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Carotenoid Intake and Risk of Colorectal Adenomas in a Cohort of Male Health Professionals

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Abstract

Purpose—Carotenoids have been hypothesized to prevent carcinogenesis through their antioxidant and pro-vitamin A properties. We examined associations between intakes of specific carotenoids and risk of colorectal adenomas.

Methods—Among 29,363 men who reported having a lower bowel endoscopy between 1986–2006, 3,997 cases of colorectal adenoma were identified in the Health Professionals Follow-up Study. Participants completed food frequency questionnaires every 4 years; dietary information was cumulatively updated. The associations between carotenoid intakes and risk of colorectal adenomas overall and by anatomic site, stage, smoking status and alcohol consumption were investigated using multivariate logistic regression models.

Results—Total β-carotene and dietary β-carotene, lycopene and lutein/zeaxanthin intakes and the total carotenoid score were inversely associated with colorectal adenoma risk. The odds ratios (95% confidence intervals) comparing the highest vs. lowest quintile of intake were 0.78 (0.69–0.88) for total β-carotene, 0.72 (0.64–0.81) for dietary β-carotene, 0.83 (0.74–0.93) for lycopene, 0.86 (0.76–0.96) for lutein/zeaxanthin, and 0.87 (0.77–0.97) for the total carotenoid score. Associations for α-carotene and β-cryptoxanthin intakes were null. We did not find significant differences in the associations between intakes of each carotenoid and risk of colorectal adenoma by anatomic site or stage (all p-values, test for common effects > 0.10). The inverse associations we observed for total β-carotene and dietary β-carotene, lycopene, and lutein/zeaxanthin intakes and the total carotenoid score with adenoma risk also did not vary by smoking status and alcohol consumption.

Conclusion—This study found that a diet high in carotenoids was associated with a reduced risk of colorectal adenomas.

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Keywords

carotenoids; nutrition; colorectal adenomas; colorectal cancer; epidemiology

Introduction

Colorectal cancer is the third leading cause of non-cutaneous cancer and cancer death among men and women in the United States (1). Colorectal adenomas are precursor lesions of colorectal cancer (2). Therefore, identifying potential modifiable lifestyle factors (including diet) that can reduce the risk of colorectal adenomas may be an effective approach to prevent the development of colorectal cancer.

Carotenoids are red, orange and yellow fat-soluble pigments that are rich in fruit and vegetables (3). The carotenoids found most commonly in diet and human plasma are α-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein/zeaxanthin (3). Their most common dietary sources in the US are carrots for α-carotene and β-carotene, oranges/orange juice for β-cryptoxanthin, tomatoes/tomato products for lycopene, and spinach for lutein and zeaxanthin (4). Carotenoids have been speculated to prevent cancer through their antioxidant properties and provitamin A activity (3).

However, epidemiological evidence for an association between carotenoids and risk of colorectal carcinogenesis has been inconclusive. A large pooled study including 11 prospective cohort studies (5) found no significant associations with risk of colorectal cancer with relative risks comparing the highest versus lowest quintile of intake ranging from 0.92 to 1.04 across the five carotenoids. The World Cancer Research Fund/American Institute for Cancer Research report also concluded that the evidence for an association between carotenoid intake and risk of colorectal cancer is limited (6).

Colorectal adenomas are precursors to cancers and may provide insights to the early steps of carcinogenesis. The data on intake of individual carotenoids and colorectal adenoma risk are inconsistent (7–16). This may be partly due to the unavailability of a comprehensive food composition data for individual carotenoids until the 1990s (17, 18), resulting in earlier studies (13–15) being more likely to report the results on multiple carotenoids expressed as carotene rather than on specific carotenoids. Previous case-control studies have reported non-significant associations between overall carotenoid intake and colorectal adenoma risk (14, 15). However, β-carotene intake was inversely associated with the risk of colorectal adenomas in some case-control (12, 13, 16) and cohort (11) studies. Only two studies have examined associations between intakes of carotenoids other than β-carotene, and the results were generally null (11, 16). A significant inverse association was reported only for α-carotene intake in one of the studies (11). Results from randomized controlled trials of β-carotene supplementation (7, 9, 10, 19) have been relatively null. The results observed have been further complicated by the potentially varied biologic effect of β-carotene by smoking and drinking habits. In a randomized controlled trial of β-carotene supplements, a reduction in levels of inflammatory markers and oxidative stress were observed among non-smokers, but not among current smokers (20). Further, in a randomized trial of adenoma recurrence (8), recurrence rates were significantly lower in the β-carotene supplement group compared to the placebo group in the subgroup of nonsmokers and nondrinkers, but were significantly higher in the β-carotene supplement group in the subgroup of smokers who consumed more than 10g/d of alcohol. In a previous case-control study, a significant inverse association between β-carotene intake and risk of colorectal adenomas was observed in nonsmokers, but a non-significant positive association was observed in past and current smokers (21). In contrast, observational studies examining associations between dietary carotenoid intakes

and risk of colorectal cancer have not observed statistically significant differences in the associations by smoking status and/or alcohol consumption levels (22–24).

Therefore, we examined the associations between intake of the 5 major carotenoids and risk of colorectal adenomas in the Health Professionals Follow-up Study, a large cohort study with repeated dietary assessments and long term follow up.

Materials and Methods

Study population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective cohort study that began in 1986. Study participants consist of 51,529 male health professionals, aged 40 to 75 y, who completed a detailed questionnaire on demographics, medical history, dietary intake and lifestyle factors in 1986. Every 2 years, follow-up questionnaires have been mailed to participants to update information on lifestyle factors and medical history. Every 4 years, diet has been assessed with a semi-quantitative food frequency questionnaire (SFFQ). The follow-up rate of the HPFS cohort is more than 90% of the total possible person-years. This study was approved by the institutional review board at the Harvard School of Public Health.

Dietary assessment

Every 4 years starting in 1986, participants completed a self-administered SFFQ to provide their usual dietary intake information over the past year. The baseline SFFQ included questions on consumption of 131 food items, and use of vitamin/mineral supplements, as well as open-ended sections for brand names and foods not specifically listed on the questionnaire. There were minor changes in the number of food items and the specific foods assessed on subsequent SFFQ. Nutrient intakes were computed by multiplying the frequency of intake of each food on the SFFQ with the nutrient content of the specified portion of that food. The carotenoid content of the food was based on the information in the USDA-National Cancer Institute carotenoid database, including the updated values for tomato products (17, 25, 26). For β-carotene, we analyzed intakes from foods and supplements combined (total intake) and intakes from foods only (dietary intake). For the other carotenoids, we only analyzed intakes from foods only (dietary intake) because supplemental intake of these carotenoids was not assessed until 1998. We used the residual method to adjust intakes for total energy intake (27).

The validity and reproducibility of the FFQ have been described previously (28, 29). The correlation between total carotene intake estimated from the FFQ and intake estimated from 2, seven-day diet records administered 6 months apart, was 0.64 (28). The correlations between estimated dietary intake from the FFQ and plasma levels among non-smokers were 0.47 for α-carotene, 0.35 for β-carotene, 0.43 for β-cryptoxanthin, 0.47 for lycopene, and 0.40 for lutein (29).

Outcome ascertainment

On each biennial questionnaire, participants reported whether they had been diagnosed with a colorectal polyp within the last 2 years. For those men who reported polyps on their questionnaire, we requested permission to receive and review their medical records from which study investigators extracted information about the type, location, size, and histology of the polyps. We defined cases as men with their initial diagnosis of adenomatous polyps. Advanced adenomas were defined as adenomas 1cm or larger in size, with tubulo-villous or villous histology, and/or with high grade dysplasia; non-advanced adenomas were defined as

tubular and small (<1 cm). If a participant had multiple adenomas, we classified them according to the adenoma with the largest size and most advanced stage.

Exclusions

In our analyses, because adenomas are frequently asymptomatic (30) and identified during endoscopic procedures, we excluded participants who had not received a large bowel endoscopy during follow-up to reduce the potential for inclusion of cases in our population of non-cases. We further excluded men with a history or diagnosis before 1986 of ulcerative colitis, cancer (except for nonmelanoma skin cancer) or colorectal polyps. Among the cases, none was diagnosed with colorectal cancer prior to diagnosis of colorectal adenomas. We also excluded participants who reported implausible energy intakes (less than 800kcal/day or above 4200kcal/day) and had greater than 70 missing responses on the baseline SFFQ. After applying the exclusion criteria, the study population consisted of 29,363 men who underwent a large bowel endoscopy during follow-up. Among the 21,602 men for whom data on type of lower bowel endoscopy was available, 1,023 (5%) had received sigmoidoscopy only and 20,579 (95%) had received at least one colonoscopy.

Statistical analysis

We used logistic regression analyses to calculate odds ratios and 95% confidence intervals to assess the association between intake of each carotenoid and risk of colorectal adenoma among men who had had a large bowel endoscopy during follow-up. We analyzed both baseline and cumulatively averaged intake data. For the analyses using the updated dietary and lifestyle data, we used data collected up to the 2 year interval prior to the most recent endoscopy for noncases and to diagnosis for cases. We included in the model the cumulatively averaged value for the dietary variables and the most recently reported value for the other lifestyle variables. We categorized intakes of each carotenoid into quintiles. In addition to analyzing associations for the specific carotenoids separately, we also analyzed total carotenoid intake using two methods. In the first method, we created a total carotenoid intake variable by summing the intake of the specific carotenoids. In the second method, because intake levels differed across specific carotenoids, we calculated a total carotenoid score by summing the quintile score for each carotenoid yielding a score ranging from 5–25.

We conducted age-adjusted and multivariate analyses. In the multivariate models, we adjusted for all established or suspected risk factors (6) (see table 2 for a list of the confounding variables and their categorizations). We performed additional analyses in which intakes of dietary fiber and dietary folate were included in the main model. To test for a linear trend in adenoma risk with increasing carotenoid intake, we analyzed intake of each carotenoid as a continuous variable which reflected the median value for each quintile of intake; the coefficient for that variable was evaluated using the Wald statistic.

Further, we tested for non-linearity of the association between intake of each carotenoid and risk of adenomas to evaluate whether carotenoid intake could be modeled as a continuous term in our analyses. We compared the model fit between the model with the linear term and cubic spline terms and the model without spline terms (31–33). We observed evidence that the association between intake of each carotenoid and risk of adenomas was nonlinear. Therefore, we did not model carotenoid intakes as continuous variables.

In subgroup analyses, we stratified the cases according to adenoma location (proximal colon, distal colon, rectum), size (<1cm, ≥1cm) and stage (non-advanced, advanced). We tested whether the effects of carotenoids varied by adenoma subtype using a contrast test (34, 35). Furthermore, we examined whether the carotenoid-adenoma associations varied by smoking habits, alcohol consumption, fat intake, BMI, and age (36–38). We used the

likelihood ratio test to compare the model with and without the cross-product term between the intake of each carotenoid and the effect modifier.

Results

Among the 29,363 men in this cohort who received at least one endoscopy during follow-up between 1986 and 2006, 3,997 men were diagnosed with colorectal adenomas. More men had adenomas in the colon (n=3,107), compared to the rectum (n=510). There were 1,780 men who were diagnosed with only non-advanced colorectal adenomas, while 1,679 men had at least one advanced adenoma (≥1cm and/or tubulo-villous/villous histology and/or high grade dysplasia). Intakes of dietary α-carotene, β-carotene, β-cryptoxanthin and lutein/zeaxanthin were positively correlated (Pearson correlation r>0.25) with the strongest correlations being observed between intakes of dietary β-carotene with α-carotene (r=0.74) and lutein/zeaxanthin (r=0.57). Dietary β-carotene intake was highly correlated with total β-carotene intake (r = 0.92); correlations between total β-carotene intake with dietary intakes of the other carotenoids were similar to the correlations observed for intakes of dietary β-carotene with the other carotenoids. Lycopene intake was weakly correlated with intakes of the other carotenoids (r<0.22.). At baseline, men in the highest quintile of the total carotenoid score were less likely to smoke, more physically active, slightly more likely to have a family history of colorectal cancer, and more likely to use multivitamins than those in the lowest quintile of the total carotenoid score (Table 1). For dietary factors, the men in the highest quintile of the total carotenoid score consumed less processed meat and red meat, drank less alcohol, and had higher intakes of total calcium, total vitamin D, total folate and dietary fiber, compared to the men in the lowest quintile.

In the age-adjusted analyses, cumulatively-averaged total β-carotene intake and dietary intakes of the 5 specific carotenoids were associated with 4–28% reduced risks of colorectal adenoma, comparing the highest quintile with the lowest (Table 2). In the multivariate analyses, statistically significant inverse associations were observed for total β-carotene and dietary β-carotene, lycopene, and lutein/zeaxanthin intakes with multivariate ORs comparing the highest vs lowest quintile ranging from 0.72–0.86. When we adjusted for smoking habits using total pack years of smoking instead of pack years of smoking before age 30, the multivariate results did not change substantially (data not shown). The results for analyses using only baseline information were similar to or weaker than those using the cumulatively averaged intake data with significant inverse associations being observed only for total and dietary β-carotene intake (multivariate OR comparing the highest with lowest quintile ranged from 0.86 to 0.87). Similar results were observed when we limited the analyses to cases who were diagnosed on their first endoscopy (n=2438 cases; data not shown). The associations comparing men in the highest vs. the lowest quintile were similar when overall carotenoid intake was modeled either as total carotenoid intake (multivariate OR, 0.81 95% CI 0.72–0.91, data not shown) or as a total carotenoid score (multivariate OR, 0.87, 95% CI 0.77–0.97, Table 2). When the total carotenoid score was calculated using dietary, rather than total β-carotene intake, the result was essentially unchanged (multivariate OR 0.82, 95% CI 0.73–0.92).

To examine whether the potential associations observed were due to other constituents present in common food sources of carotenoids, we conducted additional analyses in which either dietary folate or dietary fiber intake was included in the multivariate model. When dietary fiber intake was added to the model, the results (not shown) were similar to the multivariate results presented. In contrast, with the addition of dietary folate intake to the model, the association for each carotenoid was attenuated (not shown) with the largest changes occurring for lutein/zeaxanthin and β-cryptoxanthin intakes. After adjustment for dietary folate intake, a null association was observed between lutein/zeaxanthin intake and

colorectal adenoma risk (multivariate OR comparing the highest vs. the lowest quintile, 1.09, 95%CI 0.96–1.24), and a significant 49% increased risk of colorectal adenomas was observed among men in the highest quintile of β-cryptoxanthin intake compared to the lowest (multivariate OR, 1.49, 95%CI 1.30–1.70). To reduce potential misclassification of carotenoid intakes among users of multivitamins (and β-carotene supplements for the analyses of dietary β-carotene intake), we conducted sensitivity analyses in which we restricted the study population to never users of multivitamins (and never users of β-carotene supplements for the dietary β-carotene analyses). The strength of the association among never-users of multivitamins (N of cases = 1547) for each of the carotenoids was similar to that reported for the entire population; however none of the associations was statistically significant.

We examined the association between intake of each carotenoid separately and risk of proximal colon, distal colon and rectal adenomas due to potentially varied associations by anatomic site (32, 33). Total β-carotene intake, dietary β-carotene, lycopene and lutein/zeaxanthin intakes, and the total carotenoid score were observed to have significant inverse associations with adenomas of the distal colon and rectum (multivariate ORs comparing the highest vs. lowest quintile ranged between 0.56 and 0.78), but significant associations with adenomas of the proximal colon remained only for dietary β-carotene intake. However, the differences in the associations by anatomic site were not statistically significant (p-value, test for common effects for the highest quintile > 0.10, Table 3). When we restricted the study population to include only those men who had received a only colonoscopy (n=5,068, 17% of study population), the associations between intake of the specific carotenoids and risk of adenomas in the proximal colon were similar to those presented in Table 3; the multivariate ORs ranged from 0.89–1.02 across the five carotenoids comparing the highest to lowest quintile. Similarly, when we limited the study population to only men who were diagnosed with adenomas in 2001 or later or who had received an endoscopy in 2001 or later (because Medicare coverage of colonoscopies began in 2001) (N of cases = 2000), the strength of the association did not change appreciably for total β-carotene and dietary α-carotene, β-carotene, β-cryptoxanthin and lutein/zeaxanthin intakes; the association for lycopene intake was attenuated toward the null. However, none of the associations was statistically significant except for lutein/zeaxanthin intake (data not shown).

Individuals with large adenomas or adenomas with villous histology are more likely to develop colorectal cancer than individuals with small and tubular adenomas (34). Therefore, we examined whether the associations for each carotenoid differed between risk of non-advanced and advanced adenomas. For each of the carotenoids examined, differences in the results by stage were not statistically significant (Table 4). However, for total β-carotene and dietary β-carotene intake, there was a suggestion of a stronger inverse association with the risk of non-advanced adenomas compared to advanced adenomas. When we stratified the cases by adenoma size, the results (data not shown) were similar to those observed in the analyses by size and villous histology.

Because alcohol intake and cigarette smoking may modify the effect of β-carotene supplementation on adenoma recurrence (8, 38), we examined the association between intake of each carotenoid and risk of adenomas across different strata defined by smoking status and alcohol consumption level. For each carotenoid, risk estimates among ever smokers and never smokers were generally of similar magnitude (all p-values, test for interaction > 0.08; Table 5). When we stratified participants by alcohol consumption, only the association between β-cryptoxanthin intake and adenoma risk varied significantly according to the level of alcohol consumption (p-value, test for interaction=0.01). However, the direction of the association was inconsistent across the alcohol intake categories with a significantly positive association being observed among men drinking less than 10g/d of

alcohol and non-significant inverse associations being observed for nondrinkers and drinkers who consumed at least 10g/d of alcohol. (Table 6). We jointly classified men by both smoking habits (never, ever smoker) and alcohol consumption (0, >0-<10, and ≥10g/d of alcohol)(8). However, unlike a previous study (8), no evidence of a synergistic interaction was found for any of the carotenoids (p- value, test for interaction > 0.12, data not shown). For example, the multivariate ORs (95% CI) for the highest versus lowest quintile of dietary β-carotene intake were 0.77 (0.48–1.23) in never smokers and nondrinkers (N of cases=282) and 0.66 (0.52–0.85) in ever smokers who drank at least 10 g/d of alcohol (N of cases=1090; p-value, test for interaction = 0.44).

We further evaluated whether associations between carotenoid intake and risk of colorectal adenoma varied by several colorectal cancer risk factors. The association for lutein/zeaxanthin intake was modified by age (p-value, test for interaction = 0.02) with a stronger inverse association being observed in older participants (multivariate OR comparing the highest vs. lowest quintile, 0.80, 95%CI 0.69–0.94) compared to younger participants (multivariate OR, 0.93, 95%CI 0.78–1.11). Age did not modify the associations between intakes of the other carotenoids and colorectal adenoma risk (all p-values, test for interaction > 0.17). The association between intake of each of the carotenoids and risk of colorectal adenoma was not modified by BMI (all p-values, test for interaction > 0.35), fat intake (all p-values, test for interaction > 0.45) and family history of colorectal cancer (all p-values, test for interaction > 0.10) (data not shown).

Discussion

In this analysis of 29,363 male health professionals who had received at least one endoscopy during follow-up, intakes of total β-carotene and dietary β-carotene, lycopene and lutein/zeaxanthin were each inversely associated with the risk of colorectal adenomas. The inverse associations we observed were not significantly different by adenoma characteristics or lifestyle factors including smoking status and alcohol consumption.

Tissue samples from colorectal adenomas or tumors have shown lower levels of carotenoids compared to non-involved mucosa suggesting that carotenoids may play a role in preventing the development of colorectal adenomas (39, 40). A protective role of carotenoids against the development of colorectal adenomas has been proposed through their antioxidant properties and, for α-carotene, β-carotene and β-cryptoxanthin, by their conversion to vitamin A (41, 42). As antioxidants, carotenoids may scavenge free radicals (3), thereby reducing oxidative stress and DNA damage, a crucial step in carcinogenesis and neoplastic transformation. In addition, provitamin A carotenoids have been shown to delay the progression of damaged cells into S phase and overall colonic crypt cell proliferation, allowing more time for DNA repair and the induction of apoptosis and thereby reducing the risk of carcinogenic initiation (43).

Few studies have examined associations between intakes of specific carotenoids and colorectal adenoma risk. Two (12, 13) of 4 case-control studies of colorectal adenomas that evaluated intake of only β-carotene (12) or carotene (13–15) found inverse associations. In one previous case-control study of colorectal adenomas that evaluated intake of the 5 major carotenoids, only β-carotene intake was inversely associated with adenoma risk; associations for the other carotenoids were null (16). Among 7 case-control studies that have examined associations with serum carotenoids (39, 44–49), 4 (44–46, 49) found inverse associations but the specific carotenoid with the significant association differed in each study. One prospective study has examined the association between intakes and serum levels of specific carotenoids and risk of adenoma recurrence (11). In that study, total carotenoid intake was associated with a 40% reduced risk of adenoma recurrence comparing the highest to the

lowest quartile of intake (P-value for trend =0.03). Among the 5 specific carotenoids examined in the study, significant inverse associations were observed only for α-carotene and β-carotene intake but for β-carotene, the inverse association was limited to the recurrence of multiple adenomas. The results for the serum carotenoids were similar to those for carotenoid intake in that study. In 3 (7, 9, 10) randomized controlled trials of participants with a previous adenoma, there was no significant effect of β-carotene supplementation compared to placebo on adenoma recurrence. However, in another trial, the Polyp Prevention Study, β-carotene supplementation significantly reduced adenoma recurrence compared to placebo only within individuals who were both non-smokers and non-drinkers (8). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a trial of male smokers, β-carotene supplementation increased the risk of colorectal cancer (50), although a null association was observed for adenomas (7, 9, 10).

Strengths of our study include the use of multiple dietary questionnaires over time to reduce misclassification of carotenoid intake, long follow-up, and high follow-up rates. Recall bias was reduced in our study. Data on dietary and confounding variables were assessed on questionnaires collected prior to the follow-up cycle in which the adenoma was diagnosed. In addition, because adenomas tend to be asymptomatic, behavior change due to preclinical symptoms before diagnosis of adenoma was not likely to occur. We adjusted for many potential colorectal cancer risk factors in our analyses to account for confounding. We reduced the likelihood of including individuals with undiagnosed adenomatous polyps in our population of non-cases because all participants included in these analyses had received an endoscopy after enrollment. Further, we only included cases confirmed by pathology report to reduce potential errors in self-report of adenoma diagnoses. Finally, due to the large sample size and extensive information collected on the size, location, and histology of the adenomas, we were able to examine whether the associations differed by adenoma characteristics which may have different malignant potential.

Our study has several limitations. Measurement error in assessing carotenoid intake may have attenuated the associations observed. One source of measurement error is that the bioavailability of carotenoid intake varies by cooking methods and the presence of other nutrients such as fat (27, 38). In addition, plasma concentrations of carotenoids are affected not only by intake levels but also by their absorption, transport and metabolism once ingested (51–53). Thus, intake levels of carotenoids may not directly affect the biologically relevant levels of carotenoids in the body. However, intake of each of the 5 carotenoids was founded to have a modest positive correlation with the corresponding plasma level (correlations: 0.35–0.47) (29), and we further tried to reduce the influence of measurement error on the associations observed by using cumulatively averaged intake data collected prior to diagnosis. Due to the lack of information on supplement use for most of the carotenoids over the follow up period, our analyses focused on dietary intake (from food only). Another limitation is that the associations that we observed for specific carotenoids might have been due to other compounds that are also present in fruit and vegetables as further adjustment for folate intake attenuated the associations observed for each of the carotenoids.

Our study population underwent both colonoscopies and flexible sigmoidoscopies. However, when we restricted our population to men who were presumed to have had a colonoscopy because they reported having an endoscopy after the year 2000 (when Medicare started covering colonoscopies), the strength of the association for most of the carotenoids was similar to that observed for the whole population. The notable exception was for lycopene intake which became null. Finally, if colorectal adenomas were diagnosed at the first endoscopy, dietary intake assessed for those cases might not represent intake prior to development of the colorectal adenoma. However, adenomas are generally

asymptomatic (30). As a result, participants might not have changed their dietary habits appreciably before diagnosis and so we updated dietary information up to the follow-up cycle prior to the follow-up cycle in which the cases were diagnosed with an adenoma.

In conclusion, we observed inverse associations between total β-carotene intake, dietary β-carotene, lycopene and lutein/zeaxanthin intakes, and the total carotenoid score and the risk of colorectal adenomas. Our results provide some support that a diet high in carotenoids may prevent the incidence of colorectal cancers at an early stage of disease progression.

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Table 1

Age-adjusted baseline characteristics of participants in the Health Professionals Follow-up Study by quintiles of the total carotenoid score* in 1986

	Total carotenoid Score		
	Quintile 1	**Quintile 3**	**Quintile 5**
Age (years, mean)†	54	54	54
Body mass index (kg/m^2, mean)	25.6	25.4	25.3
Current smokers (%)	12%	7%	5%
Pack years of smoking before age 30 (years, mean)	6	5	5
Physical activity (METs/wk‡, mean)	17	21	27
Family history of colorectal cancer (%)	8%	9%	10%
Current aspirin user (≥ 2 times /week) (%)	29%	29%	28%
Current multivitamin user (%)	35%	41%	47%
Nondrinkers of alcohol(%)	23%	21%	23%
Mean daily intake			
Energy (Kcal)	2019	1968	1965
Processed meat (servings)	0.46	0.35	0.23
Red meat§ (servings)	0.73	0.6	0.44
Alcohol among drinkers (g)	17	14	11
Calcium with supplements (mg)	857	894	961
Vitamin D with supplements (IU)	358	408	464
Dietary fiber (g)	17	21	27
Folate with supplements (μg)	386	479	591

*The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin

†Value is not age adjusted

‡Physical activity was estimated as the sum of the average time/week spent in each activity × the MET value for that activity. MET stands for metabolic equivalent and is defined as the ratio of the work metabolic rate to a standard resting metabolic rate ((caloric need/kg body weight/hour activity)/(caloric need/kg body weight/hour at rest)).

§Red meat corresponds to intake of beef, pork or lamb as a main dish.

Table 2

Odds ratios (95% confidence intervals) of colorectal adenomas by quintiles of energy-adjusted carotenoid intake in the Health Professionals Follow-up Study, 1986–2006

Carotenoid	Quintile of carotenoid intake					
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	*P* for trend*
Dietary α-carotene						
Median intake (μg/d)	351	561	767	1070	1686	
No. of cases	856	868	769	787	717	
Age-adjusted †	1	1.03 (0.93–1.14)	0.91 (0.82–1.01)	0.94 (0.85–1.04)	0.86 (0.77–0.96)	<0.001
Multivariate‡	1	1.02 (0.92–1.14)	0.89 (0.79–0.99)	0.94 (0.84–1.06)	1.01 (0.90–1.14)	0.91
Total β-carotene (diet+supplement)						
Median intake (μg/d)	2513	3758	4887	6378	9567	
No. of cases	882	845	823	746	701	
Age-adjusted	1	0.97 (0.87–1.07)	0.95 (0.85–1.05)	0.85 (0.76–0.94)	0.80 (0.72–0.89)	<0.001
Multivariate	1	0.90 (0.80–1.00)	0.89 (0.79–0.99)	0.80 (0.72–0.90)	0.78 (0.69–0.88)	<0.001
Dietary β-carotene (diet only)						
Median intake (μg/d)	2457	3644	4701	6067	8938	
No. of cases	915	865	793	765	659	
Age-adjusted	1	0.95 (0.86–1.05)	0.87 (0.78–0.96)	0.84 (0.76–0.93)	0.72 (0.65–0.80)	<0.001
Multivariate	1	0.93 (0.83–1.03)	0.84 (0.75–0.94)	0.83 (0.74–0.93)	0.72 (0.64–0.81)	<0.001
Dietary β-cryptoxanthin						
Median intake (μg/d)	85	143	195	255	357	
No. of cases	850	844	790	804	709	
Age-adjusted	1	1.01 (0.91–1.12)	0.95 (0.86–1.06)	1.00 (0.90–1.11)	0.87 (0.78–0.97)	0.01
Multivariate	1	1.05 (0.94–1.17)	1.03 (0.92–1.15)	1.10 (0.98–1.23)	1.06 (0.94–1.20)	0.26
Dietary lycopene						
Median intake (μg/d)	3420	5238	6777	8775	12667	
No. of cases	781	806	805	794	811	
Age-adjusted	1	1.00 (0.90–1.11)	0.98 (0.88–1.09)	0.95 (0.85–1.05)	0.96 (0.86–1.07)	0.34
Multivariate	1	0.90 (0.81–1.01)	0.85 (0.76–0.95)	0.80 (0.72–0.90)	0.83 (0.74–0.93)	<0.001

Carotenoid	Quintile of carotenoid intake					*P* for trend*
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	
Dietary lutein+zeaxanthin						
Median intake (μg/d)	1537	2348	3040	3886	5635	
No. of cases	882	781	782	817	735	
Age-adjusted	1	0.88 (0.79–0.97)	0.88 (0.79–0.98)	0.93 (0.84–1.03)	0.82 (0.74–0.91)	<0.001
Multivariate	1	0.87 (0.78–0.97)	0.86 (0.77–0.96)	0.92 (0.82–1.02)	0.86 (0.76–0.96)	0.06
Total carotenoid score§						
Median score	3	7	10	13	16	
No. of cases	929	756	818	743	751	
Age-adjusted	1	0.94 (0.84–1.04)	0.90 (0.81–0.99)	0.88 (0.79–0.98)	0.81 (0.73–0.90)	<0.001
Multivariate	1	0.90 (0.81–1.01)	0.89 (0.80–1.00)	0.90 (0.81–1.01)	0.87 (0.77–0.97)	0.02

Abbreviation= OR, odds ratio; CI, confidence interval

** P* for trend was calculated using the Wald test statistic.

†Adjusted for age : 5-year categories.

‡Adjusted for age (5-year categories), pack years of smoking before age 30 (continuous), smoking status (never/past/current), physical activity (quintiles), family history of colorectal cancer (yes/no), time period of endoscopy during follow-up (yes/no), aspirin use (never/past/current), multivitamin use (never/past/current), body mass index (quintiles), energy intake (quintiles), processed meat consumption (quintiles), red meat consumption (quintiles), alcohol consumption (quintiles), calcium intake from foods and supplemental sources (quintiles), and vitamin D intake from foods and supplemental sources (quintiles). For analyses of total β-carotene intake, multivitamin use was not included in the model because multivitamins are a source of supplemental β-carotene and dietary intake of calcium and vitamin D was used because major source of calcium and vitamin D supplement is multivitamin, which is a source of supplemental β-carotene.

§The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin.

Table 3

Multivariate* odds ratios (95% confidence intervals) of colorectal adenomas by location† and quintiles of energy-adjusted carotenoid intake in the Health Professionals Follow-up Study, 1986~2006

Carotenoid	Quintile of carotenoid intake						*P* for common effects by adenoma location for quintile 5§
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	*P* for trend‡	
Dietary α-carotene							
proximal colon	1	1.03 (0.86–1.22)	0.95 (0.80–1.14)	0.89 (0.74–1.06)	1.04 (0.86–1.25)	0.94	0.24
distal colon	1	1.05 (0.89–1.25)	0.91 (0.76–1.09)	1.04 (0.87–1.24)	1.10 (0.91–1.33)	0.31	
rectum	1	1.00 (0.76–1.33)	0.87 (0.65–1.17)	0.78 (0.57–1.07)	0.80 (0.57–1.11)	0.08	
Total β-carotene (diet+supplement)							
proximal colon	1	0.96 (0.81–1.15)	0.95 (0.80–1.14)	0.86 (0.71–1.04)	0.87 (0.72–1.05)	0.09	0.14
Distal colon	1	0.88 (0.74–1.05)	0.86 (0.73–1.03)	0.79 (0.66–0.95)	0.70 (0.58–0.85)	<.001	
rectum	1	0.86 (0.65–1.15)	0.76 (0.56–1.02)	0.64 (0.47–0.89)	0.62 (0.44–0.86)	0.002	
Dietary β-carotene (diet only)							
proximal colon	1	0.91 (0.76–1.08)	0.86 (0.72–1.02)	0.79 (0.65–0.94)	0.73 (0.60–0.88)	<.001	0.38
Distal colon	1	0.93 (0.79–1.10)	0.83 (0.70–0.99)	0.87 (0.72–1.04)	0.72 (0.59–0.88)	0.001	
rectum	1	1.02 (0.77–1.35)	0.72 (0.53–0.98)	0.67 (0.49–0.92)	0.56 (0.39–0.79)	<.001	
Dietary β-cryptoxanthin							
proximal colon	1	1.10 (0.92–1.30)	0.99 (0.83–1.19)	1.12 (0.93–1.34)	1.04 (0.86–1.25)	0.73	0.73
distal colon	1	1.05 (0.88–1.26)	1.15 (0.96–1.37)	1.08 (0.90–1.30)	1.16 (0.96–1.40)	0.15	
rectum	1	1.01 (0.75–1.35)	0.92 (0.67–1.25)	1.11 (0.81–1.51)	1.09 (0.79–1.52)	0.46	
Dietary lycopene							
proximal colon	1	0.97 (0.81–1.16)	0.99 (0.83–1.18)	0.92 (0.77–1.10)	0.88 (0.73–1.06)	0.12	0.28
distal colon	1	0.75 (0.62–0.89)	0.67 (0.56–0.81)	0.65 (0.54–0.78)	0.71 (0.59–0.85)	<.001	
rectum	1	0.99 (0.73–1.35)	0.94 (0.69–1.29)	0.78 (0.56–1.08)	0.78 (0.56–1.08)	0.05	
Dietary lutein+zeaxanthin							
proximal colon	1	0.85 (0.71–1.02)	0.91 (0.76–1.08)	0.96 (0.80–1.14)	0.91 (0.76–1.09)	0.75	0.10
distal colon	1	0.82 (0.69–0.97)	0.85 (0.72–1.02)	0.89 (0.74–1.06)	0.77 (0.64–0.93)	0.03	
rectum	1	0.81 (0.61–1.08)	0.71 (0.53–0.96)	0.79 (0.59–1.07)	0.62 (0.45–0.85)	<.001	
Total carotenoid score‖							

Carotenoid	Quintile of carotenoid intake						*P* for common effects by adenoma location for quintile 5[§]
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	*P* for trend[‡]	
proximal colon	1	0.96 (0.81–1.15)	0.89 (0.75–1.06)	0.97 (0.81–1.17)	0.91 (0.76–1.10)	0.40	0.44
distal colon	1	0.85 (0.71–1.01)	0.89 (0.75–1.05)	0.88 (0.73–1.05)	0.79 (0.66–0.96)	0.04	
rectum	1	0.89 (0.67–1.19)	0.87 (0.65–1.16)	0.65 (0.47–0.91)	0.74 (0.53–1.02)	0.02	

Abbreviations = OR, Odds ratio; CI, confidence interval

[*] Adjusted for the same variables as in the multivariate model in table 2

[†] The area from the cecum through the sigmoid colon is considered the colon. Within the colon, adenomas located from the cecum to the splenic flexure were considered proximal colon adenomas (1468 cases), the remaining adenomas in the colon were defined as distal colon adenomas (1639 cases). Rectal adenomas were defined as adenomas located in the rectum and the rectosigmoid junction (510 cases).

[‡] *P* for trend was calculated using the Wald test statistic was used.

[§] *P* for common effects by adenoma location for quintile 5 was calculated using a contrast test.

[/] The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin.

Table 4

Multivariate* odds ratios (95% confidence intervals) of non-advanced and advanced stage† of colorectal adenomas by quintiles of energy-adjusted carotenoid intake in the Health Professionals Follow-up Study, 1986∼2006

Carotenoid	Quintile of carotenoid intake						*P* for common effects by stage for quintile 5§
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	*P* for trend‡	
Dietary α-carotene							
Non-advanced stage	1	0.96 (0.82–1.13)	0.85 (0.72–1.00)	0.81 (0.69–0.95)	0.95 (0.80–1.13)	0.39	0.50
Advanced stage	1	1.12 (0.95–1.32)	0.91 (0.76–1.08)	1.07 (0.90–1.27)	1.03 (0.86–1.24)	0.86	
Total β-carotene (diet+supplement)							
Non-advanced stage	1	0.81 (0.69–0.95)	0.76 (0.65–0.90)	0.75 (0.64–0.89)	0.71 (0.60–0.85)	<.001	0.20
Advanced stage	1	1.00 (0.85–1.19)	1.01 (0.85–1.20)	0.81 (0.68–0.98)	0.84 (0.70–1.02)	0.01	
Dietary β-carotene (diet only)							
Non-advanced stage	1	0.87 (0.75–1.02)	0.69 (0.59–0.82)	0.79 (0.67–0.94)	0.66 (0.55–0.78)	<.001	0.35
Advanced stage	1	1.02 (0.86–1.20)	0.99 (0.84–1.17)	0.84 (0.70–1.00)	0.74 (0.61–0.90)	<.001	
Dietary β-cryptoxanthin							
Non-advanced stage	1	1.04 (0.89–1.22)	0.98 (0.83–1.16)	1.07 (0.90–1.26)	1.11 (0.93–1.32)	0.23	0.99
Advanced stage	1	1.08 (0.91–1.28)	1.16 (0.97–1.37)	1.15 (0.97–1.37)	1.11 (0.92–1.34)	0.24	
Dietary lycopene							
Non-advanced stage	1	0.90 (0.76–1.07)	0.83 (0.70–0.98)	0.85 (0.72–1.00)	0.82 (0.69–0.97)	0.03	0.58
Advanced stage	1	0.91 (0.77–1.08)	0.84 (0.70–1.00)	0.80 (0.67–0.96)	0.88 (0.74–1.04)	0.14	
Dietary lutein+zeaxanthin							
Non-advanced stage	1	0.79 (0.68–0.93)	0.76 (0.65–0.90)	0.85 (0.72–1.00)	0.79 (0.67–0.93)	0.05	0.20
Advanced stage	1	0.95 (0.80–1.13)	0.99 (0.83–1.17)	0.94 (0.79–1.12)	0.93 (0.77–1.11)	0.42	
Total carotenoid score/							
Non-advanced stage	1	0.76 (0.65–0.90)	0.80 (0.68–0.94)	0.79 (0.67–0.94)	0.83 (0.70–0.98)	0.04	0.51
Advanced stage	1	1.04 (0.88–1.23)	0.99 (0.83–1.17)	0.99 (0.83–1.18)	0.90 (0.75–1.09)	0.28	

Abbreviations = OR, Odds ratio; CI, confidence interval

*Adjusted for the same variables as in the multivariate model in table 2.

†Non-advanced stage adenomas were defined as adenomas smaller than 1cm in diameter and with tubular histology (No. of cases =1780) and advanced stage adenomas were defined as adenomas 1cm or larger in diameter or having tubulo-villous or villous histology or carcinoma in situ (No. of cases =1679)

[‡] *P* for trend was calculated using the Wald test statistic.

[§] *P* for common effects by stage for quintile 5 was calculated using a contrast test.

[/] The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin

Table 5

Multivariate* odds ratios (95% confidence intervals) of colorectal adenomas by quintiles of energy-adjusted carotenoid intake stratified by smoking status† in the Health Professionals Follow-up Study, 1986~2006

	Quintile of carotenoid intake						
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)	*P* for trend‡	*P* for interaction§
Dietary α-carotene							
Never-smokers	1	0.99 (0.83–1.19)	0.92 (0.77–1.11)	0.92 (0.77–1.11)	1.00 (0.83–1.21)	0.98	0.23
Ever-smokers	1	1.04 (0.90–1.20)	0.84 (0.72–0.98)	0.95 (0.81–1.10)	0.96 (0.82–1.13)	0.50	
Total β-carotene (diet+supplement)							
Never-smokers	1	0.94 (0.78–1.12)	0.92 (0.77–1.09)	0.86 (0.72–1.04)	0.81 (0.67–0.98)	0.09	0.12
Ever-smokers	1	0.87 (0.75–1.01)	0.86 (0.73–1.00)	0.75 (0.64–0.88)	0.73 (0.62–0.87)	0.09	
Dietary β-carotene (diet only)							
Never-smokers	1	0.95 (0.80–1.13)	0.86 (0.72–1.02)	0.84 (0.70–1.00)	0.74 (0.61–0.90)	0.001	0.16
Ever-smokers	1	0.91 (0.79–1.06)	0.82 (0.71–0.96)	0.84 (0.72–0.98)	0.66 (0.56–0.79)	<.001	
Dietary β-cryptoxanthin							
Never-smokers	1	0.95 (0.79–1.14)	0.93 (0.77–1.12)	1.01 (0.84–1.22)	1.03 (0.85–1.24)	0.48	0.30
Ever-smokers	1	1.10 (0.95–1.27)	1.07 (0.92–1.25)	1.14 (0.98–1.33)	1.05 (0.89–1.24)	0.50	
Dietary lycopene							
Never-smokers	1	0.91 (0.76–1.09)	0.85 (0.71–1.02)	0.83 (0.69–1.00)	0.90 (0.75–1.08)	0.33	0.08
Ever-smokers	1	0.88 (0.75–1.02)	0.82 (0.70–0.96)	0.76 (0.65–0.89)	0.77 (0.66–0.90)	<.001	
Dietary lutein+zeaxanthin							
Never-smokers	1	0.85 (0.72–1.01)	0.87 (0.73–1.03)	0.92 (0.78–1.10)	0.77 (0.64–0.93)	0.03	0.87
Ever-smokers	1	0.88 (0.75–1.02)	0.84 (0.72–0.98)	0.88 (0.76–1.03)	0.87 (0.75–1.02)	0.21	
Total carotenoid score/							
Never-smokers	1	0.93 (0.78–1.11)	0.91 (0.76–1.09)	0.93 (0.77–1.11)	0.88 (0.73–1.06)	0.20	0.14
Ever-smokers	1	0.90 (0.78–1.05)	0.87 (0.75–1.01)	0.85 (0.73–1.00)	0.82 (0.70–0.97)	0.01	

Abbreviations = OR, Odds ratio; CI, confidence interval

*Adjusted for the same variables as in the multivariate model in table 2 except smoking status was not included in the model.

†There were 1582 cases among never smokers and 2170 cases among ever smokers.

‡ *P* for trend was calculated using the Wald test statistic.

§ *P* for interaction was calculated from the likelihood ratio test comparing the model including the cross-product term for smoking status (never-smokers vs ever-smokers) and carotenoid intake (a continuous variable with values corresponding to the median value of each carotenoid quintile category) with the model without the cross-product term

/ The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin

Table 6

Multivariate* odds ratios(95% confidence intervals) of colorectal adenomas by quintiles of energy-adjusted carotenoid intake stratified by alcohol consumption† in the Health Professionals Follow-up Study, 1986∼2006

Carotenoid	Quintile of carotenoid intake					*P* for trend‡	*P* for interaction§
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)		
Dietary α-carotene							
Non-drinkers	1	0.99 (0.72–1.36)	0.78 (0.57–1.09)	0.92 (0.67–1.25)	0.91 (0.66–1.26)	0.65	0.21
>0–<10g/d	1	1.01 (0.85–1.19)	0.93 (0.78–1.10)	0.99 (0.83–1.17)	1.10 (0.93–1.31)	0.18	
≥ 10g/d	1	1.03 (0.88–1.21)	0.86 (0.73–1.02)	0.88 (0.74–1.04)	0.92 (0.76–1.11)	0.18	
Total β-carotene (diet+supplement)							
Non-drinkers	1	0.99 (0.74–1.33)	0.98 (0.72–1.33)	0.81 (0.59–1.13)	0.61 (0.43–0.87)	0.002	0.89
>0–<10g/d	1	0.91 (0.77–1.07)	0.93 (0.79–1.10)	0.89 (0.75–1.06)	0.85 (0.71–1.01)	0.09	
≥ 10g/d	1	0.86 (0.73–1.02)	0.81 (0.68–0.96)	0.71 (0.59–0.85)	0.75 (0.62–0.91)	0.003	
Dietary β-carotene (diet only)							
Non-drinkers	1	1.20 (0.89–1.60)	0.94 (0.69–1.28)	0.77 (0.55–1.08)	0.67 (0.47–0.94)	0.00	0.32
>0–<10g/d	1	0.98 (0.83–1.15)	0.92 (0.78–1.09)	0.92 (0.77–1.08)	0.82 (0.69–0.98)	0.02	
≥ 10g/d	1	0.81 (0.68–0.95)	0.74 (0.63–0.88)	0.76 (0.64–0.91)	0.63 (0.52–0.77)	<.001	
Dietary β-cryptoxanthin							
Non-drinkers	1	0.96 (0.69–1.32)	0.87 (0.63–1.21)	1.06 (0.77–1.46)	0.95 (0.69–1.32)	1.00	0.01
>0–<10g/d	1	1.02 (0.86–1.22)	1.16 (0.98–1.38)	1.19 (1.00–1.42)	1.25 (1.05–1.48)	0.00	
≥ 10g/d	1	1.08 (0.92–1.27)	0.93 (0.78–1.10)	0.98 (0.82–1.16)	0.84 (0.69–1.03)	0.06	
Dietary lycopene							
Non-drinkers	1	0.80 (0.58–1.08)	0.85 (0.62–1.16)	0.97 (0.71–1.32)	0.90 (0.66–1.24)	0.89	0.82
>0–<10g/d	1	0.90 (0.76–1.06)	0.78 (0.66–0.92)	0.70 (0.59–0.83)	0.81 (0.69–0.96)	0.01	
≥ 10g/d	1	0.91 (0.76–1.09)	0.91 (0.76–1.09)	0.88 (0.73–1.05)	0.82 (0.68–0.98)	0.04	
Dietary lutein+zeaxanthin							
Non-drinkers	1	0.89 (0.66–1.19)	0.95 (0.70–1.29)	0.89 (0.65–1.21)	0.68 (0.49–0.95)	0.03	0.78
>0–<10g/d	1	0.91 (0.77–1.07)	0.88 (0.75–1.04)	1.03 (0.87–1.21)	0.90 (0.76–1.06)	0.55	
≥ 10g/d	1	0.80 (0.67–0.95)	0.80 (0.67–0.95)	0.80 (0.67–0.95)	0.84 (0.70–1.01)	0.23	
Total carotenoid score/							

Carotenoid	Quintile of carotenoid intake					*P* for trend[‡]	*P* for interaction[§]
	1 (referent)	2 OR (95%CI)	3 OR (95%CI)	4 OR (95%CI)	5 OR (95%CI)		
Non-drinkers	1	1.16 (0.86–1.57)	0.86 (0.63–1.18)	0.99 (0.72–1.36)	0.79 (0.56–1.11)	0.15	0.23
>0–<10g/d	1	0.91 (0.77–1.08)	0.95 (0.80–1.11)	0.98 (0.82–1.16)	0.95 (0.80–1.12)	0.78	
≥10g/d	1	0.82 (0.69–0.97)	0.81 (0.69–0.96)	0.79 (0.66–0.95)	0.77 (0.64–0.93)	0.01	

Abbreviations = OR, Odds ratio; CI, confidence interval

[*] Adjusted for the same variables as in the multivariate model in table 2 except alcohol consumption was not included in the model.

[†] There were 504 cases among Non-drinker, 1861 cases among alcohol drinkers who consumes alcohol less than 10g/d, and 1632 cases among alcohol drinkers who consumes alcohol more than 10g/d.

[‡] *P* for trend was calculated using the Wald test statistic.

[§] *P* for interaction was calculated from the likelihood ratio test comparing the model including the cross-product term for alcohol consumption (a continuous variable with values corresponding to the median value of each alcohol intake category) and carotenoid intake (a continuous variable with values corresponding to the median value of each carotenoid quintile category) with the model without the cross-product term.

[/] The total carotenoid score was derived from summing the quintile scores for total β-carotene intake and dietary intakes of α-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin.