Null Results in Brief

No Association between Fatty Acid Intake and Adenomatous Polyp Recurrence in the Polyp Prevention Trial

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Introduction

Dietary fat intake and cancer risk have been investigated in detail in many populations, although the results have been inconsistent for colorectal cancer. Several molecular mechanisms have been proposed to explain how specific dietary fatty acids could alter colorectal cancer risk due to their involvement in varying physiologic functions (1). These include apoptosis, inflammation, cell proliferation, metastasis, gene expression, signal transduction, altered estrogen metabolism, free radical production, and mechanisms related to insulin sensitivity. Most previous studies have examined the association for total fat intake, fat from animal sources, or intake of the major classes of fat (saturated, monounsaturated or polyunsaturated fat) on colorectal cancer risk. The aim of the current study was to assess the association between intake of specific fatty acids and adenoma recurrence to obtain a better understanding of the role of dietary fat and colorectal cancer risk. The fatty acids hypothesized to have an association a priori were the fish fatty acids (eicosapentanoic and docosahexanoic acid), linolenic acid, arachidonic acid, the n3:n6 ratio, saturated fat, and total fat intake.

Patients and Methods

Study Population. The Polyp Prevention Trial was a large multicenter, randomized, controlled trial of the effect of a low fat, high-fiber, high-fruit and -vegetable dietary intervention on the recurrence of large bowel adenomas. This study has been previously described in detail (2, 3). Briefly, subjects were $\geq$35 years and had one or more histologically confirmed adenomas removed during a colonoscopy done within 6 months of randomization. Study participants had no history of colorectal cancer, bowel resection, surgical resection of adenomas, polyposis syndrome, or inflammatory bowel disease. The Polyp Prevention Trial included 2,079 participants who were randomly assigned to either the intervention diet (n = 1,037) that was low in fat and high in fiber, fruit, and vegetables, or to the control group (n = 1,042) and followed their usual diet for 4 years.

Dietary Assessment. All participants (control and intervention) completed a 4-day food record at baseline (T0) and in conjunction with annual visits at the end of years 1, 2, 3, and 4. Trained, certified nutritionists reviewed all completed 4-day food records with the participants (2). A 20% sample of the 4-day food records were identified randomly with stratification by clinical center and were coded and analyzed immediately. The current analysis presents results from 372 participants who completed 4-day food records at all four time points, 181 were randomized to the intervention group and 191 to the control group.

Statistical Analysis. Odds ratios and 95% confidence intervals were estimated using logistic regression models with adenoma recurrence as the end point. Fatty acid intake (g/1,000 kcal) was treated categorically in tertiles and regression models were adjusted for age (continuous), gender (male/female), group (intervention/control), baseline nonsteroidal anti-inflammatory drug use (yes/no), body mass index (continuous), family history of colorectal cancer (yes/no), and an interaction term for group $\times$ gender. Tests for trend were done using the scores derived from the median of each tertile of fatty acid intake. Stratification of the models by group (intervention/control) did not alter the results. In addition, models without adjustments for group showed similar results.

Results and Discussion

Total fat intake at baseline and the average intake over the 4-year interval were not statistically significantly associated with adenoma recurrence. Total fat and individual fatty acid intakes were similar to those in previous studies that have examined the association with colorectal adenoma recurrence. Increasing total fat and saturated fat intake, calculated as the average of years 1, 2, and 3 (T1-T3), were not associated with a statistically significant increase in the odds of recurrence. Although a previous analysis (4) of a larger cohort from the Polyp Prevention Trial found a statistically significant decrease in risk of multiple adenomas and fish intake assessed by a food frequency questionnaire, we found no association of fish fatty acid intake (eicosapentaenoic acid plus docosahexanoic acid; T1-T3) and odds of recurrence. These results remained the same when the analysis was repeated for those with an end point of multiple adenomas. Although the average of four 4-day food records was used to assess dietary intake in this population, it should be noted that it is particularly challenging to assess fatty acid intake. Food composition databases may not accurately reflect the individual fatty acid content as the composition varies between brands and over time

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Table 1. Association among tertiles of total fat intake, total saturated fatty acid, total fish fatty acids, arachidonic acid, linolenic acid, and the *n*3:*n*6 ratio assessed using 4-day food diaries and recurrence of large bowel adenomas in the Polyp Prevention Trial (*n*= 372)

Tertile	Intake	Odds ratio* (95% confidence interval) for intake at baseline T0 (g/1,000 kcal)	*n*	Odds ratio* (95% confidence interval) for average intake, T1-T3 (g/1,000 kcal)	*n*
Total fat					
1	≤58.22	1.0	124	1.0	209
2	58.23-84.16	1.94 (1.13-3.32)	124	1.43 (0.79-2.60)	118
3	≥84.17	1.36 (0.78-2.37)	124	1.60 (0.77-3.32)	45
P_{trend}		0.28		0.15	
Saturated fatty acid					
1	≤18.99	1.0	124	1.0	217
2	19.00-27.45	1.60 (0.94-2.74)	124	1.27 (0.72-2.24)	98
3	≥27.46	1.24 (0.71-2.14)	124	1.87 (0.94-3.72)	57
P_{trend}		0.52		0.09	
Arachidonic acid					
1	≤0.10	1.0	124	1.0	143
2	0.11-0.15	1.14 (0.67-1.93)	124	0.88 (0.52-1.47)	140
3	≥0.16	0.88 (0.51-1.52)	124	1.26 (0.71-2.22)	89
P_{trend}		0.60		0.41	
Linolenic acid					
1	≤1.01	1.0	124	1.0	171
2	1.02-1.50	0.98 (0.58-1.66)	124	1.61 (0.97-2.67)	142
3	≥1.51	0.86 (0.51-1.47)	124	0.92 (0.48-1.78)	59
P_{trend}		0.57		0.87	
Fish fatty acids†					
1	≤0.03	1.0	124	1.0	95
2	0.04-0.10	1.05 (0.62-1.77)	124	0.67 (0.38-1.20)	142
3	≥0.11	0.74 (0.43-1.26)	124	0.69 (0.40-1.18)	59
P_{trend}		0.18		0.35	
*n*3:*n*6 ratio					
1	≤0.099	1.0	124	1.0	60
2	0.0994-0.12	1.24 (0.73-2.11)	124	0.65 (0.34-1.25)	121
3	≥0.121	0.97 (0.56-1.66)	124	0.76 (0.40-1.44)	191
P_{trend}		0.79		0.73	

Note: Baseline (T0) intakes used to develop cut points for tertiles of intake at T0 and T1-T3.
*Adjusted for age, group, gender, group × gender, baseline nonsteroidal anti-inflammatory drug use, body mass index (kg/m^2), and family history of colorectal cancer.
† Includes eicosapentanoic acid (C20:5) plus docosahexanoic acid (C22:6).

depending on the type of oil used to manufacture spreads and processed foods which may vary due to availability and production costs (5). A large variability in the *n*-3 fatty acid content between different species of fish adds to the complexity of assessing intake accurately. In addition, the presence of endogenously produced fatty acids and differences in fatty acid metabolism as well as other lifestyle factors increase the complexity of this relationship. Finally, it is possible that this study failed to observe a statistically significant association due to the small sample size. We did a Monte-Carlo study with 2,000 simulated data sets to evaluate the power to detect meaningful associations between the biomarkers and adenoma recurrence. Calculations were based on a sample size of n = 372 (an equal number in each of the three tertiles) and an assumed 30% recurrence in the lower tertile. With these assumptions, we would have 87% power to detect an odds ratio of 1.50 and 2.25 for the second and third tertiles, respectively, using a two-sided trend test conducted at the 0.05 significance level. Thus, with our sample size, we can be assured that there are no substantial trends (Table 1).

We anticipated that the 4-day food records, which would assess the amount and type of fat/oil used in food preparation and the specific type of oily fish eaten, would capture usual fatty acid intake as well as total and saturated fatty acid intake. We hypothesized that differences in intake of specific fatty acids would increase or decrease risk of adenoma recurrence, as underlying mechanisms regarding the possible role of specific fatty acids and colorectal cancer have been proposed (1, 6). However, our findings do not support this hypothesis.

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