data; 111, 1222 nM), 139 mM for daidzein (40, 477 nM), and 55 nM for equol for equol producers (16, 187 nM). Figure 1 shows the relationship between serum concentrations of these phytoestrogens and food intake, and Table 1 shows the parameters of association (r_s, b). Tofu intake was significantly associated with serum concentrations of genistein and daidzein (coefficients of determination (R^2) = 0.081 and 0.082, respectively). Intake of miso soup was almost significantly associated with daidzein concentration. Multivariate regression modeling with tofu and miso soup intake slightly reduced the R^2 for genistein (0.065) and daidzein (0.074). Intake of boiled beans was not associated with serum concentrations of either. In determining the relationship between dietary intake and equol concentration, we calculated r_s for all subjects and limited b to equol-producers. We found that serum concentration of equol was associated with intake of tofu among all subjects.

Serum genistein and daidzein concentrations were strongly correlated (r = 0.91, p = 0.0001, Figure 2). Serum daidzein and equol concentrations among equol producers were moderately correlated (r = 0.40, p = 0.0001, Figure 3). Among the 113 equol producers, the geometric mean concentrations of daidzein were 142 nM for equol-producers (n = 113) and 137 nM for nonequol-producers (n = 38), and they did not differ (p = 0.90). Foods consumed significantly by equol-producers than by nonequol-producers included pork (p = 0.0014 by Wilcoxon's test), margarine (p = 0.019), Chinese cabbage (p = 0.034), and tofu (p = 0.037), and nearly significant for milk (p = 0.051), *Kamaboko* (p = 0.099), and seaweed (p = 0.056).

Foods showing a significant association with serum equol concentration after adjustment for serum daidzein concentration included pork, butter, margarine, cheese, coffee, ham, and seaweeds, and nearly significant for tofu, potatoes, and milk. Those Spearman's partial correlation coefficients are listed in Table 2.

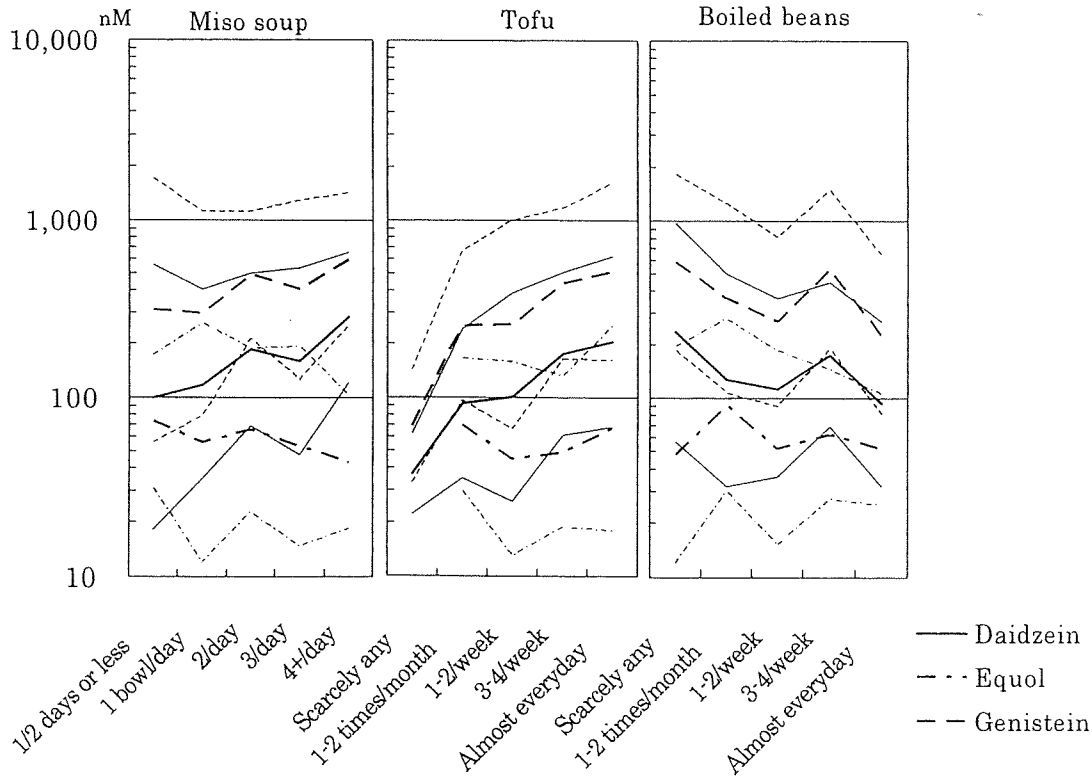

Figure 1. Association of food intake and serum phytoestrogen concentrations.
Bold lines show the geometric means of each category of food intake. Thin lines show the mean ± SD of log-transformed data.

Table 1. Spearman's correlation coefficients and regression coefficients of food intake for phytoestrogens.

	Genistein		Daidzein		Equol †	
Food item	Spearman's correlation coefficient	Regression coefficient	Spearman's correlation coefficient	Regression coefficient	Spearman's correlation coefficient	Regression coefficient
Miso-soup	0.09	0.14	0.16+	0.19+	0.03	-0.07
Tofu	0.30**	0.34**	0.27**	0.35**	0.21 *	0.12
Boiled beans	-0.11	-0.11	-0.12	-0.11	-0.04	-0.07

+ : p<0.1, *: p<0.05, **: p<0.01.

†: Spearman's correlation coefficient was calculated for all subjects, and regression coefficient was limited to equol-producers.

DISCUSSION

This study was primarily designed to validate the food frequency questionnaire and serum concentrations of phytoestrogens in the nested case-control study as a part of the JACC Study.[4] Controls of the nested case-control study were thought to represent the general population of the JACC study, and adequate to the sample set of this study. However, additional discussion such as about equol producing may be limited; e.g., most subjects of the JACC Study lived in rural areas, where dietary habits may be different from those in urban areas; subjects who donated blood samples were around 30% of whole respondents to the baseline questionnaire survey, therefore, they may be more health-conscious.

Quantitative stability of phytoestrogens during long-term storage at -80℃ is not established, so we assumed it from the viewpoint of molecular structure of isoflavones. Ranges of those serum levels in this study were comparable to those found in previous studies in Japan.[5,7,9]

We have shown here that serum concentrations of genistein and daidzein were each associated with dietary tofu intake, and slightly associated with miso soup intake. Genistein and daidzein are contained mainly in soybeans, the main ingredients of tofu and miso soup. Dietary habits of tofu and miso soup intake can be clearly evaluated in the general population, such as in the male subjects of this study, thus showing clear associations. The dietary category of boiled beans includes beans other than soybeans, and it may be difficult for study subjects to evaluate their intake of this food. We were therefore unable to determine an association between dietary intake of boiled beans and serum concentrations of phytoestrogens. Natto (fermented soybeans), one of the main foods containing soybeans in Japan, was not listed in the baseline survey questionnaire.

It is meaningful that an association was shown between long-term intake of soybean products and the concentrations of genistein and daidzein in a one-point serum sample despite the short half-lives of these phytoestrogens (6-8 hrs).[5] Frequent intake of phytoestrogen-rich foods may be required to maintain their blood concentration. An unusually large intake of these foods prior to taking a blood sample may result in unusually high blood concentrations of phytoestrogens, whereas abstention from these foods for long periods of time may result in unusually low blood concentrations of phytoestrogens. Our results show that these events were not frequent enough to diminish the association between dietary intake and phytoestrogen concentration, suggesting that dietary intake of these foods is stable. The absence of natto from the list of foods, however, may explain, at least in part, the low validity of association observed in this study.

Validity studies of serum phytoestrogen concentrations with respect to food intake have been scarce in Japan. One study reported that Spearman's correlation coefficients of serum daidzein concentration with dietary intake of natto, miso, and tofu ranged from 0.19 to 0.23, whereas the correlation coefficient of

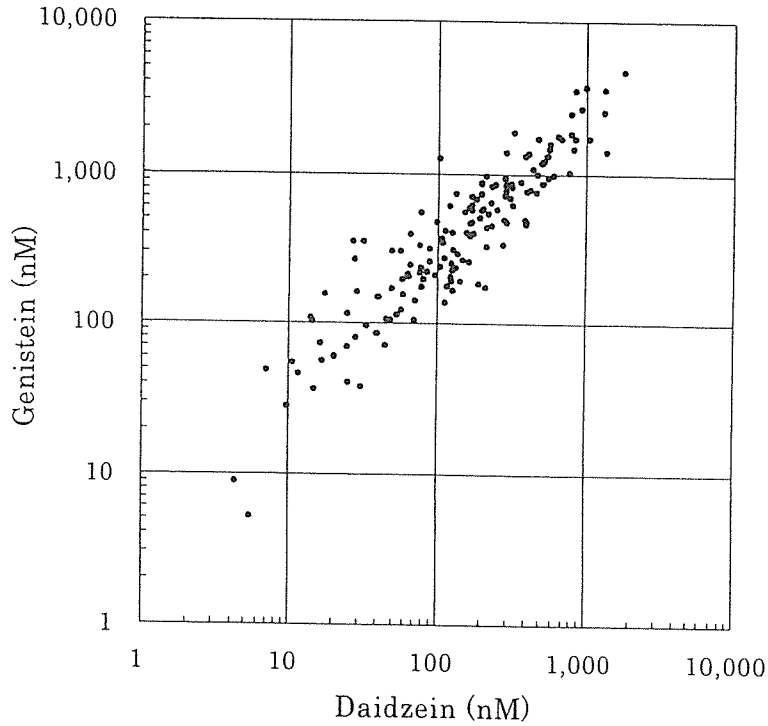

Figure 2. Correlation between serum daidzein and genistein concentrations.

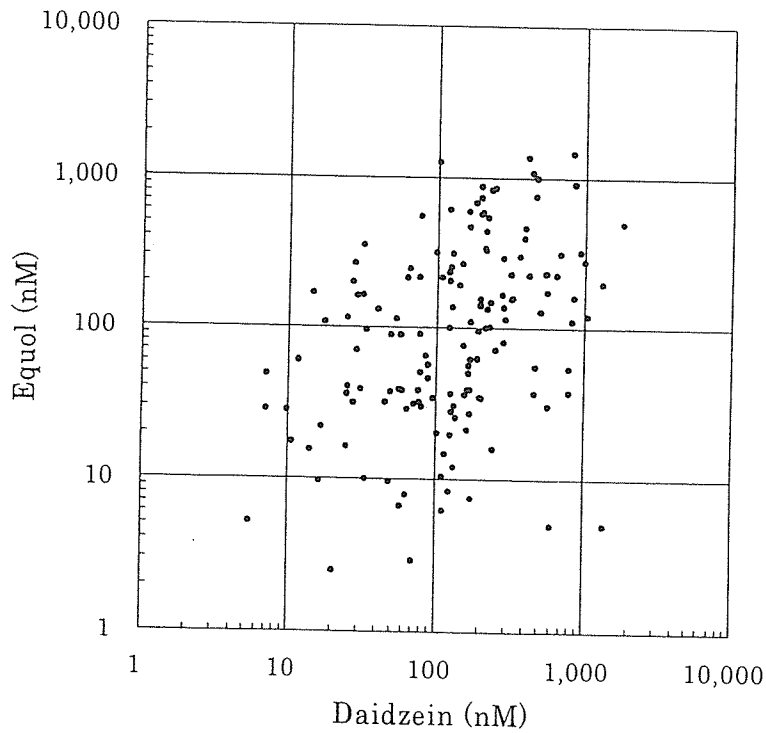

Figure 3. Correlation between serum daidzein and equol concentrations among equol-producers.

Table 2. Spearman's partial correlation coefficients between serum equol concentration and frequency of food intake adjusted for serum daidzein concentration.

Food	Spearman's partial correlation coefficients
Pork	0.34 **
Butter	0.31 **
Margarine	0.29 **
Cheese	0.29 **
Coffee	0.19 *
Ham	0.18 *
Seaweeds	0.17 *
Tofu	0.17 +
Potatoes	0.15 +
Milk	0.14 +

+: $p<0.1$, *: $p<0.05$, **: $p<0.01$.
Food list is arranged in order of p value.

serum daidzein concentration with daidzein intake estimated from dietary records was 0.37 and with daidzein intake estimated by a food frequency questionnaire was 0.26.[7] Our results were quite consistent with these earlier findings.

Equol is produced by intestinal microflora and absorbed.[2] We observed no differences in serum daidzein concentrations between equol-producers and nonequol-producers, suggesting that the ability to produce equol did not depend on daidzein intake. Among equol-producers, we did observe a slight dependence of serum equol concentration on serum daidzein concentration. Equol excretion has been reported to correlate positively with the intake of total fat and meat, and the fat-fiber ratio,[2,8] suggesting that consumption of more fat and meat creates a colonic environment capable of sustaining equol-producing microflora. It is also possible, however, that equol is contained in the meat of animals consuming soy-, alfalfa-, or clover-supplemented feed.[2] Our results indicate that consumption of fat and meat is associated with serum equol concentrations. Among Japanese people, who have a lower fat and meat intake than Western people, the effect of fat and meat on serum equol concentration may be clearer.

Coffee consumption was also correlated with serum equol concentration, although intake of other beverages, including various teas, did not show this association. The correlation between coffee consumption and serum equol concentration was still observed after adjustment for intake of pork, cheese, and butter (r_s = 0.21, p = 0.078). Residual confounding should be considered. That is, coffee consumption may be associated with a Western diet, which involves the consumption of more fat and meat than a Japanese diet. Another Japanese study showed that green tea consumption was higher among equol-producers than nonequol-producers, but the two groups showed no differences in coffee and tea consumption.[9] Our study, however, did not show this relationship (r_s = -0.11, p = 0.22 for Japanese tea).

When we examined the difference in food intake between equol-producers and nonequol-producers, we found that equol producers consumed significantly higher quantities of some foods, including pork, margarine, Chinese cabbage, and tofu. This was similar to the results of correlation analysis. We regard the latter as more valid because it took serum equol concentration into account when considering serum daidzein concentration.

In conclusion, we have shown here that serum genistein and daidzein concentrations were significantly associated with dietary intake of tofu, and slightly with intake of miso soup. Therefore, food frequency questionnaire for soy bean products and serum phytoestrogen concentrations seemed to be valid in the JACC Study. Consumption of fat, meat, and coffee may be associated with equol production by intestinal microflora in the sample set of this study.

MEMBER LIST OF THE JACC STUDY GROUP

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Colorectal Cancer and Serum C-reactive Protein Levels: a Case-control Study Nested in the JACC Study

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BACKGROUND: Recently, it has been hypothesized that inflammation increases the risk of colorectal cancer. We investigated whether serum levels of C-reactive protein (CRP), a biomarker of inflammation, are associated with colorectal cancer, using serum samples collected in the Japan Collaborative Cohort Study (JACC Study).

METHODS: We conducted a nested case-control study in the JACC Study, investigating the relationship between the risk for colorectal cancer and serum levels of CRP determined by a high-sensitivity CRP enzyme immunoassay. The subjects recruited were 141 patients with colorectal cancer (63 males and 78 females) and 327 controls with no history of cancer (148 males and 179 females). Each case of colorectal cancer was matched for sex, age and participating institution to 2 or 3 controls. We used t-test to analyze mean differences in CRP levels between colorectal cancer cases and controls. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using a conditional logistic regression model after adjusting for the potential confounding factors.

RESULTS: Serum CRP levels were not clearly associated with the risk of colorectal cancer. The OR of the highest serum CRP levels was 1.18 (95% CI: 0.68-2.06) for colorectal cancer and 1.42 (95% CI: 0.73-2.74) for colon cancer, compared to subjects with lowest serum levels. The OR for incidence of colorectal cancer showed a similar trend, but the difference was not significant. Thus, high serum CRP levels did not appear to increase the risk of colorectal cancer.

CONCLUSIONS: The present results suggest that high serum CRP levels are not associated with the risk of colorectal cancer in the JACC Study.

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Key words: C-Reactive Protein, Colorectal Neoplasms, Odds Ratio, nested case-control studies.

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Recently, the incidence of colorectal cancer, which is closely related to lifestyle factors, such as diet, exercise, smoking, and alcohol consumption, has increased for both sexes.[1-3] Consistent with the hypothesis that inflammation increases the risk of colon cancer,[4,5] administration of aspirin or non-steroidal anti-inflammatory drugs, has been shown to decrease the risk of colorectal cancer.[6,7] Also, it has been reported that serum levels of C-reactive protein (CRP), which is associated with inflammation and synthesized by hepatocytes during acute inflammation,[8,9] are elevated in persons who subsequently develop colon cancer.[10,11]

There have been no previous reports of the relationship between high serum CRP levels and the risk for colorectal cancer in a population-based cohort study of Japanese. In the present study, we used sera from the Japan Collaborative Cohort (JACC) Study to investigate whether high serum CRP levels are associated with the risk of colorectal cancer in Japanese.

METHODS

Subjects

The subjects in the JACC Study were 110,792 residents of 45 districts of Japan, ranging in age from 40 to 79 years.[12] The colorectal cancer cases were defined as incident or deceased (International Statistical Classification of Diseases and Related Health Problem 10th Revision: C18, C19, and C20). Incident cases were recruited from 24 participating institutions: in 21 participating institutions, cases were followed-up from baseline to the end of 1997; in the other 3 participating institutions, cases were followed-up from baseline to the end of 1994, 1995, and 1996, respectively. Dead subjects were enrolled from 45 participating institutions, and were followed-up from baseline to the end of 1999.

Peripheral blood samples were collected from 39,242 subjects (about 35% of respondents to the questionnaire survey) and stored in deep freezers at about -80℃ for 13 to 15 years. During follow-up, 76 deaths from colorectal cancer (50 colon and 26 rectum) and 185 incident cases of colorectal cancer (123 colon and 62 rectum) were identified among subjects who had provided serum samples at baseline; 25 of those subjects (23 cases with history of any cancer and 2 cases with lacking a serum sample) were excluded from this study. For each case of colorectal cancer, 2 or 3 controls were matched for sex, age (as near as possible), and participating institution from among the surviving subjects without incident cancer or history of cancer. The study subjects were 141 colorectal patients (63 males and 78 females) and 327 controls (148 males and 179 females); i.e., out of an initial enrollment of 236 cancer cases and 661 controls, we excluded 95 cases and 218 controls who lacked sufficient serum volume for CRP determination, and we exclude 116 controls who were not suitably matched to patients for sex, age and participating institution. The cases and controls had similar sex distributions, and the age distribution was narrower for subjects aged from 40 to 49 years than for the other age group (Table 1). Colorectal cancer cases and controls also had similar distributions of smoking and alcohol consumption.

Informed consent for participation was obtained individually from study subjects, with the exception of participating institutions with few participants, in which case informed consent was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. The Ethics Committees of Medical Care and Research of Fujita Health University and Nagoya University School of Medicine approved the protocol of this study.

Table 1. Baseline chracteristics of cases of colorectal cancer and controls.

Item		Cases (%)	Controls (%)
Number		141 (100)	327 (100)
Sex	Males	63 (44.7)	148 (44.3)
	Females	78 (55.4)	179 (54.7)
Age (year)	40-49	12 (8.5)	29 (8.9)
	50-59	44 (31.2)	117 (35.8)
	60-69	60 (42.6)	128 (39.1)
	70-79	25 (17.7)	53 (16.2)
Smoking habit	Current smoker	30 (21.3)	79 (24.2)
	Former smoker	21 (14.9)	43 (13.1)
	Never smoker	83 (58.9)	182 (55.7)
	Unknown	7 (5.0)	23 (7.0)
Alcohol consumption	Current drinker	67 (47.5)	144 (44.0)
	Former drinker	1 (0.7)	9 (2.8)
	Never drinker	68 (48.2)	191 (58.4)
	Unknown	5 (3.5)	13 (4.0)

Methods

Serum CRP levels were determined by enzyme immunoassay, using a high-sensitivity C-reactive protein enzyme immunoassay test kit (Diagnostic Automation Inc., Calabasas, CA, USA).[13] Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. All statistical analyses were performed using the Statistical Analysis System® package. Geometric mean differences in serum CRP levels between cases and controls were examined using *t*-tests. Odds ratios (ORs) and their 95% confidence intervals (CIs) for colorectal cancer were calculated using a conditional logistic regression model. The ORs were computed to categorize cases according to the tertiles of serum CRP levels in the controls. Previous findings suggest that serum CRP levels are affected by daily smoking, daily alcohol consumption, and BMI.[13] In the present study, we considered the potential confounding effects of smoking (never, former, or current smoker or unknown), alcohol consumption (never, former, current drinker or unknown), and BMI (continuous variable). To test for linear trends in OR over tertiles, each tertile was coded as 0, 1, or 2 and was then incorporated into conditional logistic regression models as a single variable. Two-side probabilities less than 0.05 were considered to indicate statistical significance.

RESULTS

Geometric mean values of serum CRP levels did not significantly differ between colorectal cancer cases (0.43 mg/L; ranges of 25% and 75%: 0.20-110mg/L, n = 141) and controls (0.45 mg/L; ranges: 0.20-1.03mg/L, n = 327), and also did not significantly differ between incident cases (0.37mg/L; ranges: 0.20-1.05mg/L, n = 104) and controls (0.45mg/L; ranges: 0.19-1.03 mg/L, n = 251). There was no clear association between serum CRP levels and the risk of colorectal cancer. In addition, geometric mean serum CRP levels of colon cancer cases (0.49mg/L, ranges: 0.20-1.05 mg/L, n = 101) were nearly equal to those for controls (0.49 mg/L, ranges: 0.23-1.00 mg/L, n = 237). The OR of the highest serum CRP levels for colorectal cancer was 1.07 (95% CI: 0.64-1.78), compared to the subjects with the lowest serum levels (Table 2). Also, the OR of the highest serum CRP levels was 1.18 (95% CI: 0.68-2.06) after adjusting for additional confounding factors, compared to the subjects with the lowest serum levels. The OR of the highest serum CRP levels for incident cases of colorectal cancer was 0.97 (95% CI: 0.51-1.83) after adjusting for the confounding factors, compared to the subjects with the lowest serum levels. In addition, the OR of the highest serum CRP levels was 1.42 (95% CI: 0.73-2.74) for colon cancer cases or 0.90 (95% CI: 0.30-2.30) for rectal cancer cases, compared to the lowest serum levels, but the difference was not significant. Higher serum CRP levels were not apparently associated with higher risk for colorectal cancer.

Table 2. Odds ratio (OR) and 95% confidence interval (CI) for colorectal cancer risk by serum C-reactive protein (CRP) level for the nested case-control study in the JACC Study.

Study cases	Ranks for serum CRP level	Ranges (mg/L)	No. Cases	No. Controls	Crude OR	Crude 95% CI	Crude p for trend	Adjusted* OR	Adjusted* 95% CI	Adjusted* p for trend
Overall for colorectal cancer	T1 (lowest)	- 0.26	47	110	1.00	(reference)		1.00	(reference)	
	T2	0.27 - 0.80	46	107	1.00	0.60-1.66		1.13	0.66-1.94	
	T3 (highest)	0.81 -	48	110	1.07	0.64-1.78	0.80	1.18	0.68-2.06	0.57
Incidence for colorectal cancer	T1 (lowest)	- 0.26	37	84	1.00	(reference)		1.00	(reference)	
	T2	0.27 - 0.80	35	84	0.93	0.52-1.65		1.05	0.57-1.94	
	T3 (highest)	0.81 -	32	83	0.91	0.50-1.66	0.77	0.97	0.51-1.83	0.98
Overall for colon cancer	T1 (lowest)	- 0.26	34	79	1.00	(reference)		1.00	(reference)	
	T2	0.27 - 0.80	30	78	0.90	0.50-1.62		1.09	0.57-2.07	
	T3 (highest)	0.81 -	37	80	1.16	0.64-2.08	0.61	1.42	0.73-2.74	0.29

*: Adjusted for smoking and alcohol consumption, and body mass index.

DISCUSSION

The JACC Study for Evaluation of Cancer Risk, sponsored by the Ministry of Education, Science, Sports, and Culture of Japan (Monbusho), was conducted to collect information from 110,792 subjects and sera from 39,242 subjects, aged from 40 to 79 years, in 45 districts of Japan from 1988 to 1990.[12] In the present study, we investigated effects of serum CRP, which is a biomarker of inflammation and has recently been suggested to play a role in risk of colorectal cancer, using sera collected in the JACC Study. It has previously been shown that CRP is an acute phase protein that is produced as the result of activity of interleukin-6 (IL-6), IL-8, and tumour necrosis factors (TNF).[8,14,15] Prostaglandins including prostaglandin E_2 (PGE_2) are synthesized in an arachidonic acid cascade initiated by cycloxygenase-2 (COX-2) enzyme, production of which is induced by inflammation.[15,16] As levels of CRP have been shown to reliably predict cardiovascular events,[17] and CRP and IL-6 have been shown to be associated with total and non-cardiovascular mortality,[18-20] it has also been hypothesized in the review that inflammation can increase the risk of cancer.[21] Recently, it has been reported that plasma CRP concentrations are elevated in subjects who subsequently developed and curative resection of colorectal cancer [5,10,11,22] and that PGE_2 levels appear to serve as a predictor of tumor recurrence in-patients with colorectal cancer.[23] Moreover, evidence indicates that the selective effects of PGE_2 consist of inhibiting secretion of IL-2, TNF-β and interferon gamma (IFN-γ) by helper T-1 (Th1) cells, and inhibiting secretion of IL-3 without affecting the secretion of IL-4 and IL-5 by helper T-2 (Th2) cells.[15]

It has been reported that the geometric mean values of plasma CRP concentrations were significantly higher for 172 colorectal incident cases (2.49mg/L) than for 342 controls (1.96mg/L; $p = 0.01$).[5] Although the assay for serum CRP determination was different from that of the present study, serum CRP levels were not significantly higher for colorectal cancer cases than for controls. This is similar to the present findings for colon cancer cases, which the odds ratio of the highest serum CRP levels was 1.4 for colon cancer and 0.9 for rectal cancer, compared to the subjects with the lowest serum CRP levels. Higher serum CRP levels were not clearly associated with increased risk of colorectal or colon cancer.

As serum CRP levels have previously been shown to be associated with acute inflammation,[8,9,11,22] the present lack of positive associations between higher serum CRP levels and increased risk of colorectal cancer may be due in part to the population-based method used in the present follow-up study. In addition, this lack of positive association may be due to sampling bias of serum CRP levels caused by the differences in serum treatment among the 45 study districts of the JACC Study. The present findings also differ from those of exactly matched case-control study, possibly due to the limited number of analytical cases at each participating institution, because of the high frequency of serum sample volumes that are inadequate for serum CRP measurement and the impossibility of creating matched case-control pairs at all participating institution. Also, the present data suggests that incidence cases of colorectal cancer have a slightly different trend in odds ratio from that of the overall colorectal cancer cases. Further studies, in which a distinction is made between incident cases of colorectal cancer and death from colorectal cancer, are needed to clarify the relationship between high serum CRP levels and the risk for colorectal cancer.

MEMBER LIST OF THE JACC STUDY GROUP

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Glucose Intolerance and Colorectal Cancer Risk in a Nested Case-Control Study among Japanese People

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BACKGROUND: Glucose intolerance may increase the risk of developing colorectal cancer.
METHODS: In a sero-epidemiological nested case-control study, conducted as part of the Japan Collaborative Cohort Study (JACC Study) for Evaluation of Cancer Risk, we measured serum glycoalbumin in 123 patients with colorectal cancer and 279 controls. Conditional logistic regression was used to evaluate the risk of colorectal cancer.
RESULTS: There were trends towards an association between high levels of glycoalbumin and an increased risk of colorectal cancer in men (odds ratio [OR] = 2.39; 95% confidence interval [CI]; 0.89-6.36) and between high levels of glycoalbumin and a decreased risk of colorectal cancer in women (OR = 0.41; 95% CI, 0.14-1.04).
CONCLUSIONS: A high level of glycoalbumin may increase the risk of colorectal cancer in men. The finding that high levels of glycoalbumin in women decreased their risk of colorectal cancer was inconsistent with previous reports, and may have been the result of limitations in the procedure in selecting samples and statistical power.
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Key words: Glucose Intolerance, glycoalbumin, Colorectal Neoplasms, Cohort Studies, Epidemiology.

Glucose intolerance or an elevated serum concentration of insulin is thought to be a risk factor for the development of colorectal cancer.[1-7] This association is based on the hypothesis that hyperinsulinemia promotes colon carcinogenesis.[1] In vitro, insulin acts as a growth factor for colonic epithelial cells and a mitogen for tumor cell growth.[1] The incidence rates of glucose intolerance and diabetes mellitus are increasing in Japan, and this, together with increased fat intake and sedentary working conditions, may be associated with the recently observed increase in the incidence of colorectal cancer and death from this disease in Japan. However, no prospective epidemiological study of the association between these biomarkers and colon cancer risk has been performed in the general population in Japan.

To determine the association between glucose intolerance and colorectal cancer in Japan, we carried out a nested case-control study using stored sera from the Japan Collaborative Cohort

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Study (JACC Study) for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho).

METHODS

The general aspects of the study population, procedures for conducting the baseline survey using a self-administered questionnaire, collecting serum samples, and following-up in the JACC study have been described previously.[8] Diagnosis of colorectal cancer was defined by codes C18, C19, and C20, in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.[9] Subjects were followed until the end of 1999 for death in all 45 study areas and until the end of 1997 for incidence in the 24 study areas in which incident cases were surveyed using a cancer registry, but follow-up was censored earlier in some areas.

We identified 220 incidents or deaths from colorectal cancer in the study subjects who donated serum samples, who did not have colorectal cancer and who were not being treated for diabetes mellitus at the time of the baseline survey. For each of these 220 patients, we randomly selected two or three control individuals, matched for study area, sex and age, from the study subjects who remained alive and cancer free (602 controls). We could not measure serum glycoalbumin in all eligible cases and controls due to a lack of sufficient volume of serum from some of the subjects. Consequently, glycoalbumin was measured in 117 cases and 263 controls (samples from 51 subjects who died from colon cancer originated from all study areas and samples from 91 who died from or were diagnosed with colorectal cancer were from the 24 above-described study areas). The procedure used in this study to select the measured samples for glycoalbumin among primarily detected cases of colorectal cancer was not as stringent as that used in regular epidemiological studies, and the statistical power was limited by an insufficient number of samples, limiting the interpretation of the results of this analysis.

Serum concentrations of glycoalbumin were determined in 2003 using autoanalyzers (JCA-BM12, JEOL Ltd., Akishima, Japan) at SRL laboratory (Hachioji, Japan), with those performing the measurement blinded to the case-control status of samples. The coefficient of variance was 0.5-0.8% for glycoalbumin. Fasting status at the time of blood donation was not recorded.

The difference in means between cases and controls was examined by t-test, and that in proportion was examined by chi-square test. The risk of colorectal cancer was evaluated by odds ratios (ORs) and 95% confidence intervals (CIs) estimated in the conditional logistic model. The ORs were computed according to tertiles of assayed substances among controls by sex. ORs were further adjusted for potential confounders such as serum total cholesterol, body mass index (BMI), walking habits in daily life, and history of diabetes mellitus. Linear trends of ORs were examined using the medians of tertiles in the conditional logistic model. Calculations were conducted using SAS® software (SAS Institute, Cary, NC) in the Academic Center for Computing and Media Studies, Kyoto University.

Individual written or oral consent, or consent from community representatives, was obtained, or a poster notification/opting-out system was applied.[8] The Ethical Boards of Nagoya University School of Medicine and Fujita Health University approved this study.

RESULTS

The mean ± standard deviation ages at baseline were 60.8 ± 8.4 years of age in male cancer cases, 60.0 ± 8.4 years in male controls, 61.1 ± 7.4 years in female cancer cases, and 60.7 ± 7.1 years in female controls. The distributions of serum glycoalbumin and total cholesterol concentrations, as well as BMI, are shown in Table 1. The mean concentrations of those substances did not differ between cases and controls. The distributions of walking habits in daily life and history of diabetes mellitus are shown in Table 2.

Table 3 shows the ORs and 95% CIs of colorectal cancer adjusted for matching variables - sex, age, and study area. High levels of glycoalbumin showed a trend towards association with an increased risk of colorectal cancer in men (OR = 2.39, p=0.081

Table 1. Distribution of measured variables.

		Cases		Controls		
		No.	Median (25, 75 percentile)	No.	Median (25, 75 percentile)	p
Males						
Glycoalbumin	%	58	15.9 (14.5, 17.8)	133	15.5 (14.2, 17.4)	0.58
Total cholesterol	mg/dL	58	193 (170, 215)	133	189 (163, 206)	0.29
Body mass index		58	22.6 (20.9, 24.6)	133	22.7 (21.2, 24.8)	0.75
Females						
Glycoalbumin	%	59	15.4 (14.3, 16.8)	130	15.7 (15.0, 16.9)	0.33
Total cholesterol	mg/dL	59	201 (181, 240)	130	209 (186, 227)	0.77
Body mass index		59	23.7 (21.6, 25.7)	130	23.0 (21.4, 25.5)	0.42

P values were examined by t-test.

Table 2. Distribution of other potential confounding factors.

	Males			Females		
	Case	Control	p	Case	Control	p
Walking habit in daily life (/day)						
One hour or more	24	46		27	53	
30 minites to 1 hr	7	16		11	14	
Around 30 min	5	12		4	19	
Almost none	4	10	0.72	4	15	0.16
History of diabetes mellitus						
Yes	2	7		2	4	
No	54	122	0.59	48	122	0.78

P values were examined by chi-square test.
Data from subjects who did not respond or who were ineligible are not shown.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of glycoalbumin.

	Males					Females				
	Category	Cases/ controls	OR	95% CI	p	Category	Cases/ controls	OR	95% CI	p
Colon and rectum (C18,C19,C20)	<14.6 (%)	15 47	1.00	0.66, 3.75	0.30	<15.2 (%)	27 47	1.00	0.40, 1.77	0.65
	14.6-16.2	18 46	1.57	0.89, 6.36	0.081	15.2-16.5	17 37	0.84	0.16, 1.04	0.060
	16.2+	25 25	2.39	Trend p=0.088		16.5+	15 46	0.41	Trend p=0.061	
Colon (C18)	<14.7 (%)	9 31	1.00	0.58, 5.36	0.31	<15.1 (%)	21 34	1.00	0.19, 1.28	0.15
	14.7-16.3	14 33	1.77	0.88, 10.3	0.076	15.1-16.3	10 33	0.50	0.26, 1.58	0.34
	16.3+	18 32	3.03	Trend p=0.082		16.3+	15 35	0.64	Trend p=0.28	
Rectum (C19,C20)	<14.5 (%)	6 13	1.00	0.20, 3.18	0.76	<15.6 (%)	7 11	1.00	0.14, 3.90	0.73
	14.5-16.2	5 15	0.81	0.19, 7.37	0.83	15.6-20.2	5 9	0.53	0.01, 1.64	0.11
	16.2+	7 13	1.21	Trend p=0.85		20.2+	1 10	0.28	Trend p=0.11	

for the highest tertile). The association seemed to be stronger for cancer of the colon than of the rectum, although both sites had a similar tendency. In contrast, high levels of glycoalbumin showed a trend towards association with a decreased risk of colorectal cancer in women (OR = 0.41, p=0.060 for the highest tertile). This tendency was similar for both colon and rectal cancer. Classified analyses by incidence of colon cancer and colon cancer deaths showed similar results (data not shown).

Adjusting for total cholesterol, BMI, or walking habits in daily life did not substantially change the OR in either sex. Adjusting for history of diabetes mellitus slightly enhanced the association between glycoalbumin level and risk of colorectal cancer (OR = 0.39; 95% CI, 0.15-1.02) in females, but had little effect in males.

DISCUSSION

Glycosylated protein levels reflect average glucose concentrations during a period that depends on the half-life of the protein. Glycoalbumin concentration is thought to reflect the average blood glucose concentration in the previous 1 to 2 weeks (half life=approximately 14 days), whereas glycohemoglobin A1c (HbA1c) concentration is thought to reflect average blood glucose concentration during the previous 2 to 3 months (half life=120 days).[10] Although an indicator that reflects long-term status is better for epidemiological studies, we assayed glycoalbumin because only serum samples were stored in the JACC Study.

Many epidemiologic studies have found an association between glucose intolerance and increased risk of colorectal cancer.[1-7] Insulin is thought to influence colorectal carcinogenesis through

its links with the insulin-like growth factors (IGFs) and IGF binding proteins (IGFBPs), which are overexpressed in many tumors.[6] An insulin-associated decrease in IGFBP-1 and resultant increase in free IGF-1 may increase the risk of colorectal cancer.[1,6] Thus, carcinogenesis is considered to be promoted by hyperinsulinemia. Glucose intolerance is not necessarily accompanied by hyperinsulinemia. However, it has been reported that elevated glucose or HbA1C levels were associated with colon cancer risk in Western countries.[2,3,6,7] Hence we examined the association between glucose intolerance and colorectal cancer in Japanese people.

In this study, a high level of glycoalbumin was associated with an increased risk of colorectal cancer in men. The association with rectal cancer, however, was weak. These results appear to be in accord with the previous finding that glucose intolerance was more strongly associated with colon than with rectal cancer (the OR for the highest HbA_{1C} quartile relative to the lowest was 2.10 for proximal colon, 1.61 for distal colon, and 0.91 for rectum).[6] Although a previous study has reported that a high blood glucose level increased the risk of colorectal cancer in women (RR = 1.98 for 8.0+ mM in non-fasting individuals) and an insignificant relative risk was shown in men (RR = 0.98),[3] our study detected apparently diverse effects between sexes and a reduced risk for colon cancer in women with glucose intolerance.

The analysis of the whole cohort of the JACC Study indicated that a history of diabetes mellitus significantly increased the risk of colorectal cancer death in women (RR =1.70, 95% CI; 1.03-2.82), but did not increase the risk in men (RR = 0.85, 95% CI; 0.51-1.42) (unpublished data). As for the risk of colorectal cancer incidencce, RR = 1.19 (95% CI; 0.68-2.07) in men, and RR = 1.65 (95% CI; 0.88-3.10) in women. These findings are not consistent with the result of the present study; rather they are consistent with previous reports by other study groups.[2,3,6,7] This inconsistency may be due to inadequate sample selection procedures and insufficient statistical power in the present work.

Adjustment for potential confounders, including serum total cholesterol, BMI, walking habits, and history of diabetes mellitus, had a minimal effect on our results.

In conclusion, a high level of glycoalbumin may increase the risk of colorectal cancer in men. The interpretation of the results was, however, limited by procedural inadequacies and insufficient statistical power.

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Alcohol Consumption and Colorectal Cancer Risk: Findings from the JACC Study

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BACKGROUND: Because alcohol drinking is a potential risk factor for colorectal cancer, the trend in alcohol consumption in Japan may partly explain the increase in incidence and mortality rates of this malignancy until 1990-1995.
METHODS: We analyzed data from the Japan Collaborative Cohort Study. From 1988 to 1990, 23,708 men and 34,028 women, aged 40-79 years, completed a questionnaire on lifestyle factors including drinking habits. Incidence rate ratios (IRR) were estimated by using proportional hazards models.
RESULTS: During the mean follow-up of 7.6 years through December 1997, we documented 418 incidents of colon cancer and 211 of rectal cancer. Male ex- or current drinkers demonstrated a twofold risk for colon cancer compared with nondrinkers: the multivariate-adjusted IRR was 2.01 (95% confidence interval [CI] 1.09-3.68) for ex-drinkers and 1.97 (95% CI: 1.28-3.03) for current drinkers. The dose-response relationship between alcohol consumption and the risk, however, was not clear. Female ex-drinkers were at an increased risk without statistical significance. For rectal cancer, we found a slightly lower risk in light current drinkers who consumed less than 22 g ethanol per day: the multivariate IRR was 0.61 (95% CI: 0.33-1.13) for men and 0.69 (95% CI: 0.27-1.74) for women. Although the IRR for all current drinkers was almost unity in men, an increasing trend in risk was detected with increasing alcohol consumption in current drinkers (trend p = 0.027).
CONCLUSIONS: Taking the findings from our study and other prospective investigations into consideration, more attention should be paid to alcohol consumption in the prevention of colon cancer in Japan.
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Key words: Alcohol Drinking, Colon Neoplasms, Rectal Neoplasms, Cohort studies.

The age-adjusted incidence and mortality rates of colorectal cancer in Japan increased linearly until 1990-1995, and thereafter leveled off.[1,2] These trends have been generally ascribed to changes in diet, particularly to an increase in fat or meat consumption and a decrease in the intake of dietary fiber.[3-5]

Alcohol consumption, however, also grew rapidly in Japan before the 1990s. Because drinking is a potential risk factor for colorectal cancer,[6,7] this increase in consumption may partly explain the increase in incidence and mortality rates of this malignancy until 1990-1995. Nevertheless, little attention has been paid to drinking habits in relation to the prevention of colorectal cancer in Japan compared with dietary factors.

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We therefore examined the association of drinking with the risk of colorectal cancer, using the dataset from the Japan Collaborative Cohort Study (JACC Study) for Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), a nation-wide prospective study.

METHODS

Study Cohort

The JACC Study started in 1988 to 1990, when 110,792 inhabitants aged 40 to 79 years completed a baseline questionnaire.[8,9] They were enrolled from 45 study areas throughout Japan, mostly as they underwent municipal health check-ups. Informed consent for participation was obtained individually from each participant, except in a few study areas where informed consent was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. The Ethics Committee of Medical Care and Research of Fujita Health University approved this investigation.

Subjects for the present analysis were restricted to 61,557 individuals who lived in 22 study areas, where information on cancer incidence is available, and questions to estimate alcohol intake were included in the questionnaire. Of the total, we excluded 57 with a previous history of colorectal cancer and 3,764 of unknown drinking status (nondrinkers, ex-drinkers, or current drinkers), leaving 57,736 subjects (23,708 men and 34,028 women) for the analysis.

Drinking Habits and Other Exposure Data

The baseline questionnaire covered lifestyle factors including smoking and drinking habits, physical activity, and consumption of selected foods, as well as medical history, education, family history of cancer, height and weight, and occupation held the longest. For alcohol intake, subjects were asked to report their drinking status (nondrinkers, ex-drinkers, or current drinkers). Ex-drinkers or current drinkers were asked the frequency of alcohol consumption with four possible responses: less than once/week, 1-2 times/week, 3-4 times/week, or almost every day. They also report the average intake at each time in a Japanese drink ('gou'). One Japanese drink is equivalent to 22 g ethanol. We estimated daily alcohol intake by multiplying the average amount on each occasion by the frequency of drinking alcoholic beverages.

Follow-up

We used population registries in the municipalities to determine the vital and residential status of subjects. We ascertained the incidence of cancer by means of linkage with the records of population-based cancer registries, supplemented by a systematic review of death certificates.[8] In some study areas, medical records in local major hospitals were also reviewed. The follow-up was conducted from the time of the baseline survey through the end of 1997 except in one area (to the end of 1994). During the study period, only 3.3% (n = 1,921) of the participants were lost to follow-up due to relocation.

The mortality-to-incidence ratio for colorectal cancer was 0.28 in the cohort covered by cancer registries. This figure is comparable with those in acceptably-accurate population-based cancer registries in Japan (0.23 to 0.51),[10] and indicates that a reasonably high proportion of colorectal cancer cases were identified.

Statistical Analysis

We categorized subjects into groups by drinking status and alcohol consumption and compared background characteristics between the groups by the one-way analysis of variance or the χ^2 test.

We counted person-time of follow-up for each participant from the date of filling out the baseline questionnaire to the development of colorectal cancer, death from any cause, emigration to outside the study area, or the end of the follow-up period, whichever came first. Those who died from causes other than colorectal cancer or moved out of the study areas were treated as censored cases.

The incidence rate ratios (IRR) for colon or rectal cancer according to drinking status and alcohol intake at baseline were estimated by gender using proportional hazards models,[11] with adjustment for age and other potential confounders.[6] The level of alcohol consumption in current drinkers was categorized into four groups in men (0.0-0.9, 1.0-1.9, 2.0-2.9, and 3.0+ Japanese drinks/day [=0-153,154-307, 308-461, and 462+ g ethanol/week]) and two groups in women (0.0-0.9 and 1.0+ Japanese drinks/day [= 0-153 and 154+ g ethanol/week]). The potential confounding factors adjusted included area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), education (attended school until the age of <16, 16-18, or 19+), family history of colorectal cancer in parents or siblings (yes or no), body mass index (<20.0, 20.0-24.9, or 25.0+ kg/m^2 for men, and <20.0, 20.0-24.9, 25.0-29.9, or 30.0+ kg/m^2 for women), smoking habits (never smokers, ex-smokers, or current smokers), walking time (≤30 or 30+ minutes/day), sedentary work (yes or no), and consumption of green leafy vegetables (≤2 times/week, 3-4 times/week, or every day), and beef (almost never, 1-2 times/month, 1-2 times/week, or 3+ times/week). Missing values for each covariate were treated as an additional category of the variable and were included in the proportional hazards model.

The dose-response relationship among current drinkers was assessed by the regression model assigning scores (0, 1, 2, or 3) to the levels of alcohol consumption. All p values were two-sided, and all the analyses were performed using the Statistical Analysis System®.[12]

RESULTS

During the mean follow-up of 7.6 (standard deviation 1.9) years, we identified 418 incident cases of colon cancer (220 in men and 198 in women) and 211 cases of rectal cancer (150 in men and 61

Table 1. Background characteristics of subjects according to drinking habits by sex.

Characteristics	Drinking habits						
			Current drinkers (Japanese drinks/day)*				
	Non-drinkers	Ex-drinkers	0.0 - 0.9	1.0 - 1.9	2.0 - 2.9	3.0+	p
Men							
Number of subjects	4,395	1,644	4,250	5,451	4,285	1,823	
Age (years)†	59.7 ± 10.7	63.4 ± 9.3	57.0 ± 10.4	57.9 ± 10.3	55.5 ± 9.4	53.9 ± 9.1	< 0.001
Attended school until age of 19 or more (%)	18.4	20.9	24.3	19.1	17.5	16.1	< 0.001
Family history of colorectal cancer (%)‡	2.3	2.0	2.6	1.9	2.5	2.3	0.31
Body mass index (kg/m²)†	22.5 ± 3.0	22.3 ± 4.2	22.7 ± 3.4	22.6 ± 2.7	22.8 ± 2.7	22.9 ± 2.8	< 0.001
Current smokers (%)	48.0	43.8	44.5	50.5	61.4	68.6	< 0.001
Daily walking time 30+ min. (%)	67.2	66.3	67.2	70.1	68.9	69.1	0.008
Sedentary work (%)	32.9	28.2	32.4	32.9	33.5	29.0	< 0.001
Consumption of green leafy vegetables, daily (%)	29.5	33.8	29.7	29.1	27.5	26.1	< 0.001
Consumption of beef 3+ times/week (%)	8.8	8.4	8.3	8.6	8.3	10.7	0.085
Women				(1.0+)			
Number of subjects	25,269	649	4,407		874§		
Age (years)†	58.5 ± 10.1	59.2 ± 10.0	55.6 ± 9.7		54.7 ± 9.8		< 0.001
Attended school until age of 19 or more (%)	10.7	10.8	13.1		9.3		< 0.001
Family history of colorectal cancer (%)‡	2.7	2.2	3.0		2.4		0.38
Body mass index (kg/m²)†	22.9 ± 3.3	23.0 ± 3.4	22.9 ± 4.0		23.0 ± 3.2		0.44
Current smokers (%)	3.3	21.5	7.4		28.8		< 0.001
Daily walking time 30+ min. (%)	71.0	70.2	73.0		70.0		0.045
Sedentary work (%)	34.7	30.2	33.8		30.5		0.021
Consumption of green leafy vegetables, daily (%)	34.4	33.7	34.6		31.1		0.24
Consumption of beef 3+ times/week (%)	10.2	10.6	12.9		14.6		< 0.001

* : One Japanese drink ('gou') is equivalent to 22 g ethanol. The categories of 0.0-0.9, 1.0-1.9, 2.0-2.9, 3.0+, and 1.0+ Japanese drinks/day correspond to those of 0-153, 154-307, 308-461, 462+, and 154+ g ethanol/week.

† : Values are means ± standard deviation.

‡ : Family history in parents and/or siblings.

§ : Women who consumed 1.0+ Japanese drinks/day are grouped into one category.

Table 2. Incidence rate ratios (IRR) for cancers of the colon and rectum according to drinking habits at baseline by sex.

Sex	Drinking habits	Person-years	Colon					Rectum				
			No. of cases	IRR1*	95% CI†	IRR2*	95% CI†	No. of cases	IRR1*	95% CI†	IRR2‡	95% CI†
Men	Nondrinkers	33,018	24	1.00	(reference)	1.00	(reference)	30	1.00	(reference)	1.00	(reference)
	Ex-drinkers	11,291	19	2.01	1.10 - 3.67	2.01	1.09 - 3.68	14	1.19	0.63 - 2.24	1.25	0.66 - 2.38
	Current drinkers§	135,710	177	2.10	1.37 - 3.23	1.97	1.28 - 3.03	106	1.01	0.67 - 1.51	1.01	0.67 - 1.52
	0.0-0.9 (Japanese drinks/day)‖	32,636	43	2.09	1.27 - 3.45	2.01	1.22 - 3.33	16	0.62	0.34 - 1.14	0.61	0.33 - 1.13
	1.0-1.9	41,446	63	2.32	1.45 - 3.71	2.22	1.38 - 3.56	35	1.02	0.63 - 1.67	1.01	0.62 - 1.65
	2.0-2.9	33,315	36	1.87	1.11 - 3.15	1.75	1.04 - 2.96	29	1.18	0.71 - 1.98	1.21	0.72 - 2.04
	3.0+	14,145	20	2.68	1.47 - 4.88	2.40	1.31 - 4.40	12	1.25	0.63 - 2.47	1.32	0.67 - 2.63
				Trend p = 0.76¶		Trend p = 0.85¶			Trend p = 0.038¶		Trend p = 0.027¶	
Women	Nondrinkers	193,562	149	1.00	(reference)	1.00	(reference)	50	1.00	(reference)	1.00	(reference)
	Ex-drinkers	4,573	6	1.64	0.73 - 3.71	1.56	0.68 - 3.60	1	0.82	0.11 - 5.92	0.78	0.11 - 5.78
	Current drinkers§	58,957	43	1.13	0.81 - 1.60	1.03	0.72 - 1.45	10	0.74	0.37 - 1.46	0.71	0.35 - 1.42
	0.0-0.9 (Japanese drinks/day)‖	32,068	22	1.12	0.72 - 1.76	1.06	0.67 - 1.68	5	0.69	0.28 - 1.75	0.69	0.27 - 1.74
	1.0+	6,253	5	1.39	0.57 - 3.38	1.22	0.49 - 3.03	2	1.48	0.36 - 6.11	1.53	0.36 - 6.47
				Trend p = 0.64¶		Trend p = 0.96¶			Trend p = 0.36¶		Trend p = 0.36¶	

* : IRR1: adjusted for age.

† : CI: confidence interval.

‡ : IRR2: adjusted for age, area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), education (attended school until the age of < 16, 16-18, or 19+), family history of colorectal cancer in parents or siblings (yes or no), body mass index (< 20.0, 20.0-24.9, or 25.0+ kg/m^2 for men, and < 20.0, 20.0-24.9, 25.0-29.9, or 30.0+ kg/m^2 for women), smoking habits (never smokers, ex-smokers, or current smokers), walking time (≤ 30 or 30+ minutes/day), sedentary work (yes or no), and consumption of green leafy vegetables (≤ 2 times/week, 3-4 times/week, or every day), and beef (almost never, 1-2 times/month, 1-2 times/week,or 3+ times/week).

§ : Including subjects with unknown alcohol consumption.

‖ : One Japanese drink ('gou') is equivalent to 22 g ethanol. The categories of 0.0-0.9, 1.0-1.9, 2.0-2.9, 3.0+, and 1.0+ Japanese drinks/day correspond to those of 0-153, 154-307, 308-461, 462+, and 154+ g ethanol/week.

¶ : The test for a trend in current drinkers.

in women).

Table 1 summarizes the background characteristics of the subjects according to drinking habits by gender. At baseline, nondrinkers, ex-drinkers, and current drinkers accounted for 18.5%, 6.9%, and 74.5% of men and 74.3%, 1.9%, and 23.8% of women, respectively (Daily alcohol consumption was unknown in some of the current drinkers). Heavy drinkers (3.0+ Japanese drinks/day) in men and moderate to heavy drinkers (1.0+ Japanese drinks/day) in women tended to be younger and less educated, are likely to be current smokers, and consume less green leafy vegetables and more beef. Ex-drinkers in both genders tended to be older and not to have been engaged in sedentary work. The proportion of current smokers was relatively high in female former drinkers.

Male ex- or current drinkers demonstrated a twofold risk for colon cancer compared with nondrinkers: the multivariate-adjusted IRR (IRR2 in Table 2) was 2.01 (95% CI: 1.09-3.68) for ex-drinkers and 1.97 (95% CI: 1.28-3.03) for current drinkers. The dose-response relationship between alcohol consumption and the risk, however, was not clear. Female ex-drinkers were at a somewhat increased risk, but it was far from significant.

For rectal cancer, we found a slightly lower risk in light current drinkers who consumed less than one Japanese drink/day in both genders: the IRR2 was 0.61 (95% CI: 0.33-1.13) for men and 0.69 (95% CI: 0.27-1.74) for women. Although the IRR2 for all current drinkers was almost unity in men, an increasing trend in risk was detected with an increasing alcohol consumption in current drinkers (trend $p = 0.027$). The IRR2 was 0.61, 1.01, 1.21, and 1.32 for <1.0, 1.0-1.9, 2.0-2.9, and 3.0+ Japanese drinks/day, respectively.

The age-adjusted IRRs (IRR1) were almost the same as the multivariate rate ratios (IRR2). We repeated the analyses in Table 2 after excluding the first two years of follow-up from the risk period but the findings remained materially unchanged. The IRR2 for colon cancer was 2.07 (95% CI: 1.05-4.10) in male ex-drinkers, 1.94 (95% CI: 1.19-3.15) in male current drinkers, 1.64 (95% CI: 0.66-4.11) in female ex-drinkers, and 1.01 (95% CI: 0.68-1.50) in female current drinkers. The corresponding figures for rectal cancer were 1.46 (95% CI: 0.72-2.95) for male ex-drinkers, 0.95 (95% CI: 0.60-1.51) for male current drinkers, and 0.89 (95% CI: 0.42-1.87) for female current drinkers. No case of rectal cancer was found in female former drinkers in this analysis.

DISCUSSION

In a large-scale prospective study, we observed an association of drinking habits with the risk of colon cancer in men. A dose-response relationship in current drinkers, however, was not evident. For rectal cancer, a "J-shaped" association was found between alcohol intake and the risk, that is, the rate ratio was lowest in light drinkers.

In Japan, per adult ethanol consumption increased from 5.86 L/year in 1965 to 8.30 L/year in 1999 (available at http://www.ncc.go.jp/jp/statistics/2003/index.html). The alcohol drinking has been common in men and has also become more popular in women.[13] If alcohol intake actually enhances the risk of colorectal cancer, therefore, its attributable risk will be large, and controlling alcohol drinking will be of great importance for the primary prevention of this cancer in Japan. Given that male former or current drinkers have twice the risk of colon cancer as nondrinkers, and the distribution of drinking habits in our cohort is applicable to the general Japanese population, the population attributable risk percent would be 45%. This may imply that nearly half of all male colon cancer is ascribable to alcohol drinking.

Alcohol intake can cause malabsorption of folate and block its release from the hepatocyte. In addition, alcohol metabolite acetaldehyde may inactivate methyltetrahydrofolate or inhibit methionine synthase. These anti-folate effects may lead to DNA hypomethylation.[7] Alcohol may also have specific carcinogenic effects; the colonic bacteria can produce substantial levels of acetaldehyde at ethanol concentrations that are common in the colonic mucosa of drinkers.[7]

A positive association of drinking habits with the risk of colon or colorectal cancer has been rather consistently found in cohort studies in Japan, particularly in men. Hirayama[14] reported an increasing risk of cancer of the sigmoid colon with the increasing frequency of alcohol consumption in his Six-Prefecture Cohort Study: the relative risks in men compared with nondrinkers were 2.03, 3.83, and 5.42 for infrequent, occasional, and daily drinkers, respectively. Murata et al.[15] also report a significantly elevated risk of colon cancer among alcohol drinkers in a male cohort, although without a clear dose-response relation.

In the Japan Public Health Center-based prospective study,[16] another population-based cohort study, regular drinking of 150+ g/week of ethanol (about 1+ Japanese drinks/day) showed an increased risk of colorectal cancer only in men: relative risks compared with nondrinkers were 1.4 for 150-299 g/week and 2.1 for 300+ g/week. In a cohort of the Takayama Study,[17] a positive dose-response relationship between alcohol consumption and colon cancer risk was observed for men and women. Thus, our study may well add further evidence for the role of alcohol intake in the development of colon cancer. Female current drinkers may not be associated with colorectal cancer because of the less intake of alcohol in our population; the median intake in the category of 0.0-0.9 Japanese drinks/day was 0.32 drinks in men and 0.15 drinks in women.

However, the decreased risk of rectal cancer in light drinkers in the present study does not seem to be supported by previous reports. One possibility is that the light drinkers had unknown characteristics that confounded the association between alcohol consumption and the risk. We may have failed to exclude all the confounding factors, although we adjusted for selected risk or protective factors, and the adjustment did not substantially alter the results.

The higher risk for colon cancer than for rectal cancer was observed in three prospective studies in Japan[14,15,17] but not in the