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Dietary lignan and proanthocyanidin consumption and colorectal adenoma recurrence in the Polyp Prevention Trial

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Lignans and proanthocyanidins are plant polyphenols that have shown protective properties against colorectal neoplasms in some human studies. Using logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) to prospectively evaluate the association between lignan and proanthocyanidin intake, estimated from databases linked to a food frequency questionnaire, and adenoma recurrence in 1,859 participants of the Polyp Prevention Trial. Overall, individual or total lignans or proanthocyanidins were not associated with colorectal adenoma recurrence. However, in sex-specific analyses, total lignan intake was positively associated with any adenoma recurrence in women (highest *vs.* lowest lignan intake quartile OR = 2.07, 95% CI: 1.22–3.52, *p* trend = 0.004) but not in men (*p* interaction = 0.04). To conclude, dietary lignan and proanthocyanidin consumption were not generally related to colorectal adenoma recurrence; however, high lignan intake may increase the risk of adenoma recurrence in women.

Polyphenols have generated interest as components of fruits and vegetables that show cancer protective properties.[1,2] On the basis of their chemical structure, polyphenols are divided into subclasses, the most pertinent being tannins (proanthocyanidins, hydrolysable tannins), lignans, stilbenes, phenolic acids and flavonoids.[3] We previously showed that the flavonoid subgroups flavonols and isoflavonoids and the flavan-3-ol epigallocatechin-3-gallate (EGCG) decrease the risk of advanced adenoma recurrence in the Polyp Prevention Trial (PPT).[4,5]

Lignans are diphenolic compounds present in the fibrous portion of plants, which are (partially or fully) converted by microbial gut flora to enterolactone and enterodiol.[6] The richest dietary sources of lignans are flax or linseed and sesame seed (3.5 g/kg).[7] Beverages (wine, tea, coffee and orange juice), cereals, bread, legumes, fruits (strawberries, peaches and oranges) and vegetables (broccoli, squash and cabbage) are, despite having 100–1,000-fold lower lignan contents than flax or sesame seed, the major dietary sources of lignans.[8–11] The antioxidative, anti-inflammatory and phytoestrogenic properties of lignans and their metabolites, as well as their ability to inhibit proliferation, invasion and angiogenesis and to promote apoptosis[12–17] suggest a plausible role for them in chemoprevention of colorectal carcinogenesis. Results from human studies are mixed with lignan consumption being associated with increased risk of colorectal cancer in a Canadian case-control study but a decreased risk in an English nested case-control study.[11,18] The association between lignan intake and colorectal cancer may differ between men and women, as sex modified the association between enterolactone concentrations and colorectal cancer in both a Danish and an English nested case-control study.[18,19] Dietary fiber and fat may modify the association between lignan intake and colorectal cancer by altering the intestinal microflora and, thus, the conversion of plant lignans to the more bioactive enterolactone and enterodiol[20]; as such, lignan intake and enterolactone concentration produced opposing results in relation to colorectal cancer in the English nested case-control study.[18] Furthermore, dietary lipids may alter the effect of lignans on the metabolism of steroid hormones,[6,21] which are involved in the etiology of colorectal tumorigenesis, as lignans and lipids are both involved in steroid hormone synthesis and metabolism.

Key words: cancer prevention, colorectal adenoma, colorectal cancer, lignans, proanthocyanidins

Abbreviations: BMI: body mass index; CI: confidence interval; EGCG: epigallocatechin 3-gallate; FFQ: food frequency questionnaire; IQR: interquartile range; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; PPT: Polyp Prevention Trial; USDA: U.S. Department of Agriculture.

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Proanthocyanidins (*e.g.*, condensed tannins) are polymers of elementary flavan-3-ol units and are common constituents of U.S. diets.[22–24] The main dietary sources of proanthocyanidins are fruits (grapes, apples and plums), legumes (dry beans), beverages (red wine, tea, cocoa and fruit juices) and chocolate.[23,25,26] Their antioxidant, anti-mutagenic, anti-inflammatory and antimicrobial activity, along with their ability to chelate metal ions, proteins and toxins, promote apoptosis and inhibit proliferation supports their role in chemoprevention of colorectal cancer in animal and *in vitro* studies.[22,27,28] The results from human studies, however, are less convincing: a Scottish and an Italian case-control study reported an inverse association between proanthocyanidin intake and colorectal cancer risk[29,30]; whereas another Scottish case-control study, as well as the prospective Iowa Women's Health Study reported no association with colorectal cancer.[31,32]

The objective of our study was to prospectively evaluate whether consumption of lignans and proanthocyandins, overall or stratified by gender and key dietary factors, was associated with colorectal adenoma recurrence in the PPT. To our knowledge, this is the first study to prospectively evaluate this relationship.

Material and methods

Study design and population

The PPT was a 4-year randomized, multi-center, nutritional intervention trial to evaluate whether an intervention designed to encourage consumption of a high-fibre, high-fruit and high-vegetable, and low-fat diet would decrease the risk of adenoma recurrence. Details of the study have been previously described.[33–35] To be eligible for the study, participants had at least one histologically confirmed colorectal adenoma identified by complete colonoscopy in the 6 months before study entry. Our study included 1,859 participants of the control ($n = 930$) and the intervention arm ($n = 929$) that had a colonoscopy at baseline (T0) and at the end of the four year trial (T4), as well as dietary data for any of the first 3 years of the study (T1, T2 or T3). The institutional review boards of the National Cancer Institute and each participating center approved the study and all participants provided written informed consent.

Adenoma assessment

At baseline (T0), 1 year later (T1), and 4 years after baseline (T4), participants had a full colonoscopy. Participants who missed the T1 colonscopy (8.2%) had a full colonscopy by the end of year T2. The first two colonoscopies were clearing colonoscopies used to remove any existing adenomas, whereas the T4 colonoscopy and any unscheduled colonoscopy after Year 2 (1.31 colonoscopies per participant after year 2) was used to determine adenoma recurrence. All colorectal lesions were evaluated for histologic features, size and degree of atypia by two independent pathologists. Adenomas detected after 2 years were considered as recurrent adenomas. Adenomas that were at least 1 cm in size, had at least 25% villous components, or showed high grade dysplasia were classified as advanced adenomas. High risk adenoma recurrence was defined as having at least three pathologically confirmed adenomas of any size or an advanced adenoma at T4.

Lignan and proanthocyanidin data

At T0 and at each of the annual follow-up visits, participants completed a self-administered modified Block-National Cancer Institute Food Frequency Questionnaire (FFQ), which asked about the frequency of intake and portion size of 119 food and beverage items during the past year.[34,35] Some FFQ food items were a single fruit or vegetable, such as apples, whereas others were grouped food items, such as "other fruits," which included grapes, plums and pineapples. Trained, certified nutritionists reviewed all FFQs with participants.[36] Compared with 24-hr dietary recalls and four-day food record data, the FFQ slightly overestimated fat and underestimated fiber, fruit and vegetable intake and had acceptable correlations for fat ($r = 0.63$), fibre ($r = 0.63$), fruit and vegetable ($r = 0.72$), dry bean ($r = 0.76$) and other macro- and micro-nutrients. With respect to foods with available lignan data, the FFQ asked three questions on legumes, one on nuts, 17 on vegetables (including soups), 11 on fruits, nine on breads/cereals, 13 on beverages and 11 on processed food consumption. The FFQ did not specifically ask questions on intakes of flaxseed, linseed or sesame seed, which are enriched in lignans, because these were rarely consumed in the U.S. when the PPT was conducted. Lignan intake was estimated for 58 of 65 food and beverage items using a Canadian phytoestrogen database and was calculated as the sum of lariciresinol, matairesinol, pinoresinol and secoisolariciresinol.[8] Three other phytoestrogen databases[10,37,38] were used for seven food items (brown or wild rice, brussel sprouts, chocolate candy, other vegetables, peas, popcorn and spaghetti) not included in the Canadian database. The four databases were similar in lignan concentrations of common foods and beverages. With respect to foods with available proanthocyanidin data, the FFQ asked 11 questions on fruits, 21 on vegetables (including soups), 12 on beverages (including beer, fruit juices, tea and wine) and one on chocolate consumption. Proanthocyanidin intake was estimated from the 2004 U.S. Department of Agriculture (USDA) comprehensive proanthocyanidin database[26] that reviewed, evaluated and summarized the existing proanthocyanidin databases and calculated the sum of monomers, dimers, trimers, 4–6 mers, 7–10 mers and polymers (>10 flavan-3-ol units). The FFQ was not specifically validated for lignan and proanthocyanidin intake using 24-hr dietary recalls and four-day food record data. Lignan and proanthocyanidin intake from dietary supplements was not included because the intake of supplements containing significant amounts of lignans and proanthocyanidins was low in the PPT.

Lifestyle data

Besides the FFQ completed at T0 and the annual follow-up visits, participants also completed an interviewer-administered

questionnaire about demographics (including age, gender and education level), physical activity, smoking (including intensity and duration of smoking), family history of cancer (including number of first-degree relatives with cancer), clinical visits, and medication and supplement use (including name, dosage and frequency of use). Regular non-steroidal anti-inflammatory drug (NSAID) use was defined as taking aspirin or non-aspirin NSAIDs such as ibuprofen, naproxen, indomethacin or piroxicam at least once per month. Hormone replacement therapy among women was defined as taking either unopposed estrogens or estrogen/progestin combinations. Physical activity was defined as self-reported time typically spent for any type of moderate or vigorous physical activity, including both occupational and non-occupational activities.

Statistical analyses

Statistical analyses were performed using SAS, version 9.1 (SAS, Cary, NC) software. Baseline participant characteristics and dietary intakes of lignans, proanthocyanidins and primary dietary sources of lignans and proanthocyanidins [at T0, and during the first 3 years of the trial (mean of T1, T2 or T3)] were evaluated by adenoma recurrence at T4 (any or high risk adenoma recurrence *vs.* no recurrence) using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. Dietary data from T4 was not used because it was collected after colonoscopy (used for assessing adenoma recurrence) in some participants. Spearman's and Pearson's correlation coefficients between lignans, proanthocyanidins and primary dietary sources of lignans and proanthocyanidins were calculated.

The association between dietary intakes of lignans and proanthocyanidins [T0 (not shown in Tables) and mean of T1, T2 and T3 (shown in the Tables)] and colorectal adenoma recurrence was evaluated by odds ratios (ORs) and 95% confidence intervals (95% CI) using multivariate logistic regression. A linear trend test was performed using the ln-transformed median value of each dietary intake quantile as a continuous variable in a logistic regression model. Participants characteristics, listed in Table 1, were evaluated as potential confounders by adding them in a stepwise manner to the model. Potential confounders remained in the model if they changed the association by >10%, had a χ^2 p value $\leq$ 0.20, and were associated with both adenoma recurrence and lignan or proanthocyanidin intake. Saturated fat intake was a confounder for the association between proanthocyanidin consumption and adenoma recurrence but not for the association between lignan consumption and adenoma recurrence. Two multivariate logistic regression models are shown: (a) crude analysis [age quartiles, sex and energy intake (continuous) during the first three trial years] and (b) multivariate analysis [age quartiles, sex, BMI, NSAID use at baseline, energy intake (continuous) and saturated fat intake (quartiles, only for proanthocyanidins) during the first three trial years].

To evaluate the statistical power to see a biologically meaningful effect of lignan and proanthocyanidin consumption on any or advanced adenoma recurrence, we used Monte Carlo simulation of 2,000 computer-generated datasets with the sample size of the trial (464 individuals in each of the four quartiles) and a true relationship described by an OR of 0.88, 0.79 and 0.70 in the second, third and fourth quartiles (relative to the first quartile) and computed the proportion that were statistically significant at the 0.05 significance level (with a two-sided trend test). Age, gender, BMI, regular NSAID use and dietary fat intake [the available variables were total fat, total saturated fat, oleic acid, linoleic acid and saturation index (proportion of saturated fatty acids on total fatty acids)] were evaluated for effect modification. For continuous variables, the median values were used as cutoffs ($\leq$ median and $>$ median). The interaction p-value for the stratified data was calculated from the interaction term between the ln-transformed median value of each dietary intake quartile as a continuous variable and the categorical variable evaluated for effect modification. All p values were considered statistically significant at either $p \leq 0.05$, or after adjusting for multiple comparisons using the Bonferroni correction at $p \leq 0.008$.

Results

At the end of the 4-year trial, 40% of participants had at least one recurrent adenoma, 12% had high risk adenoma and 7% had an advanced adenoma recurrence (Table 1). Adenoma recurrence was more common in men and older individuals, and less common in women who used hormone therapy. In addition, advanced adenoma recurrence was more common in individuals who did not regularly use NSAIDs (Table 1). Intake of lignans and proanthocyanidins was log-normally distributed and, therefore, is shown as median and quartile intakes (Table 1). At baseline, lignan and proanthocyanidin consumption as a percentage of total energy intake was higher in females than males (both $p < 0.0001$).

Compared to baseline, total daily lignan consumption increased on average from 135 to 167 μg during the first 3 years of the trial ($p < 0.0001$), those in the intervention arm increased lignan consumption by 67 ± 3 μg/day ($p < 0.0001$; in comparison to the control group: + 3 ± 2 μg/day; $p = 0.002$). The major dietary sources of lignans during the PPT (≥5% of total lignan intake) were whole grain rice or pasta (15%), broccoli (9%), coffee (8%) and spaghetti with tomato sauce (6%). The primary sources of lariciresinol, matairesinol, pinoresinol and secoisolariciresinol were broccoli (26%), whole grain rice or pasta (68%), tea (14%) and whole grain rice or pasta (14%), respectively. Except for broccoli (11.6 *vs.* 12.5 g/day for those with any *vs.* no adenoma recurrence; $p = 0.01$), intake of major sources of lignans did not vary by adenoma recurrence status (data not shown). Total proanthocyanidin intake increased from 111 to 154 mg/day from baseline during the first 3 years of the trial ($p < 0.0001$), as the intervention group increased their proanthocyanidin intake

Table 1. Proportions and medians (interquartile ranges) of participant characteristics in the Polyp Prevention Trial by adenoma recurrence at T4 ($n = 1,859$)[1]

	Adenoma recurrence (T4)						
	None	Any		High risk		Advanced	
Characteristics	Median (IQR) or %	Median (IQR) or %	p Value[2]	Median (IQR) or %	p Value[2]	Median (IQR) or %	p Value[2]
Sample size (%)	1,123 (60)	736 (40)		226 (12)		123 (7)	
Baseline (T0)							
Gender (% male)	60	72	<0.0001	76	<0.0001	72	0.01
Race (% Caucasian)	90	90	0.94	92	0.47	89	0.88
Education (% ≤high school)	24	25	0.62	28	0.24	27	0.51
Family history of colorectal cancer (% yes)[3]	27	27	0.92	31	0.29	27	1.00
Smoker (% current)	13	14	0.53	13	0.83	11	0.57
NSAID use (% yes)[4]	35	32	0.13	29	0.09	24	0.02
Supplement use (% yes)[4]	43	40	0.23	36	0.06	37	0.29
Hormone therapy (% yes)[4]	14	8	<0.0001	7	0.003	7	0.02
Age (years)	61.0 (53.0–67.0)	64.0 (56.0–70.0)	<0.0001	66.0 (60.0–71.0)	<0.0001	67.0 (60.0–72.0)	<0.0001
Body mass index (kg/m^2)	27.2 (24.5–30.1)	27.5 (25.1–30.4)	0.05	27.8 (25.2–30.9)	0.04	27.7 (25.1–31.2)	0.08
Physical activity (hr/week)[5]	8.25 (3.90–15.0)	8.36 (3.84–15.9)	0.70	8.66 (3.50–15.8)	0.98	8.38 (3.65–18.7)	0.98
Trial (T1, T2 and T3)[6]							
Daily dietary intake							
Alcohol (g)	0.96 (0.00–8.92)	1.55 (0.00–9.54)	0.30	0.99 (0.00–7.41)	0.73	0.99 (0.00–8.98)	0.87
Energy (1,000 kcals)	1.77 (1.52–2.08)	1.79 (1.54–2.09)	0.36	1.80 (1.57–2.05)	0.60	1.79 (1.57–2.02)	0.71
Total fat (g)	48.6 (36.7–64.8)	50.0 (38.2–65.8)	0.22	51.9 (41.3–65.6)	0.05	52.9 (41.6–64.7)	0.10
Saturated fat (g)	18.1 (13.1–24.8)	18.6 (13.8–25.4)	0.25	19.4 (14.4–25.5)	0.05	19.3 (14.4–25.5)	0.13
Lignans (μg)	165 (122–223)	170 (124–220)	0.97	161 (122–211)	0.49	171 (122–212)	0.68
Lariciresinol (μg)	48.4 (33.3–66.5)	48.8 (35.2–64.7)	0.91	48.4 (34.4–63.6)	0.70	49.8 (35.9–63.7)	0.93
Matairesinol (μg)	13.3 (7.05–27.4)	13.0 (6.92–27.1)	0.30	11.6 (6.61–26.6)	0.15	11.5 (6.61–26.6)	0.21
Pinoresinol (μg)	20.0 (13.2–29.2)	20.6 (13.4–29.5)	0.52	20.1 (13.4–28.9)	0.90	20.7 (13.4–28.9)	0.92
Secoisolariciresinol (μg)	77.2 (58.8–102)	77.7 (58.1–102)	0.81	75.2 (57.5–102)	0.31	77.9 (54.5–106)	0.65
Proanthocyanidins (mg)	152 (98.4–223)	154 (101–225)	0.88	151 (107–212)	0.81	150 (105–206)	0.56
Monomers (mg)	16.0 (10.3–26.0)	16.5 (10.7–25.4)	0.85	15.9 (10.6–24.2)	0.74	15.7 (10.5–23.5)	0.52
Dimers (mg)	22.3 (14.3–31.2)	22.7 (15.0–30.9)	0.85	22.4 (15.4–30.6)	0.85	22.3 (15.4–29.9)	0.67
Trimers (mg)	10.8 (7.22–16.0)	11.3 (6.91–16.0)	0.88	11.8 (7.07–15.4)	0.89	11.9 (7.12–15.0)	0.85
4–6 mers (mg)	30.5 (19.8–46.5)	31.4 (19.1–47.4)	0.77	31.8 (19.7–44.9)	0.98	30.9 (18.9–44.9)	0.69
7–10 mers (mg)	21.7 (13.3–34.0)	22.1 (13.1–34.1)	0.76	22.0 (13.6–32.0)	1.00	21.3 (13.5–31.6)	0.57
Polymers (mg)	44.1 (25.2–70.5)	43.8 (24.9–72.8)	0.96	42.7 (24.5–66.9)	0.53	42.2 (23.2–62.6)	0.41

[1]Participant characteristics stratified by adenoma recurrence have been previously presented.[4] [2]All comparisons against the no adenoma recurrence group. p Values for differences in proportions were calculated using Fisher's exact test. p Values for differences in medians were calculated using Wilcoxon rank-sum test. [3]Family history of colorectal cancer was defined as having ≥1 first-degree relative with colorectal cancer at baseline. [4]Regular non-steroidal anti-inflammatory drug (NSAID) use, hormone therapy and supplement use were tested at baseline and use throughout the first three trial years. Regular dietary supplement use was defined as taking supplement ≥1 week. Regular medication use, including NSAIDs, was defined as taking medication ≥1 month. Hormone replacement therapy included both unopposed estrogen and estrogen/progestin combinations. [5]Physical activity was defined as self-reported time typically spent for any type of moderate or vigorous physical activity. [6]T1, T2, T3: mean values per day of the first 3 years of the trial for dietary variables.

by 81 ± 3 mg/day ($p < 0.0001$; in comparison to the control group: + 0.7 ± 2 mg/day; $p = 0.05$). The primary dietary sources of proanthocyanidins during the PPT (≥5% of total intake) were apples (30.2%), other fruits (grapes, plums and pineapples: 17.3%), chocolate (14.1%), tea (9.3%) and dry beans (8.7%). Of the major dietary proanthocyanidin sources,

Table 2. Association between daily lignan intake during the trial and colorectal adenoma recurrence in the Polyp Prevention Trial ($n = 1,859$)

	Adenoma recurrence (T4)						
	No		Any		High risk		
Lignans quartiles[1] (μg/day)	*n* (%)	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]
Total Lignans							
<123	286 (61.5)	179 (38.5)	1.00[4]	1.00	57 (12.3)	1.00	1.00
123–167	287 (61.7)	178 (38.3)	0.98 (0.75–1.29)	0.99 (0.76–1.30)	61 (13.1)	1.06 (0.70–1.59)	1.07 (0.71–1.61)
168–222	266 (57.2)	199 (42.8)	1.25 (0.96–1.65)	1.26 (0.96–1.65)	58 (12.5)	1.19 (0.78–1.81)	1.21 (0.79–1.85)
>223	284 (61.2)	180 (38.8)	1.15 (0.86–1.53)	1.16 (0.87–1.56)	50 (10.8)	1.09 (0.69–1.72)	1.11 (0.70–1.75)
p trend[5]			0.17	0.15		0.59	0.55
Lariciresinol							
<34.0	296 (63.7)	169 (36.3)	1.00	1.00	54 (11.6)	1.00	1.00
34.0–48.4	268 (57.6)	197 (42.4)	1.32 (1.01–1.73)	1.32 (1.01–1.73)	57 (12.3)	1.20 (0.79–1.83)	1.21 (0.80–1.85)
48.5–66.0	272 (58.5)	193 (41.5)	1.28 (0.97–1.68)	1.29 (0.98–1.69)	67 (14.4)	1.41 (0.93–2.12)	1.40 (0.93–2.12)
>66.0	287 (61.9)	177 (38.1)	1.20 (0.90–1.60)	1.20 (0.90–1.59)	48 (10.3)	1.11 (0.71–1.74)	1.10 (0.70–1.73)
p trend			0.21	0.22		0.41	0.45
Matairesinol							
<6.99	276 (59.4)	189 (40.6)	1.00	1.00	63 (13.5)	1.00	1.00
6.99–13.1	283 (60.9)	182 (39.1)	0.92 (0.70–1.20)	0.92 (0.70–1.20)	57 (12.3)	0.86 (0.57–1.29)	0.84 (0.55–1.26)
13.2–27.3	280 (60.2)	185 (39.8)	0.99 (0.75–1.29)	0.99 (0.76–1.30)	52 (11.2)	0.86 (0.57–1.31)	0.85 (0.56–1.30)
>27.3	284 (61.2)	180 (38.8)	1.03 (0.79–1.36)	1.04 (0.79–1.37)	54 (11.6)	1.04 (0.68–1.58)	1.05 (0.68–1.60)
p trend			0.68	0.66		0.86	0.80
Pinoresinol							
<13.3	285 (61.3)	180 (38.7)	1.00	1.00	54 (11.6)	1.00	1.00
13.3–20.2	286 (61.5)	179 (38.5)	1.00 (0.76–1.31)	1.00 (0.76–1.32)	69 (12.9)	1.11 (0.73–1.68)	1.12 (0.74–1.70)
20.3–29.3	275 (59.1)	190 (40.9)	1.10 (0.84–1.45)	1.10 (0.84–1.44)	57 (12.3)	1.08 (0.71–1.66)	1.07 (0.70–1.64)
>29.3	277 (59.7)	187 (40.3)	1.10 (0.83–1.46)	1.10 (0.83–1.45)	55 (11.9)	1.04 (0.67–1.60)	1.02 (0.66–1.59)
p trend			0.40	0.42		0.88	0.94
Secoisolariciresinol							
<58.7	276 (59.4)	189 (40.6)	1.00	1.00	62 (13.3)	1.00	1.00
58.7–77.4	288 (61.9)	177 (38.1)	1.00 (0.76–1.32)	0.87 (0.66–1.14)	58 (12.5)	0.84 (0.55–1.26)	0.85 (0.56–1.29)
77.5–102	276 (59.4)	189 (40.6)	1.10 (0.84–1.44)	1.02 (0.77–1.34)	50 (10.8)	0.86 (0.56–1.32)	0.87 (0.56–1.34)
>102	283 (61.0)	181 (39.0)	1.10 (0.83–1.45)	1.01 (0.75–1.35)	56 (12.1)	0.99 (0.63–1.55)	1.02 (0.65–1.61)
p trend			0.93	0.98		0.92	0.98

[1]Lignan intake in quartiles (Q1–Q4) by the mean consumption during the first three trial years. [2]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex and average energy intake (continuous) during the first three trial years. [3]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex, average BMI (<25, 25.0–29.9, ≥30 kg/m^2), regular NSAID use at baseline and average energy intake (continuous) during the first three trial years. [4]Reference category. [5]The ln-transformed median intakes in μg/day of each quartile were used as a continuous score variable to determine the *p* value for trend.

individuals with high risk adenoma recurrence had lower tea intake than those with no adenoma recurrence (5.93 *vs.* 12.9 g/day) and lower dry bean intake (11.3 *vs.* 15.4 g/day).

Our power calculation revealed that we had 99% and 96% power to detect OR of 0.88, 0.79 and 0.70 in the second, third and fourth quartiles (relative to the first quartile) for any recurrence and for an advanced recurrence, respectively. Overall, consumption of total or individual lignans during the first 3 years of the trial was not associated with adenoma recurrence (Table 2); adjusting for dietary fiber, which was closely correlated with lignan consumption during the trial ($r = 0.77$), or saturated fat intake did not alter these association (results not shown). Similarly, consumption of proanthocyanidins, overall or for polymers of varying length, was not associated with adenoma recurrence (Table 3); adjusting for saturated fat intake, which may affect microbial

Table 3. Association between daily proanthocyanidin intake during the trial and colorectal adenoma recurrence in the Polyp Prevention Trial ($n = 1{,}859$)

	Adenoma recurrence (T4)						
	No	Any			High risk		
Proanthocyanidin quartiles[1] (mg/day)	*n* (%)	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]
Total proanthocyanidin							
<99.1	286 (61.5)	179 (38.5)	1.00[4]	1.00	49 (10.5)	1.00	1.00
99.2–153	280 (60.2)	185 (39.8)	1.09 (0.83–1.43)	1.13 (0.85–1.48)	66 (14.2)	1.39 (0.91–2.11)	1.53 (0.99–2.35)
154–223	279 (60.0)	186 (40.0)	1.13 (0.86–1.48)	1.20 (0.90–1.60)	60 (12.9)	1.29 (0.84–1.98)	1.52 (0.96–2.40)
>223	278 (59.9)	186 (40.1)	1.14 (0.86–1.52)	1.27 (0.91–1.76)	51 (11.0)	1.15 (0.73–1.82)	1.50 (0.89–2.53)
P trend[5]			0.33	0.14		0.55	0.11
Monomer							
<10.5	292 (62.8)	173 (37.2)	1.00	1.00	54 (11.6)	1.00	1.00
10.5–16.2	278 (59.8)	187 (40.2)	1.16 (0.89–1.53)	1.18 (0.89–1.35)	62 (13.3)	1.23 (0.81–1.86)	1.26 (0.82–1.92)
16.3–25.7	268 (57.6)	197 (42.4)	1.29 (0.98–1.70)	1.29 (0.98–1.71)	60 (12.9)	1.29 (0.84–1.97)	1.31 (0.85–2.03)
>25.7	285 (61.4)	179 (38.6)	1.13 (0.86–1.50)	1.14 (0.86–1.52)	50 (10.8)	1.02 (0.65–1.60)	1.04 (0.66–1.64)
p trend			0.31	0.32		0.87	0.83
Dimer							
<14.6	293 (63.0)	172 (37.0)	1.00	1.00	52 (11.2)	1.00	1.00
14.6–22.4	273 (58.7)	192 (41.3)	1.25 (0.95–1.63)	1.28 (0.98–1.69)	62 (13.3)	1.37 (0.90–2.09)	1.39 (0.91–2.12)
22.5–31.0	274 (58.9)	191 (41.1)	1.24 (0.94–1.63)	1.29 (0.97–1.73)	58 (12.5)	1.38 (0.88–2.15)	1.36 (0.87–2.14)
>31.0	283 (61.0)	181 (39.0)	1.17 (0.88–1.56)	1.25 (0.92–1.70)	54 (11.6)	1.38 (0.85–2.22)	1.39 (0.86–2.25)
p trend			0.25	0.14		0.51	0.17
Trimer							
<7.12	270 (58.1)	195 (41.9)	1.00	1.00	57 (12.3)	1.00	1.00
7.12–10.9	302 (64.9)	163 (35.1)	0.74 (0.56–0.97(	0.76 (0.58–1.00)	48 (10.3)	0.74 (0.48–1.14)	0.81 (0.52–1.25)
11.0–16.0	271 (58.3)	194 (41.7)	1.03 (0.79–1.35)	1.07 (0.81–1.43)	69 (14.8)	1.28 (0.85–1.93)	1.53 (0.99–2.37)
>16.0	280 (60.3)	184 (39.7)	0.94 (0.70–1.24)	0.98 (0.72–1.34)	52 (11.2)	0.91 (0.58–1.43)	1.12 (0.69–1.83)
p trend			0.91	0.73		0.72	0.25
4–6mers							
<19.4	274 (58.8)	192 (41.2)	1.00	1.00	55 (11.8)	1.00	1.00
19.4–30.9	298 (64.2)	166 (35.8)	0.80 (0.61–1.05)	0.83 (0.63–1.10)	54 (11.6)	0.93 (0.61–1.41)	1.01 (0.66–1.56)
31.0–46.9	276 (59.4)	189 (40.6)	1.03 (0.78–1.34)	1.09 (0.82–1.45)	67 (14.4)	1.27 (0.84–1.92)	1.50 (0.97–2.33)
>46.9	275 (59.3)	189 (40.7)	1.02 (0.77–1.36)	1.12 (0.18–1.55)	50 (10.8)	0.94 (0.60–1.92)	1.20 (0.72–2.00)
p trend			0.59	0.34		0.78	0.22
7–10mers							
<13.2	280 (60.2)	185 (39.8)	1.00	1.00	51 (11.0)	1.00	1.00
13.2–21.8	288 (62.9)	177 (38.1)	0.93 (0.71–1.22)	0.96 (0.73–1.27)	61 (13.1)	1.16 (0.76–1.77)	1.27 (0.83–1.96)
21.9–34.0	276 (59.4)	189 (40.6)	1.09 (0.83–1.42)	1.15 (0.86–1.54)	65 (14.0)	1.34 (0.88–2.03)	1.57 (1.00–2.47)
>34.0	279 (60.1)	185 (39.9)	1.04 (0.79–1.38)	1.14 (0.82–1.58)	49 (10.6)	0.99 (0.63–1.56)	1.27 (0.75–2.15)
p trend			0.57	0.32		0.75	0.19
Polymers (>10)							
<25.1	278 (59.8)	187 (40.2)	1.00	1.00	60 (12.9)	1.00	1.00
25.1–43.9	281 (60.4)	184 (39.6)	0.97 (0.74–1.26)	0.99 (0.75–1.31)	59 (12.7)	0.92 (0.61–1.39)	1.00 (0.66–1.53)
44.0–71.6	290 (62.4)	175 (37.6)	0.94 (0.72–1.23)	1.00 (0.74–1.34)	53 (11.4)	0.86 (0.57–1.31)	1.00 (0.63–1.57)
>71.6	274 (59.1)	190 (40.9)	1.07 (0.81–1.41)	1.17 (0.84–1.65)	54 (11.6)	0.93 (0.61–1.43)	1.19 (0.70–2.03)
p trend			0.76	0.46		0.64	0.62

[1]Proanthocyanidin intake in quartiles (Q1–Q4) by the mean consumption during the first three trial years. [2]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex and average energy intake (continuous) during the first three trial years. [3]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex, average BMI (<25, 25.0–29.9, ≥30 kg/m^2), regular NSAID use at baseline and average energy (continuous) and saturated fat intake (<13.4, 13.4–18.3, 18.4–25.0, >25.0 g/day) during the first three trial years. [4]Reference category. [5]The ln-transformed median intakes in mg/day of each quartile were used as a continuous score variable to determine the *p* value for trend.

Table 4. Association between daily lignan and proanthocyanidin consumption and colorectal adenoma recurrence in the Polyp Prevention Trial stratified by gender (n = 1,859)

	Adenoma Recurrence (T4)						
	No		Any		High Risk		
Intake quartiles[1]	*n* (%)	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]
Lignan (μg/day)							
Women							
<123	131 (72.8)	49 (27.2)	1.00[4]	1.00	15 (8.3)	1.00	1.00
123–167	117 (70.5)	49 (29.5)	1.20 (0.74–1.94)	1.24 (0.76–2.01)	19 (11.4)	1.53 (0.71–3.28)	1.54 (0.72–3.31)
168–222	100 (65.8)	52 (34.2)	1.68 (1.02–2.77)	1.73 (1.04–2.86)	8 (5.3)	0.87 (0.33–2.27)	0.87 (0.33–2.28)
>223	103 (65.6)	54 (34.4)	1.98 (1.17–3.35)	2.07 (1.22–3.52)	12 (7.6)	1.64 (0.64–4.17)	1.61 (0.63–4.14)
p trend[5]			0.006	0.004		0.49	0.51
Men							
<123	155 (54.4)	130 (45.6)	1.00	1.00	42 (14.7)	1.00	1.00
123–167	170 (56.9)	129 (43.1)	0.90 (0.65–1.26)	0.90 (0.65–1.26)	42 (14.0)	0.91 (0.56–1.48)	0.91 (0.56–1.50)
168–222	166 (53.0)	147 (47.0)	1.11 (0.80–1.54)	1.10 (0.79–1.52)	50 (16.0)	1.25 (0.77–2.01)	1.27 (0.78–2.06)
>223	181 (59.0)	126 (41.0)	0.91 (0.64–1.29)	0.91 (0.64–1.30)	38 (12.4)	0.96 (0.57–1.63)	0.99 (0.58–1.68)
p trend			0.87	0.87		0.81	0.74
p interaction[5]			0.05	0.04		0.83	0.83
Proanthocyanidin (mg/day)							
Women							
<99.1	106 (68.8)	48 (31.2)	1.00	1.00	16 (10.4)	1.00	1.00
99.2–153	130 (69.9)	56 (30.1)	0.95 (0.59–1.53)	0.90 (0.55–1.47)	16 (8.6)	0.73 (0.33–1.59)	0.70 (0.31–1.56)
154–223	119 (70.4)	50 (29.6)	1.03 (0.63–1.70)	0.96 (0.56–1.63)	11 (6.5)	0.64 (0.27–1.53)	0.61 (0.24–1.53)
>223	96 (65.8)	50 (34.2)	1.28 (0.75–2.20)	1.11 (0.61–2.10)	11 (7.5)	0.78 (0.31–1.99)	0.73 (0.26–2.10)
p trend			0.37	0.77		0.49	0.45
Men							
<99.1	180 (57.9)	131 (42.1)	1.00	1.00	33 (10.6)	1.00	1.00
99.2–153	150 (53.8)	129 (46.2)	1.18 (0.84–1.63)	1.26 (0.90–1.76)	50 (17.9)	1.79 (1.09–2.96)	2.11 (1.26–3.54)
154–223	160 (54.1)	136 (45.9)	1.19 (0.86–1.64)	1.36 (0.96–1.93)	49 (16.6)	1.67 (1.01–2.75)	2.12 (1.24–3.61)
>223	182 (57.2)	136 (42.8)	1.09 (0.78–1.53)	1.35 (0.91–2.00)	40 (12.6)	1.33 (0.78–2.75)	2.00 (1.08–3.70)
p trend			0.54	0.10		0.28	0.02
p interaction			0.72	0.65		0.34	0.34

[1]Lignan and proanthocyanidin intake in quartiles (Q1–Q4) by the mean consumption during the first three trial years. [2]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex and average energy intake (continuous) during the first three trial years. [3]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex, average BMI (<25, 25.0–29.9, ≥30 kg/m^2) and regular NSAID use at baseline, and average energy (continuous) and saturated fat intake (<13.4, 13.4–18.3, 18.4–25.0, >25.0 g/day; only for proanthocyanidins) during the first three trial years. [4]Reference category. [5]The ln-transformed median intakes of each quartile were used as a continuous score variable to determine the *p* value for trend. The ln-transformed median intakes of each quartile were used as a continuous score variable and sex as categorical variable to determine the *p* value for the interaction.

proanthocyanidin metabolism in the small intestine, but not dietary fibre, which was also correlated with lignan consumption during the trial (r = 0.71) did alter these associations.

After stratification by gender, total lignan intake during the first three trial years was positively associated with any adenoma recurrence in women (highest *vs.* lowest lignan intake quartile OR = 2.07, 95% CI: 1.22–3.52, *p* trend = 0.004), but not in men (OR = 0.91, 95% CI = 0.64–1.30; *p* interaction = 0.04; Table 4). Total T0 lignan intake, change in lignan intake from baseline, and fibre consumption were not associated with any adenoma recurrence in women or men (results not shown). Total proanthocyanidin intake was positively associated with high risk adenoma recurrence in men (OR = 2.00, 95% CI = 1.08–3.70, *p* trend = 0.02), but no significant interaction was noted between gender and proanthocyanidin intake (*p* interaction = 0.34; Table 4). Stratification by age, BMI or regular NSAID use did not reveal any other associations between consumption of lignans

Table 5. Association between daily lignan and proanthocyanidin consumption and colorectal adenoma recurrence in the Polyp Prevention Trial stratified by daily saturated fat intake ($n = 1{,}859$)

	Adenoma Recurrence (T4)						
	No	Any			High Risk		
Intake quartiles[1]	*n* (%)	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]	*n* (%)	OR (95% CI)[2]	OR (95% CI)[3]
Lignans (μg/day)							
Saturated fat ≤ 18.3 g/day							
<123	106 (66.3)	54 (33.7)	1.00[4]	1.00	12 (7.5)	1.00	1.00
123–167	120 (61.2)	76 (38.8)	1.36 (0.86–2.13)	1.37 (0.87–2.16)	21 (10.7)	1.67 (0.76–3.67)	1.77 (0.80–3.92)
168–222	154 (59.7)	104 (40.3)	1.62 (1.03–2.54)	1.63 (1.04–2.58)	28 (10.9)	2.00 (0.90–4.42)	2.12 (0.95–4.72)
>223	190 (60.1)	126 (39.9)	1.80 (1.10–2.95)	1.94 (1.17–3.19)	39 (12.3)	3.03 (1.29–7.11)	3.21 (1.36–7.59)
p trend[5]			0.01	0.009		0.01	0.008
Saturated fat >18.3 g/day							
<123	180 (59.0)	125 (41.0)	1.00	1.00	45 (14.8)	1.00	1.00
123–167	167 (62.1)	102 (37.9)	0.82 (0.58–1.16)	0.85 (0.60–1.20)	40 (14.9)	0.97 (0.59–1.59)	0.96 (0.58–1.58)
168–222	112 (54.1)	95 (45.9)	1.19 (0.82–1.74)	1.26 (0.86–1.85)	30 (14.5)	1.29 (0.74–2.27)	1.28 (0.73–2.25)
>223	94 (63.5)	54 (36.5)	0.78 (0.49–1.25)	0.89 (0.56–1.43)	11 (7.4)	0.61 (0.28–1.34)	0.61 (0.28–1.34)
p trend			0.85	0.86		0.62	0.61
p interaction[5]			0.35	0.32		0.02	0.01
Proanthocyanidins (mg/day)							
Saturated fat ≤ 18.3 g/day							
<99.1	109 (65.3)	58 (34.7)	1.00	1.00	12 (7.2)	1.00	1.00
99.2–153	122 (62.2)	74 (37.8)	1.20 (0.77–1.87)	1.21 (0.77–1.88)	23 (11.7)	1.73 (0.80–3.75)	1.70 (0.78–3.70)
154–223	154 (58.6)	109 (41.4)	1.52 (0.99–2.34)	1.54 (1.00–2.37)	30 (11.4)	1.90 (0.89–4.07)	1.93 (0.90–4.15)
>223	185 (60.9)	119 (39.1)	1.53 (0.95–2.45)	1.53 (0.95–2.46)	35 (11.5)	2.06 (0.90–4.70)	2.01 (0.87–4.64)
p trend			0.05	0.05		0.10	0.11
Saturated Fat >18.3 g/day							
<99.1	177 (59.4)	121 (40.6)	1.00	1.00	37 (12.4)	1.00	1.00
99.2–153	158 (58.7)	111 (41.3)	1.08 (0.76–1.54)	1.08 (0.76–1.54)	43 (16.0)	1.40 (0.84–2.34)	1.44 (0.86–2.42)
154–223	125 (61.9)	77 (38.1)	0.97 (0.66–1.43)	0.94 (0.64–1.40)	30 (14.9)	1.28 (0.72–2.25)	1.26 (0.71–2.24)
>223	93 (58.1)	67 (41.9)	1.08 (0.70–1.68)	1.10 (0.71–1.71)	16 (10.0)	0.95 (0.47–1.90)	0.99 (0.49–2.00)
p trend			0.85	0.85		0.82	0.77
p interaction			0.42	0.39		0.13	0.13

[1]Lignan and proanthocyanidin intake in quartiles (Q1–Q4) by the mean consumption during the first three trial years. Saturated fat intake below or above the median of the mean intake during the first three trial years. [2]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex and average energy intake (continuous) during the first three trial years. [3]Multivariate OR and 95% CI models were adjusted for age quartiles (<55, 55–62, 63–69, >69 years), sex, average BMI (<25, 25.0–29.9, ≥30 kg/m^2) and regular NSAID use at baseline, and average energy intake (continuous) during the first three trial years. [4]Reference category. [5]The ln-transformed median intakes of each quartile were used as a continuous score variable to determine the *p* value for trend. The ln-transformed median intakes of each quartile were used as a continuous score variable and saturated fat intake as categorical variable (≤ or > median intake) to determine the *p* value for the interaction.

and proanthocyanidins and adenoma recurrence (data not shown).

For those individuals consuming the median or below median intake of saturated fat during the trial, lignan intake was positively associated with any (OR = 1.94, 95% CI = 1.17–3.19, *p* trend = 0.009) and high risk adenoma recurrence (OR = 3.21, 95% CI = 1.36–7.59, *p* trend = 0.008; Table 5); the interaction between saturated fat and lignan intake was statistically significant for high risk adenoma recurrence ($p = 0.01$) but not for any adenoma recurrence ($p = 0.32$). The effect modification was not statistically significant for fibre (data not shown). Total proanthocyanidin intake was positively associated with any adenoma recurrence in individuals with a saturated fat intake equal to or below the median (OR = 1.53, 95% CI = 0.95–2.46, *p* trend = 0.05; Table 5).

Discussion

The objective of this study was to prospectively examine the association between consumption of lignans and proanthocyanidins and colorectal adenoma recurrence. Overall, dietary

lignan and proanthocyanidin intake was not associated with colorectal adenoma recurrence. However, when stratified by gender, high lignan intake was associated with an increased risk of any adenoma recurrence in women. Furthermore, high lignan intake was associated with an increased risk of any and high risk adenoma recurrence in individuals that consumed saturated fat at or below the median intake level. Our results suggest that high lignan intake may increase the risk of adenoma recurrence in women and individuals with low saturated fat intake.

The association between lignans and their metabolites enterolactone and enterodiol in plasma and colorectal neoplasia has been mixed in human studies. In a Canadian case-control study, lignan consumption was inversely associated with colorectal cancer.[39] Similarly, in a Dutch endoscopy-based case-control study, plasma enterodiol, but not enterolactone, concentrations were inversely associated with incident colorectal adenoma risk.[40] However, the authors could not reproduce the inverse relationship between enterodiol and colorectal cancer risk in a subsequent nested case-control study.[41] Moreover, they reported, similar to our findings, a gender specific increased risk of colorectal cancer with high enterolactone concentrations in women.[41] In contrast, both Danish and English nested case-control studies reported that high plasma enterolactone concentrations decreased the risk of colorectal cancer in women[18,19]; however, similar to our results, lignan consumption tended to be associated with increased colorectal cancer risk in the English study.[18]

Dietary lignan sources partly explain the mixed results across different studies; for example, 88% of dietary lignans were from flaxseed in the Canadian study,[11] a food item that was rarely consumed in the 1990s in the U.S. Flaxseed is not only a good dietary source of lignans but also of omega-3 fatty acids, which may protect against colorectal tumorigenesis. In addition, diet composition, specifically dietary fiber and lipids, may impact the metabolism of plant lignans to the more bioactive enterolactone and enterodiol and, therefore the association between dietary lignans and colorectal carcinogenesis.[18,20] For example, lipid consumption (in particular the consumption of saturated fats) decreases the conversion of dietary plant lignans to enterolignans[6,20]; thus, enterolignan concentrations may be higher in individuals with a low saturated fat intake, which may partly explain why the detrimental effect of high lignan consumption on adenoma recurrence can only be observed in the low saturated fat intake group. Alternatively, the lignan to lipid ratio may influence cancer risk because lignans and lipids both alter the metabolism of steroid hormones,[6,21] which are involved in the etiology of colorectal tumorigenesis. Dietary lipids may modify the effect of dietary fibre, which is closely associated with lignan consumption,[6,20] on colorectal carcinogenesis, as has been demonstrated in animal models.[42–44] The gender difference in risk of colorectal neoplasms observed in this and other studies,[18,19,41] may be related to the ability of lignans to bind to estrogen receptors and thereby antagonizing endogenously synthesized estrogen[6,18,21] but there is some evidence to suggest that this may also increase proliferation of colonic epithelial cells.[2,45]

The number of human studies that have investigated the association between proanthocyanidin consumption and risk of colorectal neoplasms is limited. A Scottish and an Italian case-control study reported an inverse association between proanthocyanidin intake and colorectal cancer risk.[29,30] In contrast, a second Scottish case-control study, as well as the prospective Iowa Women's Health Study detected no association with colorectal cancer,[31,32] which is similar to our results. Variation in dietary proanthocyanidin sources (apples and tea in most studies), may partly explain differences in associations. We previously reported that increasing dry bean intake reduced the risk of advanced adenoma recurrence in the PPT.[46] Although proanthocyanidins have been considered for prevention and therapy of cancer,[28] high proanthocyanidin intake has risks and potentially pro-carcinogenic effects. Proanthocyanidins can inhibit the growth of the intestinal microbial flora, chelate minerals and thereby decrease their absorption, inhibit intestinal enzymes, and are toxic at high concentrations.[2,45] Other dietary components may also influence the association between proanthocyanidins, especially for polymeric proanthocyanidins, and cancer risk, as only monomeric, dimeric or trimeric proanthocyanidins are absorbed.[27] This is, to our knowledge, the first study to examine the association between consumption of proanthocyanidins and risk of colorectal adenomas. The association between consumption of proanthoycyanidins and risk of colorectal cancer may vary from the association with colorectal adenomas.

Strengths of our study include the prospective, annual collection of dietary data and the use of a questionnaire that was specifically designed to accurately estimate consumption of fibre, fruit and vegetables.[34,35] The immediate review of all questionnaires by registered dieticians further improved the accuracy of dietary data,[36] and validated proanthocyanidin and lignan databases were used to estimate proanthocyanidin and lignan intake.[8,10,26,37,38] Another major strength was the complete outcome surveillance, which included colonoscopies at baseline and at the end of T1 and T4 and independent, histological characterization of all colorectal lesions by two pathologists, which minimized outcome misclassification.

Limitations of this study include that the FFQ did not specifically ask about intake of sesame and flax seed, which are enriched in lignans and have shown a protective effect in Canadian studies.[8,11,39] The use of sesame and flax seed in the U.S. was low in the 1990s; thus, we cannot exclude the possibility that at higher intake levels, the associations might be different. In addition, the FFQ was not specifically developed and validated for estimating proanthocyanidin and lignan intake and several databases were used to estimate lignan intake; however, 58 of 65 food and beverage items were estimated from a single lignan database. These results from the PPT population, which had a history of adenomas,

were nearly exclusively Caucasians engaged in a relatively healthy lifestyle, and had a comparably low lignan intake (167 μg/day) compared to the European and Canadian studies (200–1000 μg/day),[18,20,39] may be limited in their generalizability. Use of dietary supplements rich in proanthocyanidins and lignans was low in the PPT and, thus, not included in the intake estimation, which may cause random and systematic misclassification of proanthocyanidin and lignan consumption.[47] Other potential sources of random and systematic misclassification relate to dietary assessment technique, proanthocyanidin and lignan databases, variations in food quantities of recipes or grouped foods, variability in lignan and proanthocyanidin content due to climatic, growing, soil and harvesting conditions of plants and storage and preparation conditions of foods. Furthermore, participants were aware of the expected dietary patterns and in 12% of participants T3 dietary data were obtained before an unscheduled colonoscopy used for assessing adenoma recurrence.

There might be concerns regarding the size of the population; however, a Monte-Carlo study indicated that we would have 99% and 96% power to detect small to moderate sized main effects for any recurrence and for an advanced recurrence, respectively. Observed differences might have arisen by chance because this is a secondary analysis, which included stratification into subgroups, and participants were not specifically assigned to a lignan or proanthocyanidin rich diet. However, the monotonic increase in ORs for adenoma recurrence with lignan intake in women and individuals that consumed saturated fat below or equal to 18.3 g/day in combination with the biological plausibility for such an association is unlikely due to chance and supports the assertion that, despite potential dietary measurement error, the study had sufficient statistical power and participants were ranked robustly enough to observe an association.

Conclusion

In conclusion, consumption of lignans or proanthocyanidins was not associated with colorectal adenoma recurrence overall. However, high lignan intake may increase the risk of any adenoma recurrence in women and in individuals with saturated fat intake below or equal to 18.3 g/day, which suggests gender and dietary fat may modify this association. Further studies are needed to examine the importance and biological role of lignans and proanthocyanidins in colorectal carcinogenesis.

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