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Approval Sheet

Dietary omega-3 fatty acids and risk of incident sporadic colorectal adenomas: Analysis of a case-control study

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Dietary omega-3 fatty acids and risk of incident sporadic colorectal adenomas: Analysis of a case-control study

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Master of Science in Clinical Research, 2009

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ABSTRACT

Dietary omega-3 fatty acids and risk of incident sporadic colorectal adenomas: Analysis of a case-control study

Ethan W. Tolbert, M.D.

Background: Omega-3 fatty acids may reduce colorectal carcinogenesis, but results from epidemiologic studies are inconsistent. We investigated associations of omega-3 fatty acids with risk of colorectal adenomas in a case-control study, and whether they were modified by nonsteroidal anti-inflammatory drug (NSAID) use.

Methods: The MAP I study was a community-, colonoscopy-based case-control study of colorectal adenomas. Participants aged 30 – 74 years with no history of colorectal neoplasms who had outpatient colonoscopy were recruited from gastroenterology practices from 1995 to 1997. The final sample included 177 incident sporadic adenoma cases and 228 controls. Prior to undergoing colonoscopy, participants completed questionnaires eliciting demographics, medical history, and dietary intake. Multivariate-adjusted odds ratios (OR) were calculated using logistic regression models.

Results: Cases were older, more often men, and did not regularly take NSAIDs. Higher levels of omega-3 fatty acids were associated with more than a doubling of risk of adenomas. In contrast, a higher ratio of omega-3 fatty acids to total fat was associated with a significant nearly halving of adenoma risk. Higher levels of fish were also significantly associated with decreased risk of adenoms (OR 0.37; 95% CI 0.20, 0.68; $p_{trend} = 0.01$). The direct associations of omega-3 fatty acids with adenoma was stronger in those with a family history of colorectal cancer (OR 3.6; 95% CI 1.06, 12.24), and those with low total fat intakes (OR 4.45; 95% CI 1.83, 10.82). The inverse associations of fish with adenoma were stronger in those with a family history of colorectal cancer (OR 0.20, 95% CI 0.03, 0.68).

Conclusions: In summary, we found statistically significant evidence for reduced risk of colorectal adenoma with higher intakes of fish. However, our findings for omega-3 fatty acid intakes were inconsistent, likely because intakes were homogeneous within the low end of the range of omega-3 fatty intake. Further study of fish and omega-3 fatty acid associations with incident, sporadic colorectal adenoma is indicated, especially in light of widespread use of supplemental omega-3 fatty acids by the general public.

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INTRODUCTION

Recent scientific advances have contributed to our understanding of the molecular basis of colorectal cancer. While genetic factors clearly play an important role in colorectal cancer etiology, dietary factors may be the driving force behind genetic alterations that lead to developing adenomatous polyps and ultimately colorectal cancer. Omega-3 polyunsaturated fatty acids (PUFAs) are postulated to reduce colorectal carcinogenesis through the inhibition of inflammatory pathways. In this analysis we examined the association between incident precancerous adenomatous polyps, as a surrogate for future development of colorectal cancer, and dietary intake of omega-3 PUFAs from a large U.S. case-control study.

BACKGROUND

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in the United States. In 2007, there were an estimated 147,500 new cases and 53,070 deaths from colorectal cancer (1). Incidence rates for the disease vary 20-fold around the world, with the highest rates in developed countries and the lowest in India (2). Colorectal cancer can be sporadic, familial or inherited. It is believed that colorectal cancer develops as the result of a progressive accumulation of genetic and epigenetic alterations that lead to the transformation of normal colonic epithelium to colon adenocarcinoma (3). Although genetic factors clearly play a pivotal role in colorectal cancer etiology, dietary factors may be the driving force behind genetic alterations that lead to development of precancerous, adenomatous polyps and ultimately colorectal cancer. Ecological and migrant studies indicate that environmental factors and other lifestyle factors greatly influence colorectal cancer risk (4). Evidence from analytical observational studies indicates that colon cancer is highly correlated with a Western-style diet characterized by lower intake of fruits and vegetables and higher intake of red and processed meats, refined grains, sugars, and fats (5-7). Though prior epidemiologic research (8) does not corroborate the association between total fat intake and colorectal cancer suggested by ecologic comparisons, polyunsaturated fatty acids (PUFAs) are of particular interest due to their potential role in inflammation-driven colorectal carcinogenesis.

Omega-3 PUFAs have been hypothesized to influence colorectal carcinogenesis through inhibiting cyclooxygenase 2, increasing apoptotic capacity, and reducing angiogenesis (9-

13). Experimental studies report anti-inflammatory and anti-carcinogenic effects in the colon for omega-3 PUFAs [eicosapentaenoic (EPA), docosahexaenoic (DHA), and alpha-linolenic (ALA) acid] highest in fish and seed oils, and adverse effects for omega-6 PUFAs, [linoleic (LA) and arachidonic (AA) acid] found in commercially popular oils and animal products (14-24). Prospective studies and relatively short-term clinical trials have shown that omega-3 fatty acids, particularly the long-chain or marine fatty acids (DHA and EPA), decrease both biomarkers of inflammation (25-27) and rectal cell proliferation (18-21). Such evidence, coupled with the efficacy of nonsteroidal anti-inflammatory drug (NSAIDs), strong COX inhibitors, to reduce risk of colorectal neoplasia (28-31) supports the promise for omega-3 PUFAs in the prevention of colorectal cancer through modulation of similar mechanisms. Inconsistent findings and differential associations for omega-3 fatty acids are apparent across both biomarker- (32-34) and dietary assessment- (35-39) based prospective studies.

Although current observational data is largely inconclusive, given promising experimental evidence, we examined the association between incident sporadic colorectal adenomas and dietary intake of omega-3 fatty acids, among men and women from a large U.S. case-control study. Possible interactions between omega-3 fatty acid consumption and related risk factors in relation to risk of adenoma were explored. We evaluated potential effect modification by NSAID use as such drugs may circumvent the upstream effects of fatty acids in the inflammatory pathway. We hypothesized *a priori* that a higher omega-3 intake would be associated with increased risk of incident sporadic

colorectal adenomas and we expected associations to be stronger in persons who did not take NSAIDs regularly.

METHODS

Study design

The Markers for Adenomatous Polyps I (MAPI) Study was a community- and colonoscopy-based case-control study originally designed to assess biomarkers of risk for colorectal adenomas. The following is a secondary analysis of the MAP I Study data. Participants in the study were recruited from referrals for elective colonoscopy to four large gastroenterology practices in Winston-Salem and Charlotte, North Carolina, from April 1995 to March 1997. English-speaking adults, 30–74 years of age, both male and female, of any ethnic group, and those capable of signing informed consent, were eligible to participate. Subjects were excluded if they had any of the following conditions: a personal history of colonic adenomas, familial adenomatous polyposis, Gardner's syndrome, ulcerative colitis, Crohn's disease, incident colorectal cancer, or a personal history of cancer other than non-melanoma skin cancer. Of the 2,246 participants who underwent colonoscopy, 669 (30 percent) were eligible to participate in the study. Of those eligible, 36 (2 percent) refused to participate, and 617 (98 percent) were offered participation in the study. Of these, 420 (68 percent) provided informed consent prior to colonoscopy. Fifteen participants were later excluded for excess missing data in the questionnaires or implausibly low (<500 kcal/day) or high (>6,000 kcal/day) self-reported total energy intake. The final sample included 405 participants (men: $n = 189$; women: $n = 216$), of whom 177 were incident sporadic adenoma cases (men: $n = 107$; women: $n = 70$) and 228 were controls (men: $n = 82$; women: $n = 146$) without

adenomas.

Prior to undergoing colonoscopy, participants completed mailed questionnaires eliciting self-reported demographics, medical history, anthropometrics (height and weight), and a previously validated adaptation of the Willett Food Frequency Questionnaire (153 items) expanded to include additional vegetables, fruits, and low-fat food items to assess dietary intake (40, 41). Participants were asked to quantify servings and types of fish consumed, as well as amounts, sources, and types of fat (saturated, polyunsaturated, and monounsaturated) consumed. Average daily nutrient intakes from dietary (*versus* supplemental) sources in the food frequency questionnaire were assessed as average daily intakes over the past twelve months. Dietary supplements were assessed by specific questions in the food frequency questionnaire regarding multivitamin use (type and frequency) as well as use of specific vitamin and mineral supplements including omega-3 fatty acids. Total nutrient intake was calculated as the sum of dietary and supplemental intakes. For non-aspirin, nonsteroidal antiinflammatory drug (NSAID) use, participants were asked whether they currently took an NSAID (defined as once a week or more) and, if so, how many years they had done so and how many days per week, on average, they took them.

Colonoscopy and pathology

Colonoscopy of all participants was performed in the usual manner. All polyps were removed and placed in individually labeled containers. Polyp characteristics, including

location (right *versus* left colon), shape, number per individual, and *in vitro* greatest diameter, were recorded. All pathology slides for polyp specimens were evaluated by one study index pathologist using standardized criteria from the National Polyp Study (42). Polyps were categorized as adenomas, hyperplastic polyps, or "other." Further characteristics of each adenoma were noted, including histologic type (villous, tubular, or tubulovillous) and degree of dysplasia (mild, moderate, or severe).

Statistical analysis

Cases included all participants with one or more histologically confirmed adenoma regardless of their number, shape, type, degree of dysplasia, or location. All participants who had no adenomas were included as controls. The control group included participants with hyperplastic and "other" polyps, as long as no adenomas were identified. The variable 'total omega-3' was calculated as the sum of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid (ALA) plus other dietary and supplemental sources of omega-3 PUFAs. Categorical variables for total omega-3 fatty acids (low, medium, and high) were used in all analyses. Cutpoints for tertiles of various fatty acids of interest were based on the sex-specific distributions among controls. NSAID use was defined as a "yes/no" variable for use of nonaspirin NSAIDs. Age- and sex-adjusted mean baseline characteristics for cases and controls were computed for continuous variables using analysis of covariance.

Comparisons of categorical variables were performed using the chi-square test of proportions. The odds ratio (OR) with 95 percent confidence interval was calculated as a measure of association of incident sporadic adenoma with various risk factors using standard logistic regression methods for case control studies. Effect modification was assessed by comparing stratum-specific ORs (for continuous variables, the potential effect modifier was divided into tertiles). Subsequently confounding factors were assessed. The criteria for inclusion of variables in the final models included biological plausibility, fit at the ≤ 0.10 level of significance, and/or evidence of confounding as indicated by the variable's effect on the association between the primary exposure variables and adenoma. The variables considered as potential covariates included age, sex, history of a first-degree relative (mother/father, sister/brother, or daughter/son) with colorectal cancer, total energy intake (kcal/day), smoking status (current, ever, or never), alcohol consumption per day (grams per day), regular use of nonaspirin NSAIDs, physical activity (calculated as metabolic equivalent (MET)-minutes/day), height, and weight. The dietary factors considered as potential confounders included daily intake of fiber, red meat, fruits/vegetables, calcium, and vitamin D. In order to determine the final model, multivariate logistic regression models were created with all possible combinations of potential confounders, with age, sex, family history of colorectal cancer, and total energy intake included in each model. Model diagnostics were then conducted by calculating and plotting Pearson's residuals to screen for violations of the normality and homoscedasticity assumptions. To confirm the final model, automated forward and backwards selection procedures were conducted. The variables retained as covariates in final logistic models were age, total energy intake, smoking status, red meat, and

fruits/vegetables. Models for each of the primary exposure variables (categorical variables for total omega-3 fatty acids, α-linolenic acid, EPA + DHA, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and total omega-3 fatty acids in ratio with total fat, saturated fat, monounsaturated fat, and polyunsaturated fat as well as a categorical variable for fish) were evaluated. Tests for trend were completed across tertiles of the primary exposure variables using the mean value at each exposure level to scale the tests.

RESULTS

Selected characteristics of the cases and controls are shown in Table 1. On average, cases were slightly older and were more likely to be men and not regularly take NSAIDs. Cases also tended to consume more alcohol and less calcium, but these differences were not statistically significant. The range of total omega-3 fatty acid intake in this study population was 0.04-2.03 grams per day with a mean value of 0.28 (SD 0.12) grams per day and a median of 0.24 grams per day. The range of fish intake was 0-21 servings per week with a mean value of 2.0 (SD 0.53) servings per week and a median of 2.5 servings per week.

Statistically significant associations of the primary exposure variables with risk of adenomas are presented in Table 2. Higher levels of omega-3 fatty acid consumption, either total or EPA + DHA, were associated with a more than doubling of risk of adenomas, for the highest versus the lowest levels of consumption. Conversely, consumption of a higher ratio of total omega-3 fatty acids to total fat was associated with a statistically significant nearly halving of risk for adenomas. Higher levels of fish consumption were also statistically significantly associated with decreased risk of adenomatous polyps; the multivariate adjusted odds ratio for those in the highest tertile of fish consumption was 0.37 (95% CI 0.20, 0.68; $p_{trend} = 0.01$). Associations for ALA, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, and adenomas were close to the null value and not statistically significant. Findings for the ratio of omega-3 fatty acids to various types of fat were similar to those for the ratio of omega-3 fatty acids to total fat.

Multivariate stratified analyses of omega-3 fatty acids, omega-3 fatty acids in ratio with total fat, and fish intake and risk of incident, sporadic colorectal adenoma according to age, sex, family history of colorectal cancer in a first-degree relative, NSAID use, and total fat are shown in Table 3a, 3b, and 3c respectively. The direct associations of total omega-3 fatty acids with adenoma tended to be stronger in men (OR 3.2; 95% CI 1.31, 7.87), those with a family history of colorectal cancer in a first-degree relative (OR 3.6; 95% CI 1.06, 12.24), and those with low total fat intakes (OR 4.45; 95% CI 1.83, 10.82). The inverse associations of total omega-3 fatty acids in ratio with total fat also tended to be stronger in those with a family history of colorectal cancer in a first degree relative (OR 0.21; 95% CI 0.06, 0.71). The inverse associations of fish with adenoma tended to be stronger in individuals 59 or older (OR 0.28; CI 0.10, 0.81), in males (OR 0.22; 95% CI 0.09, 0.57), in those with a family history of colorectal cancer in a first degree relative (OR 0.20, 95% CI 0.03, 0.68), and in those with low total fat intakes (OR 0.19; 95% CI 0.05, 0.43).

The multivariate associations between omega-3 fatty acids, omega-3 fatty acids in ratio with total fat, and fish intake and risk of incident, sporadic colorectal adenoma according to various adenoma subtypes are reported in Table 4a, 4b, and 4c respectively. The direct associations of total omega-3 fatty acids with adenomas tended to be stronger for multiple adenomas (OR 3.29; 95% CI 1.44, 7.50), and right sided adenomas (OR 3.40; 95% CI 1.47, 7.85). The inverse associations of total omega-3 fatty acids in ratio

with total fat also tended to be stronger in those with right sided colonic lesions (OR 0.40; 95% CI 0.19, 0.84), and those with villous or tubulovillous histology (OR 0.36; 95% CI 0.13, 1.03). The inverse associations of fish with adenoma tended to be stronger in individuals with only one adenoma (OR 0.33; CI 0.15, 0.71), in those with left colon lesions (OR 0.36; 95% CI 0.17, 0.75), in those with small (<1 cm in diameter) adenomas (OR 0.27, 95% CI 0.13, 0.56), and in those with tubular histology (OR 0.29; 95% CI 0.15, 0.56). Generally speaking, the pattern was consistent with increased risk of adenomatous polyps across all adenoma characteristics as more omega-3 fatty acids were consumed. The general trend also was for lower risk of adenomatous polyps across all adenoma characteristics for those individuals consuming a higher ratio of total omega-3 fatty acids to total fat and those consuming more fish.

DISCUSSION

Although we found strong evidence for decreased risk for incident sporadic colorectal adenomas, our findings for omega-3 fatty acids were internally inconsistent. On the one hand, our data suggested increased risk among those with higher omega-3 fatty acid intakes, especially among those with low total fat intakes; on the other hand, our data suggested decreased risk among those with a high omega-3 fatty acid to total fat intake ratio—findings that are clearly contradictory. A likely explanation for these findings for omega-3 fatty acids is that, with the very low intakes within a narrow range, categorization of participants into tertiles of intake based on a food frequency questionnaire may not have been valid and yielded very unstable, internally invalid results. On the other hand, there was a more substantial range of intakes of fish, and these results are likely internally valid.

Despite strongly supportive experimental data for EPA and DHA (15, 18-21), findings of associations of these omega-3 fatty acids with colorectal neoplasms in prospective studies have been inconsistent. Of the seven prospective studies deriving marine omega-3 intake from food frequency questionnaires, two found an inverse association (35, 37) while five found no association with colorectal cancer (33, 36, 39, 43) or adenoma (44). Two prospective studies that measured blood levels of marine omega-3 fatty acids found an inverse association with colorectal cancer in both sexes (32, 34). In our study, this may have been partly due to total omega-3 intake consisting primarily of ALA and not the marine fatty acids EPA and DHA. For our study population, the intake of long-chain

marine omega-3 fatty acids, the more bioavailable source of omega-3 fatty acids (49), was very low relative to other fats and the short chain omega-3 fatty acid, ALA.

Although experimental data (13, 25) have supported the potential protective effects of both short-chain and long-chain omega-3 fatty acids, epidemiologic studies have found inconsistent associations for ALA versus DHA and EPA (11, 32, 45). Two recent studies that investigated dietary ALA intake (45) and serum ALA levels (32) found a higher risk of colorectal cancer in women but a lower risk in men with higher ALA. In our study we found an increased risk of adenomas in both men and women that appeared to be somewhat stronger in men. The potentially inefficient metabolic conversion of nutritionally essential ALA to long chain omega-3 fatty acids (46) coupled with the absence of "healthier" food sources rich in ALA, such as flax, on the FFQ may make it more difficult to evaluate the associations with ALA. More research is needed to determine whether there are differential effects of long-chain and short-chain omega-3 fatty acids in humans, particularly since ALA is currently marketed as a healthy source of omega-3 fatty acids to reduce the risk of heart disease and some cancers including colon cancer.

The typical Western diet contains 10-20 times more omega-6 than omega-3 polyunsaturated fatty acids. However, evidence suggests that human beings evolved on a diet with nearly a one to one ratio (8). Ecologic comparisons and experimental evidence suggest that a high omega-6 to omega-3 ratio is associated with increased risk of colorectal cancer via proinflammatory and procarcinogenic mechanisms (11, 16).

Current recommendations suggest an "optimal range" of 1-4:1 to an "acceptable range" of 1-8:1 (4, 8). In our analysis, we investigated the ratio of total omega-3 fatty acids to total fat intake and found an approximate 40% lower risk (OR 0.58; 95% CI 0.33, 1.00) for those in the upper tertile—a finding that was stronger among those who had a family history of colorectal cancer in a first-degree relative (OR 0.21, 95% CI 0.06, 0.71, $p_{trend} = 0.05$), or those who were regularly taking NSAIDs (OR 0.24, 95% CI 0.03, 0.59, $p_{trend} = 0.10$). This decrease in risk may be related to lower total fat intake in individuals in the highest tertile of omega-3 to total fat ratio rather than any direct protective effect of omega-3 fatty acids, a finding that corroborates the association between total fat intake and colorectal cancer suggested by ecologic comparisons (4, 6, 7).

Despite evidence for COX-2 as a key target in colorectal cancer prevention and promising findings in NSAID intervention trials (28-31, 47), anti-inflammatory drugs are not currently recommended to the general population for the prevention of colorectal cancer due to the potential risk of other adverse health effects (48, 49). However, omega-3 fatty acids may share a potential mechanism with NSAIDs to lower the risk of colorectal cancer by inhibiting the production of pro-inflammatory cytokines through cyclooxygenase. We hypothesized that if omega-3 fatty acids decrease risk of adenoma via decreasing inflammation, their associations with adenoma formation would be masked in those taking NSAIDs on a regular basis (*ie.*, we hypothesized that the associations of omega-3 fatty acids with adenomas would be more strongly inverse among those not taking NSAIDS on a regular basis). In contrast, our findings suggest that dietary intake of omega-3 fatty acids may increase the risk of colorectal adenomas

among both NSAID users and non-users. Interactions with NSAID use were not statistically significant. These findings suggest that beyond inflammatory signaling, dietary omega-3 fatty acids in their various forms and their metabolites may influence carcinogenesis either favorably or unfavorably through several other mechanisms yet to be fully investigated in human epidemiologic studies. They may modulate transcription factor activity, gene expression, signal transduction pathways, estrogen metabolism, lipid peroxidation, insulin sensitivity, and membrane permeability with subsequent effects on immunity, cell growth, differentiation, apotosis, angiogenesis, and metastasis (10-12).

Case-control and experimental studies have consistently indicated that there may be an inverse relationship between fish consumption and colorectal adenoma, particularly in women (50-52). In addition, findings from a recent meta-analysis of prospective cohort studies also found a moderate inverse association for fish intake in women (pooled RR: 0.78; 95% CI: 0.58-1.06), but a decidedly null association in men (53). In contrast to our findings for omega-3 fatty acids, associations of fish intake with adenomas were similar across age groups, both sexes, those with and without a family history of colorectal cancer, and those who did or did not regularly take an NSAID; however, the inverse association did appear substantially stronger among those with lower total fat intakes than with higher total fat intakes. This contradiction may point to the difficulty in accurately assessing nutrient intake such as omega-3 fatty acids and dietary intake of items such as fish from food frequency questionnaires. Also, the low total intake of marine omega-3 fatty acids in this study population from central North Carolina indicates a lower

consumption of species of cold water, fatty fish high in marine omega-3 fatty acids such as salmon or mackerel.

Strengths of our study included: all self-reported information was determined before case-control status was known, minimizing recall bias; detailed and specific questions on all dietary components including types and amount of fat intake were included from the food-frequency questionnaire to minimize measurement error; and both cases and controls had complete evaluation of their colon which minimizes selection bias and type 2 error.

The study has several important limitations. All dietary epidemiologic studies face difficulty in accurately measuring dietary consumption. In this study this would include omega-3 fatty acids, total fat, and fish intake using self-reported measures. Also, the study was done before the widespread availability or consumption of supplemental omega-3 fatty acids. Only one individual in the study indicated that they consumed omega-3 fatty acids as a dietary supplement. This resulted in low overall consumption of total omega-3 fatty acids across both cases and controls, leading to homogeneity of exposure, as reflected in the range, mean, and median of total omega-3 and fish intake, that may have made it difficult to detect a true association. Also, the association that was estimated may have been unstable or spurious as a result. This led to somewhat contradictory findings where the group with the highest omega-3 consumption was associated with the highest risk of adenoma, especially in total fat group; whereas, a high omega-3 to total fat ratio was associated with decreased risk in the low total fat group.

Other limitations included the potential for recall bias associated with food-frequency questionnaires. Community- and colonoscopy-based, case-control studies of colorectal adenoma also have methodological limitations inherent in their design. These include selection bias through selection of controls from among potentially symptomatic individuals referred for colonoscopy who may be at higher risk for colorectal neoplasms than the general population. In the context of omega-3 exposure, this could result in controls being more similar to cases, leading to an underestimate of the true risk of adenoma. In contrast, a strength of this investigation is that controls were selected from the population that gave rise to the cases, and the potential for differential reporting bias was limited by obtaining self-reports of exposure prior to colonoscopy and the diagnosis of adenoma. Finally the study population was 90% white, limiting the generalizability of the findings, and, given the multiple comparisons and the relatively small sample size, any associations stratified by risk factors or for associations with various adenoma characteristics should be interpreted cautiously.

In summary, consistent with other epidemiologic studies, we found statistically significant evidence for reduced risk for colorectal adenoma with higher intakes of fish. However, our findings for omega-3 fatty acid intakes were internally inconsistent and were thought to be invalid, likely because only one participant in the study took omega-3 fatty acid supplements, and dietary intakes were homogeneous within the very low end of the range of omega-3 fatty intakes that humans across the US and world consume, thus prohibiting valid, stable categorization of intakes. Further study of fish and omega-3

fatty acid intakes and their associations with incident, sporadic colorectal adenoma is indicated, especially in light of the now widespread use of supplemental omega-3 fatty acids by the general public.

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Table 1. Selected characteristics of participants, Markers of Adenomatous Polyps I Study

Characteristics	Cases (n = 177)*†	Controls (n = 228)*†	χ^2	p-value‡
Demographics				
Age (years)	58.6(0.6)	56.1(0.7)		0.02
Female (%)	39	64	25	<0.0001
White (%)	89	90	1.2	0.55
Lifestyle Factors				
Daily alcohol use (g/day)	7.6(1.1)	3.5(0.6)		0.15 ¶
Use NSAIDs § (%)	20	30	5.5	0.02
Hormone replacement therapy (%)	64	56	1.1	0.59
Dietary Factors				
Total calcium (mg/day)	750(31)	824(30)		0.08 ¶
Total vitamin D intake (IU/day)	314(19)	345(20)		0.34 ¶
Dietary vitamin D	206(9)	201(8)		0.76 ¶
Supplemental vitamin D	108(17)	143(17)		0.30 ¶
Dietary fiber intake (g/day)	23(0.7)	24(0.7)		0.23 ¶
Total fat intake (g/day)	72(3)	67(2)		0.81 ¶
Saturated fat intake (g/day)	24(1.1)	22(0.7)		0.78 ¶
Red meat intake (servings/day)	5(0.5)	4(0.2)		0.32 ¶
Fruits and vegetables (servings/day)	6.3(0.3)	6.5(0.3)		0.71 ¶
Total energy intake (kcal/day)	2043(61)	1997(52)		0.67 ¶
Total omega-3 fatty acids (g/day)	0.2(0.01)	0.3(0.03)		0.35 ¶
Polyunsaturated fat (g/day)	13.6(0.5)	14.3(0.8)		0.46
Fish (servings/week)	2.1(0.1)	2.6(0.4)		0.35

* Unless otherwise indicated, values are mean (standard error).
† Continuous variables are adjusted for age and sex. Age is adjusted for sex.
‡ Analysis of covariance for continuous variables and chi-square test of proportions for categorical variables.
§ NSAIDs, regular use of nonsteroidal antiinflammatory drugs, excluding aspirin.
¶ p-value for the transformed dietary variable comparisons.

Table 2. Associations of total omega-3 fatty acids, marine fatty acids (EPA & DHA), α-linolenic acid (ALA), total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and omega-3 fatty acids in ratio with total fat, saturated fat, monounsaturated fat, and polyunsaturated fat, and the dietary variable fish with incident sporadic colorectal adenomas.

Risk factors*	Crude Associations		Multivariate associations†	
	OR	95% CI‡	OR	95% CI‡
Total omega-3 fatty acids (gm)				
Low	1.00		1.00	
Medium	1.52	0.91, 2.53	1.33	0.78, 2.27
High	1.65	0.99, 2.76	2.38	1.32, 4.27
p_{trend}	*0.75*		*0.16*	
EPA + DHA (gm)§				
Low	1.00		1.00	
Medium	1.39	0.85, 2.28	1.54	0.91, 2.62
High	1.62	0.99, 2.67	2.21	1.24, 3.94
p_{trend}	*0.60*		*0.22*	
α-Linolenic acid (ALA) (gm)				
Low	1.00		1.00	
Medium	0.89	0.54, 1.46	0.96	0.57, 1.63
High	1.04	0.63, 1.71	1.07	0.57, 2.01
p_{trend}	*0.54*		*0.66*	
Total fat (gm)				
Low	1.00		1.00	
Medium	1.38	0.84, 2.27	1.02	0.55, 1.92
High	1.39	0.84, 2.29	1.13	0.65, 1.96
p_{trend}	*0.98*		*0.35*	
Saturated fat (gm)				
Low	1.00		1.00	
Medium	1.21	0.74, 1.99	1.00	0.59, 1.71
High	1.25	0.76, 2.07	1.26	0.68, 2.32
p_{trend}	*0.90*		*0.14*	
Monounsaturated fat (gm)				
Low	1.00		1.00	
Medium	1.37	0.83, 2.26	1.21	0.70, 2.08
High	1.29	0.78, 2.12	1.08	0.58, 2.00
p_{trend}	*0.81*		*0.27*	
Polyunsaturated fat (gm)				
Low	1.00		1.00	
Medium	1.04	0.63, 1.72	0.72	0.42, 1.23
High	0.98	0.59, 1.62	1.03	0.60, 1.77
p_{trend}	*0.80*		*0.10*	

Total omega-3/total fat				
Low	1.00		1.00	
Medium	0.75	0.46, 1.24	0.68	0.40, 1.16
High	0.63	0.38, 1.04	0.58	0.33, 1.00
p_{trend}	*0.48*		*0.37*	
Total omega-3/ saturated fat				
Low	1.00		1.00	
Medium	0.71	0.43, 1.18	0.66	0.39, 1.12
High	0.60	0.37, 1.00	0.54	0.30, 0.94
p_{trend}	*0.52*		*0.29*	
Total omega-3/ monounsaturated fat				
Low	1.00		1.00	
Medium	0.65	0.39, 1.07	0.62	0.37, 1.06
High	0.59	0.36, 0.98	0.57	0.33, 0.99
p_{trend}	*0.72*		*0.20*	
Total omega-3/ polyunsaturated fat				
Low	1.00		1.00	
Medium	0.58	0.35, 0.96	0.53	0.31, 0.90
High	0.68	0.41, 1.13	0.59	0.34, 1.02
p_{trend}	*0.54*		*0.01*	
Fish (servings/week)				
Low	1.00		1.00	
Medium	0.58	0.37, 0.94	0.64	0.38, 1.10
High	0.52	0.32, 0.83	0.37	0.20, 0.68
p_{trend}	*0.02*		*0.01*	

* Tertiles for all risk factors based on sex-specific distributions in controls.
† Covariates for all models include: age, total energy intake, smoking status, red meat consumption, and total fruits and vegetable consumption.
‡ CI, confidence interval.
§ EPA, Eicosapentaenoic acid, DHA, Docosahexaenoic acid.

Table 3a. Multivariate-adjusted, stratified associations* of omega-3 fatty acids with risk of incident, sporadic colorectal adenoma according to levels of other selected risk factors.

Risk Factors	Total omega-3 fatty acids						
	n cases/ controls	Low OR (referent)	n cases/ controls	Medium OR (95% CI)	n cases/ controls	High OR (95% CI)	p_{trend}
Age†							
<59	24/44	1.00	27/44	1.32 (0.62, 2.79)	37/38	2.59 (1.16, 5.79)	*0.10*
≥59	28/39	1.00	31/35	1.33 (0.59, 2.99)	30/28	2.14 (0.87, 5.29)	*0.52*
Sex							
Male	31/32	1.00	30/28	1.23 (0.54, 2.80)	43/20	3.20 (1.31, 7.87)	*0.06*
Female	20/52	1.00	25/51	1.54 (0.68, 3.52)	28/45	2.47 (1.00, 6.14)	*0.33*
Family history‡							
No	44/51	1.00	47/50	1.38 (0.73, 2.62)	51/46	2.05 (1.02, 4.10)	*0.49*
Yes	9/29	1.00	11/34	1.10 (0.35, 3.51)	15/18	3.60 (1.06, 12.24)	*0.05*
Use of NSAIDs§							
No	50/58	1.00	44/51	1.72 (0.53 2.04)	50/51	2.67 (1.38, 3.76)	*0.60*
Yes	4/25	1.00	13/28	1.09 (0.59, 4.04)	16/15	2.49 (0.78, 6.41)	*0.41*
Total fat intake¶							
Low	30/51	1.00	33/35	2.29 (1.07, 4.90)	31/20	4.45 (1.83, 10.82)	*0.03*
High	25/34	1.00	25/45	0.80 (0.36, 1.76)	33/43	1.15 (0.50, 2.62)	*0.65*

*Odds ratios adjusted for age, total energy intake (kcal), smoking history, red meat consumption, total fruit and vegetable consumption (less the stratifying factor).
† Age categories based on median age in the controls.
‡ Family history of colorectal cancer in a first-degree relative.
§ Use of nonsteroidal anti-inflammatory drugs at least once per week.
¶ Sex-specific tertile ranges for total fat intake (g/day) among controls.

Table 3b. Multivariate-adjusted, stratified associations* of omega-3 fatty acids in ratio with total fat with risk of incident, sporadic colorectal adenoma according to levels of other selected risk factors.

Risk Factors	Total omega-3 fatty acids/total fat						
	n cases/ controls	Low OR (referent)	n cases/ controls	Medium OR (95% CI)	n cases/ controls	High OR (95% CI)	p_{trend}
Age†							
<59	29/44	1.00	30/42	0.89 (0.43, 1.83)	35/39	0.53 (0.25, 1.10)	*0.60*
≥59	25/41	1.00	29/31	0.49 (0.22, 1.10)	29/31	0.49 (0.21, 1.14)	*0.35*
Sex							
Male	29/35	1.00	38/23	0.39 (0.18, 0.86)	39/23	0.50 (0.23, 1.08)	*0.08*
Female	23/49	1.00	23/51	1.05 (0.48, 2.31)	25/47	0.48 (0.21, 1.10)	*0.77*
Family history‡							
No	43/50	1.00	50/47	0.64 (0.35, 1.19)	47/50	0.67 (0.35, 1.26)	*0.76*
Yes	9/34	1.00	11/26	0.68 (0.18, 2.58)	17/21	0.21 (0.06, 0.71)	*0.05*
Use of NSAIDs§							
No	46/59	1.00	45/51	0.72 (0.39, 1.33)	48/49	0.64 (0.34, 1.18)	*0.66*
Yes	7/25	1.00	15/22	0.33 (0.08, 1.28)	16/22	0.24 (0.03, 0.59)	*0.10*
Total fat intake¶							
Low	32/55	1.00	35/33	0.43 (0.21, 0.89)	22/18	0.41 (0.13, 0.73)	*0.79*
High	21/32	1.00	26/39	0.91 (0.53, 1.32)	41/51	0.86 (0.40, 1.86)	*0.64*

* Odds ratios adjusted for age, total energy intake (kcal), smoking history, red meat consumption, total fruit and vegetable consumption (less the stratifying factor).
† Age categories based on median age in the controls.
‡ Family history of colorectal cancer in a first-degree relative.
§ Use of nonsteroidal anti-inflammatory drugs at least once per week.
¶ Sex-specific tertile ranges for total fat intake (g/day) among controls

Table 3c. Multivariate-adjusted, stratified associations* of fish intake with risk of incident, sporadic colorectal adenoma according to levels of other selected risk factors.

Risk Factors	Fish						
	n cases/ controls	Low OR (referent)	n cases/ controls	Medium OR (95% CI)	n cases/ controls	High OR (95% CI)	p_{trend}
Age†							
<59	21/39	1.00	39/48	0.49 (0.23, 1.03)	33/38	0.31 (0.13, 0.73)	*0.31*
≥59	15/31	1.00	38/43	0.54 (0.22, 1.30)	31/29	0.28 (0.10, 0.81)	*0.03*
Sex							
Male	23/32	1.00	43/31	0.42 (0.19, 0.94)	41/19	0.22 (0.09, 0.57)	*0.02*
Female	13/38	1.00	34/67	0.62 (0.26, 1.47)	23/41	0.33 (0.12, 0.92)	*0.34*
Family history‡							
No	29/45	1.00	63/58	0.52 (0.27, 0.99)	50/44	0.38 (0.18, 0.80)	*0.13*
Yes	7/25	1.00	14/40	0.56 (0.15, 2.14)	14/16	0.20 (0.03, 0.68)	*0.04*
Use of NSAIDs§							
No	29/46	1.00	60/71	0.62 (0.33, 1.18)	51/43	0.38 (0.18, 0.78)	*0.12*
Yes	7/20	1.00	15/28	0.38 (0.10, 1.45)	15/20	0.23 (0.03, 0.62)	*0.20*
Total fat intake¶							
Low	15/33	1.00	46/53	0.39 (0.17, 0.92)	29/18	0.19 (0.05, 0.43)	*0.01*
High	21/37	1.00	31/45	0.73 (0.33, 1.63)	35/42	0.52 (0.22, 1.25)	*0.50*

* Odds ratios adjusted for age, total energy intake (kcal), smoking history, red meat consumption, total fruit and vegetable consumption (less the stratifying factor).
† Age categories based on median age in the controls.
‡ Family history of colorectal cancer in a first-degree relative.
§ Use of nonsteroidal anti-inflammatory drugs at least once per week.
¶ Sex-specific tertile ranges for total fat intake (g/day) among controls

Table 4a. Multivariate-adjusted, stratified associations* of omega-3 fatty acids with risk of incident, sporadic colorectal adenoma according to selected adenoma characteristics.

Adenoma Characteristics	Total omega-3 fatty acids						
	n cases/ controls	Low OR (referent) †	n cases/ controls	Medium OR (95% CI) ‡	n cases/ controls	High OR (95% CI)	p_{trend}
Number of adenomas							
1	33/83	1.00	34/80	1.36 (0.72, 2.55)	36/65	1.92 (0.96, 3.85)	*0.30*
>1	25/83	1.00	22/80	1.46 (0.67, 3.19)	27/65	3.29 (1.44, 7.50)	*0.29*
Site of largest adenoma§							
Right colon	21/83	1.00	16/80	1.24 (0.57, 2.71)	25/65	3.40 (1.47, 7.85)	*0.16*
Left colon	36/83	1.00	40/80	1.42 (0.77, 2.61)	39/65	2.00 (1.03, 3.87)	*0.26*
Size of largest adenoma¶							
< 1cm	36/83	1.00	42/80	1.68 (0.94, 3.02)	38/65	2.21 (1.14, 4.26)	*0.25*
≥ 1cm	21/83	1.00	13/80	0.83 (0.35, 1.99)	27/65	2.72 (1.18, 6.27)	*0.03*
Subtype of largest adenoma							
Tubular	41/83	1.00	45/80	1.53 (0.88, 2.67)	55/65	2.51 (1.37, 4.60)	*0.09*
Villous/tubulovillous	12/83	1.00	8/80	1.05 (0.35, 3.15)	16/65	3.49 (1.23, 9.94)	*0.12*
Degree dysplasia of largest adenoma							
Mild	31/83	1.00	36/80	1.53 (0.88, 2.67)	42/65	2.51 (1.37, 4.60)	*0.12*
> Mild	24/83	1.00	20/80	1.08 (0.49, 2.36)	24/65	2.43 (1.06, 5.54)	*0.51*

* Adjusted for age, total energy intake, smoking status, red meat consumption, and total fruit and vegetable intake
† Odds ratio.
‡ Ninety-five percent confidence interval.
§ Right colon is defined as the cecum, ascending colon, hepatic flexure, and transverse colon. Left colon is defined as the splenic flexure, descending colon, sigmoid colon, and rectum.
¶ Size measured as the greatest in vivo diameter.

Table 4b. Multivariate-adjusted, stratified associations* of omega-3 fatty acids in ratio with total fat with risk of incident, sporadic colorectal adenoma according to selected adenoma characteristics.

Adenoma Characteristics	Total omega-3 fatty acids/total fat						
	n cases/ controls	Low OR (referent) †	n cases/ controls	Medium OR (95% CI) ‡	n cases/ controls	High OR (95% CI)	p_{trend}
Number of adenomas							
1	37/84	1.00	30/73	0.89 (0.48, 1.64)	36/71	0.65 (0.35, 1.21)	*0.65*
>1	21/84	1.00	29/73	0.50 (0.24, 1.02)	24/71	0.56 (0.26, 1.20)	*0.17*
Site of largest adenoma§							
Right colon	18/84	1.00	15/73	0.75 (0.34, 1.66)	25/71	0.40 (0.19, 0.84)	*0.10*
Left colon	37/84	1.00	44/73	0.63 (0.36, 1.11)	38/71	0.67 (0.37, 1.24)	*0.32*
Size of largest adenoma¶							
< 1cm	38/84	1.00	42/73	0.73 (0.41, 1.29)	44/71	0.56 (0.31, 1.00)	*0.37*
≥ 1cm	17/84	1.00	16/73	0.50 (0.23, 1.09)	20/71	0.59 (0.27, 1.33)	*0.49*
Subtype of largest adenoma							
Tubular	45/84	1.00	47/73	0.62 (0.36, 1.06)	53/71	0.56 (0.32, 0.97)	*0.22*
Villous/tubulovillous	9/84	1.00	9/73	0.44 (0.16, 1.21)	14/71	0.36 (0.13, 1.03)	*0.35*
Degree dysplasia of largest adenoma							
Mild	33/84	1.00	34/73	0.73 (0.40, 1.36)	40/71	0.56 (0.30, 1.05)	*0.40*
> Mild	23/84	1.00	25/73	0.61 (0.30, 1.26)	22/71	0.66 (0.31, 1.41)	*0.62*

* Adjusted for age, total energy intake, smoking status, red meat consumption, and total fruit and vegetable intake
† Odds ratio.
‡ Ninety-five percent confidence interval.
§ Right colon is defined as the cecum, ascending colon, hepatic flexure, and transverse colon. Left colon is defined as the splenic flexure, descending colon, sigmoid colon, and rectum.
¶ Size measured as the greatest in vivo diameter.

Table 4c. Multivariate-adjusted, stratified associations* of fish intake with risk of incident, sporadic colorectal adenoma according to selected adenoma characteristics.

Adenoma Characteristics	Fish						
	n cases/ controls	Low OR (referent) †	n cases/ controls	Medium OR (95% CI) ‡	n cases/ controls	High OR (95% CI)	p_{trend}
Number of adenomas							
1	21/70	1.00	47/98	0.43 (0.22, 0.84)	38/60	0.33 (0.15, 0.71)	*0.05*
>1	16/70	1.00	28/98	0.71 (0.34, 1.50)	27/60	0.33 (0.14, 0.78)	*0.16*
Site of largest adenoma§							
Right colon	16/70	1.00	22/98	0.72 (0.33, 1.57)	24/60	0.25 (0.10, 0.60)	*0.20*
Left colon	22/70	1.00	51/98	0.47 (0.25, 0.88)	42/60	0.36 (0.17, 0.75)	*0.03*
Size of largest adenoma¶							
< 1cm	22/70	1.00	52/98	0.45 (0.24, 0.84)	44/60	0.27 (0.13, 0.56)	*0.02*
≥ 1cm	16/70	1.00	21/98	0.84 (0.39, 1.82)	22/60	0.44 (0.18, 1.06)	*0.30*
Subtype of largest adenoma							
Tubular	30/70	1.00	52/98	0.49 (0.27, 0.87)	59/60	0.29 (0.15, 0.56)	*0.01*
Villous/tubulovillous	8/70	1.00	14/98	0.58 (0.21, 1.62)	14/60	0.33 (0.11, 1.05)	*0.30*
Degree dysplasia of largest adenoma							
Mild	19/70	1.00	45/98	0.52 (0.27, 1.02)	39/60	0.51 (0.15, 0.66)	*0.33*
> Mild	15/70	1.00	26/98	0.52 (0.27, 1.02)	33/60	0.31 (0.15, 0.66)	*0.32*

* Adjusted for age, total energy intake, smoking status, red meat consumption, and total fruit and vegetable intake
† Odds ratio.
‡ Ninety-five percent confidence interval.
§ Right colon is defined as the cecum, ascending colon, hepatic flexure, and transverse colon. Left colon is defined as the splenic flexure, descending colon, sigmoid colon, and rectum.
¶ Size measured as the greatest in vivo diameter.