly by hand and partly by mail to the JPHC study subjects in 1990 for cohort I and in 1993–1994 for cohort II. They were asked about their personal and familial medical histories, smoking, alcohol consumption, dietary habits, and other lifestyle factors (24–26). Among the eligible subjects, 45,452 men (79%) and 49,924 women (84%) returned the questionnaire. From them, we excluded subjects with a self-reported medical history of cancer and with a diagnosis of colorectal cancer before the survey began (687 men and 1,363 women). This additionally reduced the number of eligible subjects to 44,765 men and 48,561 women. Finally, we excluded subjects with incomplete alcohol and/or smoking items (2,225 men and 1,097 women), leaving 42,540 men and 47,464 women as study subjects.

Assessment of Exposure. The average frequency of alcohol consumption was reported in six categories by cohort I: "less than 1 day/month," "1–3 days/month," "1–2 days/week," "3–4 days/week," "5–6 days/week," and "everyday." Subjects consuming alcoholic beverages at least once a week were also asked about types of drinks and average consumption. Subjects in cohort II were asked about drinking status, *i.e.*, never-, ex-, or current drinkers. Ex- and current drinkers provided information on average frequency, types of drinks, and average consumption per day. The average frequency was divided into four categories: "1–3 days/month," "1–2 days/week," "3–4 days/week," and "almost everyday." We assigned a score to each category of frequency as follows: 1.5 for "1–2/week," 3.5 for "3–4/week," 6 for "5–6/week," and "everyday" in the cohort I questionnaire, and 1.5 for "1–2/week," 3.5 for "3–4/week," and 6 for "almost everyday" in the cohort II questionnaire. The amount of ethanol in each type of alcoholic beverages was calculated as follows: 180 ml sake (rice wine) as 23 g ethanol, 180 ml shochu or awamori (white spirits) as 36 g, 633 ml beer as 23 g, 30 ml whiskey or brandy as 10 g, and 60 ml wine as 6 g. Finally, weekly ethanol intake was estimated by multiplying the amount by the score.

Alcohol consumption was classified into five groups in cohort I: nondrinkers (<1 day/month), occasional drinkers (1–3 days/month), and three groups of regular drinkers (1–149 g/week ethanol, 150–299 g/week, and 300 g/week or more; Table 1). Cohort II was categorized into six groups, because nondrinkers were divided into two groups, ex- and never-drinkers. When analyzing the two cohorts together, we combined ex- and never-drinkers into nondrinkers. Three groups of regular drinkers were combined in the analyses of women (Table 2).

To evaluate the validity of alcohol consumption, we compared the estimates from the questionnaires with the 28-day dietary records (7 days in 4 seasons) provided by volunteers in each cohort. Spearman's rank correlations were 0.79 in 94 men and 0.44 in 107 women of cohort I (27), and 0.59 in 176 men and 0.40 in 178 women of cohort II. The reproducibility of the responses on alcohol intake was 0.78 in men and 0.66 in women of cohort I between 1990 and 1995 (5-year interval; Ref. 27), and 0.72 in men and 0.63 in women of cohort II between 1993 and 1997 (4-year interval). Because we also confirmed that assigning a score of 6 to "5–6/week" and "everyday" was as valid as 5.5 to "5–6/week" and 7 to "everyday" in the comparison with the dietary records in cohort I, we used the score 6 in cohort I as well as in cohort II.[3]

The questions on smoking habits included current and former smoking status, age at initiation of smoking, and average number of cigarettes smoked per day. Smoking intensity for current smokers was evaluated by pack-year defined by multiplying the years of smoking times the average number of cigarettes divided by 20 (28). We classified current smokers by the following categories of smoking intensity: <20 pack-years, 20–29 pack-years, 30–39 pack-years, and ≥40 pack-years.

A high prevalence of current smokers was found in both

[3] Unpublished observations.

Table 1 Baseline characteristics by categories on alcohol consumption and smoking status in men

	Alcohol consumption						Smoking status		
	Ex (Non)	Never (Non)	Occasional	Regular (g/week ethanol) 1–149	Regular (g/week ethanol) 150–299	Regular (g/week ethanol) 300+	Never	Ex	Current
Cohort I *n* (%)	4,191 (21.1)		2,162 (10.9)	4,578 (23.1)	4,501 (22.7)	4,426 (22.3)	4,788 (24.1)	4,543 (22.9)	10,527 (53.0)
Age (years) Mean (SD)	50.0 (6.0)		48.8 (5.9)	49.1 (5.9)	49.4 (5.9)	49.1 (5.8)	49.5 (5.6)	50.2 (6.0)	48.9 (6.0)
Family history of colorectal cancer (%)	1.0		0.9	0.8	1.3	0.9	0.9	1.1	1.0
Body mass index (kg/m^2) Mean (SD)	23.6 (3.0)		24.0 (3.2)	23.6 (2.8)	23.5 (2.7)	23.6 (2.9)	24.0 (2.9)	24.0 (2.9)	23.2 (2.8)
Current smokers (%)	47.6		46.2	45.9	57.9	63.9	–	–	–
Regular drinkers (%)	–		–	–	–	–	59.0	69.4	71.6
Physical exercise (% of 1/week or more)	15.5		19.3	21.0	16.8	16.6	19.6	21.5	15.3
Green vegetables (%)[a]	69.0		69.9	71.8	70.9	67.2	72.7	71.8	67.5
Yellow vegetables (%)[a]	49.2		48.7	49.4	44.2	42.3	51.5	50.0	42.8
Fruits (%)[a]	57.2		55.7	58.7	52.8	47.0	62.4	57.6	48.8
Beef (%)[a]	12.5		11.7	11.3	10.9	12.3	11.1	11.9	12.0
Pork (%)[a]	30.4		25.2	29.9	33.1	32.3	30.3	29.4	31.6
Chicken (%)[a]	24.1		20.2	21.5	23.0	24.1	24.3	22.3	22.4
Fish (%)[a]	44.0		37.4	49.2	54.2	56.3	49.1	49.7	49.7
Cohort II *n* (%)	952 (4.2)	4,886 (21.5)	1,936 (8.5)	5,263 (23.2)	4,785 (21.1)	4,860 (21.4)	5,461 (24.1)	5,532 (24.4)	11,689 (51.5)
Age (years) Mean (SD)	58.2 (8.3)	55.5 (8.9)	51.3 (8.3)	52.2 (8.7)	53.1 (8.6)	52.3 (8.2)	53.4 (8.3)	55.7 (8.9)	52.1 (8.6)
Family history of colorectal cancer (%)	1.8	1.5	2.2	1.6	1.4	1.4	1.1	1.7	1.7
Body mass index (kg/m^2) Mean (SD)	23.1 (3.0)	23.3 (3.6)	24.1 (3.1)	23.3 (2.8)	23.5 (2.8)	23.8 (3.1)	24.0 (2.9)	23.8 (2.9)	23.2 (3.2)
Current smokers (%)	44.4	47.6	47.6	45.8	56.7	60.5	–	–	–
Regular drinkers (%)	–	–	–	–	–	–	59.9	66.0	69.1
Physical exercise (% of 1/week or more)	20.0	17.4	18.8	21.7	19.8	19.0	22.3	24.0	16.1
Green vegetables (%)[a]	56.2	48.4	45.3	50.1	50.8	47.2	54.0	53.5	44.8
Carrot (%)[a]	41.1	33.3	31.7	32.5	30.5	29.0	37.7	35.1	27.4
Apple (%)[a]	25.0	22.0	17.8	19.8	16.2	11.9	21.3	23.5	13.6
Citrus fruits (%)[a]	42.4	44.5	38.0	40.1	34.1	27.2	42.8	43.3	31.2
Beef (%)[a]	3.9	5.2	3.5	4.1	4.1	4.8	4.5	3.5	4.8
Pork (%)[a]	16.1	16.0	14.5	14.0	16.3	18.2	16.4	14.6	16.4
Chicken (%)[a]	11.9	9.0	7.2	7.9	8.1	9.0	8.5	9.3	8.1
Fish (%)[a]	52.7	42.7	41.5	47.4	52.8	57.9	48.7	53.0	48.2

[a] Percentage of 3 days/week or more intake.

male and female regular drinkers (Tables 1 and 2). As the level of weekly regular consumption was higher, the percentage of current smokers was higher in males. As for potential confounding factors, we examined age at baseline, body mass index (kg/m^2; Ref. 29), subjects with a family history of colorectal cancer, those exercising once a week or more, and intake frequency of foods such as vegetables, fruits, meats, and fish. However, the impact of these factors showed no positive or negative trend by categories on alcohol consumption and smoking status (Tables 1 and 2). Baseline characteristics by categories on alcohol consumption have also been shown elsewhere (30).

Follow-Up. We followed study subjects until December 31, 1999. When subjects died, we used mortality data from the Ministry of Health, Labor, and Welfare. Subjects moving to other municipalities were also annually identified through residential registers in PHC areas. Among study subjects, 5.0% moved away and 0.04% were lost to follow-up during the study period.

Identification of Colorectal Cancer Incidence. After January 1, 1990 in cohort I and January 1, 1993–1994 in cohort II, incidence data on colorectal cancer were collected for the JPHC cancer registry through two data sources, local major hospitals and population-based cancer registries. Death certificates were used to supplement the information on cancer incidence.

Cases of colorectal cancer were extracted from the JPHC cancer registry based on site codes [International Classification of Diseases for Oncology, second edition (ICD-O-2) code: C180–189 (colon) and C199, 209 (rectum); Ref. 31]. Up to December 31, 1999, 772 incident cases of colorectal cancer were identified. For multiple primary cancers in colon or rectum at different times, the earliest diagnosis was applied. For those occurring simultaneously, the most advanced and most invasive diagnosis was applied. Among these incident cases, 716 were pathologically confirmed as adenocarcinoma (M: 8140, 8210, 8211, 8240, 8243, 8260, 8261, 8262, and 8263 for ICD-O-2). Such cases were additionally classified into two groups according to the depth of tumor invasion, *i.e.*, invasive cancer over a mucosal layer corresponding to code 3 (malignant, primary site) in "behavior code for neoplasms" (298 colon cases and 206 rectal cases), and noninvasive cancer within a mucosal layer corresponding to code 2 (carcinoma *in situ*; 165 colon and 38 rectum) in ICD-O-2 (the depth in 5 colon and 4 rectal tumors were unknown).

In our cancer registry system, the proportion of cases for which information was available only from death certificates was 1.0% for colorectal cancer and 3.1% for all of the cancers during the study period. These figures were considered of satisfactory quality for the present study based on the international standard (1).

Table 2 Baseline characteristics by categories on alcohol consumption and smoking status in women

	Alcohol consumption				Smoking status		
	Ex (Non)	Never (Non)	Occasional	Regular	Never	Ex	Current
Cohort I *n* (%)	16,668 (77.5)		2,567 (11.9)	2,281 (10.6)	19,934 (92.6)	369 (1.7)	1,213 (5.6)
Age (years) Mean (SD)	49.9 (5.8)		48.3 (5.8)	48.2 (5.8)	49.5 (5.8)	49.2 (6.4)	48.5 (5.9)
Family history of colorectal cancer (%)	0.8		1.5	1.1	0.9	0.6	0.8
Body mass index (kg/m^2) Mean (SD)	23.7 (3.3)		23.5 (2.9)	23.2 (2.9)	23.6 (3.2)	24.2 (3.4)	23.4 (3.8)
Current smokers (%)	4.1		6.6	16.2	–	–	–
Regular drinkers (%)	–		–	–	9.2	24.4	30.3
Physical exercise (% 1/week or more)	13.4		17.6	17.4	14.3	17.2	13.7
Green vegetables (%)[a]	78.4		75.3	78.3	78.5	71.3	72.4
Yellow vegetables (%)[a]	65.5		63.6	61.5	65.5	61.0	55.0
Fruits (%)[a]	73.7		79.1	73.0	75.4	67.0	59.2
Beef (%)[a]	10.0		9.1	11.2	9.7	13.2	14.0
Pork (%)[a]	32.4		35.6	34.6	33.1	32.7	31.4
Chicken (%)[a]	29.9		29.3	28.1	30.0	27.5	25.2
Fish (%)[a]	53.8		55.2	59.9	55.2	47.9	48.4
Cohort II *n* (%)	223 (0.9)	21,112 (81.4)	2,112 (8.1)	2,501 (9.6)	24,133 (93.0)	278 (1.1)	1,537 (5.9)
Age (years) Mean (SD)	53.7 (8.4)	54.9 (8.7)	49.1 (7.5)	50.1 (8.0)	54.0 (8.8)	53.9 (9.6)	51.4 (8.6)
Family history of colorectal cancer (%)	–	1.3	1.4	1.6	1.4	1.3	0.8
Body mass index (kg/m^2) Mean (SD)	23.6 (3.8)	23.6 (3.3)	23.5 (3.1)	23.1 (3.2)	23.5 (3.2)	23.8 (3.4)	23.2 (3.8)
Current smokers (%)	28.1	3.9	9.0	18.6	–	–	–
Regular drinkers (%)	–	–	–	–	8.5	26.7	31.2
Physical exercise (% 1/week or more)	20.2	18.5	19.6	21.5	19.1	17.9	16.0
Green vegetables (%)[a]	61.6	61.2	56.4	60.8	61.5	59.6	49.9
Carrot (%)[a]	52.2	53.0	49.2	45.9	52.9	45.8	38.4
Apple (%)[a]	29.6	33.6	31.2	30.7	33.9	26.3	21.7
Citrus fruits (%)[a]	55.2	60.9	60.9	57.6	61.6	51.3	44.8
Beef (%)[a]	6.9	4.2	5.1	5.3	4.4	5.0	5.4
Pork (%)[a]	15.8	18.8	18.8	17.3	18.8	13.8	16.2
Chicken (%)[a]	8.4	10.2	9.6	9.4	10.2	11.3	8.5
Fish (%)[a]	52.7	49.1	45.9	52.9	49.7	51.7	42.5

[a] Percentage of 3 days/week or more intake.

Statistical Analysis. Person-years of follow-up were determined from January 1, 1990 (cohort I) or 1993–1994 (cohort II) until the date of diagnosis of colorectal cancer, the date of a subject's death, the date of moving from a PHC area, or December 31, 1999, whichever occurred first. Incidence rates of colorectal cancer were calculated using person-years as the denominators and standardized with a 5-year age distribution at baseline in each cohort (40–44, 45–49, 50–54, and 55–59 in cohort I, and 40–44, 45–49, 50–54, 55–59, 60–64, and 65–69 in cohort II; Ref. 32).

Relative risks (RRs) and 95% confidence intervals (CIs) for alcohol consumption and smoking were estimated by the Cox proportional hazards model, according to the SAS PHREG procedure (33). The estimates were adjusted for the following potential confounding factors incorporated into the model: age (5-year groups), family history of colorectal cancer (anyone or none), body mass index (quartiles in each cohort), physical exercise (less than once a week and once a week or more), smoking status (when calculating RR for alcohol consumption; never-, ex-, and current smokers), alcohol consumption (when calculating RR for smoking status and intensity; nondrinkers, occasional drinkers, 1–149 g/week, 150–299 g/week, and ≥300 g/week), and PHC area. The factors relating to dietary habits, which were slightly different between both cohorts, were not considered as confounding factors, because they hardly affected the RR of alcohol consumption and smoking status. The linear trend of alcohol consumption or smoking intensity was assessed by assignment of ordinal values to categories among drinkers or current smokers, respectively. *P*s for those trends were evaluated using the two-sided test with 0.05 as the significance level.

First, we estimated the RR of all cases of colorectal cancer in each cohort, because slightly different questionnaires were used. Second, in addition to all of the cases, we combined two cohorts and calculated the RRs and the linear trends of invasive colorectal, colon, and rectal cancer to obtain more power to detect the association after confirming the same risk trend in the two cohorts. When we estimated the RR of the invasive, we defined the noninvasive as a censored case. Similarly, we considered rectal cancer as a censored case in colon cancer end point and colon cancer as a censored case in rectal cancer end point.

We also calculated the RRs of colorectal cancer for combined categories of alcohol consumption and smoking status, and tested statistical interactions, using the differences between two likelihood ratios of the models with and without the interaction terms between alcohol consumption and smoking status (34).

Table 3 Age-standardized incidence rate, multivariate-adjusted relative risk (RR), and 95% confidence interval (CI) of colorectal cancer by categories on alcohol consumption in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999)

	Ex-drinkers	Never-drinkers	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for trend among drinkers
	(Nondrinkers)			1–149	150–299	300+	
Cohort I (aged 40–59)							
No. of cases (n = 244)	42		15	39	58	90	
Person-years	39,165		20,305	42,812	42,470	41,134	
Incidence rates[a]	104.7		78.7	91.8	135.2	226.4	
RR[b] (95% CI) (n = 240)	1.0 (reference)		0.8 (0.4–1.4)	0.9 (0.6–1.4)	1.2 (0.8–1.8)	2.0 (1.4–3.0)	<0.001
Cohort II (aged 40–69)							
No. of cases (n = 213)	8	40	10	46	50	59	
Person-years	5,817	30,939	12,483	33,277	30,500	31,196	
Incidence rates[a]	99.0	109.8	92.2	149.6	166.0	207.7	
RR[b] (95% CI) (n = 207)	0.9 (0.4–2.0)	1.0 (reference)	0.9 (0.4–1.9)	1.5 (0.9–2.3)	1.6 (1.1–2.5)	2.0 (1.3–3.0)	0.024

[a] Incidence rate (per 100,000 person-years) standardized by distribution of 5-year age groups at baseline in each cohort.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (never-, ex-, and current smokers), physical exercise (less than once a week and once a week or more), and 4 Public Health Center (PHC) areas in Cohort I or 5 PHC areas in Cohort II.

The PAF was estimated by $P_e(RR_a - 1)/RR_a$, where P_e was the prevalence of exposure among incident cases and RR_a was the adjusted RR. The 95% CI of the PAFs were estimated by the formula of Greenland (35). We estimated the PAFs of drinkers to nondrinkers, current and ex-smokers to never-smokers, and drinkers currently and formerly smoked to nondrinkers never smoked.

In women, RRs were estimated only in both cohorts combined, because of the few cases and noncases in drinkers and/or smokers, and the insufficient statistical power by each cohort.

Results

Age-standardized incidence rates increased among drinkers in both cohorts (Table 3). Drinkers consuming ≥300 g/week had a higher risk of colorectal cancer compared with nondrinkers in both cohort I (RR, 2.0; 95% CI, 1.4–3.0) and cohort II (RR, 2.0; 95% CI, 1.3–3.0). We observed linear positive trends of RR according to the level of alcohol consumption ($P < 0.001$ in cohort I and $P = 0.024$ in cohort II). The risk of ex-drinkers did not substantially differ from those of nondrinkers in cohort II.

The RR of invasive cancer for alcohol consumption showed the same trend as all of the cases of colorectal cancer (RR, 2.1 in all cases and 1.7 in invasive cancer for those consuming ≥300 g/week to nondrinkers; Table 4). The association with alcohol consumption was also shown in both colon and rectal cancer, as well as in all of the cases. Statistical significance in linear trends was consistent among all endpoints. The PAF% for alcohol consumption at least occasional drinking to nondrinking was 24% (95% CI, 8–38%) in all colorectal cancer (7% to 150–299 g/week and 17% to ≥300 g/week).

Meanwhile, the RRs of current smokers for colorectal cancer were 1.5 (95% CI, 0.9–2.1) in cohort I, 1.2 (95% CI, 0.8–1.8) in cohort II, and 1.4 (95% CI, 1.1–1.8) in two cohorts combined, compared with never-smokers (Table 5 shows only the combined results). The association did not change after exclusion of noninvasive cases and did not depend on the subsite. The nonsignificant linear trend was obtained according to smoking intensity except for rectal cancer. Furthermore, long-term smoking significantly elevated the risk compared with never-smoking: RR, 1.3 (95% CI, 0.7–2.2) for ≤25 years, 1.4 (0.9–2.2) for 25–29 years, 1.4 (0.99–2.1) for 30–34 years, and 1.5 (1.1–2.0) for ≥35 years. Smoking intensity in the remote past (before age 30 years) showed no dose-response relationship (data not shown). The PAF% for currently and formerly smoking to never-smoking was 22% (95% CI, 9–36%).

Next, we assessed the joint effect of alcohol consumption and smoking status in men (Table 6). Colorectal cancer risk for drinkers of ≥300 g/week of ethanol who smoked was estimated at 3.0 (95% CI, 1.8–5.1), compared with nondrinkers who never smoked. The association did not differ between colon and

Table 4 Relative risk (RR) and 95% confidence interval (CI) of colorectal cancer by the depth of tumor invasion and the site in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Nondrinkers	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for trend among drinkers
			1–149	150–299	300+	
Person-years	74,123	32,273	75,001	71,933	71,194	
Colorectal cancer[a] (n = 447)	87	24	83	107	146	
RR[b] (95% CI)	1.0 (reference)	0.8 (0.5–1.3)	1.1 (0.8–1.5)	1.4 (1.1–1.9)	2.1 (1.6–2.7)	<0.001
Invasive colorectal cancer (n = 298)	65	18	53	72	90	
RR[b] (95% CI)	1.0 (reference)	0.9 (0.5–1.5)	1.0 (0.7–1.5)	1.3 (0.9–1.9)	1.7 (1.2–2.4)	<0.001
Colon cancer[a] (n = 299)	62	16	51	71	99	
RR[b] (95% CI)	1.0 (reference)	0.8 (0.4–1.3)	1.0 (0.7–1.4)	1.3 (0.9–1.8)	1.9 (1.4–2.7)	<0.001
Rectal cancer[a] (n = 148)	25	8	32	36	47	
RR[b] (95% CI)	1.0 (reference)	1.0 (0.5–2.3)	1.6 (0.9–2.6)	1.7 (1.01–2.8)	2.4 (1.5–4.0)	0.015

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (never-, ex-, and current smokers), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

Table 5 Relative risk (RR) and 95% confidence interval (CI) for smoking status and intensity in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Never-smokers	Ex-smokers	Current smokers	(Pack-years)				*P* for trend among current smokers
			All	<20	20–29	30–39	40+	
Person-years	78,706	76,424	169,394	32,566	45,323	41,855	46,080	
Colorectal cancer[a] (*n* = 447)	78	124	245	33	50	73	83	
RR[b] (95% CI)	1.0 (reference)	1.3 (0.98–1.7)	1.4 (1.1–1.8)	1.1 (0.8–1.7)	1.3 (0.9–1.9)	1.4 (1.05–2.0)	1.4 (0.99–1.8)	0.47
Invasive colorectal cancer (*n* = 298)	50	85	163	23	32	43	60	
RR[b] (95% CI)	1.0 (reference)	1.5 (1.02–2.1)	1.6 (1.1–2.1)	1.3 (0.8–2.2)	1.4 (0.9–2.2)	1.4 (0.9–2.1)	1.6 (1.1–2.3)	0.64
Colon cancer[a] (*n* = 299)	53	86	160	17	31	55	54	
RR[b] (95% CI)	1.0 (reference)	1.4 (0.96–1.9)	1.4 (0.99–1.9)	0.9 (0.5–1.5)	1.2 (0.8–2.0)	1.7 (1.1–2.4)	1.3 (0.9–2.0)	0.16
Rectal cancer[a] (*n* = 148)	25	38	85	16	19	18	29	
RR[b] (95% CI)	1.0 (reference)	1.2 (0.7–2.0)	1.4 (0.9–2.3)	1.6 (0.9–3.0)	1.5 (0.8–2.7)	1.0 (0.6–1.9)	1.4 (0.8–2.3)	0.48

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), alcohol consumption (nondrinkers, occasional, 1–149 g, 150–299 g, and 300 g+), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

rectum. We detected no interaction between alcohol consumption and smoking status (*P* for interaction = 0.88 in colorectum, 0.75 in colon, and 0.44 in rectum). The PAF% for alcohol consumption and/or currently or formerly smoking was estimated at 46% (95% CI, 14–66%), compared with nondrinking and never-smoking.

Female regular drinkers had no elevated risk of colorectal cancer compared with nondrinkers (RR, 0.7; 95% CI, 0.4–1.1; Table 7). Occasional drinkers to nondrinkers were inversely associated with colorectal cancer (RR, 0.5; 95% CI, 0.3–0.9). Female ex- and current smokers had a nonsignificant increased risk of colorectal cancer, as well as male ex- and current smokers (RR, 1.3; 95% CI, 0.5–3.6 for ex-smokers; RR, 1.4; 95% CI, 0.8–2.4 for current smokers).

Discussion

Our results confirmed that alcohol consumption was positively associated with colorectal cancer in a Japanese population of middle-aged and elderly men. A clear linear trend of RR was observed among drinkers. However, the RR for 24 g/day increment of alcohol consumption did not substantially differ from the result of a previous meta-analysis (36), which estimated the pooled RR at 1.32 (against 1.11, 95% CI, 1.06–1.17 in the present study; data not shown in tables).

Female regular drinkers showed no increased risk of colorectal cancer. Eighty percent of them were categorized into the lowest group (1–149 g/week ethanol). In men, the lowest group of regular drinkers showed no significant risk of colorectal

Table 6 Relative risk (RR) and 95% confidence interval (CI) for alcohol consumption and smoking status in Japan Public Health Center-based Prospective Study Cohort I men (1990–1999) and Cohort II men (1993–1999) combined

	Nondrinkers	Occasional drinkers	Regular drinkers (g/week ethanol)			*P* for interaction
			1–149	150–299	300+	
Colorectal cancer[a] (*n* = 447)						
Never-smokers (*n* = 78)	17	8	20	15	18	0.88
RR[b] (95% CI)	1.0 (reference)	1.2 (0.5–2.8)	1.3 (0.7–2.5)	1.4 (0.7–2.9)	2.2 (1.1–4.3)	
Ex-smokers (*n* = 124)	30	6	20	28	40	
RR[b] (95% CI)	1.6 (0.9–3.0)	1.2 (0.5–3.1)	1.3 (0.7–2.5)	1.9 (1.04–3.5)	3.2 (1.8–5.7)	
Current smokers (*n* = 245)	40	10	43	64	88	
RR[b] (95% CI)	1.5 (0.8–2.6)	1.1 (0.5–2.4)	1.9 (1.1–3.4)	2.2 (1.3–3.8)	3.0 (1.8–5.1)	
Colon cancer[a] (*n* = 299)						
Never-smokers (*n* = 53)	11	5	12	13	12	0.75
RR[b] (95% CI)	1.0 (reference)	1.1 (0.4–3.3)	1.2 (0.5–2.7)	1.9 (0.8–4.2)	2.2 (0.97–5.0)	
Ex-smokers (*n* = 86)	21	3	11	21	30	
RR[b] (95% CI)	1.8 (0.9–3.7)	0.9 (0.3–3.3)	1.1 (0.5–2.6)	2.2 (1.04–4.5)	3.6 (1.8–7.3)	
Current smokers (*n* = 160)	30	8	28	37	57	
RR[b] (95% CI)	1.7 (0.9–3.4)	1.3 (0.5–3.3)	1.9 (0.96–3.9)	2.0 (1.01–3.9)	3.0 (1.6–5.7)	
Rectal cancer[a] (*n* = 148)						
Never-smokers (*n* = 25)	6	3	8	2	6	0.44
RR[b] (95% CI)	1.0 (reference)	1.3 (0.3–5.4)	1.6 (0.5–4.6)	0.6 (0.1–2.9)	2.3 (0.7–7.1)	
Ex-smokers (*n* = 38)	9	3	9	7	10	
RR[b] (95% CI)	1.4 (0.5–3.8)	1.8 (0.4–7.2)	1.7 (0.5–4.7)	1.4 (0.5–4.2)	2.4 (0.9–6.6)	
Current smokers (*n* = 85)	10	2	15	27	31	
RR[b] (95% CI)	1.0 (0.4–2.8)	0.6 (0.1–3.1)	1.9 (0.7–4.8)	2.7 (1.1–6.5)	3.1 (1.3–7.5)	

[a] Including noninvasive and invasive cancers.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

Table 7 Age-standardized incidence rate, multivariate-adjusted relative risk (RR) and 95% confidence interval (CI) of colorectal cancer by categories on alcohol consumption and smoking status in Cohort I women (1990–1999) and Cohort II (1993–1999) women combined

	Alcohol consumption			Smoking status		
	Nondrinkers	Occasional drinkers	Regular drinkers	Never-smokers	Ex-smokers	Current smokers
No. of cases (n = 259)	230	12	17	239	4	16
Person-years	300,634	38,181	37,706	350,470	5,209	20,841
Incidence rate[a]	76.3	40.2	52.9	69.9	78.4	91.0
RR[b] (95% CI) (n = 253)	1.0 (reference)	0.5 (0.3–0.9)	0.7 (0.4–1.1)	1.0 (reference)	1.3 (0.5–3.6)	1.4 (0.8–2.4)

[a] Incidence rate (per 100,000 person-years) standardized by distribution of 5-year age group at baseline in both cohorts.
[b] Adjusted for age (5-year groups), family history of colorectal cancer, body mass index (quartiles in each cohort), smoking status (when calculating RR for alcohol consumption; never-, ex-, and current smokers), alcohol consumption (when calculating RR for smoking status; non-, occasional, regular drinkers), physical exercise (less than once a week and once a week or more), and 9 Public Health Center areas.

cancer. Thus, female regular drinkers may not be associated with colorectal cancer because of the small proportion of heavy drinkers.

On the basis of our estimate, 24% of colorectal cancer was attributable to alcohol consumption in men. Because relatively heavy drinkers (≥150 g/week = ≥1.5 drinks/day) contribute to a large part of the PAF, a reduction in the number of such drinkers may lead to a decrease in colorectal cancer. To our knowledge, no reported prospective studies estimated the PAF of alcohol consumption in colorectal cancer. One case-control study evaluated the PAF as 19% (37).

One reason for the high PAF may be the high prevalence of heavy drinkers. Men in the highest categories who weekly consumed ≥300 g/week of ethanol (≥3 drinks/day) accounted for 22% in our study. In the case-control study estimating the PAF (37), drinkers consuming only ≥0.7 drinks/day accounted for 33% of male controls. Moreover, based on calculation of the published numbers, in other cohort studies, the highest consumers either took at most "2 drinks/day or more" or accounted for a smaller percentage: 14% of subjects consumed ≥2.5 drinks/day in a Netherlands study (5); men accounted for 14% of person-years consuming ≥2 drinks/day in a Health Professionals Follow-up Study (6); 21% of subjects consumed ≥2 drinks/day in a Hawaiian-Japanese study (8); and only 8.7% of subjects consumed ≥3 drinks/day in a United States study (38).

Another reason may be the different distribution of the genetic polymorphisms on alcohol-related enzymes including *ALDH2* in Japanese, although we have not investigated the genetic polymorphisms in our subjects. The *ALDH2* genotypes with the atypical allele (Glu487Lys) [frequency: 0.28 in Japanese (13) *versus* <0.03 in Caucasian (39)] exert little ALDH2 activity (40) and cause a high acetaldehyde levels in blood (15). Although acetaldehyde has not been concluded to be a human colorectal carcinogen, some *in vitro* and animal studies suggest that acetaldehyde triggers carcinogenesis in the colorectum (41–43) via folate deficiency (44, 45). However, because the magnitude of RR in our study population was not higher than that of a pooled one as mentioned above (36), the effect of such genetic susceptibility may be limited.

Current and ex-smokers had an increased risk of colorectal cancer in men and women. The risk showed a nonsignificant linear trend according to smoking intensity in men. We also confirmed that the long-term smoking elevated the risk in men. Smoking intensity before age 30 years, however, failed to show the dose-response relationship seen in a previous study (19), possibly due to estimating the remote past pack-years using current numbers of cigarettes smoked per day.

Recent prospective studies consistently reported a positive association of smoking adjusted for potential confounding factors (17, 18), especially when accounting for the long induction period (19, 20). In addition, tobacco smoke includes various carcinogens such as polynuclear aromatic hydrocarbons and *N*-nitrosamines. These carcinogens in tobacco smoke are reasonable risks for colorectal carcinogenesis (46, 47). As mentioned in a recent review regarding the causality (16), evidence has been sufficiently accumulated to add colorectal cancer to the list of tobacco-associated malignancies. In the present study of a Japanese population, we could attribute 22% of colorectal cancer to currently and formerly smoking. In the Health Professionals Follow-up Study, smoking was responsible for 21% of the incidence of this cancer (19). The Cancer Prevention Study II reported that 12% of colorectal cancer deaths were attributable to smoking (21). Therefore, we can expect to reduce a large part of colorectal cancer by eliminating tobacco consumption, especially in the population with the high prevalence of smoking.

Many previous studies have defined invasive adenocarcinoma as "colorectal cancer." However, in our opinion, "colorectal cancer" should be defined as not only invasive adenocarcinoma but also noninvasive adenocarcinoma. Thus, we needed to confirm that our definition is comparable with the Western definition. As a result, the RR of all cases (including the noninvasive type) approximately corresponded to those of only the invasive type. However, 2 case-control studies showed that pack-years as smoking intensity was associated significantly with the noninvasive type rather than the invasive type (48, 49). Additional studies will be needed to determine whether or not the association of some risk factors differs in terms of these two definitions.

The major strengths of our study include its prospective design, a general population with a high response rate (80%), and the relatively low proportion of subjects lost to follow-up (0.04%). Information on alcohol consumption and smoking was collected before any subsequent diagnosis of colorectal cancer, thus avoiding the exposure recall bias inherent in case-control studies. The findings of this study can be generalized to middle-aged and elderly Japanese men, because the study subjects were selected from the general population, and there was a high response rate. Moreover, two cohorts starting at different times produced the same results.

The adjustment for the frequencies of food intake did not change the RR estimates of alcohol consumption and smoking status (data not shown). In addition, recent prospective studies have reported the weak association of fruits and vegetables (50), and meats (51). Thus, no food variables were used in the final multivariate model. However, we could not examine whether or not some nutrients, such as folate and methionine (6), affected the association of alcohol consumption and smoking status because of the inavailability of these nutrients.

In conclusion, alcohol consumption dose-dependently in-

creased the risk of colorectal cancer in men. Smoking was also associated significantly with colorectal cancer in men and not significantly in women. From the risk estimates, 46% of colorectal cancer is attributable to alcohol consumption and smoking in middle-aged and elderly Japanese men.

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