Dietary Intake of \( \omega-6 \) and \( \omega-3 \) Fatty Acids and Risk of Colorectal Cancer in a Prospective Cohort of U.S. Men and Women

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Abstract

Background: \( \omega-6 \) and \( \omega-3 \) polyunsaturated fatty acids intakes may play opposing roles in inflammation-driven colorectal carcinogenesis. We examined the relationship of these polyunsaturated fatty acids and the ratio of their intake with colorectal cancer risk in a large U.S. prospective cohort.

Design: Participants in the Cancer Prevention Study-II Nutrition Cohort completed a detailed questionnaire on diet, medical history, and lifestyle in 1999. Between 1999 and 2005, 869 incident colorectal cancer cases (452 men and 417 women) were identified among 99,080 participants (43,108 men and 55,972 women). Multivariate-adjusted rate ratios were calculated using Cox proportional hazards models.

Results: The ratio of total \( \omega-6 \) to total \( \omega-3 \) intake was not associated with colorectal cancer risk in either sex. Contrary to our initial hypothesis, total \( \omega-6 \) intake was inversely related to colorectal cancer risk in men [multivariate relative risk (95% confidence interval) for highest to lowest quartile, 0.81 (0.61-1.07); \( P_{\text{trend}} = 0.07 \)], and \( \omega-3 \)-linolenic acid, the primary contributor to total \( \omega-3 \) intake, was associated with increased risk in women for quartiles 2 through 4 versus the lowest quartile [relative risk (95% confidence interval), 1.50 (1.12-2.01), 1.40 (1.04-1.87), and 1.38 (1.02-1.85), respectively; \( P_{\text{trend}} = 0.13 \)]. In women, total \( \omega-6 \) and marine \( \omega-3 \) intake appeared to be associated with higher and lower risk, respectively, but associations were attenuated with adjustment for other risk factors.

Conclusions: The ratio of \( \omega-6 \) to \( \omega-3 \) intake was not related to colorectal cancer risk in this cohort, which may be due to unexpected findings for the individual components. Differential associations by sex warrant further investigation. (Cancer Epidemiol Biomarkers Prev 2009;18(2):516–25)

Introduction

Colorectal cancer, the third most common cancer in U.S. men and women, is highly correlated with western-style diet characterized by a constellation of dietary components including lower intakes of fruit and vegetables and higher intakes of red and processed meats, refined grains, sugars, fats, and a higher ratio of \( \omega-6 \) to \( \omega-3 \) fatty acids (1-4). Although collective epidemiologic research (5) does not corroborate the relationship between total fat intake and colorectal cancer suggested by ecologic comparisons, polyunsaturated fatty acids (PUFA) are of particular interest due to their potential role in inflammation-driven colorectal carcinogenesis. Experimental studies report anti-inflammatory and anticarcinogenic effects in the colon for \( \omega-3 \) PUFA s [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and \( \omega-3 \)-linolenic acid (ALA)], highest in fish and seed oils, and adverse effects for \( \omega-6 \) PUFA s [linoleic acid (LA) and arachidonic acid (AA)] found in commercially popular oils and animal products (6-17). Despite evidence supporting the \( \omega-6 \) to \( \omega-3 \) ratio as a biologically plausible target (9, 14, 16, 18-20), most epidemiologic studies have generally not found an association with colorectal cancer (21) and very few have been of prospective design (22, 23).

Numerous mechanisms have been proposed for the role of fatty acids in carcinogenesis and include modulation of immunity, inflammation, and cell signaling (17, 20). Lowering the \( \omega-6 \) to \( \omega-3 \) ratio is hypothesized to reduce the risk of colorectal cancer, because \( \omega-3 \) fatty acids inhibit the production of proinflammatory, \( \omega-6 \)-derived eicosanoids via the cyclooxygenase-2 enzyme (17, 18, 20, 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 (7, 10-13). Such evidence, coupled with the efficacy of nonsteroidal anti-inflammatory drug (NSAID), strong cyclooxygenase inhibitors, to reduce the risk of colorectal neoplasia (28-31), supports the promise for marine \( \omega-3 \) PUFA s in the prevention of colorectal cancer through modulation of similar mechanisms. A recent meta-analysis of prospective cohort studies investigating fish consumption and risk of colorectal cancer reported a moderately lower risk overall [pooled relative risk (RR), 0.88; 95% confidence interval (95% CI), 0.78-1.00] but stronger inverse associations...
in women and in persons consuming fish more than seven times per month (32). Inconsistent findings and differential associations by sex for both ω-6 and ω-3 fatty acids are apparent across both biomarker-based (33-35) and dietary assessment-based (22, 36-40) prospective studies.

With promising experimental evidence but current observational data largely inconclusive, we examined the association between colorectal cancer incidence and dietary intake of ω-6 and ω-3 fatty acids, both separately and in relation to one another with a ratio, among men and women from a large U.S. prospective cohort. To our knowledge, no large U.S. prospective cohort composed of both men and women has comprehensively evaluated these relationships. 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 ratio of ω-6 to ω-3 intake would be associated with increased risk of colorectal cancer and we expected associations to be stronger in persons who did not take NSAIDs regularly.

Materials and Methods

Study Cohort. Men and women in this analysis were drawn from participants in the Cancer Prevention Study (CPS)-II Nutrition Cohort, a prospective study of cancer incidence and mortality in the United States established in 1992 and described in detail elsewhere (41). At enrollment, participants completed a mailed self-administered questionnaire including information on demographic, medical, diet, and lifestyle factors. Follow-up questionnaires to update exposure information and to ascertain newly diagnosed cancers were sent in 1997, 1999, 2001, 2003, and 2005. Reported cancers were verified through medical records, registry linkage, or death certificates. The response rate for each follow-up questionnaire was at least 88%. The Emory University Institutional Review Board approves all aspects of the CPS-II Nutrition Cohort.

Follow-up for this analysis began on the date of completion of the 1999 follow-up questionnaire. The 152-item food frequency questionnaire (FFQ) first administered in 1999 provided a more comprehensive assessment of the exposures of interest than the 68-item FFQ administered at enrollment in 1992 (41). A 90% response rate was achieved for overall follow-up in 1999. Of these (151,349) persons, 87% (58,555 men and 73,643 women) returned the full-length FFQ, whereas the remaining 13% completed a shorter follow-up questionnaire with no dietary information and were therefore excluded. Of those who returned the FFQ, we excluded participants who were lost to follow-up (2,989 men and 4,056 women), who had a history of colorectal cancer (1,671 men and 1,284 women) or cancer other than nonmelanoma skin cancer (9,653 men and 11,344 women), or who provided incomplete or improbable FFQ data (1,194 men and 987 women) as indicated by implausibly high (>4,200 kcal for men and >3,500 kcal for women) or low (<800 kcal for men and <600 kcal for women) total energy intake. A total of 43,108 men and 55,972 women remained for analysis.

Follow-up for each subject began on the date of the returned 1999 survey and continued until the date of colorectal cancer diagnosis, the date of censoring due to loss to follow-up, death, report of a different cancer, or June 30, 2005, whichever came first. Individuals who self-reported colorectal cancer that could not be verified were censored at the last cancer-free survey.

Incident Colorectal Cancer. We identified and verified a total of 869 incident cases of colorectal cancer (452 in men and 417 in women) in the analytic cohort. Of these, 379 male cases and 333 female cases were initially identified by self-report (42) and subsequently verified by obtaining medical records (299 men and 269 women) or through linkage with state registries (80 men and 64 women) when complete medical records could not be obtained (41). An additional 141 cases (65 men and 76 women) were identified as primary or contributory deaths ascertained through computerized linkage with the National Death Index. The remaining cases (8 men and 8 women) were identified as a colorectal cancer case during verification of another reported cancer.

Of the 869 total cases, we identified 685 (348 male, 337 female) incident cancers of the colon (International Classification of Diseases Oncology codes: C18.0, C18.2-C18.9). Of these, 339 (157 men and 182 women) were identified as proximal (cecum to splenic flexure), 159 (87 men and 72 women) as distal (descending to sigmoid colon), 183 (102 men and 81 women) as unspecified colon, and 4 (2 men and 2 women) as overlapping lesions of the colon. We identified 169 (97 men and 72 women) cancers of the rectosigmoid junction (C19.9) or rectum (C20.9). Fifteen (7 men and 8 women) additional colorectal cases were of unknown subsite. Overlapping cases (17 men and 10 women) were counted only once in total cases.

Dietary Assessment. Diet was assessed in 1999 using a 152-item FFQ (43). Similar versions of the FFQ, administered in comparable populations, have been validated for PUFA s using biomarker and food-based comparison methods (44, 45). Validity coefficients between estimated “true” nutrient intakes and the FFQ generated using the method of triads (FFQ, adipose tissue, and seven 24-h dietary recalls) for LA and ALA were 0.89 and 0.59, respectively (45). No information was collected on flax or fish oil supplements; thus, only dietary intake was considered. Queries regarding the frequency of seafood intake included canned tuna fish, dark-meat fish (mackerel, salmon, sardines, bluefish, and swordfish), other fish (cod, haddock, and halibut), shellfish (shrimp, lobster, scallops, and clams), and breaded fish (fish sticks, cakes, or pieces). The FFQ queried about fats usually used for frying or sauteing and baking as well as type and brand of cooking oil and margarine/spread usually used at home with one open-ended question for each. Of those who indicated ever eating fried or sauteed food prepared at home, approximately one-third had invalid or missing information for cooking oil brand or type. Canola oil, the most commonly reported oil, was assigned as the default for missing values. Quartile classifications with and without individuals with unspecified cooking oil were nearly equivalent.

All individual fatty acids and other nutrient values were energy adjusted according to the residual regression
method (46). Total \(\omega-6\) fatty acid intake is the sum of LA, AA, \(\gamma\)-linolenic acid, and other minor \(\omega-6\)'s. Marine \(\omega-3\) fatty acid intake is the sum of values for DHA, EPA, and docosapentaenoic acid. Total \(\omega-3\) intake includes ALA, EPA, DHA, and docosapentaenoic acid. We computed ratios of \(\omega-6\) to \(\omega-3\) fatty acid intake for both total and marine \(\omega-3\) fatty acids and categorized each variable into sex-specific quartiles.

**Statistical Analysis.** We conducted analyses separately for men and women, as there was a statistically significant interaction between most fatty acid exposures and gender in relation to colorectal cancer risk \([P_{interaction} = 0.01-0.05, \text{except marine } \omega-3\ (P = 0.15)\] and the ratio of total \(\omega-6\) to total \(\omega-3\ (P = 0.40)\). We used Cox proportional hazards models to estimate incidence RR (95% CI) for colorectal cancer in relation to each main exposure and adjusted for age using the stratified Cox procedure with 1-year age strata. To test for any violation of the Cox proportional hazards assumption, we examined the data both graphically and by creating interaction terms between all main effect variables and time. Statistical interaction and the Cox proportional hazards assumption were assessed using the likelihood ratio test (47). \(P\) values for linear trend were estimated by creating a continuous variable using the median value within quartiles. If results appeared to strongly diverge from a linear pattern, we further examined the possible nonlinear relationship with restricted cubic splines (48). Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term with the model with the linear and cubic spline terms. Each of these tests lacked statistical significance; therefore, only the linear trend is presented. Results from two-sided \(\chi^2\) tests were considered statistically significant at \(P < 0.05\). All analyses were conducted in SAS version 9.1 (SAS Institute).

For each main exposure variable, we constructed sex-specific quartiles and examined three models. Model 1 included age and total energy intake. Model 2 included age, energy, and nondietary risk factors for colorectal cancer. Model 3 included age, energy, and nondietary and dietary risk factors for colorectal cancer. We considered as potential confounders those factors identified \textit{a priori} as established colorectal cancer risk factors based on literature review and which were also associated with fatty acid intake in the analytic cohort. Non-dietary covariates presented in the final multivariate models included colorectal screening history (never or ever colonoscopy or sigmoidoscopy by 1999), body mass index (BMI; <25, 25-30, \(\geq 30\), hormone replacement therapy (HRT) among women (never use, current estrogen replacement therapy, current estrogen/progestosterone combined replacement therapy, former use), recreational (moderate to vigorous) physical activity in metabolic equivalents (in quartiles), and anti-inflammatory drug use (total of aspirin, NSAIDs, and/or baby aspirin counted as one-fourth of a pill; never, 1-14, 15-29, \(\geq 30\) pills/mo). Dietary covariates presented in the final multivariate models included red and processed meats, low-fat dairy, whole fruit, and vegetable servings per day or per week (in sex-specific quartiles). Addition or substitution of other covariates, including alcohol, education, smoking history, multivitamin or supplement use, history of cholesterol-lowering drug use, history of diabetes, intakes (total or diet only) of calcium, vitamin D, fiber or folate, and fatty acids mutually adjusted for each other did not influence results.

We examined whether the association between fatty acid intake and colorectal cancer incidence varied by anti-inflammatory drug use (defined as \(<15\) versus \(\geq 30\) pills/mo; refs. 49, 50). We also considered effect modification by BMI (defined at BMI above or below median, 27.5), colorectal screening history (defined as never versus ever colonoscopy or sigmoidoscopy), and HRT use (defined as never versus ever use of estrogen replacement therapy or combined replacement therapy) and cross-classifications of \(\omega-6\) and \(\omega-3\) PUFAs (by tertiles). In further subanalyses, we examined associations between fatty acids and colorectal cancer after excluding individuals with missing cooking oil brand.

**Results**

Table 1 shows the mean intakes and correlation coefficients between energy-adjusted values of the different PUFAs. LA, the primary nutrient contributor to total \(\omega-6\) intake, was correlated with ALA, the primary nutrient contributor to total \(\omega-3\) intake \((r^2 = 0.76)\). Marine \(\omega-3\)-

### Table 1. Mean intakes and correlations between PUFAs in the CPS-II Nutrition Cohort, 1999

| Variable* | Total PUFA | Total \(\omega-6\) | LA | AA | GLA | Total \(\omega-3\) | ALA | Marine \(\omega-3\) | DHA | EPA | DPA |
|-----------|------------|--------------------|----|----|-----|-----------------|-----|------------------|-----|-----|-----|
| Mean intakes (g/d) | 11.50 | 11.12 | 9.91 | 0.09 | 0.01 | 1.24 | 1.06 | 0.19 | 0.12 | 0.06 | 0.02 |
| Correlation | 1.00 | 0.98 | 0.99 | 0.15 | 0.09 | 0.74 | 0.79 | -0.004 | 0.003 | -0.01 | -0.02 |
| Total \(\omega-6\) | 0.98 | 1.00 | 0.98 | 0.15 | 0.09 | 0.69 | 0.76 | -0.05 | -0.04 | -0.06 | -0.04 |
| LA | 0.99 | 0.98 | 1.00 | 0.12 | 0.07 | 0.69 | 0.76 | -0.05 | -0.05 | -0.06 | -0.06 |
| AA | 0.15 | 0.15 | 0.12 | 1.00 | 0.38 | 0.16 | 0.06 | 0.37 | 0.39 | 0.29 | 0.42 |
| GLA | 0.15 | 0.15 | 0.12 | 1.00 | 0.38 | 0.16 | 0.06 | 0.37 | 0.39 | 0.29 | 0.42 |
| Total \(\omega-3\) | 0.74 | 0.69 | 0.69 | 0.16 | 0.12 | 1.00 | 0.94 | 0.36 | 0.36 | 0.35 | 0.27 |
| ALA | 0.79 | 0.76 | 0.76 | 0.36 | 0.06 | 0.94 | 1.00 | 0.03 | 0.02 | 0.01 | 0.00 |
| Marine \(\omega-3\) | -0.004 | -0.05 | -0.05 | 0.37 | 0.23 | 0.36 | 0.02 | 1.00 | 0.99 | 0.98 | 0.84 |
| DHA | 0.003 | -0.04 | -0.05 | 0.40 | 0.23 | 0.36 | 0.02 | 0.99 | 1.00 | 0.94 | 0.81 |
| EPA | -0.01 | -0.06 | -0.06 | 0.29 | 0.22 | 0.35 | 0.01 | 0.98 | 0.94 | 1.00 | 0.83 |
| DPA | -0.02 | -0.04 | -0.06 | 0.42 | 0.32 | 0.27 | 0.84 | 0.81 | 0.83 | 1.00 | 0.00 |

*GLA, \(\gamma\)-linolenic acid; DPA, docosapentaenoic acid.

1 Pearson correlation coefficients; all correlations are significant \((P < 0.01)\) with the exception of total marine \(\omega-3\) and DHA with total PUFA, ALA with docosapentaenoic acid.
intake was not correlated with total ω-6 intake ($r^2 = -0.05$) or ALA intake ($r^2 = 0.02$). The top food contributors to ω-3 and ω-6 PUFA intake, that is, contributing >5% of total intake from a single food item, are presented in Table 2. Salad dressing was the primary food contributor to total ω-6, ALA, and therefore total ω-3 fatty acid intake. Dark fish and canned tuna were the primary food contributors to marine ω-3 fatty acid intake. Lesser food sources differed for men and women.

The distributions of baseline characteristics and other dietary factors according to quartile of total ω-6 and quartile of marine ω-3 fatty acids are provided in Table 3. The mean (SD) age at baseline was 70 (6) years in men and 68 (6) years in women. In both men and women, the range of total ω-6 intake varied 2-fold and marine ω-3 intake varied 4-fold between medians of extreme quartiles of intake (Table 3). In general, men and women with higher total ω-6, or lower marine ω-3 intake, were more likely to be overweight or obese and have a history of diabetes and less likely to be screened for colorectal cancer, college educated, physically active, or taking multivitamins or cholesterol-lowering drugs. They also generally had lower intakes of calcium, vitamin D, folate, fiber, fish, low-fat dairy, fruits, and vegetables. Heavy alcohol consumption was lower among individuals with higher intakes of total ω-6 fatty acids. Total ω-3 intake followed a less marked trend across risk factors with little difference by body size, multivitamin use, and nutrient intakes of folate, fiber, and vitamin D (data not shown).

The associations between fatty acid intake and risk of colorectal cancer among women and men are provided in Tables 4 and 5, respectively. In both women and men, there was no association between the ratio of total ω-6 to total ω-3 intake and colorectal cancer risk. In women, higher total ω-6 intake and a higher ratio of total ω-6 to marine ω-3 intake was associated with an increased risk of colorectal cancer, evident primarily in the top quartile [age- and energy-adjusted RR (95% CI), 1.37 (1.05-1.78); $P_{\text{trend}} = 0.009$ and 1.31 (1.01-1.70); $P_{\text{trend}} = 0.008$, respectively], but statistically significant associations did not hold in models adjusted for dietary factors ($P_{\text{trend}} = 0.15$ and 0.16, respectively). In women, total ω-3, driven by ALA intake, showed a statistically significant positive association with colorectal cancer for all intakes above the lowest quartile, which was only slightly attenuated following adjustment for dietary factors. This relationship was consistent across total ω-6 tertiles (data not shown). In the age- and energy-adjusted model, marine ω-3 intake in women appeared to be associated with a nonlinear reduction in colorectal cancer risk beginning in the second quartile. However, neither the linear test for trend nor the spline test for curvature (nonlinear relationship; ref. 48) was statistically significant, and RR were attenuated with multivariate adjustment. DHA, the primary contributor to marine ω-3 intake, was similarly associated with risk [multivariate RR (95% CI), 0.71 (0.54-0.92), 0.82 (0.63-1.08), and 0.85 (0.64-1.12), respectively; $P_{\text{trend}} = 0.68$; data in text only]. Likewise, dark or fatty fish (including canned tuna) intake, above the lowest quartile, was associated with a moderately lower risk of colorectal cancer in women [multivariate RR (95% CI), 0.78 (0.59-1.09), 0.77 (0.59-1.01), and 0.88 (0.65-1.19) for once to thrice per month, once per week, and more than once per week, respectively; data in text only].

Among men, no inverse associations between marine ω-3 intake and colorectal cancer risk were observed (Table 5) regardless of total ω-6 intake (data not shown). However, total ω-3 and ALA intake were slightly inversely related to risk in men ($P_{\text{trend}} = 0.09$). Also in contrast to our findings in women, the highest quartile of total ω-6 intake appeared to be associated with lower risk [RR (95% CI), 0.81 (0.61-1.07); $P_{\text{trend}} = 0.07$]. Similarly, LA, the primary contributor to total ω-6 intake, was associated with lower risk in men [multivariate RR (95% CI), 0.82 (0.63-1.08); $P_{\text{trend}} = 0.12$; data in text only]. Differential associations for ω-6 fatty acids in men and women were limited to the highest quartile of intake. These associations persisted despite adjustment for ω-3 intake (data not shown).

We detected no statistically significant interactions with NSAID use among women or men. In women who did not take NSAIDs regularly (<15 pills/mo), marine

### Table 2. Top food item contributors (>5%) to nutrient value for daily intake in the CPS-II Nutrition Cohort, 1999

| Nutrient          | Women |     | Men  |     |
|-------------------|-------|-----|------|-----|
|                   | Food  | %   | Food | %   |
| Total ω-3         | Salad dressing | 10.87 | Salad dressing | 11.04 |
|                   | Walnuts | 8.28 | Mayo, regular | 6.86 |
|                   | Mayo, regular | 7.23 | Dark fish | 6.09 |
|                   | Dark fish | 6.19 | Walnuts | 5.87 |
|                   | Margarine | 5.32 | Margarine | 5.66 |
| Short-chain ω-3 (ALA) | Salad dressing | 12.62 | Salad dressing | 12.88 |
|                   | Walnuts | 9.61 | Mayo, regular | 7.99 |
|                   | Mayo, regular | 8.38 | Walnuts | 6.85 |
|                   | Margarine | 6.07 | Margarine | 6.48 |
|                   | Cabbage/coleslaw | 5.24 |     |     |
| Long-chain, marine ω-3 | Dark fish | 39.22 | Dark fish | 38.34 |
|                   | Canned tuna | 20.1 | Canned tuna | 20.08 |
|                   | Other fish, light | 17.52 | Other fish, light | 17.39 |
|                   | Chicken/turkey | 15.2 | Shellfish | 5.11 |
|                   | Shellfish | 5.20 |     |     |
| Total ω-6         | Salad dressing | 10.57 | Salad dressing | 9.77 |
|                   | Margarine | 5.32 | Peanut butter | 5.38 |
|                   |     |     | Margarine | 5.19 |
ω-3 intake above the lowest quartile appeared to be associated with moderately lower risk [multivariate RR (95% CI), 0.78 (0.58-1.01), 0.79 (0.58-1.09), and 0.88 (0.64-1.21); \( P_{\text{trend}} = 0.59; P_{\text{interaction}} = 0.59 \); data in text only]. In women taking NSAIDs regularly (>30 pills/mo), there was no apparent association with marine ω-3 intake [multivariate RR (95% CI), 0.98 (0.52-1.84), 1.18 (0.64-2.19), and 0.90 (0.45-1.82); \( P_{\text{trend}} = 0.84 \); data in text only]. Among men not taking NSAIDs regularly, the inverse association with total ω-6 intake was stronger [multivariate RR (95% CI) for highest versus lowest quartile, 0.71 (0.50-1.00); \( P_{\text{trend}} = 0.05 \); data in text only], whereas among men taking NSAIDs regularly, there was no association [RR (95% CI), 0.89 (0.51-1.54); \( P_{\text{trend}} = 0.33; P_{\text{interaction}} = 0.26; \) data in text only]. No effect modification by BMI, colorectal screening history, or HRT use was observed.

We repeated analyses excluding men and women with missing cooking oil brand or type. In both men and women, results were weaker and not statistically significant, but in the same direction, as one would expect with a reduction in sample size (data not shown). Results were also comparable in sensitivity analysis excluding potential influential or extreme intakes outside of two interquartile ranges.

### Discussion

Ecologic comparisons and experimental evidence suggest that a high ω-6 to ω-3 ratio, a component of western-style diet, is associated with increased risk of colorectal cancer via proinflammatory and procarcinogenic mechanisms (4, 8). However, in this large prospective cohort, we observed no association between the ratio of total ω-6 to total ω-3 intake and colorectal cancer risk, which may be due, in part, to unexpected findings for total ω-6 and total ω-3 intake and their differential associations in men and women. Total ω-3 intake, primarily driven by ALA, and total ω-6 intake appeared to be associated with increased risk in women. However, in men, total ω-6 intake and ALA intake were inversely related to risk.

### Table 3. Baseline characteristics of CPS-II women and men by extreme quartile of dietary intakes of ω-6 and marine ω-3 fatty acids, 1999

|                  | Women                      |                     | Men                     |                     |
|------------------|-----------------------------|---------------------|-------------------------|---------------------|
|                  | Total ω-6 | Marine ω-3 | Total ω-6 | Marine ω-3 | Total ω-6 | Marine ω-3 | Total ω-6 | Marine ω-3 |
| Q1                | Q4         | Q1        | Q4         | Q1        | Q4         | Q1        | Q4         |
| Median intake (g/d) | 7.4        | 13.8      | 0.07       | 0.31      | 8.6        | 15.7      | 0.08       | 0.33      |
| Age at 1999 interview, mean (y) | 68.6       | 68.5      | 69.0       | 68.0      | 70.4       | 70.2      | 70.5       | 70.0      |
| Caucasian (%)     | 97.9       | 97.5      | 98.1       | 96.8      | 98.3       | 97.6      | 98.2       | 97.3      |
| College education or higher (%) | 36.5      | 30.2      | 25.2       | 43.4      | 54.9       | 47.8      | 39.0       | 64.0      |
| Family history of colon or rectal cancer (%) | 13.1      | 14.0      | 13.6       | 13.6      | 11.5       | 12.3      | 12.0       | 12.0      |
| Overweight, >30 BMI ≥25 (%) | 30.1      | 31.7      | 32.5       | 29.4      | 43.2       | 45.0      | 45.4       | 43.8      |
| Obese, BMI ≥30 (%) | 12.8       | 18.8      | 16.6       | 13.8      | 12.8       | 16.1      | 15.8       | 12.2      |
| Recreational physical activity, mean METs | 15.9       | 13.8      | 13.1       | 17.2      | 19.1       | 17.0      | 15.9       | 20.2      |
| Never use HRT (%) | 37.2       | 35.8      | 39.5       | 33.3      | —          | —         | —          | —         |
| Current ERT/CHRT use (%) | 43.5      | 49.3      | 41.8       | 47.3      | 68.2       | 65.1      | 61.2       | 71.9      |
| Colonoscopy/sigmoidoscopy screening (%) | 61.4      | 57.8      | 54.9       | 64.0      | 61.5       | 63.5      | 63.3       | 62.9      |
| NSAID use <15 pills/mo (%) | 65.9      | 65.8      | 65.9       | 66.6      | 30.2       | 27.9      | 29.4       | 27.8      |
| NSAID use ≥30 pills/mo (%) | 25.0      | 25.2      | 25.5       | 23.6      | 30.3       | 24.9      | 24.1       | 32.8      |
| Cholesterol-lowering drug use (%) | 20.9      | 18.5      | 18.5       | 20.8      | 8.2        | 14.2      | 10.8       | 11.2      |
| History of diabetes (%) | 5.2        | 8.7       | 7.0        | 6.7       | 3.7        | 4.9       | 5.6        | 2.4       |
| Current smoker (%) | 3.8        | 5.5       | 5.7        | 3.2       | 22.6       | 8.9       | 14.2       | 14.6      |
| Alcohol consumption ≥2 drinks/d (%) | 9.3        | 3.8       | 4.9        | 6.5       | 53.1       | 48.6      | 45.2       | 55.7      |
| Multivitamin use (%) | 60.7       | 54.8      | 53.1       | 63.3      | —          | —         | —          | —         |

Table 3. Baseline characteristics of CPS-II women and men by extreme quartile of dietary intakes of ω-6 and marine ω-3 fatty acids, 1999

NOTE: All values (except age) were standardized to the age distribution of the study population. All nutrients were adjusted for total energy intake.

Abbreviations: MET, metabolic equivalents; ERT or CHRT, estrogen or combined replacement therapy; total intake, intake from diet plus supplements.
observed no strong associations for marine ω-3 fatty acids in either sex. We cannot rule out chance as an explanation for our findings due to multiple associations examined and because associations were not strongly linearly related to risk.

Despite strongly supportive experimental data for EPA and DHA (7, 10-13), we did not find any robust associations for marine ω-3 fatty acids and colorectal cancer risk in this cohort. Findings from a recent meta-analysis of prospective cohort studies found a moderate protective association for fish intake in women [pooled RR (95% CI), 0.78 (0.58-1.06)] but a decidedly null relationship in men. Two recent studies investigating dietary ALA intake (33, 35) found higher risk of colorectal cancer in women but the suggestion of an inverse association for fish intake in women appeared to be associated with increased risk of colorectal cancer in men not taking aspirin (p-interaction = 0.04; ref. 35).

Unexpectedly, we found total ω-3, driven by ALA intake, to be associated with increased risk of colorectal cancer among women but the suggestion of an inverse relationship in men. Two recent studies investigating dietary ALA intake (53) and serum ALA levels (33) also found higher risk of colorectal cancer in women but lower risk in men. Although experimental data (18, 19, 25) have supported the protective effects of both short-chain and long-chain ω-3 fatty acids, epidemiologic studies have found inconsistent associations for ALA.

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Table 4. Age-, energy-, and multivariate-adjusted RR (95% CI) for incident colorectal cancer associated with ω-6 and ω-3 fatty acid intake, CPS-II Nutrition Cohort Women (1999-2005)

| Nutrient | Cases | RR* (95% CI) | P<sub>trend</sub> | RR† (95% CI) | P<sub>trend</sub> | RR‡ (95% CI) | P<sub>trend</sub> |
|----------|-------|--------------|----------------|--------------|----------------|--------------|----------------|
| Total ω-6 (g/d) | | | | | | | |
| Q1 (<8.4) | 96 | 1.00 | 0.009 | 1.00 | 0.01 | 1.00 | 0.15 |
| Q2 (8.4 to <10.0) | 94 | 0.99 (0.74-1.31) | | 0.97 (0.73-1.29) | | 0.93 (0.70-1.24) | |
| Q3 (10.0 to <12.1) | 100 | 1.06 (0.80-1.40) | | 1.05 (0.80-1.40) | | 0.97 (0.72-1.29) | |
| Q4 (≥12.1) | 127 | 1.37 (1.05-1.78) | | 1.33 (1.02-1.74) | | 1.17 (0.88-1.55) | |
| Total ω-3 (g/d) | | | | | | | |
| Q1 (<0.93) | 78 | 1.00 | 0.05 | 1.00 | 0.04 | 1.00 | 0.09 |
| Q2 (0.93 to <1.13) | 109 | 1.39 (1.04-1.86) | | 1.40 (1.04-1.87) | | 1.40 (1.05-1.88) | |
| Q3 (1.13 to <1.38) | 120 | 1.53 (1.15-2.03) | | 1.56 (1.17-2.07) | | 1.53 (1.15-2.05) | |
| Q4 (≥1.38) | 110 | 1.41 (1.06-1.89) | | 1.43 (1.07-1.92) | | 1.38 (1.02-1.85) | |
| ALA (g/d) | | | | | | | |
| Q1 (<0.78) | 77 | 1.00 | 0.04 | 1.00 | 0.04 | 1.00 | 0.13 |
| Q2 (0.78 to <0.95) | 115 | 1.52 (1.13-2.02) | | 1.52 (1.14-2.03) | | 1.50 (1.12-2.01) | |
| Q3 (0.95 to <1.19) | 112 | 1.44 (1.07-1.92) | | 1.44 (1.07-1.92) | | 1.40 (1.04-1.87) | |
| Q4 (≥1.19) | 113 | 1.47 (1.10-1.96) | | 1.46 (1.09-1.95) | | 1.38 (1.02-1.85) | |
| Marine ω-3 (g/d) | | | | | | | |
| Q1 (<0.10) | 131 | 1.00 | 0.25 | 1.00 | 0.57 | 1.00 | 0.83 |
| Q2 (0.10 to <0.15) | 97 | 0.81 (0.62-1.05) | | 0.84 (0.65-1.09) | | 0.83 (0.66-1.11) | |
| Q3 (0.15 to <0.24) | 92 | 0.79 (0.61-1.04) | | 0.84 (0.64-1.10) | | 0.86 (0.66-1.13) | |
| Q4 (≥0.24) | 97 | 0.83 (0.64-1.08) | | 0.90 (0.69-1.17) | | 0.94 (0.72-1.24) | |
| Total ω-6/total ω-3 | | | | | | | |
| Q1 (<7.6) | 96 | 1.00 | 0.63 | 1.00 | 0.90 | 1.00 | 0.48 |
| Q2 (7.6 to <8.7) | 118 | 1.25 (0.96-1.64) | | 1.23 (0.94-1.61) | | 1.18 (0.90-1.56) | |
| Q3 (8.7 to <10.0) | 99 | 1.08 (0.82-1.44) | | 1.05 (0.79-1.39) | | 0.97 (0.73-1.30) | |
| Q4 (≥10.0) | 104 | 1.13 (0.86-1.50) | | 1.08 (0.82-1.43) | | 0.96 (0.72-1.30) | |
| Total ω-6/marine ω-3 | | | | | | | |
| Q1 (<42.1) | 100 | 1.00 | 0.008 | 1.00 | 0.04 | 1.00 | 0.16 |
| Q2 (42.1 to <70.6) | 90 | 0.91 (0.68-1.21) | | 0.88 (0.66-1.18) | | 0.86 (0.64-1.14) | |
| Q3 (70.6 to <115.2) | 93 | 0.93 (0.70-1.23) | | 0.89 (0.67-1.18) | | 0.84 (0.62-1.12) | |
| Q4 (≥115.2) | 134 | 1.31 (1.01-1.70) | | 1.21 (0.93-1.58) | | 1.11 (0.84-1.45) | |

*Age- and energy-adjusted model.
†Multivariate-adjusted model controlling for age, energy, HRT (in women only), recreational physical activity, NSAID use, colorectal screening, and BMI.
‡Multivariate-adjusted model controlling for age, energy, HRT (in women only), recreational physical activity, NSAID use, colorectal screening, BMI, and red and processed meat, low-fat dairy, fruit, and vegetable intake.

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versus DHA and/or EPA (21, 33, 53). The potentially inefficient metabolic conversion of nutritionally essential ALA to long-chain ω-3’s (54) 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 potential benefits of ALA. Shared primary food sources, such as salad dressing and mayonnaise, and correlated nutrient intakes for ALA and LA have also been reported in other U.S. cohorts (55, 56). We encourage more research on this topic, particularly because ALA is currently publicized in popular media as a healthy source of ω-3 fatty acids to reduce risk of heart disease and some cancers.

We also found opposite associations in men and women for total ω-6 intake, primarily in the highest intake quartile. Among women, total ω-6 intake appeared to be directly related to colorectal cancer risk as hypothesized based on inflammatory mechanisms, but intake was inversely related to risk in men. A nested case-control study from the male PHS cohort (35) and a prospective study among Japanese men (33) also observed nonsignificant inverse trends for blood levels of ω-6 fatty acids with colorectal cancer risk, whereas prospective cohorts using intake from dietary questionnaires generally found no association in men (23, 39, 40). Although eicosanoids derived from ω-6 fatty acids are generally proinflammatory, some derivatives of LA have been shown to have anticarcinogenic effects (57, 58).

Beyond inflammatory signaling, dietary ω-6 and ω-3 fatty acids and their metabolites may influence carcinogenesis 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 fluidity with subsequent effects on immunity, cell growth, differentiation, apoptosis, angiogenesis, and metastasis (17, 20).

Sex-specific differences in results raise important questions about the effect of estrogen from either endogenous or exogenous sources on fat metabolism and vice versa. Estrogen levels may lead to alterations in normal fatty acid metabolism through changes in fatty acid utilization and oxidation (59-61). Although in our female population 98% were postmenopausal at baseline, 60% reported taking HRT at some point in their lives. Estrogen synthesis in fat tissue also contributes considerably to circulating estrogen levels in postmenopausal women (62). In other studies, HRT has been shown to improve fatty acid profiles in postmenopausal women and, to some extent, attenuate the effects of diet on health outcomes (59, 60, 63). Intake of marine ω-3 fatty acids relative to ω-6 fatty acids may also affect endogenous estrogen production, as prostaglandin products of fatty acid metabolism may regulate aromatase activity (17).

### Table 5. Age-, energy-, and multivariate-adjusted RR (95% CI) for incident colorectal cancer associated with ω-6 and ω-3 fatty acid intake, CPS-II Nutrition Cohort Men (1999-2005)

| Nutrient | Cases | RR* (95% CI) | P<sub>trend</sub> | RR* (95% CI) | P<sub>trend</sub> | RR* (95% CI) | P<sub>trend</sub> |
|----------|-------|-------------|-----------------|-------------|-----------------|-------------|-----------------|
| Total ω-6 (g/d) |       |             |                 |             |                 |             |                 |
| Q1 (<0.97) | 109  | 1.00        | 0.35            | 1.00        | 0.21            | 1.00        | 0.07            |
| Q2 (0.97 to <1.15) | 125  | 1.15 (0.89-1.48) | 1.12 (0.87-1.45) | 1.08 (0.83-1.40) |
| Q3 (1.15 to <1.38) | 116  | 1.06 (0.81-1.37) | 1.02 (0.79-1.33) | 0.97 (0.74-1.26) |
| Q4 (≥1.38) | 102  | 0.91 (0.70-1.20) | 0.88 (0.67-1.15) | 0.81 (0.61-1.07) |
| Total ω-3 (g/d) |       |             |                 |             |                 |             |                 |
| Q1 (<0.99) | 117  | 1.00        | 0.10            | 1.00        | 0.12            | 1.00        | 0.09            |
| Q2 (0.99 to <1.20) | 133  | 1.13 (0.88-1.45) | 1.15 (0.90-1.48) | 1.14 (0.89-1.46) |
| Q3 (1.20 to <1.47) | 96   | 0.81 (0.62-1.06) | 0.82 (0.63-1.07) | 0.81 (0.61-1.06) |
| Q4 (≥1.47) | 106  | 0.87 (0.67-1.14) | 0.88 (0.68-1.15) | 0.86 (0.66-1.13) |
| ALA (g/d) |       |             |                 |             |                 |             |                 |
| Q1 (<0.82) | 111  | 1.00        | 0.20            | 1.00        | 0.15            | 1.00        | 0.09            |
| Q2 (0.82 to <1.00) | 132  | 1.20 (0.93-1.54) | 1.19 (0.93-1.54) | 1.18 (0.91-1.52) |
| Q3 (1.00 to <1.26) | 104  | 0.92 (0.70-1.20) | 0.90 (0.69-1.18) | 0.88 (0.67-1.16) |
| Q4 (≥1.26) | 105  | 0.91 (0.70-1.20) | 0.90 (0.69-1.17) | 0.87 (0.66-1.14) |
| Marine ω-3 (g/d) |       |             |                 |             |                 |             |                 |
| Q1 (<0.10) | 115  | 1.00        | 0.34            | 1.00        | 0.90            | 1.00        | 0.90            |
| Q2 (0.10 to <0.16) | 108  | 1.05 (0.80-1.36) | 1.08 (0.83-1.41) | 1.09 (0.83-1.42) |
| Q3 (0.16 to <0.25) | 136  | 1.10 (0.86-1.41) | 1.19 (0.92-1.52) | 1.20 (0.93-1.55) |
| Q4 (≥0.25) | 93   | 0.87 (0.66-1.14) | 0.97 (0.73-1.28) | 1.00 (0.75-1.33) |
| Total ω-6/total ω-3 |       |             |                 |             |                 |             |                 |
| Q1 (<0.9) | 98   | 1.00        | 0.24            | 1.00        | 0.46            | 1.00        | 0.75            |
| Q2 (0.9 to <0.94) | 109  | 1.12 (0.85-1.47) | 1.08 (0.82-1.42) | 1.05 (0.80-1.38) |
| Q3 (0.94 to <1.10) | 134  | 1.37 (1.05-1.78) | 1.31 (1.01-1.70) | 1.25 (0.95-1.63) |
| Q4 (≥1.10) | 111  | 1.15 (0.88-1.51) | 1.09 (0.83-1.43) | 1.04 (0.78-1.38) |
| Total ω-6/marine ω-3 |       |             |                 |             |                 |             |                 |
| Q1 (<0.4) | 107  | 1.00        | 0.73            | 1.00        | 0.61            | 1.00        | 0.36            |
| Q2 (0.4 to <0.72) | 109  | 1.03 (0.78-1.34) | 0.98 (0.75-1.28) | 0.94 (0.72-1.24) |
| Q3 (0.72 to <1.17) | 123  | 1.15 (0.88-1.49) | 1.06 (0.81-1.37) | 1.01 (0.77-1.32) |
| Q4 (≥1.17) | 113  | 1.05 (0.80-1.37) | 0.93 (0.71-1.22) | 0.87 (0.66-1.15) |

*Age- and energy-adjusted model.  
P<sub>trend</sub> assessed by χ² test for linear trend.  
Multivariate-adjusted model controlling for age, energy, recreational physical activity, NSAID use, colorectal screening, and BMI.  
Multivariate-adjusted model controlling for age, energy, recreational physical activity, NSAID use, colorectal screening, BMI, and red and processed meat, low-fat dairy, fruit, and vegetable intake.
Although we observed no effect modification by HRT use or BMI, this relationship is complex and deserves further study.

We hypothesized that the ratio of intake of \( \omega-6 \) to \( \omega-3 \) fatty acids would be more relevant than independent measures of these fatty acid intakes given their competing roles in inflammatory pathways. When intake of \( \omega-3 \) fatty acids is sufficiently high, they are preferentially metabolized by shared metabolic and cyclooxygenase enzymes leading to ‘‘competitive inhibition’’ with \( \omega-6 \) metabolism. Similarly, high intake of \( \omega-6 \)’s, which are far more common in U.S. diets, can depress metabolism of \( \omega-3 \) fatty acids, leading to an influx of the proinflammatory class of eicosanoids (\( \omega-6 \), 14, 17, 18, 24). Five (14, 19, 53, 64, 65) of nine (22, 23, 66, 67) previous observational studies reviewed supported direct associations between a ratio of \( \omega-6 \) to \( \omega-3 \) fatty acids and colorectal cancer but tended to use retrospective designs or measured outcomes related to earlier phases of colorectal carcinogenesis, such as colorectal adenoma (64) or rectal cell proliferation (14, 19). Given the older ages of our subjects, usual diet assessed in 1999 may not reflect the etiologic period for the initiation and promotion of colorectal carcinogenesis but may reflect later stages of cancer development.

Our lack of an association for the total ratio, and only weak associations for the \( \omega-6 \) to marine \( \omega-3 \) ratio, may be due to an insufficient range of exposure. In our U.S. population, marine \( \omega-3 \) intake, the more bioavailable source of \( \omega-3 \) fatty acids (54), was very low relative to intakes of \( \omega-6 \) and ALA (short-chain \( \omega-3 \)) fatty acids. The ideal \( \omega-6 \) to \( \omega-3 \) ratio to reduce risk of cardiovascular disease and cancer is unclear (8, 55, 61, 63). The typical western diet contains 10 to 20 times more \( \omega-6 \) than \( \omega-3 \) PUFAs. In contrast, human beings evolved on a diet with a ratio of \(~1\), and current recommendations extend from an ‘‘optimal range’’ of 1:4:1 to an ‘‘acceptable range’’ of 1:8:1 (4, 8). In our study, we were able to compare those with a ratio of 12:1 with those with a ratio of 7:1, a difference that may not be meaningful compared with the ratio limited to marine \( \omega-3 \) only, which varied \( \geq 5\)-fold in our population. Experimental data indicate that a total ratio of \( <4:1 \) may be necessary for chemoprevention of colorectal cancer (19) and a recent case-control study in Scotland found a significant inverse association with colorectal cancer comparing a ratio of 3:1 to 6:1 (53).

We attempted to address limitations of previous epidemiologic studies of PUFAs and colorectal cancer. We were able to prospectively evaluate differential associations by sex suggested in the literature as well as consider plausible confounders, effect modifiers, and the relative dietary contributions of \( \omega-6 \) and short-chain (ALA) versus long-chain (marine) \( \omega-3 \) fatty acids. Adjustment for other risk factors, particularly diet, appreciably attenuated associations in our cohort, which may have been an issue in smaller studies. Limitations of our study include the 6-year follow-up time and somewhat limited power in subanalyses, particularly given interactions with sex. We did not have information on fish oil or other \( \omega-3 \) supplements for this analysis; however, their use was likely to be uncommon in 1999 given the limited evidence for their efficacy available at the time. Correlated nutrient intakes due to shared food sources may have limited our ability to assess independent associations. Although the FFQ captures brands and has been validated for fatty acids using biomarkers (44, 45), PUFAs are derived from both endogenous and exogenous sources, suggesting that a combination of dietary assessment and adipose tissue or blood biomarkers may be optimal to address measurement error and risk of misclassification (68, 69).

Although the \( \omega-6 \) to \( \omega-3 \) ratio was not related to colorectal cancer risk in this cohort, we observed differential findings by sex for individual components. Opposing associations for \( \omega-6 \) and \( \omega-3 \) fatty acids in men and women raise important questions regarding sex-specific differences in fatty acid metabolism and potential confounding by diet patterns and lifestyle choices. It is unclear whether ALA and marine \( \omega-3 \) have similar effects on colorectal risk and why this relationship may differ in men and women. Dietary intakes of ALA are generally much higher than marine \( \omega-3 \) intakes in the U.S., but ALA may not provide an adequate source of bioavailable \( \omega-3 \) (54). Additionally, many foods that contribute to ALA intake are rich in \( \omega-6 \) fatty acids, which are likely to outcompete the relatively low levels of \( \omega-3 \) in metabolic and inflammatory pathways without heavy \( \omega-3 \) supplementation and/or a significant reduction in \( \omega-6 \) intake. Perhaps this may explain, at least in part, why few observational studies in the U.S. have found strong associations for individual PUFAs or their ratios with colorectal cancer despite supportive experimental data using far higher dosages of fish oils than are found in the normal U.S. diet. Future analyses should carefully examine associations between fatty acid intake and colorectal cancer by sex and type of \( \omega-3 \) fatty acids.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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