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Total Antioxidant Capacity (TAC) intake and colorectal cancer risk in the Health Professionals Follow-up Study

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Abstract

Objective—To examine the association between total antioxidant capacity (TAC) intake and colorectal cancer incidence.

Methods—TAC intake was assessed in 1986 and every 4 years thereafter in the Health Professionals Follow-up Study, a prospective cohort study of 47,339 men. Between 1986 and 2004, 952 colorectal cancer cases were diagnosed. Cox proportional hazards regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI).

Results—Comparing the highest vs. lowest quintile, TAC intake from foods only (dietary TAC) was not associated with colorectal (multivariate-RR: 0.98; 95% CI: 0.78, 1.23) or colon (multivariate-RR: 1.20; 95% CI: 0.90, 1.61) cancer risk, but was inversely associated with rectal cancer risk (multivariate-RR: 0.58; 95% CI: 0.35, 0.96). For the same comparison, TAC intake from foods and supplements (total TAC) was not associated with colorectal (multivariate-RR: 0.91; 95% CI: 0.73, 1.14), colon (multivariate-RR: 1.01; 95% CI: 0.77, 1.33), or rectal (multivariate-RR: 0.85; 95% CI: .52, 1.38) cancer risk.

Conclusions—Dietary and total TAC intakes were not associated with colorectal and colon cancer risk. Dietary -but not total- TAC intake was inversely associated with rectal cancer risk, suggesting antioxidants *per se* may not be associated with rectal cancer risk.

Keywords

Total antioxidant capacity (TAC); FRAP; colorectal cancer; nutrition

INTRODUCTION

Antioxidant-rich foods have been hypothesized to reduce the risk of colorectal cancer [1], the third leading cause of cancer mortality in the United States [2] and worldwide [3]. A recent comprehensive review published by the World Cancer Research Fund (WCRF) concluded that there is limited evidence suggesting that consumption of fruits and non-starchy vegetables, rich sources of antioxidants and other potential cancer preventive agents, may protect against colorectal cancer [4]. In addition to examining foods rich in

antioxidants, several studies have examined relationships between intakes of single antioxidants and colorectal cancer risk. However, based on inconsistent results across studies, the WCRF review stated that no conclusion could be made regarding the influence of several antioxidants including vitamins C and E and multivitamins on colorectal cancer risk [4]. Examining overall antioxidant exposure rather than individual antioxidants may be important because the combination of antioxidants from the diet may act synergistically against oxidative stress to prevent carcinogenesis [5]. Several methodologies have been developed to quantify the total antioxidant capacity (TAC) of foods [6, 7]. One method is the ferric-reducing ability of plasma assay (FRAP) [8, 9], which measures the reduction of Fe³⁺ (ferric ion) to Fe²⁺ (ferrous ion) in the presence of antioxidants [9].

To assess the combined effect of multiple antioxidants, we examined the association between TAC intake and the risk of colorectal cancer in the Health Professionals Follow-up Study, a large prospective cohort of men.

MATERIALS AND METHODS

Study Population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective study of 51,529 male health professionals, including dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists, aged 40-75 years upon enrollment in 1986. Participants have been followed through mailed biennial questionnaires about their medical history, lifestyle, and health-related behaviors. This study was approved by the Institutional Review Board of the Harvard School of Public Health, Boston, Massachusetts.

Dietary Assessment

Diet over the past year was assessed at baseline (1986) using a 131-item food frequency questionnaire (FFQ). Dietary information was updated with subsequent similar FFQs mailed every 4 years. Nine mutually exclusive response categories were provided for the frequency of intake. Nutrient intakes were calculated by converting the frequency responses to daily intakes for each food or beverage, multiplying the daily intakes of each food and beverage with its corresponding nutrient content, and summing the contributions of all items. Supplement intake was calculated using information on multivitamin use and individual supplement use on each FFQ. The validity and reproducibility of the FFQ have been reported elsewhere [10, 11].

TAC intake was estimated using the FRAP assay which measures the reduction of Fe³⁺ (ferric ion) to Fe²⁺ (ferrous ion) in the presence of antioxidants [8, 9]. We created a TAC food composition database for the dietary questionnaires using TAC measurements assessed by the Institute of Nutrition Research, University of Oslo, Norway [9, 12, 13] (Blomhoff, R., personal communication). For those foods that were not analyzed for TAC, TAC values were imputed from similar foods. For reference, the TAC value (per 100 g) is 0.83 mmol for coffee, 0.29 mmol for apples, and 0.04 mmol for carrots. Supplemental TAC intake was imputed according to the vitamin C, vitamin E, calcium, and mineral content of individual supplements and multivitamins used (Sampson, L., personal communication).

Because nutrients are highly correlated with total energy intake, energy-adjusted nutrient intakes were calculated using the residual method [14]. To reduce the random within-person variation in diet consumption and to better reflect the long-term consumption patterns, we calculated a cumulative average intake of energy-adjusted dietary (from foods only) and total (from foods and supplements) TAC from all the dietary questionnaires available up to the start of each 2-year follow-up interval using a method previously described [15].

Exclusion of participants at baseline

Participants who did not complete the baseline (1986) FFQ were not included in these analyses. Of those participants who completed the baseline (1986) FFQ, participants with implausible energy intakes (>4200 or <800 kcal/d) or who had left >70 food items blank were excluded from the study. Participants who reported a history of ulcerative colitis or of cancer (except for nonmelanoma skin cancer) at baseline also were excluded from the analysis. Data on other inflammatory bowel diseases were not collected at baseline. Thus, 47,339 men remained for follow-up from 1986 to 2004.

Case and Death Ascertainment

On each biennial questionnaire, participants were asked whether they had been diagnosed during the previous 2 years with cancer of the colon or rectum. For reported cases of colon or rectal cancer, an authorization to obtain the medical records was requested from the participants. Information on the histologic type, anatomic location, and stage of the cancer was then extracted from medical records by study researchers blinded to exposure status. Between 1986 and 2004, 952 colorectal cancer cases (634 colon cancers, 201 rectal cancers, and 117 cancers of unknown site within the colorectum) were diagnosed among eligible men. Carcinoid or non-epithelial colorectal cancer cases were excluded from our analyses. Cases whose specific tumor site within the colorectum was unknown were included in the analyses of total colorectal cancer risk but were excluded when colon and rectal cancers were analyzed separately.

Statistical Analysis

Participants contributed follow-up time from the date they returned their baseline questionnaire to the date of diagnosis of colorectal cancer, death, or end of the study period (January 31, 2004), whichever came first. To examine associations between TAC intake and colorectal cancer risk, we estimated relative risks (RR) and 95% confidence intervals (CI) using the Cox proportional hazards regression model with age in months as the time scale and calendar year as a stratification variable. We analyzed dietary and total TAC intake modeled in quintiles. In addition to examining associations between cumulative average intake of TAC and colorectal cancer risk, we investigated associations using baseline intake of TAC. We also analyzed colon and rectal cancers separately because there is some evidence that risk factors for colon and rectal cancers may differ [16].

In the multivariate models, in addition to stratifying by age, we adjusted for known and suspected risk factors of colorectal cancer including race (Caucasian/non-Caucasian), family history of colorectal cancer (yes/no), pack years of smoking before age 30 (continuous), body mass index (<24 ; 24-26; >26 -29; >29 kg/m²), physical activity (quintiles of MET-hours/week), aspirin use (≥ 2 times per week/ <2 times/week), history of previous endoscopy (yes/no), energy intake (kilocalories/day, continuous), alcohol intake (0; >0 - <5 ; 5- <15 ; ≥ 15 g/day), red meat consumption (quintiles), total calcium intake (quintiles), dietary folate intake (quintiles), and dietary vitamin D intake (quintiles). Supplement use (ever/never) was also included as a covariate in the model when assessing dietary TAC intake; participants who reported using multivitamins or any antioxidant supplements (e.g., vitamin E, vitamin A, vitamin C, selenium, beta carotene, coenzyme Q10, and lycopene) on at least one questionnaire were considered "ever" users. For analysis of cumulative average TAC intake, the time-varying covariates were cumulatively averaged (body mass index, energy intake, alcohol intake, physical activity, red meat consumption, total calcium intake, dietary folate intake, and dietary vitamin D intake) or updated using the information collected every 2 years (all other covariates). For analysis of baseline TAC intake, baseline covariates were used in the model. As a sensitivity analysis, we also analyzed dietary TAC intake only among participants who did not use supplements during follow-up. Trend tests were

calculated by including median TAC intake in each category as a continuous variable in the model. Additional analyses were conducted, in which we stratified the participants by biannually updated variables such as smoking status (ever, never) and age (<65; ≥65 years), and by cumulative-averaged biannually updated variables such as alcohol consumption (<5; 5-15; >15g/day for the colon cancer analyses and <5; ≥5 g/day for the rectal cancer analyses), body mass index (<25; ≥25 kg/m²), and physical activity (<median value in MET-hours/week; ≥ median value) to assess whether the association between TAC intake and colon or rectal cancer risk varied by other colorectal cancer risk factors. To test the null hypothesis that there was no effect modification between each factor and TAC intake with regard to risk of colon or rectal cancer, we used the likelihood ratio test to compare the model including the different combinations of TAC intake (categorized into quartiles) and the potential effect modifier (categorized as a binary variable except for alcohol intake which was categorized in 3 groups) with a model including only TAC intake and the potential effect modifier as separate variables.

RESULTS

In this cohort of 47,339 men, the cumulative average intake was 10.76 mmol/day for energy-adjusted dietary TAC (from foods only) and 14.03 mmol/day for total TAC (from foods and supplements). In our cohort, the top 4 contributors to the baseline dietary TAC intake were caffeinated coffee (25%), decaffeinated coffee (12%), tea (10%), and orange juice (7%). Vitamin C supplement use (20%) was the main contributor to total TAC intake, followed by the top four food sources of dietary TAC intake. These 4 foods continued to be the top contributors for dietary TAC intake on all subsequent FFQs. For the rest of this paper, caffeinated coffee will be referred to as coffee and energy-adjusted TAC intake will be referred to as TAC intake. Dietary TAC intake was positively correlated with caffeine ($r=0.60$), coffee ($r=0.55$), decaffeinated coffee ($r=0.38$), and tea ($r=0.36$) consumption and only weakly correlated with vegetable ($r=0.15$), fruit ($r=0.14$), orange juice ($r=0.08$), dietary vitamin C ($r=0.20$), total vitamin C ($r=0.06$), dietary vitamin E ($r=0.08$), and total vitamin E ($r=0.05$) intake. Total TAC intake was strongly correlated with total vitamin C ($r=0.83$) and total vitamin E ($r=0.54$) intake, but less correlated with caffeine, coffee, decaffeinated coffee, tea, vegetable, fruit, orange juice, dietary vitamin C, and dietary vitamin E intake (all $r<0.3$). Men with a higher total TAC intake were more likely to drink alcohol, smoke before age 30, be more physically active, use aspirin, have higher dietary folate and total calcium intake, and eat less red meat compared to participants with lower total TAC intake (Table 1). Similar patterns generally were observed for dietary TAC intake except for physical activity which did not vary substantially by dietary TAC intake and total calcium intake which was slightly lower among men with higher dietary TAC intake (Table 1).

No statistically significant association was found between dietary TAC intake and the incidence of colorectal or colon cancer; however, a statistically significant 42% lower risk of rectal cancer was observed when comparing the highest vs. lowest quintile of dietary TAC intake [multivariate-adjusted RR (MV-RR): 0.58; 95% CI: 0.35, 0.96; P-value, test for trend = 0.02] (Table 2). No statistically significant associations comparing the highest versus lowest quintile were found between total TAC intake and the incidence of colorectal, colon, and rectal cancer. Statistically significant differences were observed between the results for colon and rectal cancer for dietary TAC intake (p-value, test for common effects between colon and rectal cancer = 0.03), but not for total TAC intake (p-value, test for common effects between colon and rectal cancer = 0.49). Additionally, no statistically significant association was found when comparing the highest vs. lowest decile of dietary and total TAC intake with colon and colorectal cancer risk (not shown). For rectal cancer, when comparing the top to the bottom decile, the association with total TAC intake was stronger than that comparing the highest vs. the lowest quintile, but not statistically significant (MV-

RR: 0.57; 95% CI: 0.30, 1.07) and was similar to that observed for dietary TAC intake (MV-RR: 0.53; 95% CI: 0.26, 1.11 comparing the top to bottom decile). In separate analyses by subsite of the colon, dietary and total TAC intakes were not associated with risk of proximal (n = 316 cases) or distal (n = 292 cases) colon cancer (not shown).

When the analysis was limited to participants who did not use antioxidant supplements at baseline or during follow-up (n=22,538; n=286 colorectal cancer cases; n=195 colon cancer cases; n=66 rectal cancer cases), the risk estimates for dietary TAC intake comparing the highest vs. lowest quintile did not change materially (MV-RR: 1.05; 95% CI: 0.70, 1.58 for colorectal cancer; MV-RR: 1.48; 95% CI: 0.86, 2.54 for colon cancer; and MV-RR: 0.53; 95% CI: 0.23, 1.22 for rectal cancer) although the associations became less precise due to the smaller number of cases. Results using baseline intake were comparable to those using cumulative average intake for both dietary and total TAC intake (not shown). Furthermore, our results did not change when we excluded cases diagnosed in the first 2 years of follow-up (n=87) (not shown). Our results also did not change when we adjusted for either overall pack years of smoking or smoking status (never, past, current) instead of pack years of smoking before age 30 in our models (not shown).

When we examined dietary TAC intake from only coffee, decaffeinated coffee, and tea combined (the primary sources of dietary TAC in this study contributing 46% of dietary TAC intake in our cohort at baseline) separately from dietary TAC intake from other food sources, an inverse association with rectal cancer risk was only observed for dietary TAC intake from coffee, decaffeinated coffee, and tea combined (MV-RR: 0.62; 95% CI: 0.33, 1.14 comparing the highest to the lowest quintile, P-value, test for trend= 0.02). Dietary TAC intake from other food sources was not associated with the risk of rectal cancer (MV-RR: 0.92; 95% CI: 0.53, 1.60 comparing the highest vs. the lowest quintile, P-value, test for trend= 0.84). For the same comparison, for colon cancer, no association was found for dietary TAC intake from coffee, decaffeinated coffee, and tea combined (MV-RR: 1.17; 95% CI: 0.84, 1.63, P-value, test for trend =0.95) or for dietary TAC intake from other food sources (MV-RR: 1.21; 95% CI: 0.87, 1.66, P-value, test for trend= 0.32).

We found that body mass index (<25; ≥25 kg/m²), age (<65; ≥65 years), physical activity (<median value in MET-hours/week; ≥ median value), and alcohol intake (<5; 5-15; >15g/day for the colon cancer analyses and <5; ≥5 g/day for the rectal cancer analyses) did not significantly modify the association between dietary or total TAC intake and colon or rectal cancer risk (all tests for interaction had P-values ≥0.20, not shown). Because cigarette smoking increases oxidative [17] whether the association between TAC intake and colorectal cancer risk varied by smoking status (ever/never smoker); owing to the small percentage of men in our cohort who are current smokers (6.5%), we combined past and current smokers into one strata. Overall, smoking status did not significantly modify the association between dietary or total TAC intake and colon or rectal cancer risk, except for a suggestive inverse association between total TAC intake and colon cancer risk was observed more among never smokers but not among ever smokers (P-value, test for interaction=0.04; all other tests for interaction with smoking status had P-values ≥0.38, data not shown).

DISCUSSION

In this large prospective study, we found an inverse association between dietary TAC intake and rectal cancer risk which was limited to TAC intake from coffee, decaffeinated coffee, and tea combined (the top 3 contributors to dietary TAC intake). No association was observed between dietary TAC intake and colorectal or colon cancer risk. Total TAC intake was not associated with risk of colorectal, colon or rectal cancer.

Antioxidants have been hypothesized to reduce cancer risk because they are scavengers of free radicals, which can cause oxidative damage to DNA, proteins, and lipids [18]. However, a recent comprehensive review published by the World Cancer Research Fund determined that no conclusion could be made regarding the influence of several antioxidants including vitamins C and E and multivitamins on colorectal cancer risk [4]. Moreover, a meta-analysis of 14 randomized trials [19] of beta-carotene, vitamins A, C, and E, and selenium supplementation given either individually or combined found no difference in gastrointestinal (defined as oesophageal, gastric, colorectal, pancreatic, and liver) cancer incidence for the intervention group when compared to the placebo group. However, in four trials, selenium appeared to be beneficial against gastrointestinal cancer risk.

A commonality among the previous observational studies and clinical trials is that the effects of only a single antioxidant or combination of only a few antioxidants were evaluated. If the concerted action of multiple antioxidants is important for limiting the adverse consequences due to oxidative stress and for preventing carcinogenesis [5], it is not surprising that null associations were observed in studies focusing on the consumption or supplementation of only a few antioxidants. In addition, the published studies have only focused on those antioxidants for which food composition data are available whereas there are numerous antioxidants in foods which have not been identified [8, 20]. Consequently, several methods (e.g., Ferric Reducing Ability of Plasma assay, Oxygen Radical Absorbance Capacity, Trolox Equivalent Antioxidant Capacity) have been developed to quantify the intake of all known and unknown antioxidants [8, 9]. We chose to analyze associations with TAC intake using the FRAP assay because the FRAP assay has been shown to directly measure total reductants in a sample [12].

Our results do not support an inverse association between total TAC intake and colorectal, colon, and rectal cancer risk. For dietary TAC intake, we found a suggestive positive, but non-significant, association with colon cancer risk and a statistically significant inverse association with rectal cancer risk. However, considering that in our study, the inverse association between dietary TAC intake and rectal cancer risk was only observed for dietary TAC intake from coffee, decaffeinated coffee, and tea combined, and not from other food sources, antioxidants *per se* may not be the relevant component driving the observed association between dietary TAC intake and rectal cancer risk. Instead, the inverse association observed for dietary TAC intake from coffee, decaffeinated coffee, and tea combined may be due to other types of compounds present in these beverages. Another reason for our findings could be that intakes of coffee, decaffeinated coffee, and tea may be measured more accurately with a FFQ than intakes of other sources of antioxidants such as vegetables. For example, in the validation study of the baseline FFQ used in this study, the correlation coefficients for coffee and tea intakes estimated by FFQ compared with intakes from two 1-week diet records exceeded 0.75 [11], whereas the correlation coefficient was 0.2 for vegetables [21].

There are several limitations to the present study. First, non-differential measurement error in our assessment of dietary and total TAC intake may have biased our results towards the null [22]. However, the repeated dietary assessments over an 18-year period reduced random within-person measurement error [14]. Secondly, the validity of TAC intake has not been examined in our cohort; however, the correlation coefficients comparing intakes assessed by the FFQ with two 1-week diet records for the major food contributors to dietary TAC intake in our study population are 0.93 for coffee (caffeinated and decaffeinated), 0.77 for tea, and 0.78 for orange juice [11]. In addition, in a study conducted in Italy, the interquartile agreement (quadratic weighted κ) between TAC intake (as assessed by FRAP intake) calculated using a FFQ, which had been developed specifically to assess antioxidant intake and TAC intake calculated using a 3 day weighted food record, was 0.49 [23]. Thirdly, TAC

intake measured by the FRAP assay, as used in our study, may not accurately represent antioxidant activity in vivo because the bioavailability of antioxidants in foods is highly variable [8] and because the in vivo system is much more complex than the in vitro system. Fourthly, we had limited power to evaluate associations between dietary or total TAC intake and rectal cancer risk.

Despite these limitations, there are several strengths to our study. First, it included a large sample of men followed for 18 years. Secondly, using TAC intake may better capture all antioxidants in the foods, i.e. known antioxidants but also all other nutrients with antioxidant properties that may not be well characterized. In addition, using TAC intake also takes into account the synergy between the different antioxidants which would be omitted when comparing one single antioxidant to the other. Thirdly, information on a wide variety of potential confounding variables was collected repeatedly during follow-up, which allowed for more complete control of confounding.

In conclusion, our findings do not support an association between TAC intake, a marker for total antioxidant intake, and the risk of colorectal, colon, and rectal cancer.

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Age-standardized baseline characteristics by quintiles of dietary and total TAC intake among 47,339 participants in the Health Professionals Follow-up Study (HPFS)

Table 1

	Dietary TAC intake (from foods; mmol/day)			Total TAC intake (from foods and supplements; mmol/day)		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Age, years (mean)	≤7.3	9.4 – 11.4	>13.9	≤8.7	11.5–14.2	>18.5
Body mass index, kg/m ² (mean)	52.3	54.6	53.7	52.7	54.2	54.0
Pack-years of smoking before age 30 (mean)	25.4	25.5	25.6	25.6	25.6	25.3
Physical activity, MET-hours/week (mean)	3.4	5.2	7.0	3.6	5.5	6.0
Family history of colorectal cancer (%)	19.2	21.7	21.5	18.9	21	24.5
Aspirin users (≥2/week) (%)	8.0	8.5	8.3	7.9	8.7	8.6
Multivitamin or antioxidant supplement users (%) ^a	24.8	29.4	31.1	23.1	29.0	33.9
Energy intake, kcal/day (mean)	52.7	52.3	51.2	28.7	47.0	87.1
Alcohol intake, g/day (mean)	1,934	2,043	1,909	1,931	2,042	1,913
Red meat intake, servings/day (mean)	6.9	12.2	14.1	7.4	12.3	12.7
Total fruit intake, servings/day (mean)	1.0	1.0	0.9	1.0	1.0	0.8
Total vegetable intake, servings/day (mean)	2.0	2.4	2.5	2.0	2.4	2.7
Coffee intake (includes decaffeinated), servings/day (mean)	2.6	3.2	3.3	2.6	3.2	3.4
Tea intake, servings/day (mean)	0.4	1.9	3.8	0.5	2.2	2.6
Dietary vitamin D intake, IU/day (mean) ^b	0.1	0.4	0.9	0.2	0.4	0.7
Dietary folate intake, mcg/day (mean) ^b	274	261	251	269	256	266
Total calcium intake, mg/day (mean) ^{bc}	329	361	370	330	358	380
Dietary fiber intake, grams/day (mean) ^b	946	881	879	861	845	1056
	20.0	21.1	21.7	19.6	20.9	22.9

^a Any multivitamin supplements or any antioxidant supplements (e.g.: vitamin E, vitamin A, vitamin C, selenium, beta carotene, coenzyme Q10, lycopene)

^b Nutrient intakes are energy-adjusted.

^c Includes the use of supplements

TABLE 2
Relative risks of colorectal, colon, and rectal cancer for quintiles of energy-adjusted dietary and total TAC intake

COLORECTAL CANCER						
DIETARY TAC (mmol/day)	≤7.3	7.4 – 9.4	9.4 – 11.4	11.4 – 13.9	>13.9	P-value, test for trend
Number of cases	148	226	217	191	170	
Person years	153046	149418	156465	150601	151922	
Age-RR (95% CI)	1.00 (Ref)	1.29 (1.04-1.59)	1.16 (0.94-1.43)	1.07 (0.86-1.33)	1.04 (0.83-1.30)	0.50
MV-RR (95% CI) ^a	1.00 (Ref)	1.27 (1.02-1.57)	1.11 (0.89-1.39)	1.03 (0.82-1.29)	0.98 (0.78-1.23)	0.19
TOTAL TAC (mmol/day)	≤8.7	8.8-11.4	11.5-14.2	14.3-18.5	>18.5	
Number of cases	176	216	200	184	176	
Person years	152668	152960	141820	161423	152581	
Age-RR (95% CI)	1.00 (Ref)	1.05 (0.86-1.28)	1.04 (0.85-1.28)	0.86 (0.70-1.06)	0.89 (0.72-1.10)	0.06
MV-RR (95% CI) ^b	1.00 (Ref)	1.03 (0.83-1.26)	1.03 (0.83-1.27)	0.85 (0.69-1.06)	0.91 (0.73-1.14)	0.17
COLON CANCER						
DIETARY TAC (mmol/day)	≤7.3	7.4 – 9.4	9.4 – 11.4	11.4 – 13.9	>13.9	
Number of cases	85	151	138	140	120	
Person years	153101	149491	156533	150649	151972	
Age-RR (95% CI)	1.00 (Ref)	1.51 (1.15-1.97)	1.29 (0.98-1.70)	1.38 (1.05-1.81)	1.27 (0.96-1.67)	0.40
MV-RR (95% CI) ^a	1.00 (Ref)	1.48 (1.12-1.94)	1.24 (0.93-1.64)	1.32 (0.99-1.75)	1.20 (0.90-1.61)	0.77
TOTAL TAC (mmol/day)	≤8.7	8.8-11.4	11.5-14.2	14.3-18.5	>18.5	
Number of cases	114	138	138	120	124	
Person years	152726	153025	141881	161480	152634	
Age-RR (95% CI)	1.00 (Ref)	1.04 (0.81-1.34)	1.13 (0.87-1.44)	0.87 (0.67-1.13)	0.97 (0.75-1.26)	0.43
MV-RR (95% CI) ^b	1.00 (Ref)	1.02 (0.79-1.31)	1.10 (0.85-1.43)	0.86 (0.66-1.13)	1.01 (0.77-1.33)	0.73
RECTAL CANCER						
DIETARY TAC (mmol/day)	≤7.3	7.4 – 9.4	9.4 – 11.4	11.4 – 13.9	>13.9	
Number of cases	43	45	49	36	28	
Person years	153137	149579	156629	150746	152053	
Age-RR (95% CI)	1.00 (Ref)	0.86 (0.56-1.31)	0.91 (0.60-1.37)	0.67 (0.43-1.05)	0.61 (0.38-0.98)	0.02
MV-RR (95% CI) ^a	1.00 (Ref)	0.84 (0.54-1.29)	0.87 (0.56-1.34)	0.64 (0.40-1.04)	0.58 (0.35-0.96)	0.02

TOTAL TAC (mmol/day)	≤8.7	8.8-11.4	11.5-14.2	14.3-18.5	>18.5
Number of cases	39	50	36	40	36
Person years	152782	153114	141982	161550	152715
Age-RR (95% CI)	1.00 (Ref)	1.11 (0.73-1.69)	0.85 (0.54-1.34)	0.84 (0.54-1.31)	0.84 (0.53-1.32)
MV-RR (95% CI)^b	1.00 (Ref)	1.09 (0.71-1.68)	0.85 (0.53-1.36)	0.86 (0.54-1.37)	0.85 (0.52-1.38)

^a Multivariate (MV) models are adjusted for age (in months), aspirin use (≥2times per week/ <2 times per week), family history of colorectal cancer (yes/no), previous endoscopy (yes/no), supplement use containing antioxidants (ever/never); body mass index (<24; 24-26; >26-29; >29 kg/m²), energy intake (kilocalories/day, continuous), alcohol intake (0; >0-<5; 5-<15; ≥15g/day), physical activity (quintiles of MET-hours/week), red meat consumption (quintiles), total calcium intake (quintiles), dietary folate intake (quintiles), dietary vitamin D intake (quintiles); pack years of smoking before age 30 (continuous), and race (Caucasian/non-Caucasian).

^b Not adjusted for supplement use.