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-
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 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 (<20.0, 20.0–24.9, or ≥25.0 kg/m²), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30 min/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/m²), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤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 carotenotes, 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 carotenotes, 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-carotenotes 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 carotenotes ($P = 0.037$), 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-carotenotes 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<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
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</tr>
<tr>
<td>Age (yr)</td>
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<tr>
<td>40–49</td>
<td>8</td>
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<tr>
<td>50–59</td>
<td>14</td>
<td>25.9</td>
</tr>
<tr>
<td>60–69</td>
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<td>37.0</td>
</tr>
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<td>70–79</td>
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<tr>
<td>Age at completion of education (yr)</td>
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</tr>
<tr>
<td>&lt;16</td>
<td>15</td>
<td>27.8</td>
</tr>
<tr>
<td>16–18</td>
<td>17</td>
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</tr>
<tr>
<td>19–</td>
<td>9</td>
<td>16.7</td>
</tr>
<tr>
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<td>24.1</td>
</tr>
<tr>
<td>Family history of colorectal cancer in parents or siblings</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3</td>
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</tr>
<tr>
<td>No</td>
<td>51</td>
<td>94.4</td>
</tr>
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<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
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<tr>
<td>Ex-smokers</td>
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<td>31.5</td>
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<tr>
<td>Current smokers</td>
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<td>3.7</td>
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<td>Consumption of beef</td>
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<tr>
<td>≤2 times/mo</td>
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<tr>
<td>1–2 times/wk</td>
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<td>≥3 times/wk</td>
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<td>5.0–5.9</td>
<td>17</td>
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<sup>a</sup>: 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

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

<sup>b</sup>: 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

<table>
<thead>
<tr>
<th>Category (µmol/l)</th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR1</td>
<td>OR2</td>
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<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>trend</td>
<td>trend</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Retinol</td>
<td></td>
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<tr>
<td>&lt;2.47</td>
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<td>2.47–3.35</td>
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<td>3.36–</td>
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<td>47</td>
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<td>trend P = 0.099</td>
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<td></td>
</tr>
<tr>
<td>β-γ-Tocopherols</td>
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<td></td>
</tr>
<tr>
<td>&lt;2.46</td>
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<td>46</td>
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<tr>
<td>2.46–3.48</td>
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<td>46</td>
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<tr>
<td>3.49–</td>
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<td>48</td>
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<tr>
<td>α-tocopherol</td>
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<td>16.51–22.52</td>
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<td>1.03–</td>
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<td>Canthaxanthin</td>
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<td>β-cryptoxanthin</td>
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<td>&lt;0.11</td>
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<td>48</td>
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<td>0.21–</td>
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<td>48</td>
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<td>trend P = 0.32</td>
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<td>0.080–</td>
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(continued)
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<th>Cases</th>
<th>Controls</th>
<th>OR^1^</th>
<th>95% CI</th>
<th>OR^2^</th>
<th>95% CI</th>
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<td></td>
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<td>&lt;0.21</td>
<td>21</td>
<td>45</td>
<td>1.00</td>
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<td>1.00</td>
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<td>0.21–0.53</td>
<td>20</td>
<td>49</td>
<td>0.79</td>
<td>0.34–1.82</td>
<td>0.69</td>
<td>0.25–1.90</td>
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<tr>
<td>0.54–</td>
<td>13</td>
<td>47</td>
<td>0.48</td>
<td>0.19–1.18</td>
<td>0.39</td>
<td>0.12–1.23</td>
</tr>
<tr>
<td>Total carotenoids</td>
<td>&lt;0.42</td>
<td>25</td>
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<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0.42–0.87</td>
<td>15</td>
<td>48</td>
<td>0.46</td>
<td>0.18–1.17</td>
<td>0.28</td>
<td>0.08–1.02***</td>
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<tr>
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<td>14</td>
<td>47</td>
<td>0.45</td>
<td>0.19–0.5***</td>
<td>0.40</td>
<td>0.14–1.17***</td>
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<td>1.00</td>
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<tr>
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<td>0.50</td>
<td>0.17–1.50</td>
</tr>
<tr>
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<td>17</td>
<td>48</td>
<td>0.66</td>
<td>0.29–1.53</td>
<td>0.60</td>
<td>0.21–1.69</td>
</tr>
<tr>
<td><strong>Provitamin A</strong></td>
<td>&lt;0.38</td>
<td>19</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
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</tr>
<tr>
<td>0.38–0.93</td>
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<td>0.46–2.69</td>
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<td>0.36–3.18</td>
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<tr>
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<td>0.59</td>
<td>0.23–1.55</td>
<td>0.46</td>
<td>0.14–1.55</td>
</tr>
<tr>
<td><strong>Total carotenoids</strong></td>
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<td>1.00</td>
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<tr>
<td>1.48–2.20</td>
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<td>48</td>
<td>0.29</td>
<td>0.12–0.72*</td>
<td>0.19</td>
<td>0.06–0.66*</td>
</tr>
<tr>
<td>2.21–</td>
<td>16</td>
<td>47</td>
<td>0.45</td>
<td>0.19–1.04***</td>
<td>0.34</td>
<td>0.11–1.00***</td>
</tr>
</tbody>
</table>

**Men**

<table>
<thead>
<tr>
<th>Category (µmol/l)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR^1^</th>
<th>95% CI</th>
<th>OR^2^</th>
<th>95% CI</th>
</tr>
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<td>20</td>
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<td></td>
<td>1.00</td>
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</tr>
<tr>
<td>0.50–0.75</td>
<td>8</td>
<td>52</td>
<td>0.42</td>
<td>0.15–1.18***</td>
<td>0.24</td>
<td>0.06–0.89***</td>
</tr>
<tr>
<td>0.76–</td>
<td>34</td>
<td>53</td>
<td>1.88</td>
<td>0.84–4.22</td>
<td>2.00</td>
<td>0.70–5.73</td>
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<tr>
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<td>1.00</td>
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<td>0.80–1.36</td>
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<td>52</td>
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<td>0.21–1.71</td>
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<td>0.61–6.34</td>
</tr>
<tr>
<td><strong>Total xanthophylls</strong></td>
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<td>1.00</td>
<td></td>
<td>1.00</td>
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</tr>
<tr>
<td>1.20–1.63</td>
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<td>0.28–1.55</td>
<td>0.68</td>
<td>0.24–1.92</td>
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<td>0.72–3.64</td>
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<td>0.71–5.68</td>
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<tr>
<td><strong>Provitamin A</strong></td>
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<td></td>
<td>1.00</td>
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<td>0.93–1.38</td>
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<td>51</td>
<td>1.07</td>
<td>0.44–2.59</td>
<td>0.98</td>
<td>0.33–2.88</td>
</tr>
<tr>
<td>1.39–</td>
<td>29</td>
<td>54</td>
<td>1.91</td>
<td>0.84–4.37</td>
<td>1.98</td>
<td>0.68–5.71</td>
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<td>0.19–2.03</td>
</tr>
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<td>53</td>
<td>1.96</td>
<td>0.79–4.87</td>
<td>2.47</td>
<td>0.73–8.34</td>
</tr>
</tbody>
</table>

**Women**

---

*a:* *P* < 0.01; **a:** *P* < 0.05; ***a:* *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/m²), 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 Combineda

<table>
<thead>
<tr>
<th>Category (µmol/l)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR1b</th>
<th>95% CI</th>
<th>OR2b</th>
<th>95% CI</th>
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<td></td>
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<td></td>
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<tr>
<td>&lt;0.10</td>
<td>38</td>
<td>95</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
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</tr>
<tr>
<td>0.11–0.30</td>
<td>34</td>
<td>100</td>
<td>0.91</td>
<td>0.46–1.84</td>
<td>0.59</td>
<td>0.29–1.40</td>
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<td>100</td>
<td>0.77</td>
<td>0.35–1.80</td>
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<td>0.28–1.44</td>
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<td>0.49</td>
<td>0.17–1.40</td>
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<td>0.27–1.53</td>
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<td>0.75</td>
<td>0.31–1.80</td>
<td>0.69</td>
<td>0.28–1.53</td>
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<td>0.59</td>
<td>0.23–1.40</td>
<td>0.73</td>
<td>0.27–1.62</td>
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<td>5.01–10.00</td>
<td>15</td>
<td>100</td>
<td>0.49</td>
<td>0.18–1.40</td>
<td>0.77</td>
<td>0.28–1.69</td>
</tr>
</tbody>
</table>

| β-γ-Tocopherols  |       |          |       |        |       |        |
| <0.25            | 32    | 98       | 1.00  |        | 1.00  |        |
| 0.25–0.50        | 44    | 90       | 0.75  | 0.41–1.38 | 0.70  | 0.36–1.29 |
| 0.51–0.75        | 42    | 100      | 0.50  | 0.26–0.99 | 0.75  | 0.38–1.40 |
| 0.76–1.00        | 36    | 100      | 0.29  | 0.12–0.76* | 0.60  | 0.26–1.38 |
| 1.01–1.25        | 32    | 100      | 0.80  | 0.40–1.61 | 0.79  | 0.37–1.40 |
| 1.26–1.50        | 28    | 100      | 0.47  | 0.20–1.02 | 0.73  | 0.34–1.48 |
| 1.51–1.75        | 21    | 100      | 0.28  | 0.09–0.86 | 0.59  | 0.23–1.48 |

| α-Tocopherol     |       |          |       |        |       |        |
| <0.10            | 42    | 96       | 1.00  |        | 1.00  |        |
| 0.11–0.30        | 33    | 100      | 0.75  | 0.41–1.38 | 0.60  | 0.29–1.22 |
| 0.31–0.60        | 41    | 101      | 0.96  | 0.49–1.89 | 0.61  | 0.27–1.39 |
| 0.61–1.20        | 39    | 101      | 0.90  | 0.46–1.80 | 0.78  | 0.36–1.70 |
| 1.21–2.50        | 33    | 100      | 0.65  | 0.33–1.29 | 0.75  | 0.35–1.54 |
| 2.51–5.00        | 28    | 100      | 0.55  | 0.27–1.11 | 0.80  | 0.37–1.73 |
| 5.01–10.00       | 22    | 100      | 0.44  | 0.19–1.00 | 0.72  | 0.34–1.53 |

| β-Cryptoxanthin  |       |          |       |        |       |        |
| <0.18            | 40    | 99       | 1.00  |        | 1.00  |        |
| 0.19–0.40        | 39    | 98       | 0.95  | 0.52–1.72 | 0.89  | 0.45–1.74 |
| 0.41–0.75        | 37    | 101      | 0.90  | 0.46–1.76 | 0.78  | 0.36–1.70 |
| 0.76–1.10        | 40    | 100      | 0.75  | 0.39–1.51 | 0.75  | 0.36–1.53 |
| 1.11–1.45        | 38    | 100      | 0.60  | 0.31–1.18 | 0.75  | 0.36–1.53 |
| 1.46–1.81        | 36    | 100      | 0.47  | 0.20–1.09 | 0.75  | 0.36–1.53 |
| 1.82–2.15        | 34    | 100      | 0.35  | 0.15–0.87 | 0.72  | 0.35–1.54 |

| 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 |
| 0.28–0.50        | 36    | 101      | 0.76  | 0.35–1.64 | 0.48  | 0.20–1.15** |

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/m²), smoking (never smokers, ex-smokers, or current smokers), alcohol drinking (never drinkers, ex-drinkers, or current drinkers), walking time (≤30, 30–60, or >60 min/day), sedentary work (yes or no), consumption of beef (<2, 2–4, 4–6, or >6 g/day), smoking time (0–1, 1–2, or >2 yrs), 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 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). Murtagh 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 carotenoids 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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