Japan Public Health Center-based prospective study.[16] A recent pooled analysis of eight cohort studies in Western countries did not show a substantial difference between cancer of the colon and rectum.[18] Further investigations would be warranted to elucidate if the contribution of alcohol differs between colon and rectal cancers in Japan.

The strengths of the present study are its prospective design and large size. We assessed drinking habits before the diagnosis of colorectal cancer; thus any errors of recall should have been non-differential between cases and non-cases. A considerable number of cases of colon and rectal cancers were identified in male current drinkers, which made it possible to assess the risk by the level of alcohol consumption.

Some methodological limitations, however, need consideration. First, the frequency and amount of alcohol consumption were based on self-reporting and may be subject to misclassification. In addition, we could not compute daily intake for some subjects due to their incomplete responses to the questionnaire. These issues in estimating alcohol intake may partly explain why we failed to uncover the dose-response relationship.

Second, information on drinking habits was collected only at baseline. If drinkers at baseline stopped drinking during the follow-up, it would have resulted in a somewhat attenuated risk for current drinkers. Although most cohort studies on drinking and the risk of colorectal cancer did not update data on the drinking habits of subjects, repeated measurements may provide more meaningful information. Finally, the number of rectal cancer cases among male and female ex-drinkers and female current drinkers was rather small as was the number of colon cancer cases in female ex-drinkers. We therefore cannot exclude an increase or a decrease in risk associated with alcohol consumption in these groups.

In conclusion, taking the findings from our study and other prospective investigations in Japan and the high percentage of male drinkers into consideration, more attention should be paid to alcohol consumption in the primary prevention of colon cancer in this country.

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Medical History of Circulatory Diseases and Colorectal Cancer Death in the JACC Study

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BACKGROUND: Host factors expressed by individual past medical history of hypertension, stroke, and myocardial infarction may have a relationship with colorectal cancer.
METHODS: As part of the Japan Collaborative Cohort Study (JACC Study) for the Evaluation of Cancer Risk sponsored by the Ministry of Education, Science, Sports and Culture of Japan (Monbusho), we conducted a follow-up study of 110,792 Japanese inhabitants aged 40-79 years to reveal the relationship of past medical history of hypertension, stroke, and myocardial infarction at the baseline in 1988-1990 with colorectal cancer death for about 10 years up to the end of 1999.
RESULTS: Past medical history of hypertension associated with an increased risk of female rectal cancer when analyzing all cancer cases with adjustment for age, body mass index, and exercise (hazard ratio [HR] = 1.97, 95% confidence interval [CI]; 1.13-3.43). Past medical history of myocardial infarction was also an increased risk for female rectal cancer (HR = 3.05, 95% CI; 1.28-7.28). Females who had a medical history of stroke had increased risk of rectal cancer without statistical significance.
CONCLUSION: There was a positive association of past medical history of hypertension and myocardial infarction and an increased risk of rectal cancer in women.
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Key words: Medical history, Hypertension, Myocardial Infarction, Colorectal Neoplasms, Cohort Studies, Epidemiology.

We reported a positive association between past medical history of hypertension and colorectal cancer in a case-control study in early 1980,[1] although it was not related to colorectal cancer in a recent case-control study in Italy.[2] Patients with hypertension, stroke and myocardial infarction may have similar lifestyle factors, such as high intake of dietary fat, less frequent physical exercise and obesity, to colorectal cancer cases. These common risk factors may contribute to the positive association between the above circulatory diseases and colorectal cancer.

Therefore, we conducted a cohort study to reveal the relationship in the Japan Collaborative Cohort Study (JACC Study) for the Evaluation of Cancer Risk sponsored by the Ministry of

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METHODS

The study population, procedures for conducting the baseline survey using a self-administered questionnaire, and follow-up methods in the JACC Study have been described previously.[3,4] Briefly, the study population was 110,792 Japanese inhabitants aged 40-79 years at 45 study areas in 1988-1990. Subjects completed a self-administered questionnaire including past medical history of hypertension, stroke, and myocardial infarction. A response to the medical history questions was selected from four alternatives such as "have never suffered from the disease", "have suffered from the disease with present treatment", "have suffered from the disease with treatment", and "have suffered from the disease without treatment". Therefore, subjects with positive medical history of hypertension, stroke and myocardial infarction were defined as those who had suffered from hypertension, stroke and myocardial infarction, respectively, irrespective of past and present treatment.

The follow-up survey was conducted using population registries in local municipalities to determine the vital and residential status of the cohort in each area. All subjects that moved out of the study areas were treated as censored subjects. All deaths that occurred in the cohort were ascertained by death certificates from local public health centers in the study areas with the authorities' permission from the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post, and Telecommunications). The causes of death were coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision[5] by verifying computer-stored data in the Ministry of Health, Labour, and Welfare with permission. A diagnosis of colon cancer was defined by code C18, while rectal cancer was C19 and C20, in the above classification.[5]

The risk of colorectal cancer was evaluated by hazard ratios (HRs) and 95% confidence intervals (CIs) estimated by the Cox proportional hazards model. Sex-specific HRs were computed after adjustment for age in all colorectal cancer cases and cases except for those who died within the first two years of the follow-up period. Sex-specific HRs were also computed after adjustment for age, body mass index (BMI) (25+, 20-25, -20 kg/m^2, and no answer) and exercise (5+, 3-4, 1-2 hours per week, seldom, and no answer) for all colorectal cancer cases and cases except for those who had died within the first two years of the follow-up period. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared provided in the self-administered questionnaire at the baseline.

Individual written or oral consent, or consent from community representatives, was obtained, or a poster notification/opting-out system was applied.[3,4] The Ethical Boards of Nagoya University School of Medicine and Fujita Health University approved this study.

RESULTS

When the data were analyzed with adjustment for age only, past medical history of hypertension increased the risk of female rectal cancer for all cancer cases (HR = 1.78, 95% CI; 1.02-3.11) and for cases except for those died within the first two years of the follow-up period (HR = 1.85, 95% CI; 1.03-3.33). Past medical history of stroke and myocardial infarction had a positive association with female rectal cancer, although there was no statistical significance. Past medical history of hypertension, stroke, and myocardial infarction also showed a positive association with male colon cancer, although none were not statistically significant. There were no other significant relationships among past medical history of hypertension, stroke, and myocardial infarction with colorectal cancer death by sex or site of cancer (colon/rectum).

Sex-specific HRs and 95% CIs of colon cancer and rectal cancer adjusted by age, BMI and exercise are shown in Table 1. Past medical history of hypertension increased the risk of female rectal cancer when analyzing all cancer cases (HR = 1.97, 95% CI; 1.13-3.43) and cases except for those died within the first two years of the follow-up period (HR = 2.08, 95% CI; 1.16-3.73). Past medical history of myocardial infarction also increased the risk of female rectal cancer when analyzing all cancer cases (HR = 3.05, 95% CI; 1.28-7.28) and cases except for those who died within the first two years of the follow-up period (HR = 3.54, 95% CI; 1.47-8.53). There were no other significant results.

DISCUSSION

There are no consistent epidemiologic reports on the relationship between past medical history of hypertension and colorectal cancer.[1,2] The present study showed a positive association between past medical history of hypertension and female rectal cancer. Females who had a medical history of hypertension had an increased risk of rectal cancer. This result supports the idea of the presence of common risk factors between colorectal cancer and hypertension. Obesity and physical inactivity are risk factors for hypertension.[6] Obesity[7,8] and physical inactivity[8,9] are also risk factors for colorectal cancer. However, the risk of rectal cancer still existed when BMI and exercise were adjusted. Therefore, there may be common risk factors other than BMI and exercise involved in the link between hypertension and rectal cancer deaths. Females who had a medical history of myocardial infarction also had increased risk of rectal cancer when BMI and exercise were adjusted. Females who had a medical history of stroke had increased risk of rectal cancer without statistical significance. This may be accounted for by hypertension, as myocardial infarction and stroke are both closely related to hypertension.

There is a hypothetical correlation between circulatory diseases and colorectal cancer, shown in Figure 1, from the viewpoint of folic acid metabolism.[10] We proposed this hypothesis because the average value of plasma homocysteine of patients with colorectal

Table 1. Sex-specific hazard ratio (HR) and 95% confidence interval (CI) of past history of hypertension, stroke, and myocardial infarction for colon and rectal cancer mortality adjusted for age, body mass index and exercise.

	All causes			All causes except for those died within the first two years of the follow-up		
	Person-years	No. of Cases	Adjusted HR* (95% CI)	Person-years	No. of Cases	Adjusted HR* (95% CI)
			Colon cancer			
Males						
Hypertension	404,090	124	1.01 (0.68 - 1.51)	322,051	110	0.99 (0.64 - 1.52)
Stroke	393,120	122	1.64 (0.72 - 3.75)	313,469	108	1.96 (0.85 - 4.50)
Myocardial infarction	394,168	120	1.25 (0.58 - 2.69)	314,282	106	1.49 (0.69 - 3.23)
Females						
Hypertension	573,184	130	0.77 (0.52 - 1.13)	459,204	121	0.82 (0.55 - 1.23)
Stroke	552,990	124	0.96 (0.24 - 3.92)	443,152	116	1.05 (0.26 - 4.23)
Myocardial infarction	555,667	128	1.08 (0.50 - 2.33)	445,254	120	1.17 (0.54 - 2.52)
			Rectal cancer			
Males						
Hypertension	404,090	109	0.98 (0.63 - 1.51)	322,051	104	0.92 (0.59 - 1.45)
Stroke	393,120	104	0.33 (0.05 - 2.34)	313,469	100	0.35 (0.05 - 2.49)
Myocardial infarction	394,168	105	0.41 (0.10 - 1.67)	314,282	101	0.44 (0.11 - 1.79)
Females						
Hypertension	573,184	54	1.97 (1.13 - 3.43)	459,204	48	2.08 (1.16 - 3.73)
Stroke	552,990	47	2.99 (0.72-12.45)	443,152	41	3.45 (0.83-14.43)
Myocardial infarction	555,667	49	3.05 (1.28 - 7.28)	445,254	43	3.54 (1.47 - 8.53)

* : Adjusted hazard ratio for all cases by age, body mass index, and exercise.

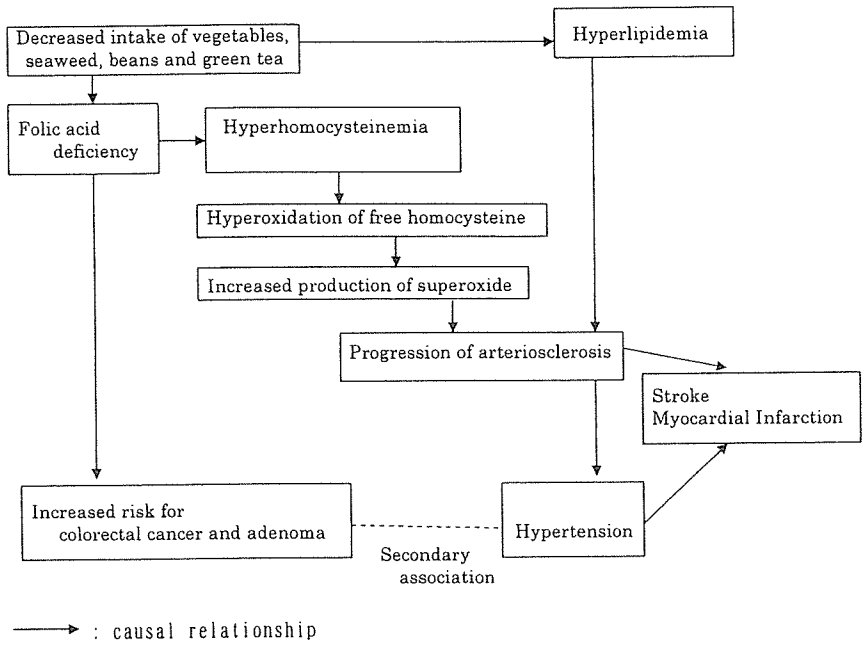

Figure 1. Hypothetical correlation among hypertension, stroke, and myocardial infarction and colorectal cancer (modified version of the original figure[10])

cancer was significantly higher than of healthy controls in a clinical case-control study.[10] Except for folic acid deficiency, oxidative stress may contribute to the relationship. We have already reported that higher levels of serum oxidized low-density lipoprotein, which is believed to play a role in the development and progression of atherosclerosis,[11] were associated with risk of colorectal cancer as part of the JACC Study.[12] Therefore, our findings that past medical history of hypertension and myocardial infarction increased the risk of female rectal cancer could be a secondary association due to folic acid deficiency and /or oxidative stress.

There is a major limitation in interpreting the present results. As we conducted a cohort study, some of the subjects who did not have a medical history of hypertension at the time of the baseline questionnaire survey may have developed hypertension and then subsequently colorectal cancer during the follow-up period. Therefore, the relationship between past medical history and colorectal cancer death might have been underestimated.

There were no consistent results by sex or site of cancer (colon/rectum) in our study. These differences should be carefully addressed by considering factors other than folic acid deficiency and /or oxidative stress, such as hormonal background.

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Serum Carotenoids, Retinol, and Tocopherols, and Colorectal Cancer Risk in a Japanese Cohort: Effect Modification by Sex for Carotenoids

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Abstract: *To examine associations of serum carotenoids, retinol, and tocopherols with colorectal cancer risk, we conducted a case-control study nested within the Japan Collaborative Cohort Study. These micronutrients were measured in prediagnostic serum samples from 116 men and women who developed colorectal cancer during an 8-yr follow-up period and from 298 matched controls. In men, the higher level of serum total carotenoids was associated with a decreased risk: The multivariate-adjusted odds ratio (OR) for the highest vs. the lowest tertile was 0.34 (95% confidence interval [CI] = 0.11–1.00; trend* P *over tertiles = 0.040). In women, the higher levels of α- and β-carotenes and total carotenoids were instead related to an increased risk: The corresponding ORs were 4.72 (95% CI = 1.29–17.3), 2.00 (0.70–5.73), and 2.47 (0.73–8.34), respectively (trend* P *= 0.007, 0.040, and 0.064, respectively). We also found a somewhat decreasing risk with increased serum retinol in all subjects and α-tocopherol in men: The ORs (95% CI) for the highest tertiles were 0.29 (0.11–0.78; trend* P *over tertiles = 0.010) and 0.29 (0.07–1.17; trend* P *= 0.098), respectively. The effects of some carotenoids on colorectal cancer risk may be modified by sex or by factors associated with sex, including smoking and drinking habits.*

Introduction

Consumption of vegetables and fruit has often been related to a decreased risk of colorectal cancer (1,2), suggesting the potential etiological importance of carotenoids and other phytochemicals contained in these foods.

Several studies have assessed dietary intake of carotenoids in relation to colorectal cancer risk but have reported inconsistent findings: Some suggested the protective effects of carotenoids (3–7) whereas others did not (8–11). In addition, only a few investigations (11–13) have examined possible associations of specific carotenoids other than β-carotene with the risk.

Studies using blood samples can assess the role of several carotenoids simultaneously (14) and allow for the bioavailability of compounds in individual subjects. Such studies may also provide possible explanations for the results of several recent cohort studies that have not demonstrated the presumed protective effects of vegetables and fruit (15,16). Nevertheless, there have been little data on the association of blood carotenoids with colorectal cancer risk.

We therefore examined the associations between serum carotenoids and the risk of colorectal cancer in a prospective study in Japan. Additionally, retinol and tocopherols, possi-

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bly important anticarcinogenic substances from foods other than carotenoids (14), were considered in relation to malignancy.

Materials and Methods

Study Population and Serum Samples

We carried out a nested case-control study as a part of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (the JACC Study; the Monbusho is the Japanese name for the Ministry of Education, Culture, Sports, Science and Technology of Japan). The details of this study are described elsewhere (17,18). The study involved 110,792 residents, aged 40–79 yr at baseline, from 45 areas all over Japan. Potential subjects for the present study were restricted to 65,184 individuals who lived in 24 study areas, where cancer registries are available. An epidemiological survey on lifestyle factors was conducted using a self-administered questionnaire from 1988 to 1990. The questionnaire addressed demographic factors, personal and family medical histories, anthropometric factors, smoking and drinking habits, physical activity, dietary habits, use of vitamin supplements, and other lifestyles. We did not collect information on carotenoid supplements since they were uncommon in Japan at the time of the baseline survey.

In addition to completing the questionnaire, those survey participants who underwent health-screening checks sponsored by municipalities were asked to donate blood samples during the same period as the questionnaire survey. Eventually, 23,863 subjects (7,793 men and 16,070 women; 36.6% of the 65,184 respondents to the questionnaire survey in the 24 study areas) provided blood samples.

Those who donated blood samples were more likely to be women (67.3%) than those not providing samples (54.8%). The former were less likely to be highly educated (those attending school until the age of ≥19; 15.8% for men and 9.3% for women) than the latter (20.7% for men and 11.6% for women). In women, the mean age was lower in subjects with blood samples (56.8 [SD, 9.4] yr) than those without them (59.4 [10.5] yr), while it was similar between the two groups of men (58.4 [9.7] and 57.9 [10.6] yr, respectively). Among subjects providing blood samples, those with a previous history of cancer (n = 409) were omitted, leaving 23,454 (7,673 men and 15,781 women) for follow-up.

Sera were separated from the samples at laboratories in or near the surveyed municipalities as soon as possible after the blood draw. Serum of each participant was divided into three to five tubes (100 to 500 μl per tube), and the tubes were stored in deep freezers at –80°C until analyzed in 2002.

Informed consent for participation was obtained individually from subjects, with the exception of those in some study areas in which 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 the protocol of this investigation including the procedures to obtain informed consent.

Case Ascertainment and Control Selection

We used population registries in the municipalities to determine the vital and residential status of the subjects. Registration of death is required by the Family Registration Law in Japan and is followed across the country. For logistical reasons, we discontinued the follow-up of subjects who had moved out of the study areas.

The cases were defined as those of incident colorectal cancer (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* C18, C19, and C20). We ascertained the incidence of cancer by means of linkage with the records of population-based cancer registries and/or checking hospital-based registries or inpatient records of hospitals treating cancer patients (17), supplemented by systematic review of death certificates. The follow-up was conducted from the time of baseline survey through the end of 1997, except for three areas (to the end of 1994, 1995, and 1996, respectively). During the study period, only 2.1% (n = 501) of the 23,454 subjects were lost to follow-up due to moving. 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 representative population-based cancer registries in Japan (0.23 to 0.51; 19) and indicates the reasonably high quality of the case identification procedure.

During the mean follow-up of 7.9 (SD, 1.5) yr, 171 incident cases of colorectal cancer were documented among the subjects who had provided serum samples at baseline. Of the cases, we excluded 46 without sufficient samples for measurement. For each case, 2 or 3 controls were selected from the population at risk without incident cancer or previous history of cancer, matching for sex, age (as near as possible), and participating institution. We had to further exclude 9 cases because appropriate controls were not available. Eventually, 116 cases of colorectal cancer (including 84 cases of colon cancer) and 298 controls were involved in the analysis.

The baseline characteristics of cases were not materially altered by this exclusion. Those of all the 171 incident cases and of the 116 cases included in the analysis were as follows, respectively: female sex, 50.3% and 53.4%; mean age ± SD, 61.4 ± 8.3 and 61.2 ± 8.8 yr in men and 62.7 ± 7.8 and 62.0 ± 7.6 yr in women; current smokers, 45.9% and 46.3% in men and 3.5% and 3.2% in women; current drinkers, 80.0% and 75.9% in men and 23.3% and 21.0% in women; multivitamin supplement users, 12.3% and 15.0% in men and 7.3% and 10.2% in women; and users of vitamin E supplement, 3.2% and 5.1% in men and 14.5% and 16.3% in women. In both sexes, the proportions of daily consumers of vegetables or fruit were comparable among all the cases and the cases involved in the analysis except for green leafy vegetables in women (38.7% of all cases and 52.8% of selected cases were daily consumers of green leafy vegetables).

Determination of Serum Carotenoids, Retinol, and Tocopherols

All the samples were analyzed by trained staff blinded to case-control status. Serum total cholesterol was determined using an autoanalyzer. Serum concentrations of carotenoids, retinol, and tocopherols were measured by high-performance liquid chromatography, as described elsewhere (14), using the same equipment for all specimens. The ranges of repeatability and day-to-day variation (coefficients of variation) were 4.6% to 6.9% and 6.3% to 20.0%, respectively, for the assays of carotenoids, retinol, and tocopherols. We could not separately measure serum levels of zeaxanthin and lutein or β- and γ-tocopherols and therefore report the combined levels as zeaxanthin/lutein and β-/γ-tocopherols, respectively. We calculated total carotenes as the sum of α- and β-carotenes and lycopene, total xanthophylls as the sum of β-cryptoxanthin, canthaxanthin, and zeaxanthin/lutein, and total provitamin A as the sum of α- and β-carotenes and β-cryptoxanthin. Total carotenoids were calculated as total carotenes plus total xanthophylls.

To assess the degradation of serum components in stored sera, we previously compared serum levels of carotenoids, retinol, and tocopherols at the time of collection and after 9 yr of storage at –80°C (Ito Y, et al., unpublished data; $n = 46$). The mean decrease in serum components was less than 15% for α- and β-carotenes and less than 20% for retinol, α-tocopherol, lycopene, β-cryptoxanthin, and zeaxanthin/lutein.

Statistical Analysis

We first analyzed the data by sex because the associations of some carotenoids with colorectal cancer risk were considerably different between men and women. The associations of micronutrients with the risk in men and women combined were examined only for the compounds without a substantial effect modification by sex. Analyses limited to colon or rectal cancer cases were not made due to the small number of cases.

Body mass index (BMI) at baseline was calculated from reported height and weight: BMI = (weight in kg)/(height in m)^2. We compared background characteristics between cases and controls by the chi-square test or the Mantel test. Mean differences between cases and controls were examined by analysis of covariance (ANCOVA) allowing for the matching after converting serum levels of carotenoids, retinol, and tocopherols to logarithmic values. Adjusted as possible confounding factors were education (age at completion of education: <16, 16–18, or ≥19 yr), family history of colorectal cancer in parents or siblings (yes or no), BMI (as a continuous variable), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/month, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (as a continuous variable).

In the study questionnaire, subjects reported the intake frequency of beef with five possible responses: almost never, 1–2 times/mo, 1–2 times/wk, 3–4 times/wk, or almost every day. If the intake frequency of a subject did not exactly fit any category, the participant chose the category he or she regarded as most appropriate. We then classified participants into three groups, that is, ≤2 times/mo, 1–2 times/wk, or ≥3 times/wk, according to the response. For walking time, the questionnaire included four possible responses: ≥1 hr/day, 30–60 min/day, about 30 min/day, or almost never. If a subject walked for 1 h or 30 min per day, the response he or she considered more appropriate was selected. The response was then dichotomized into ≤30 min/day (about 30 min/day or almost never) and ≥30 min/day (≥1 h/day or 30–60 min/day).

Whether the case-control difference was modified by sex was tested by ANCOVA, including the previously mentioned confounding variables and the product term for interaction between case-control status and sex.

Conditional logistic models were applied to calculate odds ratios (ORs) for the incidence of colorectal cancer (20). Cases and controls were categorized into three groups, according to tertile levels of carotenoids, retinol, and tocopherols among controls. However, control subjects were not precisely divided into three equal groups because some controls had identical serum values. ORs were calculated for the middle and highest tertiles vs. the lowest one, considering only matching variables (sex, age, and participating institution), or matching factors, education (age at completion of education: <16, 16–18, or ≥19 yr), family history of colorectal cancer in parents or siblings (yes or no), BMI (<20.0, 20.0–24.9, or ≥25.0 kg/m^2), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/mo, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (<4.0, 4.0–4.9, 5.0–5.9, or ≥6.0 mmol/l). We did not adjust for supplement use because we intended to assess overall bioavailability of the micronutrients using serum concentration as an indicator.

To test for linear trends in OR over tertiles, we coded each tertile as 0, 1, or 2, and then incorporated it into the logistic model as a single variable. We further statistically tested whether the effects of serum carotenoids, retinol, and tocopherols on colorectal cancer risk were modified by sex by including product terms between sex and each of the tertiles in the logistic models (21). We have also attempted to determine whether the effect modification is due to sex or due to smoking or drinking habit by multivariate analysis. Included were product terms between smoking or drinking habit (never or ever) and each of the tertiles of serum micronutrients in the conditional logistic models, in addition to those between sex and each of the tertiles.

All P values were two-sided, and all analyses were performed using the Statistical Analysis System, release 8.2 (SAS Institute Inc., Cary, NC; 22). In ANCOVA or the conditional logistic regression analysis, missing values in each cat-

egorical covariate were treated as an additional category in the variable and were included in the model.

Results

Table 1 compares baseline characteristics of colorectal cancer cases with those of controls by sex. Age distribution was quite comparable between cases and controls due to the matching: mean ages ± SD were 61.2 ± 8.8 yr in male cases, 60.5 ± 8.4 yr in male controls, 62.0 ± 7.6 yr in female cases, and 61.4 ± 7.3 yr in female controls. Compared with controls, cases were likely to have a family history of colorectal cancer and to be engaged in sedentary work in both sexes. Particularly in men, the serum level of total cholesterol tended to be higher in cases than in controls. Female case subjects tended to be leaner than control participants. All the case-control differences, however, did not reach statistical significance. Smoking and alcohol drinking habits were similarly distributed between cases and controls.

The proportion of users of multivitamin or vitamin E supplement was comparable between cases and controls except that a higher percentage of female case subjects used a vitamin E supplement than controls without a significant difference: The percentages of multivitamin use were 15.0% in male cases, 15.8% in male controls, 10.2% in female cases, and 10.6% in female controls, while those of vitamin E use were 5.1%, 5.3%, 16.3%, and 11.4%, correspondingly.

In men, the geometric means of serum concentration were significantly lower in colorectal cancer cases than in controls for zeaxanthin/lutein (by 11%), canthaxanthin (by 6%), and lycopene (by 18%; Table 2; $P < 0.05$). In women, the geometric mean was higher in cases than in controls for α-carotene by 21% ($P = 0.005$).

Of interest, the mean serum level of total carotenoids was lower in cases than in controls among men (geometric mean, 1.59 μmol/l in cases vs. 1.79 μmol/l in controls), while it was higher in cases among women (2.55 μmol/l in cases vs. 2.33 μmol/l in controls). A highly significant interaction was detected between case-control status and sex (P for interaction = 0.002). Such effect modifications by sex were found also for zeaxanthin/lutein, canthaxanthin, α-carotene, β-carotene, total carotenes, total xanthophylls, and provitamin A (P for interaction <0.05).

In men, the highest tertiles of serum canthaxanthin, total carotenes, and total carotenoids were associated with a 60–70% decreased risk compared with the lowest tertiles (Table 3): The multivariate-adjusted ORs (OR2) were 0.36 (95% confidence interval [CI] = 0.11–1.16; trend P over tertiles = 0.089) for canthaxanthin, 0.40 (95% CI = 0.14–1.17; trend $P = 0.10$) for total carotenes, and 0.34 (95% CI = 0.11–1.00; trend $P = 0.040$) for total carotenoids. In women, on the contrary, the higher levels of α- and β-carotenes and total carotenoids were related to a somewhat increased risk: The OR2 for the highest vs. the lowest tertile was 4.72 (95% CI = 1.29–17.3; trend $P = 0.007$) for α-carotene, 2.00 (95% CI = 0.70–5.73; trend $P = 0.040$) for β-carotene, and 2.47 (95% CI = 0.73–8.34; trend $P = 0.064$) for total carotenoids. The risk modification by sex for the highest tertile was statistically significant for zeaxanthin/lutein (P for interaction = 0.048), α-carotene ($P = 0.024$), total carotenes ($P = 0.037$), and total carotenoids ($P = 0.022$; data not shown in the table). Similar effect modifications by sex (i.e., low OR in men but high OR in women for the highest tertiles) were observed also for canthaxanthin (P for interaction = 0.055), β-carotene ($P = 0.056$), total xanthophylls ($P = 0.070$), and provitamin A ($P = 0.082$).

Among the carotenoids with possible effect modification by sex, all but α-carotene failed to show independent and significant ($P < 0.10$) effect modification by sex after adjustment for risk modification by smoking or drinking habit. For α-carotene, the risk modification by sex seemed to be independent of that by alcohol drinking (P for interaction between α-carotene and sex for the highest tertile = 0.096). On the other hand, an interaction was suggested between canthaxanthin and smoking ($P = 0.033$) or drinking habit ($P = 0.084$), which was independent of effect modification by sex; that is, the potential protective effects appeared to be stronger among smokers or drinkers. No significant interaction was found between carotenoids other than canthaxanthin and smoking or drinking habit after adjustment for the interaction between carotenoids and sex.

We also found a somewhat decreasing risk with increasing concentrations of serum retinol and α-tocopherol in men: The multivariate ORs (OR2) across tertiles were 1.00, 0.56 (95% CI = 0.20–1.52), and 0.31 (95% CI = 0.07–1.34) with a P for trend of 0.099 for retinol, and 1.00, 0.23 (95% CI = 0.07–0.80), and 0.29 (95% CI = 0.07–1.17) (trend $P = 0.098$) for α-tocopherol.

When we combined men and women for the substances without a substantial effect modification by sex (Table 4), the serum retinol level was inversely correlated with colorectal cancer risk. The OR2 (95% CI) over tertiles was 1.00, 0.51 (0.27–0.99), and 0.29 (0.11–0.78; trend $P = 0.010$). Subjects with a higher value of serum lycopene tended to show a lower OR (OR2 for the highest tertile = 0.48; 95% CI = 0.20–1.15; trend $P = 0.096$).

Findings for OR considering only matching variables (OR1) were generally in line with those for multivariate OR (OR2), but the OR1 tended to approach unity compared with OR2 (Tables 3 and 4). Excluding subjects without at least a 2-yr follow-up did not essentially alter the association of serum carotenoids, retinol, and tocopherols with the risk of colorectal cancer (data not shown).

Discussion

In the present study, we found that the higher serum total carotenes and total carotenoids tended to be associated with a decreased risk of colorectal cancer in men. On the contrary, women with higher levels of α- and β-carotenes and total carotenoids showed an increased risk. The female predominance in OR for the highest tertiles of serum levels was statistically or

Table 1. Distribution of Baseline Characteristics in Cases of Colorectal Cancer and Controls by Sex[a]

	Men					Women				
	Cases		Controls			Cases		Controls		
	N	%	*N*	%	*P* for Difference	*N*	%	*N*	%	*P* for Difference
Total number	54	100.0	141	100.0		62	100.0	157	100.0	
Age (yr)										
40–49	8	14.8	23	16.3	0.65	4	6.5	10	6.4	0.53
50–59	14	25.9	38	27.0		19	30.6	55	35.0	
60–69	20	37.0	53	37.6		30	48.4	74	47.1	
70–79	12	22.2	27	19.1		9	14.5	18	11.5	
Age at completion of education (yr)										
<16	15	27.8	39	27.7	0.57	14	22.6	43	27.4	0.30
16–18	17	31.5	49	34.8		32	51.6	77	49.0	
19–	9	16.7	16	11.3		7	11.3	12	7.6	
Unknown	13	24.1	37	26.2		9	14.5	25	15.9	
Family history of colorectal cancer in parents or siblings										
Yes	3	5.6	3	2.1	0.22	6	9.7	7	4.5	0.14
No	51	94.4	138	97.9		56	90.3	150	95.5	
Body mass index (kg/m^2)										
<20.0	7	13.0	19	13.5	0.42	13	21.0	20	12.7	0.16
20.0–24.9	34	63.0	93	66.0		32	51.6	83	52.9	
25.0–	13	24.1	24	17.0		16	25.8	49	31.2	
Unknown	0	0.0	5	3.5		1	1.6	5	3.2	
Smoking										
Nonsmokers	10	18.5	27	19.1	0.94	57	91.9	141	89.8	0.84
Ex-smokers	17	31.5	41	29.1		2	3.2	4	2.5	
Current smokers	25	46.3	68	48.2		2	3.2	3	1.9	
Unknown	2	3.7	5	3.5		1	1.6	9	5.7	
Alcohol drinking										
Nondrinkers	10	18.5	26	18.4	0.86	48	77.4	118	75.2	0.43
Ex-drinkers	2	3.7	8	5.7		0	0.0	4	2.5	
Current drinkers	41	75.9	105	74.5		13	21.0	29	18.5	
Unknown	1	1.9	2	1.4		1	1.6	6	3.8	
Walking time (min/day)										
≤30	10	18.5	28	19.9	0.70	9	14.5	36	22.9	0.20
≥30	30	55.6	71	50.4		40	64.5	94	59.9	
Unknown	14	25.9	42	29.8		13	21.0	27	17.2	
Sedentary work										
Yes	15	27.8	22	15.6	0.12	13	21.0	23	14.6	0.16
No	25	46.3	69	48.9		26	41.9	82	52.2	
Unknown	14	25.9	50	35.5		23	37.1	52	33.1	
Consumption of beef										
≤2 times/mo	22	40.7	53	37.6	0.66	22	35.5	61	38.9	0.85
1–2 times/wk	12	22.2	40	28.4		18	29.0	38	24.2	
≥3 times/wk	4	7.4	10	7.1		11	17.7	30	19.1	
Unknown	16	29.6	38	27.0		11	17.7	28	17.8	
Serum total cholesterol (mmol/l)										
<4.0	7	13.0	25	17.7	0.22	2	3.2	8	5.1	0.36
4.0–4.9	20	37.0	58	41.1		16	25.8	45	28.7	
5.0–5.9	17	31.5	36	25.5		25	40.3	62	39.5	
6.0–	9	16.7	18	12.8		18	29.0	38	24.2	
Unknown	1	1.9	4	2.8		1	1.6	4	2.5	

a: See text for details on the categories for walking time and consumption of beef.

Table 2. Geometric Means and 5-95 Percentiles (μmol/l) of Serum Levels of Retinol, Tocopherols, and Carotenoids in Cases of Colorectal Cancer and Controls by Sex

	Men			Women			
	Geometric Mean (5–95 percentile)			Geometric Mean (5–95 percentile)			
	Cases (N = 54)	Controls (N = 141)	P for Difference[a]	Cases (N = 62)	Controls (N = 157)	P for Difference[a]	P for Interaction Between Case-Control Status and Sex[b]
Retinol (μmol/l)	2.79 (1.37–5.45)	2.86 (1.78–4.52)	0.14	2.25 (1.47–3.89)	2.30 (1.43–4.36)	0.24	0.99
β-/γ-Tocopherols (μmol/l)	3.02 (1.32–8.51)	2.86 (1.21–6.75)	0.21	3.40 (2.05–6.63)	3.32 (1.57–6.27)	0.35	0.68
α-Tocopherol (μmol/l)	17.47 (8.80–30.13)	17.40 (6.99–30.81)	0.66	20.94 (9.38–34.82)	20.96 (9.82–34.95)	0.90	0.73
Zeaxanthin/lutein (μmol/l)	0.78 (0.32–1.77)	0.87 (0.38–2.07)	0.030	1.00 (0.46–1.76)	0.93 (0.38–1.88)	0.087	0.002
Canthaxanthin (μmol/l)	0.021 (0.008–0.057)	0.023 (0.010–0.053)	0.046	0.026 (0.013–0.055)	0.024 (0.011–0.051)	0.15	0.011
β-Cryptoxanthin (μmol/l)	0.20 (0.03–1.15)	0.18 (0.03–1.25)	0.62	0.32 (0.09–1.19)	0.32 (0.05–0.88)	0.74	0.99
Lycopene (μmol/l)	0.11 (0.02–0.48)	0.14 (0.03–0.75)	0.035	0.20 (0.02–1.10)	0.22 (0.05–1.06)	0.47	0.14
α-Carotene (μmol/l)	0.047 (0.003–0.176)	0.052 (0.010–0.160)	0.33	0.091 (0.024–0.234)	0.076 (0.014–0.211)	0.005	0.003
β-Carotene (μmol/l)	0.25 (0.04–1.21)	0.32 (0.07–1.49)	0.077	0.65 (0.10–2.38)	0.55 (0.08–1.69)	0.086	0.0009
Total carotenes (μmol/l)	0.45 (0.09–1.68)	0.56 (0.13–2.12)	0.051	1.00 (0.16–3.05)	0.91 (0.18–2.43)	0.22	0.004
Total xanthophylls (μmol/l)	1.09 (0.39–3.22)	1.16 (0.44–3.18)	0.25	1.43 (0.57–2.88)	1.34 (0.57–2.72)	0.15	0.017
Provitamin A (μmol/l)	0.54 (0.09–3.58)	0.59 (0.11–2.47)	0.46	1.13 (0.19–3.37)	1.00 (0.20–2.50)	0.10	0.020
Total carotenoids (μmol/l)	1.59 (0.52–4.87)	1.79 (0.64–4.68)	0.096	2.55 (0.80–5.88)	2.33 (0.75–5.00)	0.065	0.002

a: P value for difference of the geometric mean between cases and controls adjusted for education (age at completion of education: <16, 16–18, or ≥19 yr), family history of colorectal cancer in parents or siblings (yes or no), body mass index (as a continuous variable), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/mo, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (as a continuous variable) by analysis of covariance.

b: Adjusted for education (age at completion of education: <16, 16–18, or ≥19 yr), family history of colorectal cancer in parents or siblings (yes or no), body mass index (as a continuous variable), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/mo, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (as a continuous variable) by analysis of covariance. See text for details on the categories for walking time and consumption of beef.

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Colorectal Cancer Risk by Serum Levels of Carotenoids, Retinol, and Tocopherols by Sex[a]

	Men							Women						
	Category (μmol/l)	Cases	Controls	OR1[b]	95% CI	OR2[c]	95% CI	Category (μmol/l)	Cases	Controls	OR1[b]	95% CI	OR2[c]	95% CI
Retinol	<2.47	24	46	1.00		1.00		<1.93	22	51	1.00		1.00	
	2.47–3.35	14	48	0.45	0.18–1.14***	0.56	0.20–1.52	1.93–2.58	21	53	0.89	0.41–1.93	0.87	0.33–2.27
	3.36–	16	47	0.41	0.14–1.25	0.31	0.07–1.34	2.59–	19	53	0.53	0.17–1.71	0.49	0.10–2.43
					trend $P = 0.095$		trend $P = 0.099$					trend $P = 0.34$		trend $P = 0.44$
β-/γ-Tocopherols	<2.46	15	46	1.00		1.00		<2.81	16	52	1.00		1.00	
	2.46– 3.48	21	46	1.51	0.65–3.54	2.07	0.67–6.36	2.81– 3.97	26	50	1.60	0.76–3.35	1.85	0.76–4.47
	3.49–	18	48	1.36	0.51–3.62	1.85	0.50–6.87	3.98–	20	55	1.30	0.57–2.96	1.58	0.54–4.61
					trend $P = 0.59$		trend $P = 0.41$					trend $P = 0.51$		trend $P = 0.34$
α-tocopherol	<16.51	23	46	1.00		1.00		<19.53	22	51	1.00		1.00	
	16.51–22.52	12	48	0.40	0.15–1.03***	0.23	0.07–0.80**	19.53–25.42	18	53	0.75	0.31–1.83	0.71	0.23–2.21
	22.53–	19	47	0.61	0.20–1.87	0.29	0.07–1.17***	25.43–	22	53	1.03	0.42–2.54	0.70	0.20–2.46
					trend $P = 0.41$		trend $P = 0.098$					trend $P = 0.82$		trend $P = 0.62$
Zeaxanthin/lutein	<0.71	22	45	1.00		1.00		<0.79	21	51	1.00		1.00	
	0.71–1.02	16	49	0.64	0.28–1.47	0.66	0.23–1.89	0.79–1.11	12	52	0.60	0.25–1.45	0.81	0.29–2.28
	1.03–	16	47	0.62	0.26–1.51	0.48	0.17–1.39	1.12–	29	54	1.53	0.68–3.44	1.96	0.72–5.28
					trend $P = 0.29$		trend $P = 0.18$					trend $P = 0.20$		trend $P = 0.15$
Canthaxanthin	<0.017	21	44	1.00		1.00		<0.021	16	52	1.00		1.00	
	0.017–0.029	17	49	0.68	0.30–1.57	0.48	0.17–1.33	0.021–0.031	23	48	1.64	0.69–3.91	1.54	0.56–4.22
	0.030–	16	48	0.58	0.23–1.46	0.36	0.11–1.16***	0.032–	23	57	1.49	0.63–3.53	1.83	0.62–5.35
					trend $P = 0.25$		trend $P = 0.089$					trend $P = 0.44$		trend $P = 0.28$
β-cryptoxanthin	<0.11	17	46	1.00		1.00		<0.28	26	51	1.00		1.00	
	0.11–0.32	20	48	1.11	0.45–2.73	1.02	0.34–3.03	0.28–0.46	16	53	0.57	0.25–1.31	0.43	0.15–1.22
	0.33–	17	47	0.92	0.35–2.47	0.95	0.28–3.23	0.47–	20	53	0.71	0.30–1.67	0.50	0.18–1.44
					trend $P = 0.84$		trend $P = 0.93$					trend $P = 0.49$		trend $P = 0.24$
Lycopene	<0.09	20	43	1.00		1.00		<0.13	23	52	1.00		1.00	
	0.09–0.20	17	50	0.70	0.30–1.63	0.77	0.28–2.16	0.13–0.34	16	52	0.76	0.34–1.71	0.71	0.27–1.88
	0.21–	17	48	0.73	0.29–1.87	0.57	0.19–1.71	0.35–	23	53	1.23	0.46–3.32	1.12	0.32–3.95
					trend $P = 0.51$		trend $P = 0.32$					trend $P = 0.76$		trend $P = 0.93$
α-carotene	<0.038	16	41	1.00		1.00		<0.070	17	51	1.00		1.00	
	0.038–0.079	24	53	0.99	0.46–2.16	1.10	0.41–2.93	0.070–0.102	14	51	1.03	0.39–2.73	1.36	0.38–4.87
	0.080–	14	47	0.63	0.25–1.57	0.73	0.24–2.20	0.103–	31	55	2.70	1.05–6.95**	4.72	1.29–17.3**
					trend $P = 0.30$		trend $P = 0.54$					trend $P = 0.019$		trend $P = 0.007$

(continued)

Table 3. *(Continued)*

	Men							Women						
	Category (μmol/l)	Cases	Controls	OR1[b]	95% CI	OR2[c]	95% CI	Category (μmol/l)	Cases	Controls	OR1[b]	95% CI	OR2[c]	95% CI
β-carotene	<0.21	21	45	1.00		1.00		<0.50	20	52	1.00		1.00	
	0.21–0.53	20	49	0.79	0.34–1.82	0.69	0.25–1.90	0.50–0.75	8	52	0.42	0.15–1.18***	0.24	0.06–0.89**
	0.54–	13	47	0.48	0.19–1.18	0.39	0.12–1.23	0.76–	34	53	1.88	0.84–4.22	2.00	0.70–5.73
					trend $P = 0.11$		trend $P = 0.10$					trend $P = 0.029$		trend $P = 0.040$
Total carotenes	<0.42	25	46	1.00		1.00		<0.80	21	52	1.00		1.00	
	0.42–0.87	15	48	0.46	0.18–1.17	0.28	0.08–1.02***	0.80–1.36	14	52	0.77	0.32–1.81	0.59	0.21–1.71
	0.88–	14	47	0.45	0.19–1.05***	0.40	0.14–1.17***	1.37–	27	53	1.78	0.74–4.28	1.96	0.61–6.34
					trend $P = 0.070$		trend $P = 0.10$					trend $P = 0.16$		trend $P = 0.21$
Total xanthophylls	<0.95	22	46	1.00		1.00		<1.20	21	52	1.00		1.00	
	0.95–1.41	15	47	0.64	0.28–1.46	0.50	0.17–1.50	1.20–1.63	12	52	0.66	0.28–1.55	0.68	0.24–1.92
	1.42–	17	48	0.66	0.29–1.53	0.60	0.21–1.69	1.64–	29	53	1.62	0.72–3.64	2.01	0.71–5.68
					trend $P = 0.34$		trend $P = 0.34$					trend $P = 0.17$		trend $P = 0.14$
Provitamin A	<0.38	19	46	1.00		1.00		<0.93	18	52	1.00		1.00	
	0.38–0.93	22	48	1.12	0.46–2.69	1.07	0.36–3.18	0.93–1.38	15	51	1.07	0.44–2.59	0.98	0.33–2.88
	0.94–	13	47	0.59	0.23–1.55	0.46	0.14–1.55	1.39–	29	54	1.91	0.84–4.37	1.98	0.68–5.71
					trend $P = 0.23$		trend $P = 0.20$					trend $P = 0.078$		trend $P = 0.12$
Total carotenoids	<1.48	28	46	1.00		1.00		<2.06	20	52	1.00		1.00	
	1.48–2.20	10	48	0.29	0.12–0.72*	0.19	0.06–0.66*	2.06–2.95	12	52	0.75	0.29–1.92	0.62	0.19–2.03
	2.21–	16	47	0.45	0.19–1.04***	0.34	0.11–1.00***	2.96–	30	53	1.96	0.79–4.87	2.47	0.73–8.34
					trend $P = 0.054$		trend $P = 0.040$					trend $P = 0.057$		trend $P = 0.064$

a: $*P < 0.01$; $**P < 0.05$; $***P < 0.10$. Controls were not precisely divided into three even groups because of identical measurement values.

b: Considering only matching variables (age and participating institution) by using conditional logistic models.

c: Adjusted for education (age at completion of education: <16, 16–18, or ≥19 yr), 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), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/mo, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (<4.0, 4.0–4.9, 5.0–5.9, or ≥6.0 mmol/l) by using conditional logistic models. See text for details on the categories for walking time and consumption of beef.

Table 4. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Colorectal Cancer Risk by Serum Levels of Carotenoids, Retinol, and Tocopherols in Men and Women Combined[a]

	Category (μmol/l)	Cases	Controls	OR1[b]	95% CI	OR2[c]	95% CI
Retinol	<2.11	45	95	1.00		1.00	
	2.11–3.01	37	103	0.63	0.34–1.14	0.51	0.27–0.99*
	3.02–	34	100	0.42	0.18–0.98*	0.29	0.11–0.78*
					trend $P = 0.039$		trend $P = 0.010$
β-/γ-Tocopherols	<2.65	32	98	1.00		1.00	
	2.65–3.61	44	89	1.53	0.87–2.69	1.48	0.77–2.81
	3.62–	40	110	1.21	0.65–2.26	1.17	0.56–2.44
					trend $P = 0.57$		trend $P = 0.65$
α-Tocopherol	<17.86	42	96	1.00		1.00	
	17.86–23.85	33	101	0.75	0.41–1.38	0.60	0.29–1.22
	23.86–	41	101	0.96	0.49–1.89	0.61	0.27–1.39
					trend $P = 0.99$		trend $P = 0.30$
β-Cryptoxanthin	<0.18	40	99	1.00		1.00	
	0.18–0.40	39	98	0.95	0.52–1.72	0.89	0.45–1.74
	0.41–	37	101	0.90	0.46–1.76	0.78	0.36–1.70
					trend $P = 0.75$		trend $P = 0.53$
Lycopene	<0.10	38	85	1.00		1.00	
	0.10–0.27	42	112	0.83	0.47–1.45	0.70	0.37–1.31
	0.28–	36	101	0.76	0.35–1.64	0.48	0.20–1.15**
					trend $P = 0.46$		trend $P = 0.096$

a: $*P < 0.05$; $**P < 0.10$. Analysis was restricted to antioxidants with no substantial effect modification by sex. Controls were not precisely divided into three even groups because of identical measurement values.

b: Considering only matching variables (sex, age, and participating institution) by using conditional logistic models.

c: Adjusted for education (age at completion of education: <16, 16–18, or ≥19 yr), 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), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 or ≥30 min/day), sedentary work (yes or no), consumption of beef (≤2 times/mo, 1–2 times/wk, or ≥3 times/wk), and serum total cholesterol level (<4.0, 4.0–4.9, 5.0–5.9, or ≥6.0 mmol/l) by using conditional logistic models. See text for details on the categories for walking time and consumption of beef.

marginally significant for several carotenoids. Such effect modifications by sex were also detected when we compared geometric means of serum concentrations between cases and controls. In addition, we found a somewhat decreasing trend in risk with increasing serum levels of retinol in men or men and women combined, and of α-tocopherol in men.

There is little evidence of any relationship between blood levels of carotenoids and colorectal cancer risk. Malila et al. (11) reported no association of serum β-carotene with the risk of colorectal cancer in an 8-yr prospective study of male smokers. For colorectal adenomas, the precursors of colorectal cancers, Erhardt et al. (23) found that the plasma lycopene level was significantly lower in the adenoma group than in the control group. They also reported a lower plasma β-carotene level, although not significant, in adenoma cases. Their findings are, in part, consistent with ours that the geometric mean of serum lycopene concentration was significantly lower in male cases of colorectal cancer than in corresponding controls, and subjects with a higher level of serum lycopene were at a somewhat lower risk in the analysis with men and women combined. Shikany and coworkers (24), however, revealed no associations between any individual carotenoid or total carotenoids in plasma and adenomatous polyps in a case-control study. The study, however, included only adenomas of the distal colon and rectum, while subjects in the study by Erhardt et al. (23) underwent a total colonoscopy.

In line with some previous studies on α-tocopherol and retinol, we found a somewhat decreasing trend in risk with increasing serum levels of α-tocopherol and retinol in men. A pooled analysis of data from five cohorts revealed a 30% reduction in colorectal cancer risk for the highest quartile of serum α-tocopherol concentration compared with the lowest after adjustment for serum cholesterol level (25). Ingles et al. (26) found that a high α-tocopherol to γ-tocopherol ratio was associated with a decreased risk of large colorectal adenomas. Furthermore, in a controlled trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, α-tocopherol supplementation conferred a modest preventive effect against colorectal cancer in older male smokers (27). Breuer-Katschinski et al. (28) found an inverse association between serum concentration of vitamin A and colorectal adenoma in a case-control study, although the risk was not correlated with the serum vitamin E level.

Malila and colleagues (11), however, did not support the possible protective effects of α-tocopherol or retinol against colorectal cancer in a prospective study using serum samples before the intervention of the ATBC study. More data, particularly from prospective studies, should be accumulated to assess the relationship between blood levels of tocopherols or

retinol and the risk of not only colorectal adenoma but also cancer of the colorectum.

The low risk in men and the high risk in women associated with higher serum levels of some carotenoids can be interpreted in several ways. First, men and women may biologically differ in the effects of carotenoids on colorectal cancer. In women, blood carotenoid levels seem to be regulated by sex hormones to some extent and thus may have implications different from those of men for cancer risk (29). Murtaugh et al. (30) detected no association between dietary β-carotene and rectal cancer risk in a case-control study in the analysis by sex. Among female subjects, however, they found an increased risk associated with combination of lower presumed estrogen status (postmenopausal without hormone replacement therapy) and low intake of β-carotene. This suggests that sex hormones may modify the action of carotenoids. However, the authors also reported a negative association of dietary lycopene with rectal cancer risk only in women, which may be somewhat inconsistent with our findings, that is, the elevated risk in women with higher serum levels of selected carotenoids. Further investigations on possible interactions between sex hormones and carotenoids are warranted.

Second, lifestyles more prevalent in Japanese men than in women, such as smoking or alcohol drinking, may interact with the effect of carotenoids. Smoking and drinking habits have been related to decreased blood levels of carotenoids (31,32), and the lowered levels may not be enough to exert protective effects against colorectal cancer. Although it was not feasible to examine the interaction between these lifestyle factors and carotenoids in the present study due to the limited number of nonsmoking or nondrinking men, the greater risk reduction by intake of vegetables and fruits in smokers has been observed for cancer of the lung (33) and stomach (34). Supplementation of β-carotene, however, conferred a modest increase in the risk of colorectal adenoma recurrence in smokers while decreasing the risk in nonsmoking and nondrinking subjects (35). Although the effect modification by sex for carotenoids might be confounded by smoking or drinking habit, the very strong correlations between sex and these lifestyles prevented us from drawing clear conclusions, even with the multivariate analysis; for example, the female subjects were almost all nonsmokers. Studies in nonsmokers or nondrinkers would be required to address this issue.

On balance, the greater risk of colorectal cancer in women with higher serum concentrations of carotenes cannot be explained by the two interpretations mentioned previously. The third hypothesis is that blood levels of some carotenoids may have a U-shaped association with colorectal cancer risk regardless of sex. Too much carotene intake could increase the risk of malignancy (36). β-Carotene has not only antioxidant activity but also prooxidant actions, especially at high concentrations and/or under high oxygen tension (37). Although the colon is in an anaerobic environment, higher oral intake of β-carotene can lead to its accumulation in the colonic mucosa (38), and its tissue concentration may reach a level at which β-carotene acts as a prooxidant. In the present study, women generally demonstrated higher levels of serum carotenoids than men. A part of female subjects may have had such high blood levels that it increased their risk of colorectal cancer, while men with relatively higher levels may have shown a lower risk.

The strength of our study derives principally from its prospective design in that blood samples were collected before diagnosis of colorectal cancer. Using serum samples allowed objective measurements of dietary factors, considering inter-individual variations of their bioavailability. Some methodological limitations, however, need elucidation.

First, the sample size was relatively small to examine the sex-specific effects of carotenoids, retinol, and tocopherols on colorectal cancer risk. These significant effect modifications by sex for some carotenoids, therefore, must be confirmed by larger studies.

Second, the serum levels of carotenoids, retinol, and tocopherols varied widely between study areas: The coefficients of variation computed by one-way analysis of variance ranged from 69.6% (total xanthophylls) to 285.3% (lycopene) in men and from 87.4% (canthaxanthin) to 290.9% (lycopene) in women. These variations between areas may partly be due to not only the difference in dietary intake but also to the difference in procedures after drawing blood. The cases and controls, however, are still comparable because of the matching for participating institutions. Further, even when excluding a study area with the values furthest from the means, the overall directions of associations for some carotenoids, namely, inverse associations in men and positive ones in women, were not altered.

Finally, we could not include all the potentially confounding factors. For example, the limitation of samples prevented us from considering serum folate. Folate has been linked to the reduced risk of colorectal cancer in alcohol drinkers (39) and is rich in green leafy vegetables that also contain much carotenoid. Adjustment for consumption of green leafy vegetables, however, strengthened the inverse associations of some carotenoids with colorectal cancer risk in men: The multivariate-adjusted ORs for the middle and highest tertiles were 0.42 (95% CI = 0.15–1.20) and 0.20 (95% CI = 0.06–0.72) for canthaxanthin (trend $P = 0.014$), 0.23 (95% CI = 0.06–0.90) and 0.22 (95% CI = 0.06–0.81) for total carotenes (trend $P = 0.023$), and 0.17 (95% CI = 0.05–0.60) and 0.24 (95% CI = 0.07–0.82) for total carotenoids (trend $P = 0.011$), respectively. Moreover, the positive associations of serum levels of α- and β-carotenes and total carotenoids with colorectal cancer risk in women cannot be ascribed to the confounding by folate.

In conclusion, the effect of some carotenoids on colorectal cancer risk may be modified by sex or by factors associated with sex, including lifestyle factors such as smoking and drinking habits. The male low risk and female high risk associated with the higher blood levels, if confirmed, could provide another interpretation to the relationship between vegetable and fruit consumption and the risk of colorectal cancer. The observed decreasing trend in risk with an elevating se-

rum retinol (in men or men plus women) and α-tocopherol (in men) may support the possible protective effects of these substances against colorectal cancer.

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Mortality in the JACC Study till 1999

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BACKGROUND: We have been conducting a cohort study named "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)" since 1988. The aim of this paper is to describe the mortality of our JACC cohort in the follow-up period from 1988 through 1999, to compare it with the mortality, especially cancer deaths, of the Japanese population in the same period and to compare the causes of mortality by district among the cohort.
METHODS: We conducted a follow-up study of 110,792 Japanese inhabitants aged 40-79 years in 1988-1990 for about 10 years to the end of 1999.
RESULTS: Of 46,465 males, 37,750 (81.2%) were alive, 7,238 (15.6%) were dead and 1,477 (3.2%) had moved out of the study areas. The figures were 57,016 (88.6%), 4,940 (7.7%) and 2,371 (3.7%) among 64,327 females, respectively. The mean follow-up period was 9.9 years. The proportion of cancer deaths by site in our cohort members was almost same as the Japanese population aged 40-79 years old in 1995. Sex-specific standardized mortality ratios of total deaths, all cancer deaths, and most cancers in our cohort were less than 100 in both males and females for total cohort and the cohort by district.
CONCLUSION: Our cohort members appeared to be almost the same or slightly healthier and less likely to die from total causes and cancers than the general population.
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Key words: Japan Collaborative Cohort Study (JACC Study), Cancer, Mortality

A large-scale population based cohort study named "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)"[1] was initiated in 1988. The purpose of this study is to address the relationship between recent Japanese lifestyles and cancer. There were no other cohort studies in Japan at that time since Hirayama's large-scale cohort study[2] on cancer which was initiated in 1965 and terminated in 1982, even though the Japanese lifestyle, especially dietary habits, have dramatically changed since the end of the Second World War in 1945.[3] Epidemiologic studies using questionnaires on smoking, drinking and diet are important. However, those using biological markers can provide much more informative evidence for cancer pathogenesis. Therefore, another purpose of the JACC Study is to investigate the relationship between biological markers and cancer risk.

This paper will aim to describe the mortality of our JACC cohort in the follow-up period from 1988 through 1999, to compare it with the mortality, especially cancer deaths, of the Japanese population in the same period and to compare the causes

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