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Dietary flavonol, flavone and catechin intake and risk of colorectal cancer in the Netherlands Cohort Study

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Dietary flavonoids are hypothesized to be protective against colorectal cancer, yet findings have been inconsistent. We examined the association of dietary flavonol, flavone and catechin intake with colorectal cancer endpoints within the Netherlands Cohort Study (NLCS). In addition, we explored whether body mass index (BMI) may be an effect modifier of this association. The NLCS includes 120,852 men and women who were 55–69 years and completed a self-administered questionnaire at baseline in 1986. A case-cohort approach was used for data processing and analysis. After 13.3 years, 1,444 male and 1,041 female colorectal cancer cases were available for estimation of hazard ratios and 95% confidence intervals for quintiles of flavonoid intake. After adjustment for potential confounders, no association of total flavonol and flavone intake and total catechin intake with colorectal cancer endpoints was observed. Analyses stratified for BMI showed significant inverse trends in the association of total catechin intake, (+)-catechin intake and (–)-epicatechin intake with rectal cancer in men with a BMI $\geq$ 25 kg/m^2 and in the association of total catechin intake and intake of kaempferol, myricetin and all individual catechins with colorectal cancer, in particular colon cancer, in women with a BMI < 25 kg/m^2. In conclusion, our findings generally do not support an association of dietary flavonol, flavone and catechin intake with colorectal cancer endpoints. Dietary catechin intake may be associated with a decreased rectal cancer risk in overweight men. Dietary flavonol and catechin intake may be associated with a decreased colorectal cancer risk in normal weight women.

Key words: cohort studies; flavonoids; colonic neoplasms; rectal neoplasms

Colorectal cancer is one of the most common forms of cancer in the Western world. Most colorectal cancers occur as sporadic (*i.e.*, nonhereditary) forms for which main risk factors lie in diet and lifestyle.[1] The modifiable potential of dietary and lifestyle factors offers opportunities for prevention.

Flavonoids are polyphenolic compounds present in foods and beverages from plant origin that are thought to possibly protect against cancer. In cell line and animal studies, flavonoids were shown to have an antioxidant effect, to interfere with or eliminate carcinogens, to inhibit cell proliferation, to induce apoptosis and to inhibit angiogenesis.[2,3] Specific to colorectal carcinogenesis, such findings are still accumulating.[4–7]

Whether dietary intake of flavonoids is protective against colorectal cancer in humans cannot be easily extrapolated from cell line and animal findings. In this perspective, epidemiologic studies on the association of flavonoid intake with colorectal cancer risk are important, yet to date these have been limited. Those studies on flavonoid intake and colorectal cancer risk that were conducted yielded inconsistent results.[8–17]

The most studied flavonoid subgroups are flavonols, flavones and catechins (also known as flavan-3-ols or flavanols). Major contributors to flavonol intake are quercetin, kaempferol and myricetin. Flavones include luteolin and apigenin. Most abundant within the subgroup of catechins are (+)-catechin, (–)-epicatechin, (+)-gallocatechin (GC), (–)-epigallocatechin (EGC), (–)-epicatechin gallate (ECG) and (–)-epigallocatechin gallate (EGCG). Flavonols and catechins can be found in fruits, vegetables, tea and red wine, with tea containing all major catechins and flavonols. Flavones are only present in some vegetables.[18–21] Fruit and vegetable intake as well as tea intake, like flavonoid intake itself, have been hypothesized to be protective against cancer but have not consistently been found to be associated with a reduction in colorectal cancer risk.[22–25]

We examined the association of dietary flavonol, flavone and catechin intake with colorectal cancer endpoints within the Netherlands Cohort Study on diet and cancer (NLCS). In addition, we explored whether body mass index (BMI) may be an effect modifier of this association. Total flavonol and flavone intake, total catechin intake, and intake of the individual flavonols quercetin, kaempferol and myricetin and the individual catechins (+)-catechin, (–)-epicatechin, GC, EGC, ECG and EGCG were studied.

Material and methods

Study population and design

The Netherlands Cohort Study on diet and cancer (NLCS) comprises 58,279 men and 62,573 women who were 55–69 years and completed a mailed self-administered questionnaire at baseline in 1986. A case-cohort approach was used for data processing and analysis, enumerating incident cancer cases from the entire cohort and calculating the accumulated person-time at risk from a random subcohort of 5,000 members who were selected immediately after baseline and followed up for migration and vital status. All subcohort members contributed to the person-time at risk until they became colorectal cancer cases or otherwise censored. The study design has been described in detail elsewhere.[26]

Incident colorectal cancer cases were ascertained through annual record linkage with PALGA[27] (the Netherlands nationwide pathology registry) and the Netherlands population-based cancer registry. The completeness of cancer follow up has previously been estimated to be >96%[28]. After computerized linkage, visual inspection with additional information is performed to separate the computer matches into true and false positives. The use of this two-stage procedure has previously yielded a high sensitivity (*e.g.*, 98%) and a maximized positive predictive value.[29]

After 13.3 years of follow up, 1,444 male and 1,041 female incident colorectal cancer cases and 2,191 male and 2,247 female

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TABLE I – MEAN (STANDARD DEVIATION) INTAKE OF FLAVONOIDS AND OTHER POPULATION CHARACTERISTICS AT BASELINE IN MALE SUBCOHORT MEMBERS AND CASES

Characteristic	Subcohort members	Colorectal cancer cases	Cases by subsite	
			Colon	Rectum
N[1]	1,853	1,271	820	326
Total flavonol and flavone intake (mg/day)	26.6 (12.4)	27.0 (12.2)	26.8 (12.0)	27.2 (13.2)
Quercetin intake (mg/day)	18.3 (9.0)	18.5 (8.8)	18.3 (8.6)	18.9 (9.6)
Kaempferol intake (mg/day)	6.8 (3.8)	6.9 (3.9)	7.0 (3.8)	6.8 (4.1)
Myricetin intake (mg/day)	1.4 (1.0)	1.5 (1.0)	1.5 (0.9)	1.4 (1.0)
Total catechin intake (mg/day)	57.3 (36.7)	58.9 (37.2)	60.1 (36.6)	55.6 (38.2)
(+)-catechin intake (mg/day)	4.4 (2.8)	4.5 (2.8)	4.5 (2.5)	4.4 (3.1)
(−)-epicatechin intake (mg/day)	13.0 (7.1)	13.4 (7.0)	13.5 (6.9)	12.9 (7.1)
(+)-gallocatechin intake (mg/day)	2.8 (2.1)	2.9 (2.1)	2.9 (2.1)	2.7 (2.1)
(−)-epigallocatechin intake (mg/day)	4.6 (3.2)	4.7 (3.3)	4.8 (3.2)	4.4 (3.4)
(−)-epicatechin gallate intake (mg/day)	18.7 (14.0)	19.2 (4.3)	19.8 (14.0)	17.9 (14.6)
(−)-epigallocatechin gallate intake (mg/day)	13.8 (10.4)	14.2 (10.6)	14.6 (10.4)	13.3 (10.8)
Age (years)	61.2 (4.2)	62.1 (4.1)	62.3 (4.2)	61.6 (4.0)
Family history of colorectal cancer (%yes)	5	10	10	9
Smoking status (%)				
Never	13	11	11	10
Ex	53	60	62	56
Currently	35	29	27	34
Alcohol intake (%)				
0 g/day	15	12	13	11
0.1–29 g/day	70	70	70	67
≥30 g/day	15	18	17	22
Occupational physical activity at longest held job (%)				
<8 kJ/min	59	63	68	54
8–12 kJ/min	26	24	22	29
>12 kJ/min	15	13	12	17
BMI (kg/m^2)	24.9 (2.6)	25.2 (2.7)	25.2 (2.7)	25.1 (2.5)
Processed meat intake (g/day)	17.0 (17.2)	17.8 (17.5)	17.8 (17.5)	17.4 (16.7)

BMI, body mass index.
[1] N without subjects with missing values on population characteristics.

subcohort members were available for analysis. These numbers were obtained after excluding subjects who reported a history of cancer at baseline other than nonmelanoma skin cancer and subjects with incomplete or inconsistent questionnaires. A subdivision can be made into 920 male and 758 female colon cancer cases (International Classification of Diseases for Oncology, first edition codes 153.0 through 153.9) and 376 male and 196 female rectal cancer cases (code 154.1). The remaining cases were rectosigmoid cancer cases (code 154.0) and were only included when analyzing risk of overall colorectal cancer.

The NLCS has been approved by the institutional review boards of the TNO Nutrition and Food Research Institute (Zeist) and Maastricht University (Maastricht).

Questionnaire

Information on food habits and other risk factors was collected at baseline from all cohort members using a mailed self-administered questionnaire. For the dietary part, the questionnaire included a semi-quantitative food-frequency questionnaire (FFQ) assessing regular consumption of 150 food-items in the preceding year. For each item, subjects were asked to indicate how often, on a scale of seven frequency categories ranging from never/less than once per month to 6–7 times per week, a specified quantity of each food or beverage was consumed. Questions on vegetables were specified with respect to season. In an open-ended question, subjects were asked to list any foods and beverages consumed at least once per week but not included in the questionnaire. Questionnaire data were key-entered and processed in a manner blinded to subcohort or case status. The FFQ was validated and tested for reproducibility. Comparison with a 9-day dietary record showed that it was able to rank subjects adequately according to intake of the food groups and nutrients investigated.[30] The FFQ was also found to be a good indicator of nutrient intake over a period of at least 5 years.[31]

Ascertainment of flavonol, flavone and catechin intake

Daily flavonol and flavone intake and daily catechin intake in the present population were calculated by multiplying the reported consumption frequency and consumed quantity on the FFQ by the flavonoid content of each food (in mg/100 g of edible portion) or beverage (in mg/100 ml). Flavonol and flavone content of foods and beverages were derived from a food composition table composed of data gathered in the Netherlands by Hertog et al.[18,19] Catechin content of foods and beverages were derived from a food composition table composed of data gathered in the Netherlands by Arts et al.[20,21] Both the tables were constructed after determining flavonol and flavone content and catechin content in different types and varieties/brands of vegetables, fruits, pulses (*e.g.*, legumes), processed foods, wine, tea, juices, coffee, chocolate milk and beer. Account was taken of season and purchasing location by multiple sampling. Briefly, according to the gathered data, flavonols are particularly present in onions, kale, apples, pears, tea, wine and fruit juices. Catechins are particularly present in broad beans, berries, grapes, black chocolate, tea and red wine. Of the flavones, luteolin was only detected in sweet red pepper and apigenin was not detected at all. Hence, flavone intake in the present population exclusively refers to luteolin intake. In addition, because luteolin intake in the present population was low, luteolin intake was summed with total flavonol intake and no separate variable was created.

Ascertainment of BMI and other covariates

BMI (kg/m^2) was calculated from the baseline questionnaire by dividing self-reported weight (kg) by self-reported height squared (m^2). Self-reported weight and height have been shown to be a valid and reliable manner of assessment in other studies with adult populations.[32–35] Information on other covariates that were considered potential confounders on the basis of previous research was also available from the baseline questionnaire. Daily intake of nutrients other than flavonols, flavones or catechins was calculated

TABLE II – MEAN (STANDARD DEVIATION) INTAKE OF FLAVONOIDS AND OTHER POPULATION CHARACTERISTICS AT BASELINE IN FEMALE SUBCOHORT MEMBERS AND CASES

Characteristic	Subcohort members	Colorectal cancer cases	Cases by subsite	
			Colon	Rectum
N^1	2,053	948	695	175
Total flavonol and flavone intake (mg/day)	29.1 (12.7)	28.7 (12.2)	28.6 (12.2)	28.7 (12.2)
Quercetin intake (mg/day)	19.7 (8.9)	19.4 (8.5)	19.4 (8.5)	19.5 (8.2)
Kaempferol intake (mg/day)	7.7 (4.1)	7.6 (4.1)	7.6 (4.1)	7.6 (4.3)
Myricetin intake (mg/day)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)
Total catechin intake (mg/day)	67.0 (39.2)	65.4 (37.4)	65.3 (37.6)	65.6 (37.7)
(+)-catechin intake (mg/day)	4.7 (2.5)	4.6 (2.4)	4.6 (2.4)	4.6 (2.4)
(−)-epicatechin intake (mg/day)	15.0 (7.5)	14.6 (6.9)	14.5 (7.0)	14.7 (6.6)
(+)-gallocatechin intake (mg/day)	3.3 (2.2)	3.2 (2.1)	3.2 (2.1)	3.2 (2.2)
(−)-epigallocatechin intake (mg/day)	5.3 (3.4)	5.2 (3.3)	5.2 (3.3)	5.3 (3.5)
(−)-epicatechin gallate intake (mg/day)	22.2 (15.0)	21.7 (14.5)	21.7 (14.5)	21.7 (14.7)
(−)-epigallocatechin gallate intake (mg/day)	16.5 (11.1)	16.1 (10.8)	16.1 (10.8)	16.1 (11.0)
Age (years)	61.4 (4.3)	62.5 (4.0)	62.5 (4.1)	62.4 (3.8)
Family history of colorectal cancer (%yes)	6	10	10	9
Smoking status (%)				
Never	57	59	61	58
Ex	21	21	21	19
Currently	22	19	18	22
Alcohol intake (%)				
0 g/day	32	34	34	34
0.1–29 g/day	64	62	61	63
≥30 g/day	4	5	5	3
Nonoccupational physical activity (%)				
<30 min/day	23	28	29	33
30–60 min/day	31	31	30	31
60–90 min/day	23	23	23	23
>90 min/day	22	18	18	13
BMI (kg/m^2)	25.0 (3.5)	25.1 (3.5)	25.1 (3.6)	25.0 (3.6)
Processed meat intake (g/day)	11.3 (12.5)	11.2 (11.8)	11.2 (11.9)	11.3 (11.8)

BMI, body mass index.
[1]*N* without subjects with missing values on population characteristics.

using the Dutch food composition table 1986–1987.[36] Considered as potential confounders were age, family history of colorectal cancer, smoking status, alcohol intake, occupational physical activity at longest held job (only for men), nonoccupational physical activity, socioeconomic status by educational level, total energy intake, fiber intake, folate intake, β-carotene intake, vitamin C intake, vitamin E intake, vegetable intake, intake of pulses, fruit intake, grain intake, meat and poultry intake, processed meat intake, calcium intake, energy-adjusted total fat intake by the residual method,[37] coffee consumption and a previous gallbladder operation. In addition, for women, we also considered oral contraceptive (OC) use, duration of OC use, use of hormonal therapy after menopause, duration of use of hormonal therapy after menopause, parity, age at menarche, age at menopause and age at first child birth.

Statistical analyses

To estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI), survival analysis was done using Cox proportional hazards model using the statistical package Stata version 9.2 (Stata Corp., College Station, TX). HRs were based on comparing the hazard rate of overall colorectal cancer, colon cancer or rectal cancer across quintiles of flavonoid intake with that in the lowest quintile. Sex-specific quintiles of intake were computed according to the distribution of intake in the subcohort. To account for the additional variance introduced by sampling the subcohort from the entire cohort, standard errors were estimated using the robust Huber–White sandwich estimator.[38] The proportional hazards assumption was tested using the scaled Schoenfeld residuals.[39] When according to this test the proportional hazards assumption seemed to be violated, hazard curves were inspected visually and analyses were done for short and long follow up by splitting up the follow-up time at 7 years. An ordinal score value based on the median value within each quintile in the subcohort was used to test for trend across quintiles. HRs and 95% CIs were estimated with an age-adjusted and a multivariate model. Potential confounders considered on the basis of previous research that introduced a >10% change in HRs or contributed significantly were included as covariates in the multivariate model. All analyses were conducted separately for men and women because this enhances comparability with previous studies as several were conducted with cohorts including only men or only women.[10,11,13,16,17] None of the potential confounders considered introduced a >10% change in HRs. The potential confounders that contributed significantly and were thus included in the final multivariate model were age (years), family history of colorectal cancer (yes or no), smoking status (never, ex, currently), alcohol intake (0 g/day, 0.1–29 g/day, ≥30 g/day), occupational physical activity at longest held job in men (<8 kJ/min, 8–12 kJ/min, >12 kJ/min), nonoccupational physical activity in women (<30 min/day, 30–60 min/day, 60–90 min/day, >90 min/day), BMI (kg/m^2) and processed meat intake (in g/day). Interaction of flavonoid intake and BMI was tested using cross-product terms between quintiles of flavonoid intake on one hand and BMI as a dichotomous variable (categories being BMI < 25 kg/m^2 and BMI ≥ 25 kg/m^2) on the other hand. To check whether BMI may be an intermediate factor, we compared HRs and 95% CIs estimated with the final multivariate model with HRs and 95% CIs estimated with a multivariate model not adjusted for BMI. To check whether early symptoms of disease could have influenced the results, analyses were repeated excluding the first 2 years of follow up. In all analyses, statistical significance was indicated by a p-value <0.05 for two-sided testing.

Results

Mean (standard deviation) flavonoid intake and other population characteristics for the subcohort and cases are shown in Table I for men and in Table II for women. Men in the subcohort had a mean total flavonol and flavone intake of 26.6 (12.4) mg/day and a mean total catechin intake of 57.3 (36.7) mg/day. Women in the

TABLE III – HAZARD RATIOS (HR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION OF TOTAL FLAVONOL AND FLAVONE INTAKE AND TOTAL CATECHIN INTAKE WITH COLORECTAL CANCER ENDPOINTS IN MEN

	Q1 (lowest) (ref.)	Q2	Q3	Q4	Q5 (highest)	*p* for trend[1]
			Quintiles of total flavonol and flavone intake (mg/day)			
Person-years	4,285	4,397	4,302	4,274	4,392	
Range	1.4–16.0	16.0–22.5	22.4–28.3	28.2–36.1	36.0–105.0	
Colorectum						
N cases	239	264	234	253	281	
Age-adjusted HR (95% CI)	1.00	1.01 (0.80–1.28)	0.90 (0.71–1.14)	0.95 (0.75–1.21)	1.03 (0.82–1.30)	0.87
Multivariate HR (95% CI)[2]	1.00	0.95 (0.75–1.21)	0.81 (0.63–1.04)	0.89 (0.70–1.14)	0.97 (0.76–1.23)	0.83
Colon						
N cases	148	171	164	159	178	
Age-adjusted HR (95% CI)	1.00	1.05 (0.81–1.37)	1.04 (0.80–1.36)	0.97 (0.74–1.27)	1.04 (0.80–1.35)	0.96
Multivariate HR (95% CI)[2]	1.00	1.00 (0.76–1.30)	0.96 (0.73–1.26)	0.92 (0.70–1.21)	0.97 (0.74–1.27)	0.72
Rectum						
N cases	68	66	50	67	75	
Age-adjusted HR (95% CI)	1.00	0.91 (0.63–1.30)	0.70 (0.47–1.04)	0.94 (0.65–1.35)	1.02 (0.71–1.45)	0.73
Multivariate HR (95% CI)[2]	1.00	0.92 (0.64–1.33)	0.69 (0.46–1.04)	0.95 (0.65–1.37)	1.04 (0.72–1.49)	0.67
			Quintiles of total catechin intake (mg/day)			
Person-years	4,219	4,326	4,319	4,473	4,314	
Range	<24.2	24.1–44.4	44.3–62.8	62.8–84.4	84.3–290.1	
Colorectum						
N cases	242	257	241	249	282	
Age-adjusted HR (95% CI)	1.00	1.02 (0.81–1.29)	0.91 (0.72–1.15)	0.88 (0.69–1.11)	1.00 (0.79–1.27)	0.72
Multivariate HR (95% CI)[2]	1.00	1.01 (0.79–1.28)	0.85 (0.67–1.09)	0.85 (0.67–1.08)	0.99 (0.77–1.25)	0.65
Colon						
N cases	140	163	167	163	187	
Age-adjusted HR (95% CI)	1.00	1.13 (0.86–1.47)	1.12 (0.86–1.46)	1.01 (0.78–1.32)	1.16 (0.89–1.52)	0.48
Multivariate HR (95% CI)[2]	1.00	1.12 (0.85–1.47)	1.06 (0.80–1.39)	0.98 (0.74–1.28)	1.13 (0.86–1.48)	0.65
Rectum						
N cases	80	66	53	59	68	
Age-adjusted HR (95% CI)	1.00	0.76 (0.54–1.09)	0.60 (0.42–0.88)	0.66 (0.45–0.95)	0.75 (0.53–1.07)	0.11
Multivariate HR (95% CI)[2]	1.00	0.78 (0.54–1.11)	0.62 (0.42–0.90)	0.69 (0.47–1.01)	0.80 (0.56–1.14)	0.24

Q, quintile; ref., reference category.
[1]Based on an ordinal score value based on the median value within each quintile in the subcohort.–[2]Adjusted for age, family history of colorectal cancer, smoking status, alcohol intake, occupational physical activity at longest held job, BMI and processed meat intake.

subcohort had a mean total flavonol and flavone intake of 29.1 (12.7) mg/day and a mean total catechin intake of 67.0 (39.2) mg/day.

Tables III and IV show the age-adjusted and multivariate HRs (95% CIs) for the association of total flavonol and flavone intake and total catechin intake with colorectal cancer endpoints for men and women, respectively. Results of the age-adjusted and multivariate analyses were comparable. Multivariate estimates showed no dose-response relationship of total flavonol and flavone intake and total catechin intake with colorectal cancer endpoints. For intake of individual flavonols and catechins, also no dose-response relationship with colorectal cancer endpoints was observed (data shown in Supporting Information Table VII for men and Table VIII for women).

The results of stratified multivariate analyses in subjects with a BMI < 25 kg/m^2 and in subjects with a BMI ≥ 25 kg/m^2 are shown in Table V for men and in Table VI for women. In men with a BMI ≥ 25 kg/m^2, there was a significant inverse trend in the association of total catechin intake with rectal cancer (quintile 4 *vs.* 1, HR= 0.52, 95% CI 0.29–0.94; quintile 5 *vs.* 1, HR = 0.63, 95% CI 0.36–1.08; p for trend = 0.04). In this group, a significant inverse trend in HRs for rectal cancer was also observed for intake of the individual catechins (+)-catechin and (–)-epicatechin. For intake of other individual catechins, there was an indication of an inverse trend in HRs for rectal cancer, but none were statistically significant (data shown in Supporting Information Table IX). Contrary to men, a significant inverse trend in the association of total catechin intake with colon cancer was observed in women with a BMI < 25 kg/m^2 (quintile 5 *vs.* 1, HR = 0.62, 95% CI 0.43–0.91; p for trend = 0.04). Significant inverse trends in HRs for colon cancer in this group were also observed for intake of myricetin, GC, EGC and EGCG. For kaempferol intake and intake of all other individual catechins, there was an indication of an inverse trend in HRs for colon cancer, but none were statistically significant. HRs significantly lower than 1.00 were mostly present in the highest quintile of intake. For rectal cancer, associations in women with a BMI < 25 kg/m^2 seemed to be inverse as well, with HRs in the highest quintile of intake being similarly decreased as those for colon cancer. However, no statistically significant associations with rectal cancer were observed, possibly because of a lack of power. For overall colorectal cancer in women with a BMI < 25 kg/m^2, significant inverse trends in HRs were observed for total catechin intake, and intake of kaempferol, myricetin and all individual catechins (data shown in Supporting Information Table X).

Tests for interaction of total flavonol and flavone intake and total catechin intake on one hand and BMI on the other hand were not significant. However, for intake of individual flavonols and catechins, in men, a significant interaction of EGC intake and BMI was observed for colon cancer and significant interactions of (−)-epicatechin intake and EGC intake on one hand and BMI on the other hand were observed for rectal cancer (data shown in Supporting Information Table IX). In women, significant interactions of kaempferol intake, (+)-catechin intake, EGC intake and EGCG intake on one hand and BMI on the other hand were observed for overall colorectal cancer, in particular colon cancer (data shown in Supporting Information Table X).

Comparison of HRs and 95% CIs estimated with the final multivariate model with HRs and 95% CIs estimated with a multivariate model not adjusted for BMI, to check whether BMI may be an intermediate factor, did not yield essential differences (data not shown). Exclusion of the first two years of follow up gave comparable results. Observed changes in HRs were not uniformly away from or closer to the null (data not shown).

TABLE IV – HAZARD RATIOS (HR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION OF TOTAL FLAVONOL AND FLAVONE INTAKE AND TOTAL CATECHIN INTAKE WITH COLORECTAL CANCER ENDPOINTS IN WOMEN

	Q1 (lowest) (ref.)	Q2	Q3	Q4	Q5 (highest)	p for trend[1]
			Quintiles of total flavonol and flavone intake (mg/day)			
Person-years	5,016	5,005	5,170	5,121	5,172	
Range	0.6–18.4	18.3–25.0	24.9–31.1	31.0–38.4	38.3–93.6	
Colorectum						
N cases	205	175	205	172	191	
Age-adjusted HR (95% CI)	1.00	0.86 (0.67–1.10)	0.98 (0.77–1.24)	0.80 (0.63–1.03)	0.89 (0.70–1.14)	0.30
Multivariate HR (95% CI)[2]	1.00	0.85 (0.66–1.10)	0.98 (0.76–1.25)	0.80 (0.62–1.03)	0.90 (0.70–1.16)	0.40
Colon						
N cases	154	129	140	137	135	
Age-adjusted HR (95% CI)	1.00	0.85 (0.65–1.12)	0.87 (0.67–1.13)	0.88 (0.67–1.15)	0.84 (0.64–1.10)	0.29
Multivariate HR (95% CI)[2]	1.00	0.84 (0.64–1.11)	0.86 (0.66–1.13)	0.87 (0.66–1.15)	0.85 (0.65–1.12)	0.35
Rectum						
N cases	37	30	46	24	38	
Age-adjusted HR (95% CI)	1.00	0.84 (0.51–1.37)	1.24 (0.79–1.95)	0.64 (0.38–1.09)	0.99 (0.62–1.59)	0.75
Multivariate HR (95% CI)[2]	1.00	0.85 (0.52–1.41)	1.30 (0.82–2.06)	0.68 (0.40–1.17)	1.08 (0.67–1.75)	0.94
			Quintiles of total catechin intake (mg/day)			
Person-years	5,093	5,086	5,091	5,069	5,144	
Range	<36.2	36.2–51.6	51.6–75.4	75.3–95.9	95.9–287.3	
Colorectum						
N cases	206	182	168	219	173	
Age-adjusted HR (95% CI)	1.00	0.89 (0.69–1.13)	0.78 (0.61–1.00)	1.01 (0.79–1.28)	0.78 (0.61–1.00)	0.15
Multivariate HR (95% CI)[2]	1.00	0.90 (0.70–1.16)	0.79 (0.61–1.02)	1.02 (0.79–1.30)	0.79 (0.61–1.02)	0.20
Colon						
N cases	150	138	122	156	129	
Age-adjusted HR (95% CI)	1.00	0.95 (0.72–1.24)	0.79 (0.60–1.05)	0.99 (0.76–1.29)	0.82 (0.62–1.07)	0.22
Multivariate HR (95% CI)[2]	1.00	0.96 (0.73–1.26)	0.79 (0.59–1.05)	1.00 (0.76–1.31)	0.82 (0.62–1.09)	0.25
Rectum						
N cases	37	34	28	47	29	
Age-adjusted HR (95% CI)	1.00	0.92 (0.57–1.49)	0.76 (0.46–1.26)	1.20 (0.77–1.89)	0.74 (0.45–1.23)	0.51
Multivariate HR (95% CI)[2]	1.00	0.97 (0.60–1.58)	0.79 (0.48–1.32)	1.26 (0.80–1.98)	0.80 (0.48–1.33)	0.69

Q, quintile; ref., reference category.
[1]Based on an ordinal score value based on the median value within each quintile in the subcohort.–[2]Adjusted for age, family history of colorectal cancer, smoking status, alcohol intake, nonoccupational physical activity, BMI and processed meat intake.

Discussion

We examined the association of dietary flavonol, flavone and catechin intake with colorectal cancer endpoints within the NLCS after 13.3 years of follow up. In addition, we explored whether BMI may be an effect modifier of this association. The present data generally showed no association of flavonol, flavone and catechin intake with risk of overall colorectal cancer, colon cancer and rectal cancer. The association of flavonol and flavone intake, but not catechin intake, with colorectal cancer risk was investigated within the NLCS once before after 4.3 years of follow up and in that analysis no significant associations emerged.[9] This is congruent with several other cohort studies that did not observe an association.[8,10,12,13,16,17]

In contrast, there are some studies with findings that support an inverse association of flavonol, flavone and/or catechin intake with colorectal cancer endpoints. Two case–control studies, for example, found a significant inverse trend for colorectal cancer risk for flavonol intake[14,15] and one also for flavone intake.[14] Arts et al.[11] observed a significant inverse trend in the association of total catechin intake and intake of individual catechins with rectal cancer risk in the Iowa Women's Health Study. In addition, a nonrandomized trial comparing flavonoid supplement use with nonuse suggested flavonoid supplement use of 2–5 years reduced the recurrence rate of colon neoplasia in patients with resected colon cancer. Flavonoid supplements in this study consisted of a mixture of 10 mg apigenin and 10 mg EGCG and were taken by resected colon cancer cases and polypectomized adenoma patients.[40] Other evidence for a potential effect of dietary flavonoids comes from the Polyp Prevention Trial which examined the effectiveness of a 4-year low-fat, high-fiber, high-fruit and high-vegetable diet on adenoma recurrence. In this randomized trial, greater flavonol consumption was associated with a decreased risk of advanced adenoma recurrence.[41]

In those two case–control studies that observed a significant inverse trend in the association of flavonol intake with colorectal cancer risk, consumption in the highest quintile was >28.5 mg/day[14] and >36.7 mg/day[15] relative to <13.2 mg/day and <16.0 mg/day, respectively, in the lowest quintile. In this study, total flavonol and flavone intake was comparable with intake in these studies, *i.e.*, >36.0 mg/day in men and >38.3 mg/day in women in the highest quintile relative to <16.0 mg/day and <18.4 mg/day, respectively, in the lowest quintile. Detection of an association of total flavonol and flavone intake with colorectal cancer endpoints in this study therefore does not seem to have been limited by a relatively small contrast in intake, which is most importantly determined by the reference category. Conversely, there may have been a relatively small contrast in catechin intake in our study, namely >84.3 mg/day in men and >95.9 mg/day in women in the highest quintile relative to <24.2 and <36.2 mg/day, respectively, in the lowest quintile. In the study that observed a significant inverse association of total catechin intake with rectal cancer risk using data from the Iowa Women's Health study, mean intake in subsequent quintiles was 3.6, 8.7, 14.8, 24.7 and 75.1 mg/day.[11] However, another study within the Iowa Women's Health Study, in which there was a similarly high contrast in catechin intake (*i.e.*, >134.8 mg/day in the highest quintile relative to <6.7 mg/day in the lowest quintile) but a longer follow-up time, found no association.[16]

In exploring whether BMI may be an effect modifier of the association of flavonol, flavone and catechin intake with colorectal cancer endpoints, selected flavonoids were found to be inversely associated with rectal cancer risk in overweight men and with colorectal cancer risk in normal weight women. Contrary to our findings, a prior case–control study that looked into the association of

TABLE V – MULTIVARIATE HAZARD RATIOS (HR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION OF TOTAL FLAVONOL AND FLAVONE INTAKE AND TOTAL CATECHIN INTAKE WITH COLON AND RECTAL CANCER IN MEN WITH A BMI < 25 KG/M^2 AND A BMI ≥ 25 KG/M^2

	Q1 (lowest) (ref.)	Q2	Q3	Q4	Q5 (highest)	*p* for trend[1]	*p* for interaction
			Quintiles of total flavonol and flavone intake (mg/day)				
BMI < 25 kg/m^2							
Person-years	2,466	2,235	2,338	2,382	2,356		
Range	1.8–16.0	16.0–22.5	22.4–28.2	28.2–36.1	36.0–105.0		
BMI ≥ 25 kg/m^2							
Person-years	1,819	2,162	1,964	1,892	2,036		
Range	1.4–16.0	16.0–22.5	22.4–28.3	28.2–36.1	36.0–103.3		
Colon, BMI < 25 kg/m^2							
N cases	73	89	78	79	84		
HR (95% CI)[2]	1.00	1.14 (0.79–1.66)	0.94 (0.64–1.40)	0.92 (0.62–1.36)	0.97 (0.66–1.43)	0.58	
Colon, BMI ≥ 25 kg/m^2							
N cases	75	82	86	80	94		
HR (95% CI)[2]	1.00	0.86 (0.58–1.26)	0.97 (0.65–1.43)	0.93 (0.63–1.39)	0.97 (0.66–1.42)	0.93	0.73
Rectum, BMI < 25 kg/m^2							
N cases	39	27	23	37	42		
HR (95% CI)[2]	1.00	0.69 (0.40–1.17)	0.55 (0.31–0.97)	0.92 (0.56–1.50)	1.05 (0.64–1.71)	0.43	
Rectum, BMI ≥ 25 kg/m^2							
N cases	29	39	27	30	33		
HR (95% CI)[2]	1.00	1.27 (0.74–2.18)	0.94 (0.52–1.70)	1.02 (0.57–1.83)	1.10 (0.62–1.94)	0.99	0.40
			Quintiles of total catechin intake (mg/day)				
BMI < 25 kg/m^2							
Person-years	2,367	2,345	2,196	2,458	2,412		
Range	<24.2	24.1–44.3	44.3–62.8	62.9–84.3	84.4–290.1		
BMI ≥ 25 kg/m^2							
Person-years	1,852	1,981	2,123	2,015	1,902		
Range	<24.2	24.2–44.4	44.3–62.8	62.8–84.4	84.3–233.4		
Colon, BMI < 25 kg/m^2							
N cases	66	88	75	81	93		
HR (95% CI)[2]	1.00	1.34 (0.92–1.96)	1.11 (0.75–1.65)	1.05 (0.71–1.55)	1.15 (0.78–1.70)	0.89	
Colon, BMI ≥ 25 kg/m^2							
N cases	74	75	92	82	94		
HR (95% CI)[2]	1.00	0.95 (0.64–1.42)	1.06 (0.72–1.56)	0.97 (0.65–1.43)	1.14 (0.77–1.70)	0.53	0.67
Rectum, BMI < 25 kg/m^2							
N cases	40	29	22	36	41		
HR (95% CI)[2]	1.00	0.73 (0.44–1.23)	0.57 (0.32–1.00)	0.89 (0.53–1.48)	0.96 (0.58–1.57)	0.77	
Rectum, BMI ≥ 25 kg/m^2							
N cases	40	37	31	23	27		
HR (95% CI)[2]	1.00	0.85 (0.51–1.41)	0.67 (0.40–1.15)	0.52 (0.29–0.94)	0.63 (0.36–1.08)	0.04	0.23

Q, quintile; ref., reference category; BMI, body mass index.
[1]Based on an ordinal score value based on the median value within each quintile in the subcohort.–[2]Adjusted for age, family history of colorectal cancer, smoking status, alcohol intake, occupational physical activity at longest held job, BMI and processed meat intake.

6 subgroups of flavonoids (among which flavonols, flavones and catechins) with colorectal cancer risk in normal weight and overweight individuals found no association in either group.[14] A plausible explanation for the different findings for men and women in strata of BMI in our study may involve effects of insulin-like growth factor 1 (IGF-1) and estrogens. IGF-1 may be an intermediate factor through which flavonoids decrease colorectal cancer risk as IGF-1 inhibits apoptosis and promotes cell cycle progression[42] and EGCG was found to lower IGF-1 levels.[43] Following this, it might be that flavonoids only significantly decrease risk when IGF-1 levels are relatively high, which, seeing that adipose tissue secretes IGF-1,[42] might be the case in women and overweight men but not normal weight men. In overweight postmenopausal women, however, estrogen levels are higher than in normal weight postmenopausal women[44] and the potentially protective effects of estrogens against colon cancer[45] may overshadow potential effects of flavonoids. This explanation fits with our observation of a decreased risk in overweight men and normal weight women, but is limited by that it does not explain why only rectal cancer risk was decreased in men as opposed to colorectal cancer risk in women. To shed more light on BMI as a potential effect modifier of the association of flavonoid intake with colorectal cancer risk and the possible mechanisms underlying this, more studies are needed. In these, it would also be interesting to check whether BMI may be an intermediate factor. Although our present results did not indicate this, Hughes et al.[46] recently found higher total dietary intake of flavonols/flavones and catechins to be associated with a lower increase in BMI over time in women in our cohort and more body fatness or a higher BMI in itself is an established risk factor for colorectal cancer.[47]

Strengths of this study include the prospective design and high completeness of follow up of cancer incidence, which minimize the probability of recall bias and selection bias to occur. In addition, the large number of male and female colorectal cancer cases provided sufficient power to detect associations and to do stratified analyses. The assessment of many potential risk factors at baseline furthermore enabled us to adjust for risk factors for colorectal cancer that could potentially confound the studied associations. Adequate control for potential confounders is important because flavonol, flavone and catechin intake could merely be indicating an overall healthy lifestyle and therefore be associated with a decreased colorectal cancer risk rather than being a direct protective factor.[17] Still, despite the fact that we adjusted for a number of potential confounders, the possibility that residual confounding may have affected our results has to be acknowledged.

A limitation of this study may be that flavonol, flavone and catechin intake was based on a single measurement of dietary intake at baseline, which may not be representative of intake over 13.3 years. The FFQ however was shown to be representative of dietary habits over a period of at least 5 years.[31] In addition, when analyses were done for short and long follow up after splitting up the

TABLE VI – MULTIVARIATE HAZARD RATIOS (HR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION OF TOTAL FLAVONOL AND FLAVONE INTAKE AND TOTAL CATECHIN INTAKE WITH COLON AND RECTAL CANCER IN WOMEN WITH A BMI < 25 KG/M^2 AND A BMI ≥ 25 KG/M^2

	Q1 (lowest) (ref.)	Q2	Q3	Q4	Q5 (highest)	*p* for trend[1]	*p* for interaction
			Quintiles of total flavonol and flavone intake (mg/day)				
BMI < 25 kg/m^2							
Person-years	2,904	2,500	2,877	2,922	3,122		
Range	0.6–18.4	18.3–25.0	24.9–31.1	31.0–38.4	38.3–93.6		
BMI ≥ 25 kg/m^2							
Person-years	2,112	2,506	2,293	2,199	2,050		
Range	2.2–18.4	18.3–25.0	24.9–31.1	31.1–38.3	38.3–82.1		
Colon, BMI < 25 kg/m^2							
N cases	74	69	67	74	76		
HR (95% CI)[2]	1.00	1.13 (0.76–1.67)	0.87 (0.59–1.29)	1.00 (0.68–1.48)	0.90 (0.62–1.32)	0.48	
Colon, BMI ≥ 25 kg/m^2							
N cases	80	60	73	63	59		
HR (95% CI)[2]	1.00	0.64 (0.42–0.95)	0.84 (0.56–1.25)	0.74 (0.49–1.12)	0.79 (0.53–1.19)	0.46	0.30
Rectum, BMI < 25 kg/m^2							
N cases	22	19	28	13	20		
HR (95% CI)[2]	1.00	1.05 (0.55–2.01)	1.34 (0.73–2.46)	0.62 (0.30–1.29)	0.86 (0.45–1.64)	0.37	
Rectum, BMI ≥ 25 kg/m^2							
N cases	15	11	18	11	18		
HR (95% CI)[2]	1.00	0.71 (0.32–1.59)	1.28 (0.61–2.70)	0.81 (0.36–1.80)	1.49 (0.72–3.10)	0.26	0.50
			Quintiles of total catechin intake (mg/day)				
BMI < 25 kg/m^2							
Person-years	2,700	2,756	2,743	2,872	3,254		
Range	0.3–36.2	36.2–51.6	51.6–75.3	75.3–95.9	95.9–247.2		
BMI ≥ 25 kg/m^2							
Person-years	2,393	2,330	2,348	2,197	1,890		
Range	<36.1	36.7–51.6	51.8–75.4	75.5–95.8	96.1–287.3		
Colon, BMI < 25 kg/m^2							
N cases	84	63	67	78	68		
HR (95% CI)[2]	1.00	0.76 (0.51–1.12)	0.78 (0.53–1.16)	0.83 (0.57–1.22)	0.62 (0.43–0.91)	0.04	
Colon, BMI ≥ 25 kg/m^2							
N cases	66	75	55	78	61		
HR (95% CI)[2]	1.00	1.28 (0.86–1.92)	0.78 (0.51–1.20)	1.20 (0.81–1.78)	1.12 (0.74–1.71)	0.68	0.11
Rectum, BMI < 25 kg/m^2							
N cases	21	23	14	27	17		
HR (95% CI)[2]	1.00	1.14 (0.60–2.15)	0.67 (0.33–1.35)	1.22 (0.66–2.24)	0.65 (0.33–1.28)	0.26	
Rectum, BMI ≥ 25 kg/m^2							
N cases	16	11	14	20	12		
HR (95% CI)[2]	1.00	0.74 (0.33–1.64)	0.96 (0.45–2.04)	1.33 (0.67–2.66)	1.03 (0.47–2.27)	0.51	0.63

Q, quintile; ref., reference category; BMI, body mass index.
[1]Based on an ordinal score value based on the median value within each quintile in the subcohort.–[2]Adjusted for age, family history of colorectal cancer, smoking status, alcohol intake, nonoccupational physical activity, BMI and processed meat intake.

follow-up time at 7 years, no marked differences in associations were observed. As mentioned earlier, no association with colorectal cancer risk for total flavonol and flavone intake was observed within the NLCS after 4.3 years of follow up.[9] If for some reason misclassification of intake occurred, it may be more likely that intake is underestimated instead of overestimated because flavonol and flavone intake as well as catechin intake have been reported to be higher at older age.[48,49] Reports however were based on cross-sectional data and actual age effects may not be clearly distinguishable from time effects.[49] In any case, misclassification is likely to be independent of the outcome and any form of nondifferential misclassification, *i.e.*, under- or overestimation, would most likely lead to attenuation of the associations.

In conclusion, the present findings generally do not support an association of dietary flavonol, flavone and catechin intake with colorectal cancer endpoints. Dietary catechin intake may be associated with a decreased rectal cancer risk in overweight men. Dietary flavonol and catechin intake may be associated with a decreased colorectal cancer risk in normal weight women.

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