Dietary intake of PUFAs and colorectal polyp risk[1–4]

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ABSTRACT

Background: Marine-derived n−3 (omega-3) PUFAs may reduce risk of developing colorectal cancer; however, few studies have investigated the association of n−3 PUFA intakes on colorectal polyp risk.

Objective: The objective of this study was to examine the associations of dietary PUFA intake on risk of colorectal adenomatous and hyperplastic polyps.

Design: This was a colonoscopy-based case-control study that included 3166 polyp-free control subjects, 1597 adenomatous polyp cases, and 544 hyperplastic polyp cases. Dietary PUFA intake was calculated from food-frequency questionnaires and tested for association by using unconditional logistic regression. The urinary prostaglandin E_2 metabolite, which is a biomarker of prostaglandin E_2 production, was measured in 896 participants by using liquid chromatography and tandem mass spectrometry.

Results: n−6 PUFAs were not associated with adenomatous or hyperplastic polyps in either men or women. Marine-derived n−3 PUFAs were associated with reduced risk of colorectal adenomas in women only, with an adjusted OR of 0.67 (95% CI: 0.47, 0.97) for the highest quintile of intake compared with the lowest quintile of intake (P-trend = 0.01). Dietary intake of α-linolenic acid was associated with an increased risk of hyperplastic polyps in men (P-trend = 0.03), which was not seen in women. In women, but not in men, dietary intake of marine-derived n−3 PUFAs was negatively correlated with urinary prostaglandin E_2 production (r = −0.18; P = 0.002).

Conclusion: Higher intakes of marine-derived n−3 PUFAs are associated with lower risk of adenomatous polyps in women, and the association may be mediated in part through a reduction in the production of prostaglandin E_2. This trial was registered at clinicaltrials.gov as NCT00625066. *Am J Clin Nutr* 2012;95:703–12.

INTRODUCTION

CRC[5] is the fourth most common cancer and the second leading cause of cancer-related death in the United States (1). Early identification and prevention are important strategies to reduce CRC mortality (2). Chemoprevention, especially through dietary agents, has great promise for the primary prevention of CRC (3). The identification and evaluation of bioactive nutrients that might reduce colorectal neoplasm remain important priorities with substantial public health implications, and one such functional food that has received considerable attention is n−3 PUFA. The n−3 PUFAs included α-linolenic acid (18:3n−3) and the marine-derived n−3 PUFAs EPA (20:5n−3), docosapentanoic acid (22:5n−3), and DHA (22:6n−3). Although there is evidence to suggest that n−3 PUFAs have antiinflammatory properties (4), in the Western diet, n−6 PUFAs, particularly linoleic acid (18:2n−6), account for ∼89% of the total PUFA energy intake (5). Dietary linoleic acid can be metabolized through a series of desaturation and elongation reactions into arachidonic acid (20:4n−6) (6).

Arachidonic acid is the parent compound for multiple inflammatory eicosanoids (7). In the cyclooxygenase pathway, arachidonic acid is converted into various bioactive lipid molecules including prostaglandin E_2 (8). Animal models of CRC have shown the connection between tumor formation and arachidonic acid with a positive correlation between increasing tissue concentrations of arachidonic acid, increased prostaglandin E_2 production, and increased intestinal tumor number and size (9–12). In addition, upregulation of cyclooxygenase-2 occurs in 50% of colon adenomas and 85% of colon cancers and is considered a key and early oncogenic event in colorectal carcinogenesis (13). n−3 PUFAs are converted to eicosanoids through the same enzymatic pathways as arachidonic acid but produce series 3 eicosanoids that have less inflammatory actions compared with those of arachidonic acid–derived series 2 eicosanoids (7, 14, 15).

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[5] Abbreviations used: CRC, colorectal cancer; FFQ, food-frequency questionnaire; PGEM, prostaglandin E_2 metabolite.

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Despite a consistent cancer inhibitory effect of marine-derived n−3 PUFAs in animal models, results from epidemiologic studies have been mixed (16–19). In addition, few studies have investigated the effect of marine-derived n−3 PUFAs on CRC precursors such as adenomas. In this article, we report the results of a large colonoscopy-based case-control study that involved 5307 patients in whom we evaluated the association of dietary PUFA intake and colorectal polyp risk. Finally, we have recently shown that dietary n−3 PUFA intake was correlated with in vivo production of prostaglandin E_2 as measured by urinary PGEMs in a cohort of Chinese women (20). In this study, we have investigated the association of dietary PUFA intake and prostaglandin E_2 production in a Western population in relation to adenoma risk.

SUBJECTS AND METHODS

Study population

Participants in this study were part of the Tennessee Colorectal Polyp Study, which is a colonoscopy-based case-control study conducted in Nashville, TN. Study methods have been published elsewhere (21). Briefly, eligible participants, aged between 40 and 75 y old, were identified from patients scheduled for a colonoscopy at the Vanderbilt Gastroenterology Clinic between 1 February 2003 and 31 April 2010 and the Veterans' Affairs Tennessee Valley Health System Nashville campus between 21 August 2003 and 30 May 2007. Patients with genetic CRC syndromes (such as hereditary nonpolyposis CRC or familial adenomatous polyposis) or a previous history of inflammatory bowel disease, adenomatous polyps, or any cancer other than nonmelanoma skin cancers were excluded from the study. Most of the participants were recruited at the time of the colonoscopy (n = 11,863). For potential participants who were missed at the time of the colonoscopy, recruitment occurred after the procedure (n = 722), which occurred in <6% of subjects and resulted when study staff members were not available to meet the participant at recruitment. In 12,585 eligible individuals, 7621 subjects provided a written informed consent and participated in at least one component of the study (61%). Individuals who did not agree to participate were slightly younger than subjects who agreed to participate (mean age: 57.6 ± 8.2 y compared with 58.0 ± 7.5 y, respectively; $P < 0.0001$) and were more likely to be men than women (60.7% compared with 57.6%, respectively; $P < 0.0001$). The study was approved by the Vanderbilt University Institutional Review Board, the Veterans' Affairs Institutional Review Board, and the Veterans' Affairs Research and Development Committee.

Outcome assessment

Results of patient colonoscopies were recorded by using standardized data-entry forms. Information on the number, locations, and sizes of polyps were collected. Polyps were classified as adenomatous (which included villous, tubulovillous, tubular, sessile serrated, and traditional serrated on the basis of a histologic review), hyperplastic, mixed, or other. Almost 9% of adenomatous polyps (139 of 1597 adenomatous polyps) were classified as either a sessile or traditional serrated adenoma and were categorized as adenomatous polyps for analysis. A polyp was considered an advanced adenoma if it met one of the following 3 criteria: *1*) size >1.0 cm, *2*) a >25% villous component, or *3*) contained a high-grade dysplasia.

Exposure assessment

A standardized telephone interview was conducted by trained interviewers after the colonoscopy to obtain information on medication use, demographics, medical history, family history, reproductive history, anthropometric measures, and lifestyle. Interviewers were blinded to the results of the colonoscopy. Participants also completed a self-administered mail survey by using a semiquantitative 108-item FFQ that was developed to capture the diet in the southeastern United States and developed by using the NHANES III database (22). Although this FFQ has previously been shown to have moderate correlations to biomarkers of carotenoids and α-tocopherol, it has not been validated with respects to fatty acid intake (23). The FFQ also contains 5 items that surveyed eating habits and 13 items that were used to capture vitamin and supplement use. In study participants, 5332 subjects (70%) had completed both the telephone interview and the FFQ, and these subjects were included in the current analysis. The usual dietary intake of PUFAs was estimated by using USDA food-composition tables. Total n−6 PUFA was calculated by adding the total daily intake of linoleic acid and arachidonic acid. Total marine-derived n−3 PUFAs were calculated by combining EPA, docosapentanoic acid, and DHA. We also calculated the ratio or total n−6 PUFA divided by marine-derived n−3 PUFAs.

Laboratory assays

Urinary PGEM (11 α-hydroxy-9,15-dioxo-2,3,4,5-tetranorprostane-1,20-dioic acid) concentrations were measured by using liquid chromatography and tandem mass spectrometry by using the method previously described by Murphey et al (24) to quantify endogenous prostaglandin E_2 production. Briefly, 0.75 mL urine per subject was titrated to a pH of 3 by using 1 mol HCl/L. PGEM in the sample was derivatized with methoxyamine HCl. Methoximated PGEM was extracted by using the described solid-phase extraction technique. Liquid chromatography was performed by using a Waters Acquity BEH C18 column (50 × 2.0 mm, 1.75 μm) attached to a Waters Acquity UPLC (Waters Corp). Column effluent was directed to a TSQ Quantum Ultra triple quadrupole mass spectrometer (Thermo Fisher Scientific) for analysis. Endogenous PGEM was quantified by using the [$^2H_6$]-*O*-methyloxime PGEM internal standard, and PGEM results were reported as nanograms per milligram of urinary creatinine. Laboratory staff was blinded to case status of the urine samples and the identity of the quality control samples included in the study. In this study, the CVs were 6.1% for between-batch samples and 7.8% for within-batch samples.

Statistical analyses

From a study sample of 5332 potentially eligible participants, 25 participants with missing smoking, alcohol, or educational status data were excluded. Our final study included 5307 participants categorized as 3166 polyp-free control subjects and

TABLE 1
Demographic and lifestyle characteristics by case status and sex[1]

Characteristics	Men				Women			
	Control subjects (n = 1715)	Adenomatous (n = 1141)	Hyperplastic (n = 363)	P	Control subjects (n = 1451)	Adenomatous (n = 456)	Hyperplastic (n = 181)	P
Age (y)	58.5 ± 7.6[2]	59.7 ± 7.1	58.4 ± 6.8	0.01	56.4 ± 7.6	57.8 ± 7.8	55.4 ± 6.9	0.15
Race (%)				0.25				0.23
White	90.5	88.2	90.5		89.5	86.5	89.7	
African American or black	7.6	10.0	7.8		8.5	10.4	9.3	
Other	2.0	1.9	1.8		2.0	3.2	1.0	
Smoking (%)				<0.0001				<0.0001
Current	13.2	28.3	31.2		7.0	17.8	25.1	
Former	42.1	38.8	44.8		26.7	26.5	33.9	
Never	44.8	32.9	24.0		66.3	55.7	41.0	
Alcohol consumption (%)				0.06				0.10
Current	24.6	25.1	29.1		13.5	15.2	14.9	
Former	29.3	32.5	30.6		9.1	11.3	13.7	
Never	46.1	42.4	40.3		77.4	73.6	71.4	
Family history of colorectal cancer or polyps (%)	21.2	24.5	21.7	0.12	31.0	35.0	35.1	0.23
Educational attainment (college graduate; %)	45.9	38.0	36.7	<0.0001	55.4	51.8	49.0	0.07
Regularly exercised in the past 10 y (%)	57.0	48.7	49.5	<0.0001	60.2	58.8	58.2	0.66
BMI (kg/m^2)	28.3 ± 5.0	29.1 ± 7.1	29.1 ± 5.0	0.06	27.5 ± 6.3	28.2 ± 6.2	28.3 ± 7.6	0.01
Ever use of HRT (%)[2]	—	—	—		37.4	40.0	39.3	0.41
Study site (%)				<0.0001				0.14
Academic center	59.1	54.1	47.4		96.7	96.5	93.6	
VA	40.9	45.9	52.6		3.3	3.5	6.4	
Indication for colonoscopy screening (%)	71.0	70.3	69.7	0.86	71.8	68.9	68.4	0.32
NSAID use (%)								
Current	58.9	55.1	57.5	0.08	43.4	37.5	46.2	0.03
Former	6.0	6.6	8.5		8.9	6.4	7.1	
Never	35.1	38.4	33.9		47.7	56.2	46.7	
Total energy intake (kcal/d)	2491 ± 1067	2647 ± 1184	2624 ± 1178	0.0004	1605 ± 624	1627 ± 674	1642 ± 674	0.37
Linoleic acid intake (g/d)	18.81 ± 9.3	18.73 ± 10.1	18.91 ± 10.2	0.98	11.51 ± 5.6	11.60 ± 5.8	11.46 ± 5.9	0.83
Arachidonic acid intake (g/d)	0.12 ± 0.09	0.12 ± 0.09	0.12 ± 0.09	0.75	0.08 ± 0.05	0.08 ± 0.05	0.08 ± 0.06	0.87
α-Linolenic acid intake (g/d)	1.65 ± 0.82	1.68 ± 0.92	1.71 ± 0.95	0.01	0.93 ± 0.47	0.97 ± 0.50	0.97 ± 0.53	0.17
Marine-derived n−3 PUFA intake (g/d)	0.17 ± 0.20	0.16 ± 0.18	0.14 ± 0.14	0.05	0.10 ± 0.11	0.09 ± 0.11	0.09 ± 0.09	0.009
Calcium intake (mg/d)	1118 ± 593	1063 ± 659	1046 ± 572	<0.0001	830 ± 454	784 ± 455	755 ± 412	0.0005
Total fish intake (g/d)	17.9 ± 22.1	16.8 ± 21.9	17.9 ± 23.6	0.40	15.8 ± 19.2	12.3 ± 16.8	14.4 ± 20.8	0.002

[1] HRT, hormone replacement therapy; NSAID, nonsteroidal antiinflammatory drug; VA, Veterans Affairs Hospital.
[2] Mean ± SD (all such values).

2141 polyp cases including 1597 cases with any adenomatous polyps and 544 cases with hyperplastic polyps only.

We compared age-adjusted differences between cases and control subjects by using ANOVA for continuous variables or the Cochran-Mantel-Haenszel chi-square test for categorical variables. Unconditional logistic regression models were used to estimate risk of colorectal polyps associated with PUFA intakes. Dietary intakes of fatty acids were adjusted for energy intakes by using the residual method (25). Dietary PUFAs were categorized into quintiles on the basis of the sex-specific distribution of the energy-adjusted nutrient intakes in polyp-free control subjects. All models were adjusted for age (continuous), race (white or nonwhite), BMI (continuous), total energy intake (continuous), cigarette use (current use, former use, or never used), regular alcohol use (current use, former use, or never used), study site, educational attainment (high school or less or some college, college graduate, or graduate or professional education), regular physical activity in the past 10 y (yes or no), family history of CRC or adenomatous polyp (yes or no), indication for colonoscopy (screening or diagnostic), year of colonoscopy, total daily dietary calcium intake (continuous), nonsteroidal antiinflammatory drug intake (current of noncurrent use), and use of hormone replacement therapy (ever, never, or women only). We calculated tests for trend by rank ordering exposure categories and including the variable within the model as a continuous term. We constructed separate logistic regression models with

TABLE 2
Dietary PUFA intake and colorectal polyps stratified by sex

	Any adenomatous polyps				Hyperplastic polyps only			
	Men		Women		Men		Women	
Dietary intake	Cases/control subjects	OR (95% CI)[1]	Cases/control subjects	OR (95% CI)[2]	Cases/control subjects	OR (95% CI)[1]	Cases/control subjects	OR (95% CI)[2]
	n		*n*		*n*		*n*	
Linoleic acid								
Q1[3]: Men (range, 3.4–10.6 g/d; median, 8.3 g/d); women (range, 2.1–6.8 g/d; median, 5.6 g/d)	246/343	1.00 (referent)	92/291	1.00 (referent)	75/343	1.00 (referent)	42/291	1.00 (referent)
Q2: Men (range, 10.7–14.6 g/d; median, 12.7 g/d); women (range, 6.9–9.2 g/d; median, 8.1 g/d)	209/343	0.91 (0.71, 1.18)	86/290	0.95 (0.66, 1.37)	66/343	0.99 (0.67, 1.46)	37/290	0.82 (0.49, 1.36)
Q3: Men (range, 14.7–18.7 g/d; median, 16.5 g/d); women (range, 9.3–11.8 g/d; median, 10.4 g/d)	204/343	0.88 (0.67, 1.14)	74/290	0.84 (0.58, 1.24)	65/343	1.01 (0.68, 1.50)	33/290	0.73 (0.43, 1.24)
Q4: Men (range, 18.8–24.7 g/d; median, 21.0 g/d); women (range, 11.9–15.3 g/d; median, 13.2 g/d)	222/343	0.90 (0.69, 1.16)	105/290	1.14 (0.80, 1.64)	74/343	1.10 (0.75, 1.63)	32/290	0.66 (0.39, 1.14)
Q5: Men (range, 24.8–67.8 g/d; median, 30.4 g/d); women (range, 15.4–48.5 g/d; median, 18.6 g/d)	260/343	1.02 (0.79, 1.31)	99/290	1.08 (0.75, 1.56)	83/343	1.22 (0.83, 1.77)	37/290	0.70 (0.42, 1.19)
P-trend		0.69		0.45		0.81		0.16
Arachidonic acid								
Q1: Men (range, 0–0.053 g/d; median, 0.037 g/d); women (range, 0.0–0.037 g/d; median, 0.027 g/d)	229/343	1.00 (referent)	100/291	1.00 (referent)	71/343	1.00 (referent)	39/291	1.00 (referent)
Q2: Men (range, 0.054–0.079 g/d; median, 0.066 g/d); women (range, 0.038–0.056 g/d; median, 0.047 g/d)	200/343	0.95 (0.73, 1.23)	91/290	0.90 (0.64, 1.28)	56/343	0.85 (0.57, 1.27)	38/290	1.09 (0.65, 1.82)
Q3: Men: range, 0.080–0.109 g/d; median, 0.093 g/d); women (range, 0.057–0.077 g/d; median, 0.067 g/d)	251/343	1.18 (0.91, 1.53)	82/290	0.83 (0.58, 1.19)	92/343	1.30 (0.90, 1.89)	25/290	0.73 (0.41, 1.28)
Q4: Men (range, 0.110–0.159 g/d; median, 0.131 g/d); women (range, 0.078–0.107 g/d; median, 0.090 g/d)	223/343	1.01 (0.78, 1.31)	94/290	0.94 (0.66, 1.34)	72/343	1.01 (0.68, 1.49)	44/290	1.32 (0.80, 2.19)
Q5: Men (range, 0.160–1.23 g/d; median, 0.214 g/d); women (range, 0.108–0.433 g/d; median, 0.139 g/d)	238/343	0.95 (0.73, 1.22)	89/290	0.83 (0.59, 1.18)	72/343	0.92 (0.63, 1.35)	35/290	0.98 (0.59, 1.64)
P-trend		0.46		0.40		0.85		0.81
α-Linolenic acid								
Q1: Men (range, 0.3–0.9 g/d; median, 0.8 g/d); women (range, 0.1–0.5 g/d; median, 0.4 g/d)	218/343	1.00 (referent)	78/291	1.00 (referent)	60/343	1.00 (referent)	32/291	1.00 (referent)
Q2: Men (range, 1.0–1.2 g/d; median, 1.1 g/d); women (range, 0.6–0.7 g/d; median, 0.7 g/d)	222/343	1.04 (0.81, 1.35)	86/290	1.15 (0.79, 1.67)	73/343	1.31 (0.88, 1.95)	35/290	1.15 (0.67, 1.99)
Q3: Men (range, 1.3–1.6 g/d; median, 1.4 g/d); women (range, 0.8–0.9 g/d; median, 0.8 g/d)	195/343	0.91 (0.70, 1.19)	74/290	0.95 (0.64, 1.42)	61/343	1.10 (0.73, 1.67)	30/290	0.88 (0.49, 1.57)
Q4: Men (range, 1.7–2.1 g/d; median, 1.9 g/d); women (range, 0.9–1.2 g/d; median, 1.1 g/d)	222/343	0.98 (0.75, 1.28)	113/290	1.46 (1.00, 2.14)	72/343	1.28 (0.85, 1.92)	39/290	1.23 (0.70, 2.15)
Q5: Men (range, 2.2–6.7 g/d; median, 2.7 g/d); women (range, 1.3–4.6 g/d; median, 1.5 g/d)	284/343	1.11 (0.87, 1.43)	105/290	1.34 (0.92, 1.96)	97/343	1.51 (1.03, 2.21)	45/290	1.24 (0.73, 2.11)
P-trend		0.09		0.12		0.03		0.57

(Continued)

TABLE 2 (*Continued*)

	Any adenomatous polyps				Hyperplastic polyps only			
	Men		Women		Men		Women	
Dietary intake	Cases/control subjects	OR (95% CI)[1]	Cases/control subjects	OR (95% CI)[2]	Cases/control subjects	OR (95% CI)[1]	Cases/control subjects	OR (95% CI)[2]
Marine-derived n−3 PUFAs[4]								
Q1: Men (range, 0.00–0.042 g/d; median, 0.022 g/d); women (range, 0.0–0.023 g/d; median, 0.012 g/d)	268/343	1.00 (referent)	106/291	1.00 (referent)	83/343	1.00 (referent)	38/291	1.00 (referent)
Q2: Men (range, 0.043–0.082 g/d; median, 0.063 g/d); women (range, 0.024–0.051 g/d; median, 0.037 g/d)	217/343	0.96 (0.74, 1.24)	96/290	1.01 (0.71, 1.43)	86/343	1.29 (0.89, 1.87)	34/290	1.09 (0.63, 1.87)
Q3: Men (range, 0.083–0.140 g/d; median, 0.111 g/d); women (range, 0.052–0.087 g/d; median, 0.067 g/d)	218/343	0.99 (0.76, 1.28)	98/290	0.98 (0.69, 1.40)	60/343	0.90 (0.61, 1.35)	37/290	1.26 (0.74, 2.26)
Q4: Men (range, 0.141–0.246 g/d; median, 0.179 g/d); women (range, 0.088–0.140 g/d; median, 0.107 g/d)	227/343	1.03 (0.80, 1.32)	88/290	0.89 (0.62, 1.27)	80/343	1.24 (0.86, 1.81)	52/290	1.76 (1.06, 2.91)
Q5: Men (range, 0.247–3.883 g/d; median, 0.342 g/d); women (range, 0.141–1.01 g/d; median, 0.232 g/d)	211/343	0.94 (0.73, 1.21)	68/290	0.67 (0.47, 0.97)	54/343	0.83 (0.56, 1.24)	20/290	0.68 (0.38, 1.23)
P-trend		0.18		0.01		0.12		0.27
Ratio of total n−6 to marine-derived n−3 PUFAs								
Q1: Men (range, 6–71; median, 50); women (range, 7–71; median, 49)	199/343	1.00 (referent)	95/291	1.00 (referent)	60/343	1.00 (referent)	32/291	1.00 (referent)
Q2: Men (range, 72–117; median, 92); women (range, 72–120; median, 93)	215/343	1.01 (0.78, 1.31)	85/290	0.98 (0.69, 1.40)	65/343	1.12 (0.75, 1.68)	44/290	1.34 (0.80, 1.25)
Q3: Men (range, 118–187; median, 142); women (range, 121–210; median, 158)	232/343	1.08 (0.82, 1.42)	65/290	0.74 (0.50, 1.09)	70/343	1.18 (0.77, 1.78)	34/290	0.86 (0.49, 1.53)
Q4: Men (range, 188–389; median, 256); women (range, 211–42; median, 289)	226/343	0.92 (0.68, 1.25)	94/290	1.09 (0.73, 1.63)	72/343	1.12 (0.71, 1.75)	33/290	0.84 (0.45, 1.56)
Q5: Men (range, 390–78,588; median, 713); women (range, 428–118,125; median, 848)	269/343	0.95 (0.67, 1.34)	117/290	1.30 (0.88, 1.92)	96/343	1.38 (0.83, 2.28)	38/290	0.81 (0.43, 1.54)
P-trend		0.18		0.04		0.79		0.27

[1] Adjusted for age, race, BMI, total energy intake, smoking status, alcohol use, study site, educational status, physical activity, family history of colorectal neoplasm, indication for colonoscopy, year of study, calcium intake, and aspirin use.

[2] Adjusted for age, race, BMI, total energy intake, smoking status, alcohol use, study site, educational status, physical activity, family history of colorectal neoplasm, indication for colonoscopy, year of study, calcium intake, aspirin use, and hormone replacement therapy.

[3] Q, quintile.

[4] EPA + docosapentanoic acid + DHA.

a dependent variable of nonadvanced adenoma or advanced adenoma. Because of the small number of serrated adenomas, we were not able to robustly model serrated adenoma as a dependent variable; however, the removal of serrated adenomas from our category of adenomatous polyps did not appreciably change our results (data not shown). To formally tests for possible interactions between dietary PUFAs and sex, we included the cross product of sex with the dietary intake of each PUFA (dichotomized at the median intake) within our models and used the likelihood ratio test to evaluate potential multiplicative interactions of the 2 variables by comparing the models with and without the cross-product term of these variables.

As part of an ongoing substudy of the Tennessee Colorectal Polyp Study, urinary PGEM concentrations were determined for 598 male and 283 female participants. Participants were eligible for this study if they reported no use of nonsteroidal antiinflammatory drugs 48 h before urine collection. Cases were matched to control subjects on the basis of age, sex, race, and study site. We identified participants who had urinary PGEM determinations and had complete FFQ data. Because urinary PGEM data were skewed to high values, we normalized the distribution by log transformation of urinary PGEM data. We calculated partial Spearman's correlation coefficients between log-transformed urinary PGEM concentrations and the total marine-derived n−3 PUFA dietary intake. Partial Spearman's correlation coefficients were adjusted for age and total energy intake. Log-transformed urinary PGEM concentrations were compared across dietary quintiles of marine-derived n−3 PUFAs by using the ANOVA test. All statistical calculations were performed with SAS software (version 9.2; SAS Institute).

RESULTS

Demographic and lifestyle characteristics stratified by case status and sex are presented in **Table 1**. In men and women, smoking was more common in adenomatous and hyperplastic polyp cases than in control subjects. The daily calcium and marine-derived n−3 PUFA intake was higher in control subjects than in adenomatous and hyperplastic polyp cases for men and women. In men, but not in women, the dietary intake of α-linolenic acid was lower in control subjects than in colorectal polyp cases.

There was no association between dietary intakes of linoleic acid and arachidonic acid for either adenomatous or hyperplastic polyps (**Table 2**). In men, there was a significant trend of increased risk of hyperplastic polyps with increasing dietary intake of α-linolenic acid (P-trend = 0.03). Compared with men who reported the lowest intake of α-linolenic acid, men who reported the highest intake of α-linolenic acid had an adjusted OR of 1.51 (95% CI: 1.03, 2.21) for hyperplastic polyps. No associations were seen in men between the intake of α-linolenic acid and adenomatous polyp risk. There were no associations shown between the intake of marine-derived n−3 PUFAs and adenomatous or hyperplastic polyp risk in men. Compared with women who reported the lowest intake of marine-derived n−3 PUFAs, women who reported the highest intake of marine-derived n−3 PUFAs had an OR of 0.67 (95% CI: 0.47, 0.97) for adenomatous polyp risk. There was a significant trend between increasing marine-derived n−3 PUFA intake and decreased adenomatous polyp risk in women (P-trend = 0.01). In women, but not in men, there was a significant trend (P-trend = 0.04) with an increasing dietary ratio of total n−6 PUFAs to marine-derived n−3 PUFAs and colorectal adenoma risk. There was no evidence of a significant interaction between sex and linoleic acid (P = 0.15), arachidonic acid (P = 0.72), α-linolenic acid (P = 0.14), marine-derived n−3 PUFA intake (P = 0.40), or the ratio of n−6 PUFAs to marine-derived n−3 PUFAs (P = 0.17) and any adenomatous polyp risk. For hyperplastic polyp risk, there was no evidence of a significant interaction between sex and linoleic acid (P = 0.54), arachidonic acid (P = 0.25), α-linolenic acid (P = 0.69), marine-derived n−3 PUFA intake (P = 0.38), or the ratio of n−6 PUFAs to marine-derived n−3 PUFAs (P = 0.17).

When stratified by nonadvanced and advanced adenomas, there was no evidence in a difference of risk by type of adenoma although a borderline significant trend (P-trend = 0.07) was shown with increasing dietary α-linolenic acid intake in women and nonadvanced adenomas (*see* supplemental material under "Supplemental data" in the online issue.) Women who reported the highest intake of marine-derived n−3 PUFAs had lower risk of both nonadvanced (OR: 0.69; 95% CI: 0.46, 1.04) and advanced (OR: 0.57; 95% CI: 0.29; 1.14) adenomas than did women with the lowest intake (P-trend = 0.03 and 0.09, respectively).

The dietary intake of marine-derived n−3 PUFAs in women was negatively correlated to urinary PGEM concentrations (r = −0.18, P = 0.002) (**Table 3**). This correlation was our hypothesized relation with increasing intakes of marine-derived n−3 PUFA associated with lower concentrations of PGEM. There were no significant differences between quintiles of intake of marine-derived n−3 PUFA and concentrations of urinary PGEM in men (**Figure 1**). Women in the highest quintile of marine-derived n−3 PUFAs intake had lower concentrations of PGEM than did women in the lowest quintiles of intake (P = 0.01).

DISCUSSION

In this large, colonoscopy-based case-control study of colorectal polyps, we showed the dietary intake of marine-derived n−3 PUFAs to be associated with a decreased risk of adenomatous polyps in women, but not in men, although women consumed less fish than did men. Women in the highest quintile of marine-derive n−3 PUFA intake consumed, on average, 3 servings of fish per week compared with 0.5 servings of fish per week for women in the lowest quintile. For women, this higher intake of marine-derived n−3 PUFAs was associated with lower production of prostaglandin E_2, which may suggest that the alteration of eicosanoid production is an important mechanism that underlies the chemopreventive effects of marine-derived n−3 PUFAs. In a previous, nested case-control study of CRC in Chinese women, we showed a significant correlation between the dietary ratio of n−6 to n−3 PUFAs and urinary PGEM (r = 0.12, P = 0.03) (20), which was similar to the correlation we showed between this ratio and urinary PGEM production in women in this study (r = 0.21, P = 0.003). Comparisons between these 2 populations are difficult because of their very different background dietary patterns.

This sex-specific effect of marine-derived n−3 PUFAs on colorectal neoplasm risk is intriguing and has been previously reported in animal models of CRC (26). Although our results from the FFQ suggested that women consumed lower concentrations of

TABLE 3
Urinary PGEM and dietary intake of PUFAs adjusted for age and total energy intake[1]

	Men (n = 598) (range: 0.4–286 ng PGEM/mg creatinine; median: 13.2 ng PGEM/mg creatinine)	Women (n = 283) (range: 0.5–94 ng PGEM/mg creatinine; median: 7.1 ng PGEM/mg creatinine)
Linoleic acid		
Men: range, 3.3–67.3 g/d; median, 16.9 g/d; women: range, 2.3–30.0 g/d; median, 10.1 g/d	0.006 (−0.07, 0.09)	0.009 (−0.11, 0.12)
P	0.83	0.88
Arachidonic acid		
Men: range, 0.001–0.50 g/d; median, 0.1 g/d; women: range, 0.008–0.25 g/d; median, 0.06 g/d	−0.01 (−0.09, 0.07)	0.05 (−0.06, 0.17)
P	0.81	0.36
α-Linolenic acid		
Men: range, 0.34–6.4 g/d; median, 1.5 g/d; women: range, 0.17–3.5 g/d; median, 0.8 g/d	0.03 (−0.05, 0.11)	0.09 (−0.03, 0.20)
P	0.51	0.14
Marine-derived n−3 PUFAs[2]		
Men: range, 0–1.4 g/d; median, 0.1 g/d; women: range, 0–0.9 g/d; median, 0.06 g/d	−0.04 (−0.12, 0.04)	−0.18 (−0.29, −0.07)
P	0.39	0.002
Ratio of n−6 PUFAs to marine-derived n−3 PUFAs		
Men: range, 12–53,381; median, 157; women: range, 16–61,662; median, 169	0.04 (−0.04, 0.12)	0.21 (0.10–0.32)
P	0.38	0.003

[1] All values are partial Spearman's correlation coefficients; 95% CIs in parentheses. PGEM, prostaglandin E_2 metabolite.
[2] Marine-derived n−3 PUFAs = EPA + docosapentanoic acid + DHA.

marine-derived n−3 PUFAs than did men, this result may not translate into lower tissue concentrations of n−3 PUFAs. Sex differences in tissue concentrations of n−3 PUFAs that are independent of dietary intake have been described, but the mechanism that underlies this effect is still unclear (27–29). In human consumption studies that used stable isotopes, women showed an increased conversion of α-linolenic acid to DHA compared with that of men (30, 31). Estrogen appears to contribute to this effect via the activation of peroxisome proliferator activated receptor-α with the subsequent increased expression of desaturases and elongases (32, 33). These differences could have clinical implications as shown by the favorable effects of dietary α-linolenic acid on sudden cardiac death risk that have been reported for women more so than for men (34, 35). Nevertheless, we did not find any evidence of decreased risk of colorectal polyps with an increasing dietary intake of α-linolenic acid, and, in fact, an increasing intake of α-linolenic acid was associated with increased polyp risk.

Human studies on the association of marine-derived n−3 PUFAs and CRC have been largely observational. In a meta-

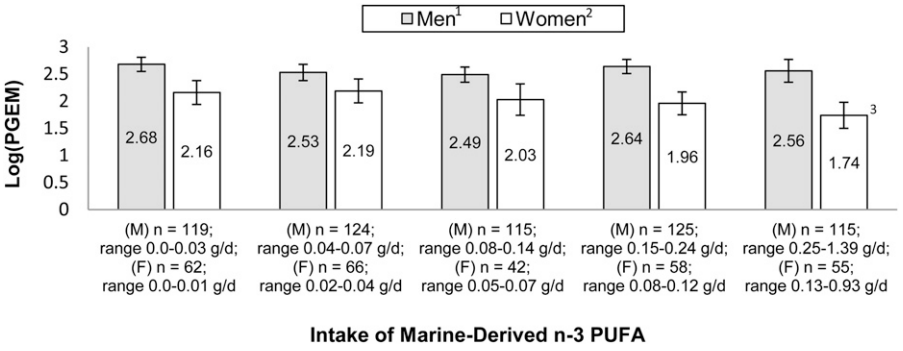

FIGURE 1. Mean (95% CI) concentrations of urinary PGEM by quintile of dietary marine-derived n−3 PUFA intake. [1]*P*-trend in men = 0.23; [2]*P*-trend in women = 0.04; [3]first (lowest) quintile compared with the fifth quintile, $P = 0.01$. PGEM, prostaglandin E_2 metabolite.

analysis by Geelen et al (16), 14 prospective cohort studies were pooled together for an RR of 0.88 (95% CI: 0.78, 1.00) for the highest compared with the lowest fish-consumption category for CRC risk. Fewer studies have evaluated marine-derived n−3 PUFAs and colorectal adenoma risk. In a large, prospective study conducted in the United States, a higher intake of marine-derived n−3 PUFAs as determined by using a FFQ was not associated with reduced risk of distal colorectal adenoma risk; however, there was an inverse association between a higher dietary intake of marine-derived n−3 PUFAs and large adenomas that did not reach statistical significance (OR: 0.74: 95% CI: 0.54, 1.01) (36). In our study, when stratified by adenomatous polyp location, we showed no major differences between the association of marine-derived n−3 PUFAs and adenomatous polyp risk of either distal or proximal polyps (data not shown).

Two studies have evaluated fatty acid exposure on the basis of dietary biomarkers and colorectal adenoma risk. A Dutch study that included 52 sporadic adenoma cases and 57 polyp-free control subjects estimated dietary fatty acid exposure by measuring adipose tissue fatty acid contents obtained from the buttocks (37). The adjusted OR for the highest compared with lowest tertile was 0.3 (95% CI: 0.1, 1.1) with a borderline significant *P*-trend of 0.07. Ghadimi et al (38) conducted a case-control study of 203 adenomas and 179 control subjects and measured serum fatty acid concentrations by using gas chromatography. The study showed a protective trend with increasing serum DHA concentrations and colorectal adenomas in both men and women. The study was conducted in Japan, where the baseline consumption of marine-derived n−3 PUFAs is much higher than in the United States. If there is a threshold effect related to absolute concentrations of marine-derived n−3 PUFAs consumed, which has been suggested in some studies (39), then we may not have seen an effect on the basis of the concentrations on intake in men in our population.

An increase in EPA intake results in higher tissue concentrations of EPA with a possible reduction in tissue concentrations of arachidonic acid (14, 40–42). The implication of this PUFA substitution on eicosanoid production has been shown in several experimental models. In human HCA-7 CRC cells, the incorporation of EPA from cell-culture medium resulted in reduced synthesis of prostaglandin E_2 (43).The feeding of fish oil in mouse models reduced concentrations of prostaglandin E_2 in response to azoxymethane (15), whereas in *fat-1* transgenic mice, which endogenously synthesize n−3 PUFAs from dietary n−6 PUFAs, the concentrations of prostaglandin E_2 in response to experimental colitis were markedly decreased compared with those of wild-type mice (44). Finally, in a small randomized clinical trial in humans, fish-oil supplements lowered the rectal mucosal tissue production of prostaglandin E_2 more than did a placebo (45). Thus, emerging evidence suggests that prostaglandin E_2 production can be manipulated on the basis of dietary PUFA intake; however, future work is necessary to link these findings to clinical outcomes.

Few studies exist that have evaluated dietary risk factors for hyperplastic polyps. When dietary fat has been evaluated, it is generally a composite outcome of total fat (46–48) or animal fat (49, 50) and not by individual fatty acids, which make comparisons with our study difficult. In our study, only α-linolenic acid was associated with an increased risk of hyperplastic polyps. These results were surprising given the presumed antiinflammatory action of α-linolenic acid (4). Indeed, flaxseed oil, which is a dietary source of α-linolenic acid, reduced adenoma formation in APC^{Min} mice (51). Thus, our results could have been a chance finding and would need to be confirmed in other studies. Our findings of a lack of association of dietary marine-derived n−3 PUFAs on hyperplastic, as opposed to adenomatous, polyp risk would be expected if the beneficial effects of n−3 PUFAs are mediated through a reduction in prostaglandin E_2. The overexpression of cyclooxygenase-2 has been well documented in adenomatous polyps but has been much less commonly described in hyperplastic polyps, which suggests that prostaglandin E_2 may not play as important a role in hyperplastic polyp development (52–54).

Our study had several strengths. First, the Tennessee Colorectal Polyp Study is one of the largest colonoscopy-based case-control studies of colorectal polyps conducted, which provided adequate power for sex-specific analyses. In addition, only patients with complete colonoscopies were included within the study, which ensured a truly polyp-free control group.

There were several weaknesses to the study. As a case-control study, dietary exposure could be subject to recall bias. However, this bias might have been mitigated because the vast majority of participants were unaware of their adenomatous polyp diagnosis at the time of interview. A second limitation was our ascertainment of dietary PUFA use was based on FFQs, which have been shown to have a wide range of correlations with various biomarkers of fatty acid intake from 0.15 for α-linolenic acid to 0.50 for EPA (55–58). In addition, the ascertainment of participant use of fish-oil supplements was added to the baseline questionnaire after study initiation and was missing in 77% of participants and, therefore, was not evaluated in this study. Thus, we may have underestimated total dietary exposure to marine-derived n−3 PUFAs.

In conclusion, we showed that women who consumed higher concentrations of marine-derived n−3 PUFAs had a lower risk of colorectal adenomas. Higher consumption of these fatty acids was also negatively correlated with prostaglandin E_2 production. Future interventional studies should be conducted to determine whether dietary manipulation of fatty acid intake can reduce colorectal neoplasm risk and whether supplementation goals may need to be sex specific.

The authors' responsibilities were as follows—HJM, MJS, QD, and WZ: designed the research; QC, WES, GLM, and RMN: conducted the research; QC and GLM: provided essential reagents or materials; HJM, MJS, and WZ: analyzed data or performed statistical analysis; HJM and MJS: wrote the manuscript; and HJM and WZ: had primary responsibility for the final content of the manuscript. None of the authors had a conflict of interest.

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