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No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma

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Abstract

Previous epidemiologic studies that have examined the relationship between renal cell carcinoma (RCC) risk and intakes of plant foods and antioxidant nutrients have yielded inconsistent results. We therefore examined the associations between intakes of fruit, vegetables, carotenoids, flavonoids, vitamin E, and vitamin C and RCC risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort. At baseline, 27,062 male Finnish smokers aged 50–69 years completed a 276-item dietary questionnaire that included questions on frequency of consumption and portion size. During up to 19 years of follow-up, 255 men developed RCC. Cox proportional hazards models were utilized to estimate relative risks (RR) and 95% confidence intervals (CI). Despite a large range in intake, no association was observed between fruit, vegetables, or antioxidant nutrients and RCC risk. For example, multivariate RRs and 95% CIs for the highest versus the lowest quartile of intake were 0.79 (0.55–1.14), 1.23 (0.85–1.79), 1.09 (0.74–1.60), 0.83 (0.57–1.21), 1.09 (0.73–1.64), and 0.99 (0.67–1.46) for fruit, vegetables, total carotenoids, total flavonoids, total vitamin E, and vitamin C, respectively (all p-values for trend > 0.05). Our results indicate that diet may not play a large role in the etiology of RCC in male smokers, although further examination of these associations in nonsmokers, women, and diverse racial populations is warranted.

Keywords

antioxidants; cohort study; diet; fruit; renal cell cancer; vegetables

Introduction

The incidence of renal cell carcinoma (RCC) is increasing both in the United States and globally 1, 2. The rise in incidence is due in part to more frequent use of ultrasonography, computed tomography, and magnetic resonance imaging, which inadvertently detect kidney cancers 3. However, the incidence of advanced and metastatic disease has also increased, suggesting that the rise is not entirely due to earlier detection 2.

Established risk factors for RCC include age, race, gender, smoking, and obesity, with most studies also demonstrating a positive association with hypertension 2, 4. Dietary factors also

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appear to play a role, with higher fruit and vegetable intake linked to lower risks of this disease in several studies[5–10]. Fruits and vegetables are rich sources of free-radical scavenging antioxidant nutrients, including carotenoids, flavonoids, and vitamin C. Vitamin E is also a powerful antioxidant, although its major food sources are not fruits and vegetables. Rather, vitamin E is found predominantly in vegetable oils and nuts [11]. Since oxidative stress is hypothesized to play a role in the development of RCC [12], higher dietary intakes and/or blood levels of these nutrients may protect against the initiation and progression of this malignancy. Studies that have examined the relationship between RCC and individual antioxidant nutrients, however, have yielded inconsistent results [6, 7, 9, 10, 13–16].

We investigated associations of fruits, vegetables, and individual antioxidant nutrients with subsequent risk of RCC in a large cohort study of male smokers. With 255 incident RCC cases available for analysis, this is one of the largest prospective studies to date examining these associations.

Materials and methods

Study design and subjects

Details of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study have been described previously [17]. Briefly, the ATBC Study was a randomized, double-blind, placebo-controlled, primary prevention trial that tested whether daily supplementation withβ-carotene (20 mg) and/or vitamin E (50 mg DL-α-tocopheryl acetate) reduced the incidence of lung and other cancers. The study population included 29,133 Caucasian male smokers from southwestern Finland, aged 50–69 years, who smoked 5 or more cigarettes per day at baseline. Subjects with a history of cancer, those with a serious disease that would limit long-term participation in a trial, or those using vitamin E, A, or β-carotene supplements in excess of predefined limits were excluded. All subjects were enrolled between 1985 and 1988 and were actively followed until trial closure on April 30, 1993 (median follow-up time = 6.1 years); passive case ascertainment continued thereafter.

The Institutional Review Boards of both the National Public Health Institute of Finland and the US National Cancer Institute approved the study and written, informed consent was obtained from each participant before randomization.

Baseline data collection

At baseline, subjects were asked to provide demographic, smoking, and occupational information, to give a history of medical examinations and diseases, and to complete a dietary questionnaire. Height, weight, and blood pressure were measured by trained personnel. The dietary questionnaire asked participants to report usual frequency of consumption and portion size over the past year for 276 foods and beverages, and was accompanied by a color picture booklet designed to assist with portion size estimation. Daily nutrient intakes were calculated using the food composition database from the National Public Health Institute in Finland. The food use questionnaire was developed specifically for use in the ATBC Study and was validated in a pilot study that collected 12 two-day food consumption records distributed evenly over a period of 6 months from 190 subjects; Pearson correlation coefficients (unadjusted) were 0.41, 0.64, 0.58, 0.47, and 0.62 for vitamin A, vitamin E, vitamin C, vegetables, and fruits, respectively [19]. A total of 27,111 men (93% of the full cohort) successfully completed the dietary questionnaire. Overnight fasting serum samples were collected from virtually all participants at baseline and stored at −70°C. Concentrations of α-tocopherol, β-carotene, and retinol were determined using high-performance liquid chromatography in the chemistry laboratory of the National Public

Health Institute (Helsinki, Finland) 20, while cholesterol levels were measured using an enzymatic assay (CHOD-PAP method, Boehringer Mannheim, Germany).

Case ascertainment

RCC cases (ICD-9 code 189.0) were identified through the Finnish Cancer Registry, which provides almost 100% case ascertainment nationwide 18. Cancers of the renal pelvis, ureter, or urethra (n=49) were not included in the present analysis. Two study physicians reviewed the medical records from hospitals and pathology laboratories independently to confirm the diagnosis of RCC. If the two disagreed, a third physician assigned a final diagnosis. A total of 255 incident cases of renal cell carcinoma were diagnosed between randomization and April 30, 2004.

Statistical analyses

Follow-up time for the 27,062 subjects included in this analysis was calculated from the date of study entry until RCC diagnosis, death, or April 30, 2004. Cox proportional hazards models were used to estimate age-adjusted and multivariate relative risks (RR) and 95% confidence intervals (CI), with the lowest quartile of dietary intake or serum nutrients serving as the referent category. P-values for linear trend were based on the median intake of each nutrient quartile, which were subsequently modeled as continuous variables. A base model was specified *a priori* and included known or suspected risk factors for RCC, including age, cigarettes smoked per day, number of years of smoking, alcohol consumption (grams/day), body mass index (kg/m^2), and measured systolic and diastolic blood pressure (mm Hg) as continuous variables, and trial intervention group (α-tocopherol versus no α-tocopherol; β-carotene versus no β-carotene), education (primary, high school, vocational, or university), self-reported history of hypertension (yes, no), and regular leisure-time physical activity (sedentary, moderate intensity activities, high intensity activities) as categorical variables. Dietary intakes were further adjusted for energy using the standard multivariate approach (models using the residual method 21 yielded similar results). Serum α-tocopherol was additionally adjusted for serum cholesterol since the latter is the major carrier of vitamin E in the bloodstream. Intakes of dietary fat, cholesterol, and red meat, as well as place of residence and height, were evaluated as confounders but did not change risk estimates by more than 10 percent. A comprehensive antioxidant index, including dietary intakes of carotenoids, flavonoids, tocopherols, and vitamin C, was created using principal components analysis; this approach has been described previously 22.

Effect modification of associations between RCC and intakes of fruit and vegetables, total carotenoids, total flavonoids, total vitamin E, and vitamin C by age (<57, ≥ 57 years), cigarettes/day (<20, ≥20), years smoked (<36, ≥ 36 years), clinical hypertension (based on measured blood pressure at baseline: <140/90, ≥ 140/90 mmHg), self-reported history of hypertension (yes, no), alcohol consumption (<11, ≥ 11 grams/day), and BMI (<25, ≥ 25 kg/m^2) was assessed in stratified analyses and by including relevant cross-product terms in multivariate models. Cut points were determined using median values for age, cigarettes/day, years smoked, and alcohol consumption. The cut point for BMI was determined based on the standard definition of overweight.

Lag analyses in which RCC cases diagnosed within the first 5 years of follow-up were removed were carried out in order to assess the impact of preclinical disease on the associations of interest. The proportional hazards assumption was verified by including a cross-product term between each nutrient and follow-up time in multivariate models (all *p*-values > 0.05). All reported *p*-values are two-tailed, with a statistical significance level of α=0.05. Statistical analyses were performed using the SAS software version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

Men with higher fruit and vegetable intake smoked less and for fewer years, were moderately heavier, had higher baseline serum levels of β-carotene, and were more highly educated and physically active than men with low intakes (Table I). Fruit and vegetable consumption was positively associated with total energy and red meat intakes and inversely associated with dietary fat, cholesterol, and alcohol consumption.

RCC was not significantly associated with fruit or vegetable intake (Table II), dietary intakes or serum levels of individual antioxidant nutrients (Table III), or a comprehensive dietary antioxidant index (Table III). Risks were unchanged when supplemental vitamin E and vitamin C were combined with dietary intakes of these nutrients (data not shown). A lag analysis in which 74 cases diagnosed within the first 5 years of follow-up were excluded showed similarly null associations when compared to the full cohort. For example, the RR and 95% CI for the highest versus the lowest quartile of total carotenoids, total vitamin E, and total fruits and vegetables were 1.08 (0.68–1.72), 1.15 (0.70–1.87) and 0.88 (0.56–1.39), respectively (all p-values for trend > 0.05).

There was no variation in the risks of RCC associated with fruit and vegetable, total carotenoid, total flavonoid, total vitamin E, or vitamin C intakes across categories of smoking dose, smoking duration, history of hypertension, or alcohol intake (data not shown). A significant interaction was observed, however, between total vitamin E intake and BMI ($p = 0.01$), with men in the normal range BMI group exhibiting a suggestively increased risk of RCC with higher vitamin E intake (RR and 95% CI for highest versus lowest quartile = 1.36 (0.68–2.72), p trend = 0.12); this was not observed among men in the overweight and obese BMI category (RR and 95% CI = 0.96 (0.58–1.58), p trend = 0.96). A borderline significant interaction ($p = 0.05$) was also observed between fruit and vegetable intake and age such that younger men exhibited a decreased risk of RCC at higher levels of total fruit and vegetable intake (RR and 95% CI for highest versus lowest quartile = 0.55 (0.30–0.99), p trend = 0.02), with no such effect noted in older men (RR and 95% CI = 1.42 (0.86–2.35), p trend = 0.17).

Discussion

Our findings are consistent with many other prospective studies that have reported no association between increased fruit and vegetable consumption and RCC risk[23–28]. Case-control studies have yielded more conflicting findings [6–9, 13–15, 29–33]. In contrast to most reports, a study that combined data from the Nurses' Health Study and the Health Professionals Follow-up Study and included a total of 248 RCC cases showed that higher fruit and vegetable consumption was associated with a significantly reduced risk of RCC in men (RR and 95% CI for ≥6 versus < 3 servings per day = 0.45 (0.25–0.81)), but not in women [10]. Furthermore, there was an interaction with smoking status such that the protective effect was only evident in nonsmoking males. Our cohort was comprised exclusively of smokers, which might have precluded the detection of any modest yet beneficial effects of fruit and vegetable intake on RCC risk.

It is unclear why beneficial associations between fruit and vegetable intake and RCC risk were observed in younger but not older men in our cohort. Our study is not the first to demonstrate such a finding; in a case-control study conducted in Italy, Galeone et al. noted a significant inverse association between vegetable fibre intake and RCC risk in subjects < 60 years of age, with no such relation apparent in older individuals [34]. We are not aware of any heterogeneity in the biology of RCC across age subgroups. While such differences may indeed exist, it is more likely that our finding is due to chance.

Although oxidative stress appears to play a role in the development of RCC 12, antioxidants have been inconsistently related to RCC in past prospective and case-control studies[6–10, 13–16, 35, 36]. Most of these studies investigated α-tocopherol, vitamin C, and individual carotenoids, but did not examine flavonoids or combinations of individual antioxidant nutrients. We found no evidence for a protective effect of any antioxidant nutrient on RCC risk.

Strengths of our study include its prospective design, which limits recall bias, use of a validated dietary questionnaire that was created specifically for the ATBC study, availability of pre-randomization serum β-carotene, retinol, and α-tocopherol concentrations for virtually all participants, the large number of incident RCC cases, and our ability to control for a large number of important confounders.

A possible limitation is that our results may not be generalizable to females, nonsmokers, or non-White ethnicities. We also relied on a single measure of dietary intake and serum nutrient concentrations, which may not adequately reflect lifetime dietary habits. In addition, FFQs may only be valid when asking about food intake over the past few days; when compared to food records or 24 hour recalls, their validity can be somewhat poor, especially for energy intake 37. The correlation coefficients in our study, however, ranged between 0.50 and 0.76 for individual antioxidants, suggesting good agreement between data from the FFQ and food consumption records. Random misclassification in FFQ data could have biased our results toward the null, especially if the true association between fruits, vegetables, and or antioxidant nutrients and RCC risk was modest.

In conclusion, our results suggest that increased consumption of fruit, vegetables, and antioxidant nutrients does not reduce the risk of RCC in adult male smokers, although the lack of effect in our study may be partially attributable to misclassification of dietary intakes associated with the use of FFQs. Future studies should continue to address whether higher intakes of plant foods and antioxidants might be beneficial for RCC in nonsmokers, women, and diverse racial populations.

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TABLE I

BASELINE CHARACTERISTICS (MEANS AND PROPORTIONS) BY QUARTILES OF TOTAL FRUIT AND VEGETABLE INTAKE IN THE ATBC STUDY

Characteristics	**Quartile of total fruit and vegetable intake (g/day)**			
	1	**2**	**3**	**4**
	<132.4	**132.4–207.9**	**208.0–303.8**	**>303.8**
No. of participants	6765	6766	6766	6765
Age (years)	57.6	57.3	57.1	56.7
Body mass index (kg/m^2)	26.0	26.3	26.3	26.6
Cigarettes/day	21.9	20.4	20	19.5
No. years smoked	37.2	36.1	35.8	34.6
Serum α-tocopherol (mg/L)	11.3	11.7	12.2	12.5
Serum β-carotene (ug/L)	177	200	223	253
Serum cholesterol (mmol/L)	6.26	6.25	6.25	6.21
Daily dietary intake				
Vitamin E (total, mg)[1]	10.5	11.6	12.4	13.7
Carotenoids (total, ug)[1]	1137	1689	2285	3422
Red meat (g)[1]	61.4	66.0	67.1	70.3
Cholesterol (mg)[1]	593	587	582	568
Fat (g)[1]	110	107	105	100
Total energy (kcal)	2511	2716	2879	3153
Alcohol (g/day)	19.9	18.1	17.2	16.8
Education level (% > primary)	14	19	23	31
Physical activity (% active)[2]	46	58	62	68
History of hypertension (% yes)	18	19	19	21

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

[1]Adjusted for total energy intake

[2]Defined as moderate or heavy physical activity during leisure time

TABLE II

AGE-ADJUSTED AND MULTIVARIATE[1] RR AND 95% CI FOR RCC ACCORDING TO QUARTILES OF FRUIT AND VEGETABLE INTAKE. THE ATBC STUDY, 1985–2004

	Quartile of intake				*p* trend
	1	2	3	4	
Fruit and vegetables (g/d)					
Mean	86	170	252	425	
No. cases	66	70	58	61	
Age-adjusted RR (95% CI)	1.00 (ref)	1.03 (0.74–1.44)	0.84 (0.59–1.20)	0.87 (0.62–1.24)	0.42
Multivariate RR (95% CI)	1.00 (ref)	1.07 (0.76–1.51)	0.88 (0.61–1.27)	0.92 (0.63–1.35)	0.83
Fruits (g/d)					
Mean	29	80	134	257	
No. cases	76	54	65	60	
Age-adjusted RR (95% CI)	1.00 (ref)	0.69 (0.49–0.97)	0.82 (0.59–1.14)	0.75 (0.53–1.05)	0.33
Multivariate RR (95% CI)	1.00 (ref)	0.71 (0.50–1.01)	0.83 (0.59–1.17)	0.79 (0.55–1.14)	0.53
Citrus Fruits (times/d)					
Mean	0.01	0.13	0.25	0.56	
Number of cases	69	57	70	59	
Age-adjusted RR (95% CI)	1.00 (ref)	0.88 (0.62–1.25)	0.88 (0.63–1.23)	0.83 (0.58–1.17)	0.37
Multivariate RR (95% CI)	1.00 (ref)	0.88 (0.62–1.26)	0.92 (0.66–1.29)	0.85 (0.60–1.22)	0.48
Juices (g/d)					
Mean	0.0	10	69	278	
Number of cases	67	70	49	69	
Age-adjusted RR (95% CI)	1.00 (ref)	1.23 (0.88–1.72)	0.77 (0.53–1.11)	1.11 (0.79–1.55)	0.96
Multivariate RR (95% CI)	1.00 (ref)	1.28 (0.91–1.80)	0.81 (0.56–1.18)	1.23 (0.87–1.74)	0.56
Vegetables (g/d)					
Mean	39	76	116	202	
No. cases	59	60	66	70	
Age-adjusted RR (95% CI)	1.00 (ref)	1.00 (0.70–1.43)	1.08 (0.76–1.53)	1.13 (0.80–1.60)	0.94
Multivariate RR (95% CI)	1.00 (ref)	1.05 (0.73–1.51)	1.16 (0.81–1.67)	1.23 (0.85–1.79)	0.64
Cruciferous Vegetables (times/d)					
Mean	0.01	0.06	0.12	0.33	

	Quartile of intake				p trend
	1	2	3	4	
Number of cases	57	68	61	69	
Age-adjusted RR (95% CI)	1.00 (ref)	1.16 (0.81–1.64)	1.01 (0.70–1.45)	1.21 (0.85–1.72)	0.40
Multivariate RR (95% CI)	1.00 (ref)	1.14 (0.80–1.63)	1.02 (0.71–1.46)	1.24 (0.87–1.79)	0.31
Root Vegetables (g/d)					
Mean	5.5	15	27	57	
Number of cases	58	66	71	60	
Age-adjusted RR (95% CI)	1.00 (ref)	1.11 (0.78–1.58)	1.18 (0.84–1.67)	0.98 (0.68–1.40)	0.76
Multivariate RR (95% CI)	1.00 (ref)	1.15 (0.80–1.64)	1.25 (0.88–1.78)	1.05 (0.72–1.53)	0.92

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; 95% CI, 95% confidence interval; RR, relative risk.

[1] All factors adjusted for age, BMI (kg/m^2), education level (primary, high school, vocational, university), measured systolic and diastolic blood pressure, self-reported history of hypertension (yes, no), leisure-time physical activity (low, medium, high), years of smoking, total number of cigarettes per day, trial intervention group (α-tocopherol, no α-tocopherol; β-carotene, no β-carotene), total energy intake (kcal/day), and alcohol consumption (grams/day).

TABLE III

AGE-ADJUSTED AND MULTIVARIATE[1] RR AND 95% CI FOR RCC ACCORDING TO QUARTILES OF DIETARY AND SERUM ANTIOXIDANT NUTRIENTS. THE ATBC STUDY, 1985–2004

	Quartile of dietary intake or serum concentration				*p* trend
	1	**2**	**3**	**4**	
Total carotenoids (ug/d)					
Mean	2330	3791	5383	9127	
No. cases	62	61	68	64	
Age-adjusted RR (95% CI)	1.00 (ref)	0.97 (0.68–1.38)	1.05 (0.75–1.49)	0.98 (0.69–1.38)	0.64
Multivariate RR (95% CI)	1.00 (ref)	1.02 (0.71–1.46)	1.16 (0.81–1.66)	1.09 (0.74–1.60)	0.98
α-Carotene (ug/d)					
Mean	124	327	616	1435	
Number of cases	55	65	70	65	
Age-adjusted RR (95% CI)	1.00 (ref)	1.15 (0.81–1.65)	1.22 (0.86–1.74)	1.12 (0.78–1.60)	0.7
Multivariate RR (95% CI)	1.00 (ref)	1.18 (0.83–1.70)	1.29 (0.90–1.85)	1.20 (0.83–1.75)	0.45
β-Carotene (ug/d)					
Mean	775	1386	2151	4221	
Number of cases	61	54	76	64	
Age-adjusted RR (95% CI)	1.00 (ref)	0.86 (0.59–1.23)	1.19 (0.85–1.66)	0.98 (0.69–1.40)	0.76
Multivariate RR (95% CI)	1.00 (ref)	0.91 (0.62–1.31)	1.30 (0.91–1.84)	1.10 (0.76–1.60)	0.41
β-Cryptoxanthin (ug/d)					
Mean	2.8	14	31	83	
Number of cases	68	64	63	60	
Age-adjusted RR (95% CI)	1.00 (ref)	0.93 (0.66–1.31)	0.90 (0.64–1.27)	0.87 (0.61–1.23)	0.45
Multivariate RR (95% CI)	1.00 (ref)	0.94 (0.66–1.32)	0.95 (0.67–1.35)	0.90 (0.63–1.28)	0.60
γ-carotene (ug/d)					
Mean	7.5	24	44	94	
Number of cases	52	70	63	70	
Age-adjusted RR (95% CI)	1.00 (ref)	1.31 (0.91–1.87)	1.17 (0.81–1.69)	1.29 (0.90–1.85)	0.33
Multivariate RR (95% CI)	1.00 (ref)	1.37 (0.95–1.97)	1.22 (0.84–1.78)	1.38 (0.95–2.01)	0.21
Lutein and Zeaxanthin (ug/d)					
Mean	867	1225	1535	2133	

	Quartile of dietary intake or serum concentration				*p* trend
	1	**2**	**3**	**4**	
Number of cases	62	67	72	54	
Age-adjusted RR (95% CI)	1.00 (ref)	1.04 (0.74–1.47)	1.11 (0.79–1.56)	0.84 (0.58–1.20)	0.35
Multivariate RR (95% CI)	1.00 (ref)	1.10 (0.77–1.57)	1.21 (0.83–1.77)	0.97 (0.62–1.53)	0.94
Lycopene (ug/d)					
Mean	147	460	825	1743	
Number of cases	55	63	68	69	
Age-adjusted RR (95% CI)	1.00 (ref)	1.12 (0.78–1.60)	1.20 (0.84–1.72)	1.21 (0.84–1.72)	0.33
Multivariate RR (95% CI)	1.00 (ref)	1.17 (0.81–1.68)	1.25 (0.87–1.80)	1.30 (0.89–1.88)	0.20
Retinol (ug/d)					
Mean	573	1007	1562	2859	
No. cases	68	61	64	62	
Age-adjusted RR (95% CI)	1.00 (ref)	0.90 (0.63–1.27)	0.93 (0.66–1.31)	0.90 (0.64–1.32)	0.29
Multivariate RR (95% CI)	1.00 (ref)	0.96 (0.67–1.37)	1.02 (0.71–1.46)	1.00 (0.69–1.46)	0.58
Total flavonoids (ug/d)					
Mean	4758	9020	15192	39663	
No. cases	69	63	67	56	
Age-adjusted RR (95% CI)	1.00 (ref)	0.89 (0.63–1.25)	0.93 (0.66–1.30)	0.77 (0.54–1.10)	0.32
Multivariate RR (95% CI)	1.00 (ref)	0.94 (0.66–1.32)	0.98 (0.69–1.40)	0.83 (0.57–1.21)	0.47
Catechin (ug/d)					
Mean	176	600	1528	7367	
Number of cases	70	68	61	56	
Age-adjusted RR (95% CI)	1.00 (ref)	0.93 (0.67–1.30)	0.82 (0.58–1.16)	0.75 (0.53–1.07)	0.13
Multivariate RR (95% CI)	1.00 (ref)	0.94 (0.67–1.32)	0.87 (0.61–1.24)	0.79 (0.54–1.13)	0.21
Epicatechin (ug/d)					
Mean	214	965	2605	12845	
Number of cases	61	64	74	56	
Age-adjusted RR (95% CI)	1.00 (ref)	1.03 (0.72–1.46)	1.17 (0.83–1.64)	0.88 (0.61–1.26)	0.29
Multivariate RR (95% CI)	1.00 (ref)	1.06 (0.75–1.52)	1.22 (0.86–1.73)	0.93 (0.64–1.35)	0.41
Kaempferol (ug/d)					
Mean	130	311	757	4256	

	Quartile of dietary intake or serum concentration				p trend
	1	2	3	4	
Number of cases	64	70	62	59	
Age-adjusted RR (95% CI)	1.00 (ref)	1.05 (0.75–1.48)	0.91 (0.64–1.29)	0.87 (0.61–1.23)	0.33
Multivariate RR (95% CI)	1.00 (ref)	1.09 (0.77–1.54)	0.97 (0.67–1.39)	0.92 (0.63–1.33)	0.47
Myricetin (ug/d)					
Mean	241	496	858	1936	
Number of cases	65	75	57	58	
Age-adjusted RR (95% CI)	1.00 (ref)	1.12 (0.80–1.56)	0.83 (0.59–1.19)	0.85 (0.60–1.21)	0.17
Multivariate RR (95% CI)	1.00 (ref)	1.19 (0.85–1.67)	0.90 (0.63–1.31)	0.96 (0.66–1.39)	0.49
Quercetin (ug/d)					
Mean	3344	5511	7756	13195	
Number of cases	67	67	66	55	
Age-adjusted RR (95% CI)	1.00 (ref)	0.98 (0.70–1.37)	0.94 (0.67–1.32)	0.79 (0.55–1.12)	0.16
Multivariate RR (95% CI)	1.00 (ref)	1.01 (0.72–1.43)	0.98 (0.69–1.41)	0.86 (0.58–1.27)	0.39
Total vitamin E (mg/d)					
Mean	6.5	9.4	12	20	
No. cases	68	53	68	66	
Age-adjusted RR (95% CI)	1.00 (ref)	0.75 (0.52–1.08)	0.97 (0.69–1.35)	0.95 (0.67–1.33)	0.96
Multivariate RR (95% CI)	1.00 (ref)	0.82 (0.56–1.19)	1.10 (0.75–1.60)	1.09 (0.73–1.64)	0.47
α-Tocopherol (mg/d)					
Mean	5.6	8.1	11	17	
Number of cases	64	58	68	65	
Age-adjusted RR (95% CI)	1.00 (ref)	0.88 (0.62–1.25)	1.03 (0.73–1.45)	0.99 (0.70–1.40)	0.82
Multivariate RR (95% CI)	1.00 (ref)	0.96 (0.67–1.40)	1.19 (0.82–1.74)	1.17 (0.77–1.76)	0.36
γ-Tocopherol (mg/d)					
Mean	1.8	4.3	8.0	19	
Number of cases	69	65	45	76	
Age-adjusted RR (95% CI)	1.00 (ref)	0.92 (0.66–1.30)	0.64 (0.44–0.94)	1.10 (0.79–1.52)	0.40
Multivariate RR (95% CI)	1.00 (ref)	0.92 (0.65–1.30)	0.65 (0.44–0.96)	1.10 (0.78–1.55)	0.36
β-Tocopherol (mg/d)					
Mean	0.39	0.66	0.92	1.48	

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	Quartile of dietary intake or serum concentration				p trend
	1	2	3	4	
Number of cases	55	65	78	57	
Age-adjusted RR (95% CI)	1.00 (ref)	1.16 (0.81–1.66)	1.37 (0.97–1.94)	1.00 (0.69–1.45)	0.99
Multivariate RR (95% CI)	1.00 (ref)	1.25 (0.86–1.81)	1.53 (1.05–2.21)	1.16 (0.76–1.78)	0.55
δ-Tocopherol (mg/d)					
Mean	0.18	0.47	1.16	5.19	
Number of cases	61	74	44	76	
Age-adjusted RR (95% CI)	1.00 (ref)	1.19 (0.85–1.67)	0.71 (0.48–1.04)	1.24 (0.89–1.75)	0.13
Multivariate RR (95% CI)	1.00 (ref)	1.20 (0.85–1.69)	0.73 (0.49–1.09)	1.24 (0.87–1.76)	0.15
α-Tocotrienol (mg/d)					
Mean	0.93	1.56	2.16	3.35	
Number of cases	62	62	62	69	
Age-adjusted RR (95% CI)	1.00 (ref)	0.96 (0.68–1.37)	0.96 (0.67–1.36)	1.07 (0.76–1.50)	0.66
Multivariate RR (95% CI)	1.00 (ref)	1.07 (0.75–1.54)	1.13 (0.78–1.65)	1.36 (0.90–2.04)	0.13
γ-Tocotrienol (mg/d)					
Mean	0.06	0.14	0.23	0.46	
Number of cases	60	71	52	72	
Age-adjusted RR (95% CI)	1.00 (ref)	1.18 (0.83–1.66)	0.86 (0.59–1.25)	1.21 (0.85–1.71)	0.36
Multivariate RR (95% CI)	1.00 (ref)	1.18 (0.84–1.68)	0.90 (0.61–1.31)	1.23 (0.87–1.76)	0.31
β-Tocotrienol (mg/d)					
Mean	1.31	2.09	2.77	4.09	
Number of cases	52	76	67	60	
Age-adjusted RR (95% CI)	1.00 (ref)	1.40 (0.98–1.99)	1.23 (0.86–1.76)	1.09 (0.75–1.58)	0.97
Multivariate RR (95% CI)	1.00 (ref)	1.57 (1.08–2.27)	1.46 (0.97–2.19)	1.42 (0.88–2.31)	0.30
δ-Tocotrienol (mg/d)					
Mean	0.01	0.03	0.07	0.21	
Number of cases	66	58	66	65	
Age-adjusted RR (95% CI)	1.00 (ref)	0.85 (0.60–1.21)	0.96 (0.68–1.35)	0.95 (0.67–1.34)	0.99
Multivariate RR (95% CI)	1.00 (ref)	0.88 (0.62–1.26)	1.01 (0.71–1.44)	1.02 (0.71–1.47)	0.68
Vitamin C (mg/d)					
Mean	50	78	104	161	

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	Quartile of dietary intake or serum concentration				*p* trend
	1	**2**	**3**	**4**	
No. cases	66	53	75	61	
Age-adjusted RR (95% CI)	1.00 (ref)	0.78 (0.54–1.11)	1.09 (0.78–1.52)	0.88 (0.62–1.24)	0.59
Multivariate RR (95% CI)	1.00 (ref)	0.81 (0.56–1.18)	1.16 (0.82–1.65)	0.99 (0.67–1.46)	0.93
Antioxidant index					
Mean	−4.26	−1.66	0.62	5.28	
No. cases	53	71	72	59	
Age-adjusted RR (95% CI)	1.00 (ref)	1.31 (0.92–1.87)	1.31 (0.92–1.87)	1.05 (0.73–1.53)	0.98
Multivariate RR (95% CI)	1.00 (ref)	1.26 (0.88–1.81)	1.26 (0.87–1.81)	1.00 (0.68–1.48)	0.78
Serum β-carotene (ug/L)					
Mean	75	141	213	425	
No. cases	67	59	63	66	
Age-adjusted RR (95% CI)	1.00 (ref)	0.86 (0.61–1.20)	0.87 (0.62–1.22)	0.86 (0.62–1.20)	0.28
Multivariate RR (95% CI)	1.00 (ref)	0.83 (0.58–1.19)	0.88 (0.62–1.26)	0.91 (0.63–1.32)	0.60
Serum retinol (ug/L)					
Mean	439	541	617	759	
No. cases	64	65	58	68	
Age-adjusted RR (95% CI)	1.00 (ref)	0.92 (0.65–1.28)	0.89 (0.63–1.25)	1.06 (0.76–1.47)	0.77
Multivariate RR (95% CI)	1.00 (ref)	0.95 (0.67–1.35)	0.87 (0.61–1.25)	1.03 (0.72–1.47)	0.84
Serum α-tocopherol (mg/L)					
Mean	8.4	10.7	12.5	16.4	
No. cases	54	66	69	66	
Age-adjusted RR (95% CI)	1.00 (ref)	1.33 (0.92–1.93)	1.45 (0.98–2.13)	1.57 (1.02–2.43)	0.91
Multivariate RR[2] (95% CI)	1.00 (ref)	1.17 (0.80–1.70)	1.35 (0.92–2.01)	1.37 (0.88–2.14)	0.81

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; 95% CI, 95% confidence interval; RR, relative risk.

[1] All factors adjusted for age, BMI (kg/m^2), education level (primary, high school, vocational, university), measured systolic and diastolic blood pressure, self-reported history of hypertension (yes, no), leisure-time physical activity (low, medium, high), years of smoking, total number of cigarettes per day, trial intervention group (α-tocopherol, no α-tocopherol; β-carotene, no β-carotene), and alcohol consumption (grams/day). Dietary factors further adjusted for total energy intake (kcal/day).

[2] Further adjusted for serum cholesterol.