Flavonoid Intake and Risk of Pancreatic Cancer in Male Smokers (Finland)

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Abstract

Extending research on the protective effect of flavonoids in cell culture and animal studies, we examined the association between consumption of flavonoids and flavonoid-rich foods and development of exocrine pancreatic cancer within the α-Tocopherol, β-Carotene Cancer Prevention Study cohort. Of the 27,111 healthy male smokers (50-69 years) who completed a self-administered dietary questionnaire at baseline, 306 developed exocrine pancreatic cancer during follow-up (1985-2004; median, 16.1 years). Intakes of total flavonoids, three flavonoid subgroups, seven individual flavonoids, and flavonoid-rich foods were estimated from a validated food frequency questionnaire. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models. Overall, flavonoid intake was not significantly associated with pancreatic cancer. However, in stratified analysis, greater total flavonoid intake was associated with decreased pancreatic cancer risk in participants randomized during the trial to placebo (fourth versus first quartile: hazard ratio, 0.36; 95% confidence interval, 0.17-0.78; P_{trend} = 0.009) and not to supplemental α-tocopherol (50 mg/d) and/or β-carotene (20 mg/d; $P_{interaction}$ = 0.002). Similar patterns and significant interactions were observed for flavonols, flavan-3-ols, kaempferol, quercetin, catechin, and epicatechin. Our data suggest that a flavonoid-rich diet may decrease pancreatic cancer risk in male smokers not consuming supplemental α-tocopherol and/or β-carotene. (Cancer Epidemiol Biomarkers Prev 2008;17(3):553–62)

Introduction

In the United States, pancreatic cancer is the fourth most common cause of cancer mortality (~33,400 deaths annually) among men and women (1). There is no effective screening test for pancreatic cancer, which contributes to its high fatality and 5-year survival rate of <5.0% (2). Successful treatment options for pancreatic cancer are limited because of its late stage of diagnosis, resistance to chemotherapy and radiotherapy, and the challenges involved with surgical resection (3). Therefore, prevention offers the greatest promise to decrease mortality rates of pancreatic cancer.

Smoking is estimated to be the strongest modifiable risk factor for pancreatic cancer accounting for ~25% to 30% of all cases (4). The association between diet and pancreatic cancer is less conclusive (5). A recent meta-analysis of case-control studies estimated that high fruit and vegetable consumption decreased the risk of pancreatic cancer by 28% and 20%, respectively (6). However, most prospective cohort studies have not shown a protective influence for fruits and vegetables on pancreatic cancer (7-17).

Flavonoids are a group of bioactive polyphenols distributed widely in the plant kingdom that are especially enriched in certain fruits and vegetables (18, 19). Three major flavonoid subgroups are flavonols, flavan-3-ols (also called catechins), and flavones. Kaempferol, myricetin, and quercetin are major individual flavonols and are consumed primarily from apples, beans, broccoli, and onions. Two major flavan-3-ols are catechin and epicatechin, whose primary dietary sources are tea, apples, and red wine. Parsley, thyme, and celery are the primary dietary sources of the two major flavones apigenin and luteolin. Based on the protective effect of flavonoids against pancreatic carcinogenesis in most cell culture (20-23) and animal studies (24, 25), we hypothesized that high dietary intake of flavonols, flavan-3-ols, and flavones may inhibit development of exocrine pancreatic cancer in humans. The association between flavonoid intake and pancreatic cancer development has been evaluated in three prospective cohorts. In a Finnish cohort study of 10,000 men and women, less pancreatic cancer cases were observed at higher intakes of flavonols and flavones combined; however, the study included only 29 pancreatic cancer cases and had limited power to

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observe associations (26). In the Iowa Women's Health Study cohort (n = 130 cases), intermediate (second or third versus first quartile) but not high flavan-3-ol intakes (fourth versus first quartile) were associated with ~45% reduced pancreatic cancer risk in postmenopausal women (27). A limitation of the study was that the association was examined in only the flavan-3-ol subgroup (27). In the Multiethnic Cohort Study, high flavonol intakes were associated with a 59% reduced exocrine pancreatic risk in current smokers (n = 112 cases) and not in former or never smokers during 8 years of follow-up (28). A limitation of the study was that the association was examined in only the flavonol subgroup (28). Therefore, the objective of this study was to examine the association between dietary intakes of total flavonoids, three flavonoid subgroups (flavonols, flavan-3-ols, and flavones), seven individual flavonoids (kaempferol, myricetin, quercetin, catechin, epicatechin, apigenin, and luteolin), and flavonoid-rich foods and development of exocrine pancreatic cancer in a prospective cohort of male smokers in Finland.

Materials and Methods

Study Design and Population. The α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study was a placebo-controlled, double-blind, primary prevention trial designed to determine whether α-tocopherol (50 mg/d) and β-carotene (20 mg/d) alone or in combination reduced the incidence of lung cancer in male smokers (29). Using a 2 × 2 factorial design, 29,133 eligible men, ages 50 to 69 years, in southwestern Finland, who smoked at least five cigarettes per day, were randomized to one of four intervention groups. Persons with a cancer history other than nonmelanoma skin cancer or carcinoma *in situ*, severe angina, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, receiving anticoagulant therapy, other medical problems that might limit long-term participation, or current use of supplements containing vitamin E (>20 mg/d), vitamin A (>20,000 IU/d), or β-carotene (>6 mg/d) were excluded from the study. Participants were randomized between April 1985 and June 1988. The trial ended on April 30, 1993 (median, 6.1 years). Follow-up for the present cohort analysis was through April 30, 2004, representing follow-up for up to 19.4 years (median, 16.1 years) and a total of 371,663 person-years of observation. The study was approved by the institutional review boards of both the U.S. National Cancer Institute and the National Public Health Institute in Finland. All study participants provided written informed consent before the initiation of the study. Details of the study rationale, design, and methods have been described previously (28).

Lifestyle and Dietary Data. The participating men completed a questionnaire providing sociodemographic and health information. Height, weight, and blood pressure were measured by trained nurses. In addition, participants filled out a diet history questionnaire that included 276 food items and mixed dishes and came with a portion size picture booklet that included 122 pictures of foods with three to five portion sizes. It was specifically developed for the ATBC Study participants (30). Participants were queried the frequency and the usual portion size of consumption during the previous 12 months. The diet questionnaire with the picture booklet was given to participants at the first baseline visit to be filled out at home. Two weeks later, participants returned for the second baseline visit and reviewed and completed it with a study nurse. Nutrient intake values were computed from the food consumption data of the dietary questionnaire using the food composition database at the National Public Health Institute in Finland (1998). Our study includes the 27,111 (93%) participants who satisfactorily completed the dietary questionnaire (31).

Flavonoid Data. Intakes of individual flavonoids (kaempferol, myricetin, quercetin, apigenin, luteolin, catechin, and epicatechin) were calculated using the food flavonoid database from Hertog et al. (32-34), with the exception of the flavonol intakes from berries, which were based on Finnish analyses (35). The flavonoid-rich foods presented in this report were based on their contribution to flavonoid intake in the ATBC cohort and the Dutch population (34). Wine was estimated to be half each from white and red wine and based on Finnish alcohol consumption (31). Onion intake was estimated from mixed foods recipes used for the ATBC questionnaire. Total flavonoid intake was calculated as the sum of intakes of flavonols (sum of kaempferol, myricetin, and quercetin), flavan-3-ols (sum of catechin and epicatechin), and flavones (sum of apigenin and luteolin).

We used data from the original validity and reliability study for the ATBC Study dietary questionnaire that was conducted before the beginning of the trial (30) to determine the validity and reliability for the dietary flavonoids in the present study. The relative validity estimates for flavonoids were determined by calculating Pearson correlation coefficients between log-transformed, energy-adjusted intake values from food records, which had been kept for 24 days spread randomly over 6 months, and from the average of two food frequency questionnaires, which had been filled out at the beginning and end of the 6-month period by 133 men. The validity estimates were 0.77 (total flavonoids), 0.73 (flavonols), 0.75 (kaempferol), 0.66 (myricetin), 0.68 (quercetin), 0.77 (flavan-3-ols), 0.76 (catechin), 0.76 (epicatechin), 0.30 (flavones), 0.08 (apigenin), and 0.43 (luteolin). The reliability estimates for flavonoids were determined by calculating the intraclass correlation coefficients between log-transformed, energy-adjusted intake values from three food frequency questionnaires that were filled out every 3 months by 190 men. The reliability estimates were 0.69 (total flavonoids), 0.69 (flavonols), 0.67 (kaempferol), 0.57 (myricetin), 0.68 (quercetin), 0.25 (flavan-3-ols), 0.26 (catechin), 0.26 (epicatechin), 0.08 (flavones), 0.31 (apigenin), and 0.11 (luteolin).

Case Ascertainment. Pancreatic cancer cases were ascertained from the Finnish Cancer Registry, which received their information through short forms from hospitals, physicians, pathological, cytologic and hematologic laboratories, dentists, and death certificates from Statistics Finland. Korhonen et al. (36) reported that the Finnish Cancer Registry provides nearly 100% case ascertainment in Finland and accurately reports 89% of primary pancreatic cancer cases. The diagnosis for cases through April 1999 was based on a review of all relevant

medical records and tumor specimens by an ATBC Study committee composed of physicians, oncologists, and pathologists. Pancreatic cancer cases diagnosed after April 1999 were based solely on Finnish Cancer Registry data. Only cases confirmed as incident primary exocrine adenocarcinoma of the pancreas (*International Classification of Diseases, Ninth Edition* code 157 and *International Classification of Diseases, Tenth Edition* code C25) were used for this report. Endocrine cancers (*International Classification of Diseases, Ninth Edition* code 157.4 and *International Classification of Diseases, Tenth Edition* code C254) were excluded as their etiology differs from that of pancreatic adenocarcinoma. The final data set contained 319 incident exocrine pancreatic cancer cases among cohort members of which 306 had complete dietary data. Of the 306 cases, 161 of 205 (79%) cases diagnosed through April 1999 and 67 of 101 (66%) cases diagnosed after April 1999 had microscopic diagnosis.

Statistical Analysis. All statistical analyses were done using Statistical Analysis Systems software. Follow-up time for each participant was calculated from the date of randomization until diagnosis of pancreatic cancer, death, or April 30, 2004. Intakes of flavonoids, nutrients, and dietary variables were energy adjusted by the regression residual method (37). Participants were grouped into quintiles or quartiles of energy-adjusted intakes of flavonoids and flavonoid-rich foods based on distributions from the entire cohort. For foods that were not consumed by more than a quartile of the cohort, categories for zero intakes were created.

Baseline variables examined as potential confounders in our analyses included age; height, weight, and body mass index; education; place of living; self-reported history of diabetes mellitus, pancreatitis, gallstones, or peptic or duodenal ulcers; measured blood pressure; serum cholesterol; smoking habits (years smoked, cigarettes smoked per day, pack-years); occupational and leisure physical activity; energy and alcohol intake; and energy-adjusted fat, saturated fat, carbohydrate, free sugar, fiber, β-carotene, calcium, folic acid, vitamin C, and vitamin E intake. The distributions of differing characteristics of the case and noncase participants were evaluated using Wilcoxon rank-sum tests and χ^2 tests for continuous and categorical variables, respectively. Generalized linear models adjusted for age at randomization

Table 1. Baseline characteristics of the ATBC Study according to quintiles of energy-adjusted total flavonoid consumption (*n* = 27,111, means or proportions)

Characteristic*	Quintiles of energy-adjusted total flavonoid consumption (mg/d)				
	≤6.45	>6.45-9.14	>9.14-12.8	>12.8-22.9	>22.9
Demographics					
Age at randomization (y)	57.1	57.4	57.1	57.1	57.1
Secondary school education† (%)	13.1	16.9	20.7	26.8	31.1
Lifestyle behaviors					
Years smoked	37.0	36.3	35.9	35.2	35.2
Cigarettes smoked per day	22.3	20.9	20.1	19.6	19.2
History of diabetes mellitus (%)	3.3	3.8	4.7	4.8	4.5
Family history of pancreatic cancer (%)	2.7	2.8	3.0	3.1	3.3
Mean duration of follow-up (y)	13.3	13.5	13.8	14.0	14.0
Mean daily nutrient intake					
Calories (kcal)	2,937	2,518	2,587	2,683	2,717
Total fat (g)	127	125	123	121	120
Saturated fat (g)	57.3	54.0	52.0	50.3	49.2
Mean daily flavonoid intake					
Flavonols (mg)	3.94	6.22	8.07	10.9	19.4
Kaempferol (mg)	0.145	0.315	0.501	1.04	4.79
Myricetin (mg)	0.358	0.570	0.740	1.03	1.72
Quercetin (mg)	3.44	5.34	6.83	8.83	12.9
Flavan-3-ol (mg)	0.441	1.43	2.61	5.59	22.8
Catechin (mg)	0.208	0.580	0.99	2.06	8.25
Epicatechin (mg)	0.234	0.855	1.62	3.53	14.6
Flavones (mg)	0.077	0.110	0.137	0.160	0.154
Apigenin (mg)	0.052	0.072	0.089	0.101	0.097
Luteolin (mg)	0.025	0.038	0.048	0.059	0.057
Mean daily flavonoid-rich food intake					
Fruits (g)	55.4	98.1	138	183	170
Apples (g)	5.92	17.2	31.1	48.3	42.9
Berries (g)	14.8	28.5	39.9	51.8	46.2
Citrus fruits (g)	19.3	28.5	37.1	43.8	42.2
Fruit juices (g)	32.4	75.6	97.9	123	116
Wine (g)	4.21	6.11	10.0	17.5	17.4
Vegetables (g)	235	282	309	326	314
Beans (g)	0.16	0.33	0.53	0.80	0.90
Cabbage (g)	0.78	1.37	2.11	2.88	2.92
Onions (g)	0.01	0.02	0.08	0.30	1.02
Tea (g)	−1.06	3.40	9.76	41.1	314

*Generalized linear models adjusted for age at randomization were used to estimate the means within each total flavonoid intake quintile for the continuous population characteristics and the frequency proportions for categorical population characteristics.
† Ninth grade or higher.

Table 2. HR (95% CI) for exocrine pancreatic cancer according to energy-adjusted baseline daily intake of flavonoids in the ATBC Study (*n* = 27,111), 1985-2004

Flavonoid	Quintiles of energy-adjusted intake (1 = lowest, 5 = highest)					P_{trend}
	1*	2	3	4	5	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Total flavonoids						
Range of intake (mg)	≤6.45	>6.45-9.14	>9.14-12.82	>12.82-22.88	>22.88	
No. cases/person-years	71/72,244	62/72,910	51/74,825	59/75,823	63/75,860	
Multivariate adjusted †	1	0.88 (0.62-1.24)	0.72 (0.50-1.03)	0.84 (0.59-1.19)	0.90 (0.64-1.28)	0.98
Flavonols						
Range of intake (mg)	≤5.24	>5.24-6.98	>6.98-9.09	>9.09-13.00	>13.00	
No. cases/person-years	71/71,585	67/72,895	48/74,710	57/76,184	63/76,289	
Multivariate adjusted	1	0.96 (0.68-1.34)	0.68 (0.47-0.98)	0.81 (0.57-1.16)	0.91 (0.64-1.30)	0.77
Kaempferol						
Range of intake (mg)	≤0.20	>0.20-0.34	>0.34-0.61	>0.61-1.94	>1.94	
No. cases/person-years	65/72,853	61/72,602	64/74,865	55/75,721	61/75,622	
Multivariate adjusted	1	0.93 (0.66-1.33)	0.94 (0.66-1.34)	0.82 (0.57-1.19)	0.93 (0.65-1.33)	0.84
Myricetin						
Range of intake (mg)	≤0.35	>0.35-0.54	>0.54-0.80	>0.80-1.28	>1.28	
No. cases/person-years	63/72,627	70/72,765	51/74,653	59/75,617	63/76,001	
Multivariate adjusted	1	1.10 (0.78-1.55)	0.81 (0.56-1.17)	0.93 (0.65-1.34)	1.04 (0.73-1.49)	0.88
Quercetin						
Range of intake (mg)	≤4.44	>4.44-5.86	>5.86-7.44	>7.44-9.87	>9.87	
No. cases/person-years	66/71,639	65/72,656	51/74,874	57/75,771	67/76,723	
Multivariate adjusted	1	1.02 (0.72-1.43)	0.78 (0.54-1.14)	0.89 (0.62-1.28)	1.07 (0.75-1.53)	0.69
Flavan-3-ols						
Range of intake (mg)	≤0.90	>0.90-1.82	>1.82-3.51	>3.51-9.75	>9.75	
No. cases/person-years	66/73,718	64/72,600	64/74,296	51/75,403	61/75,646	
Multivariate adjusted	1	0.96 (0.68-1.35)	0.94 (0.66-1.34)	0.76 (0.52-1.10)	0.92 (0.64-1.31)	0.72
Catechin						
Range of intake (mg)	≤0.35	>0.35-0.68	>0.68-1.30	>1.30-3.65	>3.65	
No. cases/person-years	61/73,571	72/73,026	60/74,623	54/74,799	59/75,644	
Multivariate adjusted	1	1.15 (0.81-1.62)	0.94 (0.65-1.34)	0.86 (0.59-1.25)	0.95 (0.66-1.36)	0.56
Epicatechin						
Range of intake (mg)	≤0.49	>0.49-1.10	>1.10-2.24	>2.24-6.19	>6.19	
No. cases/person-years	68/73,826	62/72,199	59/74,674	56/75,377	61/75,587	
Multivariate adjusted	1	0.91 (0.65-1.29)	0.85 (0.60-1.21)	0.82 (0.57-1.18)	0.90 (0.63-1.28)	0.83
Flavones						
Range of intake (mg)	≤0.035	>0.035-0.056	>0.056-0.087	>0.087-0.197	>0.197	
No. cases/person-years	63/73,854	58/73,367	69/73,330	54/74,959	62/76,152	
Multivariate adjusted	1	0.91 (0.64-1.30)	1.08 (0.76-1.52)	0.82 (0.57-1.18)	0.99 (0.70-1.42)	0.99
Apigenin						
Range of intake (mg)	≤0.016	>0.016-0.029	>0.029-0.046	>0.046-0.121	>0.121	
No. cases/person-years	60/75,641	68/74,379	53/73,477	61/72,451	64/75,714	
Multivariate adjusted	1	1.11 (0.78-1.57)	0.84 (0.58-1.21)	0.96 (0.67-1.37)	1.06 (0.74-1.51)	0.68
Luteolin						
Range of intake (mg)	≤0.012	>0.012-0.020	>0.020-0.036	>0.036-0.067	>0.067	
No. cases/person-years	61/72,760	70/71,750	57/73,794	52/75,936	66/77,422	
Multivariate adjusted	1	1.14 (0.81-1.61)	0.93 (0.64-1.33)	0.86 (0.59-1.25)	1.09 (0.77-1.56)	0.82

*Reference category.
† Multivariate-adjusted HRs are adjusted for age at randomization, years of smoking, total number of cigarettes per day, self-reported history of diabetes mellitus, and energy-adjusted saturated fat intake.

were used to estimate means for continuous population characteristics and frequency proportions for categorical population characteristics within energy-adjusted total flavonoids intake quintile (Table 1).

Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed using Cox proportional hazards for flavonoids or flavonoid-rich foods compared with the lowest intake quantile. For trend testing, we assigned the median value of each quantile and used these values as a continuous score variable. Potential confounders were added to individual models in a stepwise fashion and were considered a confounder if they were associated with both development of pancreatic cancer and intake of total flavonoids, had a χ^2 $P \leq 0.20$, and changed the HR by <10%. To evaluate confounding by nutrients, we calculated a median trend score variable for each nutrient based on the median value of each intake quintile of a nutrient, which then was added to individual models.

All multivariate-adjusted models were adjusted for age at randomization, years of smoking, total number of cigarettes smoked per day, self-reported history of diabetes mellitus, and energy-adjusted saturated fat intake as continuous variables. Effect modification of each flavonoid by antioxidant intake (β-carotene from food, vitamin C from food, vitamin E from food, food plus supplemental β-carotene, vitamin E from food plus supplemental α-tocopherol), study intervention group, and smoking (intensity and duration) were evaluated

using stratified analyses. Interactions were additionally evaluated by including cross-product terms in multivariable models for each flavonoid quantile trend and dichotomized variables (median split for antioxidant intakes, study intervention placebo and any supplement, and smoking intensity and duration) or all four study intervention groups (placebo, α-tocopherol, β-carotene, and α-tocopherol plus β-carotene). We also evaluated effect modification by length of follow-up by testing for statistical significance using a time-dependent interaction term (<10 and >10 years) and analyses stratified by follow-up time. All *P* values correspond to two-sided tests.

Results

Compared with noncases, participants who developed pancreatic cancer were older (58.4 versus 57.2 years; $P < 0.0001$), had a longer smoking duration (37.1 versus 35.9 years; $P = 0.01$) and greater daily intake of energy-adjusted saturated fat (54.4 versus 52.5 g; $P = 0.01$) and carbohydrates (266 versus 262 g; $P = 0.05$), and were more likely to have a history of diabetes mellitus (7.2% versus 4.2%; $P = 0.009$) and a family history of pancreatic cancer (6.9% versus 3.0%; $P = 0.003$) but did not significantly differ ($P < 0.05$) in other baseline characteristics (data not shown).

Table 3. HR (95% CI) for exocrine pancreatic cancer according to energy-adjusted baseline daily intake of flavonoid-rich foods in the ATBC Study (*n* = 27,111), 1985-2004

Food	Quintiles of energy-adjusted intake (1 = lowest, 5 = highest)					P_{trend}
	1*	2	3	4	5	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Fruits						
Range of intake (g)	≤52.33	52.34-89.90	>89.90-131.9	>131.9-191.3	>191.3	
No. cases/person-years	69/72,839	60/73,379	57/74,143	54/75,566	66/75,736	
Multivariate adjusted †	1	0.86 (0.61-1.22)	0.80 (0.56-1.15)	0.76 (0.53-1.10)	0.95 (0.67-1.34)	0.82
Apples						
Range of intake (g)	0	0.25-10.68	>10.71-25.62	25.64-49.83	>49.95	
No. cases/person-years	77/79,783	57/74,044	49/71,290	66/72,606	57/73,940	
Multivariate adjusted	1	0.85 (0.60-1.20)	0.77 (0.54-1.19)	1.01 (0.72-1.40)	0.87 (0.61-1.23)	0.88
Berries						
Range of intake (g)	≤11.53	>11.53-21.76	>21.76-34.41	>34.41-55.48	>55.48	
No. cases/person-years	71/72,894	49/73,215	63/74,209	54/75,641	69/75,704	
Multivariate adjusted	1	0.66 (0.46-0.95)	0.85 (0.60-1.19)	0.70 (0.49-1.01)	0.88 (0.63-1.24)	0.94
Citrus fruits						
Range of intake (g)	≤4.43	>4.43-13.99	14.00-27.72	>27.72-58.79	>58.80	
No. cases/person-years	65/73,301	68/72,748	54/74,620	53/75,973	66/75,020	
Multivariate adjusted	1	1.05 (0.75-1.48)	0.85 (0.59-1.22)	0.84 (0.58-1.20)	1.05 (0.74-1.49)	0.84
Fruit juices ‡						
Range of intake (g)	0	0.002-32.86	32.94-121.5	>121.5		
No. cases/person-years	88/97,529	84/90,693	74/92,057	60/91,384		
Multivariate adjusted	Reference	1.08 (0.80-1.46)	0.96 (0.71-1.31)	0.84 (0.60-1.17)		0.16
Wine ‡						
Range of intake (g)	0	0.10-23.7	>24.3			
No. cases/person-years	228/286,708	47/42,295	31/42,659			
Multivariate adjusted	Reference	1.48 (1.08-2.03)	1.02 (0.70-1.49)			0.86
Vegetables						
Range of intake (g)	≤208.3	>208.3-258.2	>258.2-307.2	>307.2-373.0	>373.0	
No. cases/person-years	70/70,018	58/72,837	58/74,554	66/75,646	54/78,608	
Multivariate adjusted	Reference	0.81 (0.57-1.15)	0.81 (0.57-1.16)	0.95 (0.67-1.33)	0.78 (0.54-1.12)	0.37
Beans ‡						
Range of intake (g)	0	>0				
No. cases/person-years	263/315,846	43/55,816				
Multivariate adjusted	Reference	0.99 (0.72-1.37)				0.95
Cabbage ‡						
Range of intake (g)	0	>0.16-4.3	>4.3			
No. cases/person-years	241/273,860	31/52,294	34/45,508			
Multivariate adjusted	Reference	0.74 (0.51-1.07)	0.98 (0.68-1.40)			0.76
Onions ‡						
Range of intake (g)	0	>0				
No. cases/person-years	303/365,588	3/6,074				
Multivariate adjusted	Reference	0.59 (0.19-1.83)				0.36
Tea ‡						
Range of intake (g)	0	3.93-157.1	>157.1			
No. cases/person-years	209/235,489	41/68,171	56/68,003			
Multivariate adjusted	Reference	0.70 (0.50-0.98)	0.96 (0.71-1.29)			0.78

*Reference category.
† Multivariate-adjusted HRs are adjusted for age at randomization, years of smoking, total number of cigarettes per day, self-reported history of diabetes mellitus, and energy-adjusted saturated fat intake.
‡ Reference category was an intake of zero. Intake values are not energy adjusted.

Table 1 provides the means and proportions of baseline characteristics of study participants by quintile of energy-adjusted total flavonoid intake. Across increasing energy-adjusted total flavonoid intake quintile, the proportion of participants with secondary education, self-reported diabetes, family history of pancreatic cancer, and intake of individual flavonoids and flavonoid-rich foods increased while participants smoked less and for fewer years, and intake of energy-adjusted fat and saturated fat decreased.

Overall, energy-adjusted intakes of total flavonoids, flavonols, flavan-3-ols, flavones, and individual flavonoids were not associated with pancreatic cancer (Table 2). Similar nonsignificant results were observed for the consumption of total fruits, apples, berries, citrus fruits, total vegetables, beans, cabbage, onions, total fruit juices, tea, and wine, although fruit juice and onions tended to display inverse associations (Table 3).

Significant interactions were observed in the multivariate-adjusted models between development of pancreatic cancer and energy-adjusted intakes of total flavonoids, two flavonoid subgroups (flavonols and flavan-3-ols), and five individual flavonoids (kaempferol, myricetin, quercetin, catechin, and epicatechin) by intervention group (placebo versus any supplement: α-tocopherol, β-carotene, or both) at $P < 0.05$ (Table 4). Participants in the three study intervention groups (that is, α-tocopherol, β-carotene, or both) were combined in one strata because we did not observe significant associations in separate strata or interactions between the three groups at $P > 0.10$ for the flavonoids (data not shown).

Among participants randomized to the placebo group, energy-adjusted intakes of total flavonoids (HR, 0.36; 95% CI, 0.17-0.78; $P_{trend} = 0.009$) and of two flavonoid subgroups, flavonols (HR, 0.54; 95% CI, 0.27-1.07; $P_{trend} = 0.04$), and flavan-3-ols (HR, 0.42; 95% CI, 0.19-0.92; $P_{trend} = 0.01$), were or tended to be associated with decreased pancreatic cancer risk when comparing the highest versus lowest intake quartiles in the multivariate-adjusted model (Table 4). Of the individual flavonoids, high intakes of kaempferol (HR, 0.37; 95% CI, 0.17-0.79; $P_{trend} = 0.009$), myricetin (HR, 0.61; 95% CI, 0.30-1.18; $P_{trend} = 0.10$), quercetin (HR, 0.59; 95% CI, 0.29-1.23; $P_{trend} = 0.06$), catechin (HR, 0.43; 95% CI, 0.20-0.95; $P_{trend} = 0.009$), and epicatechin (HR, 0.50; 95% CI, 0.23-1.06; $P_{trend} = 0.02$) were or tended to be inversely associated with development of pancreatic cancer in the placebo group (Table 4). Similar trends and patterns of interactions were not observed for flavonoid-rich foods, except for tea consumption (placebo: HR, 0.49; 95% CI, 0.24-1.04; $P_{trend} = 0.06$ and intervention: HR, 1.14; 95% CI, 0.82-1.58; $P_{trend} = 0.43$; $P_{interaction} = 0.03$).

There were no significant interactions of the flavonoid associations by follow-up time overall; however, among participants in the placebo group, the association between flavonoid intake and pancreatic cancer risk was somewhat attenuated with increasing time to cancer diagnosis (<10 years follow-up time: HR for total flavonoids, 0.14; 95% CI, 0.03-0.61; $P_{trend} = 0.006$ and ≥10 years follow-up time: HR for total flavonoids, 0.68; 95% CI, 0.25-1.85; $P_{trend} = 0.43$). Excluding the first two years of follow-up resulted in minimal changes in risk estimates and changes in patterns; however, due to the lower number of cases ($n = 75$), the length of 95% CI increased (HR for total flavonoids, 0.37; 95% CI, 0.17-0.80; $P_{trend} = 0.02$). The association between flavonoid intake and pancreatic cancer risk was not significantly modified by antioxidant intake (β-carotene from food, vitamin C from food, vitamin E from food, food plus supplemental β-carotene, or vitamin E from food plus supplemental α-tocopherol) or smoking intensity and duration.

Discussion

Overall, there was no association between flavonoid intake and pancreatic cancer risk in the ATBC Study (Table 2). However, we observed statistically significant interactions between flavonoid intake and pancreatic cancer risk by α-tocopherol and/or β-carotene trial intervention on pancreatic cancer risk (Table 4), such that among participants who received placebo, there was a statistically significant 64% reduced pancreatic cancer risk with high total flavonoid intake, relative to low intake, particularly for the flavonol kaempferol and the flavan-3-ol catechin (Table 4). Inverse trends were also observed for intakes of two flavonoid subgroups (flavonols and flavan-3-ols) and three individual flavonoids (myricetin, quercetin, and epicatechin) and pancreatic cancer among subjects in the placebo group. No associations were observed for intakes of flavones (apigenin and luteolin; Table 4). The magnitude of our flavan-3-ol and flavonol associations is similar to that observed in previous pancreatic cancer studies (27, 28). Consistent with other prospective studies, no significant associations were observed for intakes of most flavonoid-rich foods, such as fruits and vegetables (Table 3; refs. 7-17).

A major strength of the current study was its large prospective nature with long follow-up (up to 19.4 years). Dietary data were collected before diagnosis of pancreatic cancer, which eliminates recall bias and reduces reverse causation due to dietary changes as a consequence of nondiagnosed pancreatic cancer. Our study is internally valid as the cases arose from the cohort that includes the noncases and therefore does not have control selection bias. It also has a large number of cases, providing power to detect differences in food components, such as flavonoids, if they exist. The food frequency questionnaire was developed specifically for the ATBC Study population (30) and provided detailed dietary and flavonoid data that are based on Finnish nutrient databases. In particular, flavonol content of berries were analyzed from berries available in Finland (35).

Most cell culture (20-23, 38) and animal studies (24, 25, 39) in pancreatic cancer models support our results that high dietary intake of flavonols and flavan-3-ols might inhibit human pancreatic carcinogenesis. The exception is one Argentinean research group, which showed that dietary quercetin increases the incidence of pancreatic dysplastic foci in rats treated with the carcinogen nitrosomethylurea (40, 41). Potential biological mechanisms by which flavonols and flavan-3-ols inhibit pancreatic carcinogenesis are inhibition of proliferation, cell cycle arrest, induction of apoptosis, promotion of differentiation, antioxidative activity, and inhibition of angiogenesis (42). Most pertinent, flavonoids can inhibit the activity of phase I enzymes and increase the activity of phase II enzymes, thereby decreasing the metabolic activation of procarcinogens

Table 4. Multivariate adjusted HR (95% CI) for exocrine pancreatic cancer according to energy-adjusted baseline intake of flavonoids by intervention group (placebo versus α-tocopherol, β-carotene, or both) in the ATBC Study (*n* = 27,111), 1985-2004

Flavonoid	Quartiles of intake (1: lowest, 4: highest)				P_{trend}	$P_{interaction}$
	1*	2	3	4		
		HR (95% CI)	HR (95% CI)	HR (95% CI)		
Total flavonoids						
Range of intake (mg)	≤7.10	>7.11-10.74	>10.74-18.69	>18.69		
Placebo						
No. cases/person-years	27/22,521	21/23,168	22/23,965	9/24,802		
Multivariate adjusted †	1	0.83 (0.46-1.48)	0.88 (0.49-1.57)	0.36 (0.17-0.78)	0.009	
Supplement						
No. cases/person-years	65/67,622	47/68,926	49/70,453	66/70,207		
Multivariate adjusted	1	0.70 (0.48-1.02)	0.73 (0.50-1.06)	0.98 (0.69-1.39)	0.39	0.002
Flavonols						
Range of intake (mg)	≤5.69	>5.69-7.95	>7.95-11.70	>11.70		
Placebo						
No. cases/person-years	27/22,099	24/23,161	15/24,572	13/24,623		
Multivariate adjusted	1	0.94 (0.54-1.64)	0.58 (0.30-1.10)	0.54 (0.27-1.07)	0.04	
Supplement						
No. cases/person-years	58/67,503	53/68,922	44/70,067	72/70,715		
Multivariate adjusted	1	0.91 (0.62-1.32)	0.75 (0.51-1.12)	1.24 (0.87-1.78)	0.11	0.004
Kaempferol						
Range of intake (mg)	≤0.24	>0.24-0.44	>0.44-1.29	>1.29		
Placebo						
No. cases/person-years	26/22,785	20/23,291	24/23,608	9/24,770		
Multivariate adjusted	1	0.82 (0.45-1.50)	1.00 (0.56-1.77)	0.37 (0.17-0.79)	0.009	
Supplement						
No. cases/person-years	60/68,092	50/68,572	57/70,623	60/69,920		
Multivariate adjusted	1	0.79 (0.54-1.15)	0.89 (0.61-1.28)	0.95 (0.66-1.38)	0.67	0.006
Myricetin						
Range of intake (mg)	≤0.40	>0.40-0.66	>0.66-1.12	>1.12		
Placebo						
No. cases/person-years	26/23,051	24/23,194	15/23,987	14/24,224		
Multivariate adjusted	1	0.95 (0.54-1.66)	0.60 (0.32-1.14)	0.61 (0.31-1.18)	0.10	
Supplement						
No. cases/person-years	54/67,738	52/68,423	56/70,335	65/70,712		
Multivariate adjusted	1	0.96 (0.65-1.40)	1.02 (0.70-1.48)	1.21 (0.83-1.75)	0.21	0.02
Quercetin						
Range of intake (mg)	≤4.82	>4.82-6.61	>6.61-9.10	>9.10		
Placebo						
No. cases/person-years	23/22,043	28/23,420	16/24,225	12/24,767		
Multivariate adjusted	1	1.27 (0.72-2.22)	0.74 (0.38-1.41)	0.59 (0.29-1.23)	0.06	
Supplement						
No. cases/person-years	58/67,664	48/68,432	52/70,255	69/70,856		
Multivariate adjusted	1	0.84 (0.57-1.23)	0.90 (0.61-1.31)	1.20 (0.84-1.73)	0.16	0.007
Flavan-3-ols						
Range of intake (mg)	≤1.12	>1.12-2.51	>2.51-6.76	>6.76		
Placebo						
No. cases/person-years	23/23,138	24/22,802	23/23,920	9/24,596		
Multivariate adjusted	1	1.12 (0.63-2.00)	1.06 (0.59-1.91)	0.42 (0.19-0.92)	0.01	
Supplement						
No. cases/person-years	60/68,694	53/68,699	52/69,845	62/69,970		
Multivariate adjusted	1	0.85 (0.58-1.23)	0.82 (0.56-1.20)	1.00 (0.69-1.44)	0.54	0.005
Catechin						
Range of intake (mg)	≤0.43	>0.43-0.92	>0.92-2.53	>2.53		
Placebo						
No. cases/person-years	22/22,882	26/23,061	22/23,837	9/24,676		
Multivariate adjusted	1	1.27 (0.71-2.27)	1.05 (0.57-1.92)	0.43 (0.20-0.95)	0.009	
Supplement						
No. cases/person-years	61/68,999	53/68,649	51/69,780	62/69,779		
Multivariate adjusted	1	0.83 (0.57-1.20)	0.79 (0.54-1.15)	0.97 (0.68-1.40)	0.60	0.005
Epicatechin						
Range of intake (mg)	≤0.63	>0.63-1.56	>1.56-4.35	>4.35		
Placebo						
No. cases/person-years	22/23,335	25/22,716	22/23,731	10/24,674		
Multivariate adjusted	1	1.25 (0.70-2.23)	1.10 (0.60-2.01)	0.50 (0.23-1.06)	0.02	
Supplement						
No. cases/person-years	65/68,449	48/68,579	53/70,313	61/69,866		
Multivariate adjusted	1	0.71 (0.49-1.04)	0.77 (0.53-1.11)	0.91 (0.63-1.30)	0.68	0.01

(*Continued on the following page*)

Table 4. Multivariate adjusted HR (95% CI) for exocrine pancreatic cancer according to energy-adjusted baseline intake of flavonoids by intervention group (placebo versus α-tocopherol, β-carotene, or both) in the ATBC Study (*n* = 27,111), 1985-2004 (Cont'd)

Flavonoid	Quartiles of intake (1 = lowest, 4 = highest)				P_{trend}	$P_{interaction}$
	1*	2	3	4		
		HR (95% CI)	HR (95% CI)	HR (95% CI)		
Flavones						
Range of intake (mg)	≤0.041	>0.041-0.069	>0.069-0.148	>0.148		
Placebo						
No. cases/person-years	21/23,565	16/22,621	25/23,729	17/24,540		
Multivariate adjusted	1	0.80 (0.42-1.53)	1.24 (0.69-2.23)	0.89 (0.46-1.69)	0.80	
Supplement						
No. cases/person-years	56/68,623	58/68,586	50/69,600	63/70,398		
Multivariate adjusted	1	1.00 (0.69-1.45)	0.83 (0.57-1.22)	1.09 (0.75-1.56)	0.50	0.42
Apigenin						
Range of intake (mg)	≤0.020	>0.020-0.036	>0.036-0.082	>0.082		
Placebo						
No. cases/person-years	20/23,760	19/23,359	20/23,129	20/24,208		
Multivariate adjusted	1	0.94 (0.50-1.77)	0.96 (0.52-1.79)	1.04 (0.56-1.95)	0.79	
Supplement						
No. cases/person-years	55/70,471	59/69,268	54/67,612	59/69,856		
Multivariate adjusted	1	1.04 (0.72-1.51)	0.93 (0.64-1.36)	1.03 (0.71-1.49)	0.87	0.98
Luteolin						
Range of intake (mg)	≤0.014	>0.014-0.027	>0.027-0.057	>0.057		
Placebo						
No. cases/person-years	17/22,899	24/22,527	18/23,940	20/25,089		
Multivariate adjusted	1	1.51 (0.81-2.81)	1.15 (0.59-2.24)	1.35 (0.70-2.61)	0.67	
Supplement						
No. cases/person-years	63/67,787	54/67,743	50/70,016	60/71,662		
Multivariate adjusted	1	0.83 (0.58-1.19)	0.77 (0.53-1.12)	0.91 (0.63-1.30)	0.91	0.99

*Reference category.
† Multivariate-adjusted HRs are adjusted for age at randomization, years of smoking, total number of cigarettes per day, self-reported history of diabetes mellitus, and energy-adjusted saturated fat intake.

and increasing detoxification of carcinogens, including those from tobacco (43-45). In support of this biological mechanism, flavonol intake has shown the greatest protective association for lung cancer (18, 46, 47). Similar to our results, Hirvonen et al. (31) reported that flavonol intake was protective against lung cancer among the ATBC male smokers, and Nöthlings et al. (28) showed that flavonol intake was protective only against pancreatic cancer in current smokers. We did not observe significant interactions between flavonoid intake and smoking intensity or duration in the ATBC Study. The number of hydroxyl groups in the B ring of flavonols might explain differences in their protective effects against pancreatic carcinogenesis as myricetin (three hydroxyl groups) had the least protective effect and kaempferol (one hydroxyl group) had the strongest protective effect in current smokers in this cohort as well as in the Multiethnic Cohort Study (28). In support of our hypothesis, cell culture studies suggest that individual flavonols differ depending on the number of hydroxyl groups in biological mechanisms important for pancreatic carcinogenesis, such as proliferation, antioxidant activity, and inhibition of angiogenesis (48-50).

The association between flavonoid intake and pancreatic cancer risk was limited to the participants that received placebo only during the trial phase of the ATBC Study, which suggests that daily α-tocopherol and/or β-carotene supplements may interfere with the protective effect of flavonoids (Table 4). Although neither trial intervention significantly altered the pancreatic cancer incidence during the trial, the pancreatic cancer incident rate was 25% lower for the men who received β-carotene supplements compared with those who did not receive β-carotene and men that received α-tocopherol had a 34% increased pancreatic cancer incident rate compared with the rate for those who did not receive α-tocopherol (51). We did not observe similar effects for antioxidants from foods such as dietary β-carotene, vitamin C, or vitamin E. Average intakes of vitamin E (10.7 mg/d) and β-carotene (1.7 mg/d) were much smaller than those consumed from supplemental α-tocopherol (50 mg/d) and β-carotene (20 mg/d). Other supplement use was too low in the ATBC Study to examine associations. We are not aware of any reported interactions between high flavonoid intake and daily α-tocopherol and/or β-carotene supplements in large prospective cohorts. There is some evidence that increased flavonoid intake improves α-tocopherol concentrations and antioxidant capacity in humans (52). The lack of a protective effect of flavonoids in the supplement group might be linked to the fact that α-tocopherol, β-carotene, and flavonoids exert antioxidant as well as prooxidant activities with greater prooxidative properties at high concentrations in the presence of metal ions and endogenous reducing agents (53, 54).

There are several limitations to our study. As with all dietary intake studies, measurement error related to both the dietary assessment techniques and the nutrient database is likely present and could cause inaccurate risk estimates. However, the monotonic decreasing HR across flavonoid intake quartiles and the consistency of the reduced pancreatic cancer risk across individual

flavonols and flavan-3-ols among participants in the placebo group would support that subjects were ranked robustly enough to observe associations (Table 4). The flavonoid intake data are primarily based on flavonoid analysis of Dutch foods (32-34). It is possible that Finnish foods differ from Dutch foods in flavonoid contents. The dietary questionnaire was not specifically designed to estimate flavonoid intake, which can explain the low reliability and validity coefficients for flavones. Intakes of flavone-rich foods were based primarily on recipes because these foods are mostly used as garnishes and spices. Given further the low intake values, the lack of an association between flavones and pancreatic cancer is not wholly unexpected.

Associations between flavonoids and pancreatic cancer could be different in nonsmokers, women, and populations with high consumption of dietary supplements and therefore may not be generalizable to such populations. In the Multiethnic Cohort Study, smoking and not gender modified the association between flavonol intake and smoking status; high flavonol intake was associated with decreased risk of exocrine pancreatic cancer in current smokers and not in former and never smokers (28). Our study may have limited power to evaluate the association of flavonoid intake and pancreatic cancer and the number of pancreatic cancer cases in the placebo group was low ($n = 79$). However, our results are consistent with those reported from the Multiethnic Cohort Study that observed inverse flavonoid associations only among smokers ($n = 112$ cases; ref. 28).

Furthermore, the inverse association between flavonoid intake and pancreatic cancer risk in the placebo group is similar and statistically significant across most flavonoid categories (Table 4), which would argue against the possibility that this is a chance finding. Flavonoid intake is invariably linked to a healthful diet (that is, low total fat and saturated fat intake) because flavonoids are found only in plants, most of which are high in carbohydrates and vitamins. Although residual confounding cannot be completely excluded, our results are independent of saturated fat intake and other potential pancreatic cancer confounders that we adjusted for in the multivariate model; therefore, the protection observed with a flavonoid-rich diet may be related to the specific biological actions of flavonoids. Lastly, as data were ascertained only at baseline, those dietary intakes, smoking habits, and the prevalence of diabetes mellitus may have changed during follow-up, which could contribute to misclassification of exposure leading to attenuated risk estimates or spurious associations because of incomplete adjustment of confounders.

In conclusion, our results from the ATBC Study suggest that there is no overall association between flavonoid intake and pancreatic cancer risk (Table 2). However, the reduced risk of pancreatic in male smokers who were not randomized to the α-tocopherol and/or β-carotene intervention suggests that population subgroups might benefit from a flavonoid-rich diet. Our results should be considered with caution given the relative small number of cases in the placebo group and the lack of an established biological mechanism for the interaction that we observed. Confirmation of our results in populations that have an adequate proportion of supplement users to evaluate interactions as well as nonsmokers and women are needed before conclusions can be made about the role of flavonoid intake in pancreatic cancer development in humans.

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