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Intake or Blood Levels of n-3 Polyunsaturated Fatty Acids and Risk of Colorectal Cancer: A Systematic Review and Meta-analysis of Prospective Studies

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ABSTRACT

Background: Previous results of the association between n-3 polyunsaturated fatty acids (PUFA) and colorectal cancer were inconsistent. We conducted a systematic review and meta-analysis of prospective studies.

Methods: The PubMed and Embase databases were searched through July 10, 2019, followed by a manual search. A random-effects model was used.

Results: Twenty prospective studies, including 18,102 cases and 1,360,046 participants, were included. The pooled RR of colorectal cancer for the highest versus lowest category of n-3 PUFA intake was 0.97 [95% confidence interval (CI), 0.90–1.04]. Regarding the type of n-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intakes were inversely associated with 11% (RR = 0.89; 95% CI, 0.80–0.99) and 12% (RR = 0.88; 95% CI, 0.81–0.96) lower colorectal cancer risks, respectively, in the comparison of the highest versus lowest category. Increments of 0.1 g/day of EPA (RR = 0.95; 95% CI, 0.92–0.98) and DHA (RR = 0.97; 95% CI, 0.95–0.99) intakes were associated with a lower colorectal cancer risk. Regarding the blood levels of n-3 PUFAs, the pooled RR of colorectal cancer for the highest versus lowest category of blood levels of n-3 PUFAs was 0.79 (95% CI, 0.64–0.98). The risk of colorectal cancer decreased by 4% for every 1% increase in blood n-3 PUFA levels (RR = 0.96; 95% CI, 0.92–1.00).

Conclusions: High blood n-3 PUFA levels are inversely associated with colorectal cancer risk, and high n-3 PUFA intake is suggestively associated with lower colorectal cancer risk.

Impact: Our findings suggest that high blood n-3 PUFA levels may be associated with reduced colorectal cancer risk, but further studies are needed.

Introduction

Worldwide, colorectal cancer is the third most frequently diagnosed cancer and the fourth most common cause of death from cancer, accounting for 700,000 cancer-related deaths (1). Considering the high global burden of colorectal cancer, it is important to identify potential risk factors for colorectal cancer and develop preventive strategies against colorectal cancer. The most recent report from the World Cancer Research Fund concluded that physical activity, alcohol consumption, and body fatness are convincingly associated with the risk of colorectal cancer (2). However, most of the foods and nutrients had weak or limited evidence of an association with the risk of colorectal cancer, except for processed meat. n-3 polyunsaturated fatty acid (PUFA) intake was also categorized as "limited-no conclusion."

n-3 PUFAs include α-linolenic acid (ALA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid (EPA). Marine n-3 PUFAs, which are derived from marine sources and include DHA, DPA, and EPA, have been observed to exert potent anti-inflammatory effects and inhibit colorectal carcinogenesis (3–5). To date, many prospective studies have examined the association between the intake or blood levels of n-3 PUFAs and colorectal cancer risk (6–24). A previous meta-analysis including 8,775 colorectal cancer cases reported no association between n-3 PUFA intake and the risk of colorectal cancer (25). Since then, additional prospective studies including a large cohort study that included 6,291 cases among 476,160 subjects have investigated the association between n-3 PUFAs and the risk of colorectal cancer (18–21, 24). Dietary fat intake was mostly assessed with self-report questionnaires, which have a limitation of potential misclassification (26); n-3 PUFAs are essential fatty acids that humans cannot synthesize and should obtain through dietary intake. Thus, n-3 PUFA biomarkers, such as blood levels, may provide a more precise assessment of n-3 PUFA intake (27, 28).

Therefore, we performed a systematic review and meta-analysis of prospective studies to quantitatively assess the evidence of the association between the intake or blood levels of n-3 PUFAs and the risk of colorectal cancer.

Materials and Methods

Literature search and selection

We searched the PubMed and Embase databases from inception to July 10, 2019, to identify eligible studies published in the form of full-length articles. The following keywords were used: "(n-3 OR omega-3 OR marine OR docosahexaenoic OR eicosapentaenoic OR docosapentaenoic OR α-linolenic acid OR DHA or EPA or DPA or ALA) AND (colorectal OR colon OR rectal) AND (cancer OR neoplasms OR carcinoma)" (Supplementary Table S1). In addition, we supplemented the search by reviewing the reference lists from the retrieved articles or published reviews.

Studies were included in this meta-analysis when they met the following criteria: (i) prospective design (cohort or nested case–

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control); (ii) the exposure of interest was intake of n-3 PUFAs or blood (whole blood, plasma, or serum) levels of n-3 PUFAs; (iii) the outcome of interest was colorectal, colon, or rectal cancer; and (iv) RRs and 95% confidence intervals (CI) were provided. When more than one publication was from the same cohort, the study with the largest population and longest follow-up duration was included in the meta-analysis.

Data extraction

Two investigators (Y. Kim and J. Kim) independently extracted data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (29). Any discrepancies were addressed by examining the original studies and through discussion. The information extracted from each study is as follows: first author's last name, year of publication, country or region where the study was conducted, duration of follow-up or dates of study period, sex, baseline age, number of cases and subjects/controls or person-time, types of n-3 PUFAs (ALA, EPA, DHA, DPA), anatomic site of the tumor (colorectal, colon, rectal), adjustment for potential confounders, and RRs with corresponding 95% CIs for each category of n-3 PUFA intake or blood levels of n-3 PUFAs. When a study provided several RRs, we included the RRs that reflected the greatest degree of adjustment for potential confounders. One publication was considered as two prospective cohort studies because it provided RRs from two different cohorts (17).

Quality assessment

To assess the quality of the studies included in the meta-analysis, the Newcastle–Ottawa quality assessment scale (30) was used. The quality of each study was assessed independently by two investigators (Y. Kim and J. Kim) based on three domains: selection (representativeness of the exposed cohort; ascertainment of exposure), comparability of cohorts (adjustment for important confounders), and outcome (ascertainment of outcome; duration of follow-up; adequacy of follow-up). Any disagreements between the investigators were resolved by discussion to reach a consensus. We considered a study with scores of 10 or higher (out of 13), 7 to 9, and 6 or less as being of high, good, and low quality, respectively.

Statistical analysis

We combined study-specific RRs using a DerSimonian and Laird random-effects model (31), which considers both within- and between-study variations. For studies that reported RRs separately for different types of n-3 PUFAs (8, 24), we combined the RRs using a fixed effects model, and the pooled RRs were included in the meta-analysis. For analysis of intake, we performed an analysis of marine n-3 PUFAs (including EPA, DHA, and DPA) in addition to total n-3 PUFAs (including ALA, EPA, DHA, and DPA). We conducted subgroup analyses by sex, geographic region, cancer sites, duration of follow-up, type of fatty acids, quality score and adjustment for age, body mass index (BMI), smoking, alcohol, and physical activity to explore whether the association differed by characteristics of the study or population. To test for variations across subgroups, a meta-regression analysis was performed.

For the dose–response analysis, the method proposed by Greenland and Longnecker (32–34) was used. For each study, the median value of n-3 PUFA intake or blood levels of n-3 PUFAs in each category was assigned to each corresponding RR. Open-ended categories were assumed to have the same interval of dietary intake or blood level as the adjacent category. When n-3 PUFA intakes were provided in densities (g/1,000 kcal; ref. 11), we converted the values into absolute intakes (g/day) using median daily energy intake of the study population. We presented the RRs for a 0.5 g/day increase in n-3 PUFA intake and as a 1% increase in total fatty acids for blood levels of n-3 PUFAs. A potential nonlinear association between dietary or blood levels of n-3 PUFAs and colorectal cancer risk was also examined using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (35). The P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero.

Statistical heterogeneity among studies and inconsistencies was evaluated using the Q statistic (36) and I^2 statistic (37). A sensitivity analysis that removed one study at one time and pooled the remaining studies was also performed to explore the robustness of the results. Potential publication bias was assessed through Begg (38) and Egger (39) tests. For statistical significance, the two-tailed α was set at $P = 0.05$. All statistical analyses were performed using Stata software version 14.2 (StataCorp).

Results

Study characteristics

A total of 20 prospective studies (6–24) including 18,102 colorectal cancer cases among 1,360,046 participants were eligible for the current meta-analysis. The detailed study selection process is shown in **Fig. 1**. **Table 1** shows the general characteristics of the studies included in the present meta-analysis. Fifteen studies provided RRs of n-3 PUFA intake (6–17, 19, 20), 3 studies provided RRs of blood levels of n-3 PUFAs (22–24), and 2 studies provided RRs of both n-3 PUFA intake and blood levels of n-3 PUFAs (18, 21). The follow-up periods ranged from 3.3 years to 26 years, and the median follow-up time was 9.3 years. Eight studies were conducted in the United States (6, 10, 12, 16, 17, 20, 23), 6 studies were conducted in Asia (9, 11, 13, 14, 22, 24), 5 studies were conducted in Europe (7, 8, 15, 19, 21), and one study was conducted in Oceania (18). All studies controlled for age, and most of the studies adjusted for alcohol consumption ($n = 17$; refs. 7, 9–11, 13–24), BMI ($n = 16$; refs. 7–17, 20–23), smoking ($n = 16$; refs. 7, 9–11, 13–18, 20–24), and physical activity ($n = 16$; refs. 7, 9, 11–18, 20–24). According to the quality assessment, scores ranged from 9 to 12 indicating good or high quality.

n-3 PUFA intake

Seventeen prospective studies (6–21) that included 17,405 cases among 1,358,236 participants were included in the meta-analysis of the association between n-3 PUFA intake and the risk of colorectal cancer. The pooled RR for the highest versus lowest levels of n-3 PUFA intake was 0.97 (95% CI, 0.90–1.04; $I^2 = 34.6\%$; $P_{heterogeneity} = 0.05$), with no significant heterogeneity (**Fig. 2**; **Table 2**). The association between n-3 PUFA intake and risk of cancer was not significantly different by sex, geographical region, cancer sites, duration of follow-up, quality score, or adjustment for covariates (P for difference > 0.1 in all comparisons; **Table 2**). Regarding the type of n-3 PUFA, EPA (RR = 0.89; 95% CI, 0.80–0.99), and DHA (RR = 0.88; 95% CI, 0.81–0.96) intakes were inversely associated with lower risks of colorectal cancer. On the other hand, a non-significant positive association was observed between ALA intake and colorectal cancer risk (RR = 1.01; 95% CI, 0.92–1.12). In the dose–response analysis, 13 prospective studies (7, 9, 11–17, 19–21) including 15,838 cases among 1,198,638 participants were included. The pooled RR for a 0.5 g/day increase in n-3 PUFA intake was 1.00 (95% CI, 0.97–1.03; **Table 2**). We found no significant nonlinear

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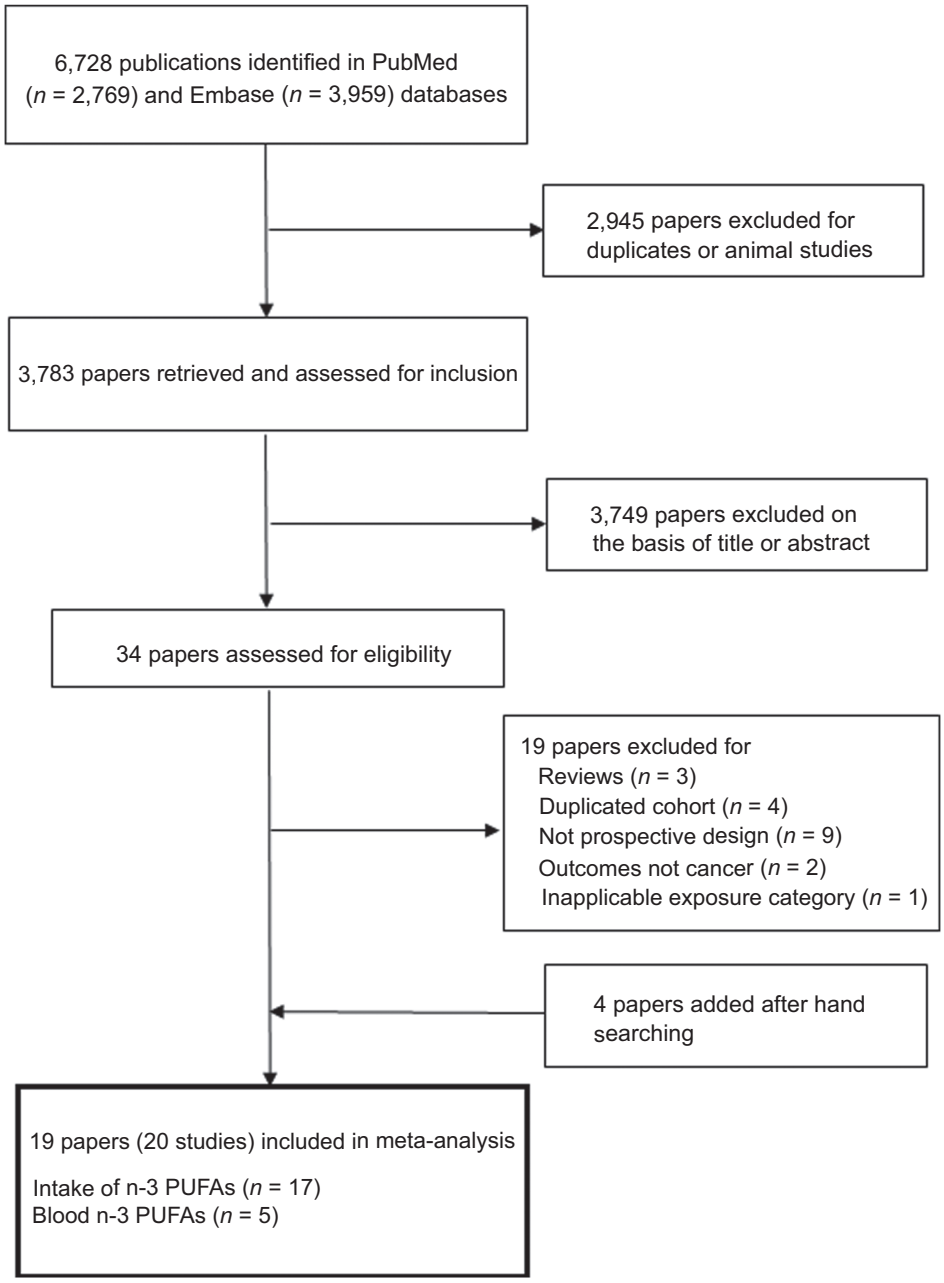

Figure 1.
Flow chart of study selection. The flow chart shows the process used to select prospective studies for the meta-analysis of the association between n-3 PUFAs and the risk of colorectal cancer.

association between n-3 PUFA intake and the risk of colorectal cancer (P for nonlinearity = 0.39; **Fig. 2**). Regarding the type of n-3 PUFA, an increase of 0.1 g/day of EPA and DHA intake was associated with 5% and 3% lower risks of colorectal cancer, respectively (**Table 2**). A significant nonlinear association was not observed for EPA (P for nonlinearity = 0.06), DHA (P for nonlinearity = 0.06), DPA (P for nonlinearity = 0.10), or ALA (P for nonlinearity = 0.48) intake (**Fig. 3**).

Thirteen prospective studies (8–14, 16–18, 20, 21) that included 16,239 cases among 1,288,528 participants were included in the meta-analysis of the association between marine n-3 PUFA intake and risk of colorectal cancer. The pooled RR for the highest versus lowest levels of marine n-3 PUFA intake was 0.98 (95% CI, 0.92–1.05; Supplementary Table S2). We found no significant difference by sex, geographic region, cancer sites, duration of follow-up, or adjustment for covariates (P for difference > 0.1 in all comparisons). Ten prospective studies (9, 11–14, 16, 17, 20, 21) with 14,884 cases and 1,164,145 participants were included in the dose–response analysis. The pooled RR for a 0.5 g/day increase in marine n-3 PUFA intake was 1.01 (95% CI, 0.95–1.07). A nonlinear association was not observed between marine n-3 PUFA intake and colorectal cancer risk (P for nonlinearity = 0.55; Supplementary Fig. S1).

Blood levels of n-3 PUFAs

Five prospective studies (18, 21–24) with 1,553 cases, among 6,937 participants were included in the meta-analysis of the association between blood levels of n-3 PUFAs and risk of colorectal cancer. The pooled RR for the highest versus lowest blood levels of n-3

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Table 1. Characteristics of prospective studies included in the meta-analysis of n-3 PUFAs and colorectal cancer.

First author, year	Country	Cohort name	Follow-up period	Age at baseline, years	Study size		Sex of subjects	Exposure	Adjustment for covariates
					Subjects	No. of cases			
Bostick, 1994	United States	The Iowa Women's Health Study	5 years	55–69	35,215	212	Female	n-3 PUFA intake	Age, total energy intake, height, parity, total vitamin E intake, a total vitamin E by age interaction term, and vitamin A supplement intake
Pietinen, 1999	Finland	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	8 years	50–69	27,111	185	Male	n-3 PUFA intake	Age, supplement group, smoking years, BMI, alcohol, education, physical activity at work, and calcium intake
Terry, 2001	Sweden	The Swedish Mammography Screening Cohort	9.6 years	40–74	61,463	460	Female	n-3 PUFA intake	Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, and vitamin D. Saturated fat, monounsaturated fat, polyunsaturated fat.
Kojima, 2005	Japan	Japan Collaborative Cohort Study	7.1 years	40–79	650	169	Male and female	Blood levels of n-3 PUFAs	Family history of colorectal cancer in first-degree relatives, BMI, education, smoking and alcohol drinking history, green leafy vegetable intake, and physical exercise. Cases and controls were matched on age and participating institution.
Oba, 2006	Japan	A community-based cohort in Japan	7 years	≥35	30,221	203	Male and female	n-3 PUFA intake	Age, height, BMI, total pack-years of cigarette smoking, alcohol intake, and physical activity
Hall, 2007	United States	Physicians' Health Study	1982–1995	40–84	460	178	Male	Blood levels of n-3 PUFAs	BMI, multivitamin use, history of diabetes, random assignment to aspirin or placebo, vigorous exercise, alcohol intake, and quartile of red meat intake. Controls were matched on age and smoking status.
Hall, 2008	United States	Physicians' Health Study	17.6 years	53.6, mean	21,406	500	Male	n-3 PUFA intake	Age, smoking, BMI, multivitamin use, history of diabetes, random assignment to aspirin or placebo, vigorous exercise, alcohol intake, and quartile of red meat intake
Butler, 2009	Singapore	Singapore Chinese Health Study	9.8 years	45–74	61,321	961	Male and female	n-3 PUFA intake	Age at interview, sex, dialect group (Cantonese, Hokkien), interview year, diabetes at baseline, smoking history, BMI, alcohol intake, education, any weekly physical activity, first-degree relative diagnosed with colorectal cancer, and total daily energy intake
Murff, 2009	China	Shanghai Women's Health Study	1996–2007	40–70	73,242	396	Female	n-3 PUFA intake	Age, energy intake, total energy-adjusted n-6 PUFA intake, energy-adjusted ratio of total n-6 PUFA to n-3 PUFA intake, BMI, current smoker, alcohol use, regular physical activity in past 5 y, total energy-adjusted red meat intake, menopausal status, hormone replacement therapy use, multivitamin use, and aspirin use
Daniel, 2009	United States	Cancer Prevention Study-II Nutrition Cohort	6 years	70 male 68 female, mean	99,080	869	Male and female	n-3 PUFA intake	Age, energy, recreational physical activity, NSAID use, colorectal screening, BMI, and red and processed meat, low-fat dairy, fruit, and vegetable intake

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Table 1. Characteristics of prospective studies included in the meta-analysis of n-3 PUFAs and colorectal cancer. (Cont'd)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, years	Study size		Sex of subjects	Exposure	Adjustment for covariates
					Subjects	No. of cases			
Sasazuki, 2011	Japan	The Japan Public Health Center	9.3 years	40–69	98,466	1,268	Male and female	n-3 PUFA intake	Age, area, BMI, smoking status, alcohol drinking, past history of or medication use for diabetes mellitus, METs, screening for colorectal cancer, total calorie, intake of calcium, vitamin D, fiber, and red meat
Key, 2012	United Kingdom	UK Dietary Cohort Consortium	1985–2006	61.7, mean	2,415	547	Male and female	n-3 PUFA intake	Age, date of diary, sex, height, weight, energy intake, alcohol intake, fiber intake, smoking, education, social class, physical activity
Kantor, 2014	United States	VITamins And Lifestyle Study	6.7 years	50–76	68,109	488	Male and female	n-3 PUFA intake	Age, sex, race/ethnicity, education, BMI, energy intake, MET-hr per wk of moderate/vigorous activity, alcohol intake, smoking history, multivitamin use, calcium intake, dietary fiber intake, fruit and vegetable intake, red/processed meat intake, aspirin use, nonaspirin NSAID drug use, family history of colorectal cancer, history of sigmoidoscopy/colonoscopy, history of polyps, hormone replacement therapy, cardiovascular disease, memory loss, use of cholesterol-lowering drugs, and omega-6 (linoleic +arachidonic) intake
Song, 2014	United States	Nurses' Health Study	24 years	30–55	76,386	1,469	Female	n-3 PUFA intake	Age, calendar year, family history of colorectal cancer, prior lower gastrointestinal endoscopy, pack-years of smoking before age 30, BMI, physical activity, current multivitamin use, postmenopausal status and hormone use, regular aspirin or NSAID use, total caloric intake, red meat, processed meat, alcohol consumption, energy-adjusted intake of folate, calcium, vitamin D, and total fiber
Song, 2014	United States	Health Professionals Follow-up Study	26 years	40–75	47,143	987	Male	n-3 PUFA intake	Age, calendar year, family history of colorectal cancer, prior lower gastrointestinal endoscopy, pack-years of smoking before age 30, BMI, physical activity, current multivitamin use, regular aspirin or NSAID use, total caloric intake, red meat, process meat, alcohol consumption and energy-adjusted intake of folate, calcium, vitamin D, and total fiber
Hodge, 2015	Australia	Melbourne Collaborative Cohort Study	9 years	40–69	41,514	395	Male and female	n-3 PUFA intake; blood levels of n-3 PUFAs	Age, education, alcohol intake, smoking status, physical activity, total energy intake and stratified by: sex, ethnicity (Southern-European migrant vs. not), and family history of cancer
Kraja, 2015	Netherlands	Rotterdam Study	14.6 years	≥55	4,967	222	Male and female	n-3 PUFA intake	Age, sex, energy-adjusted dietary fiber intake, intake of vegetable, trans fat, fruit, alcohol, and sodium

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Table 1. Characteristics of prospective studies included in the meta-analysis of n-3 PUFAs and colorectal cancer. (Cont'd)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, years	Study size		Sex of subjects	Exposure	Adjustment for covariates
					Subjects	No. of cases			
Navarro, 2016	United States	Women's Health Initiative prospective cohort	11.7 years	50–79	134,017	1,952	Female	n-3 PUFA intake	Age, total energy intake, BMI, education, family history of colorectal cancer, history of colonoscopy, current NSAID use, alcohol intake, smoking history, physical activity, ever use of hormone therapy, folate, calcium, and red meat intake, study component, randomization assignment and treatment arm
Butler, 2017	Singapore	Singapore Chinese Health Study	3.3 years	45–74	700	350	Male and female	Blood levels of n-3 PUFAs	BMI, smoking, education level, alcohol use, weekly physical activity, history of diabetes, and use of NSAIDs. The control was matched to an index case by sex, dialect group, age, date of baseline interview, and date of biospecimen collection.
Aglago, 2019	Europe	European Prospective Investigation into Cancer and Nutrition	14.9 years	51.3, mean	476,160	6,291	Male and female	n-3 PUFA intake; blood levels of n-3 PUFAs	Age, sex, center, BMI, height, physical activity, smoking, education, and intakes of energy, alcohol, red and processed meat, fiber, dairy products

Abbreviations: MET, metabolic equivalent; No., number.

PUFAs was 0.79 (95% CI, 0.64–0.98; $I^2 = 22.8\%$; $P_{heterogeneity} = 0.26$), with no significant heterogeneity (**Fig. 4**). There was no significant difference by sex, geographical region, cancer sites, duration of follow-up, type of fatty acids, quality score, or adjustment for covariates (P for difference > 0.4 in all comparisons; **Table 2**). Three prospective studies (21–23) with 808 cases among 2,032 participants were included in the dose–response analysis. A 1% increase in blood n-3 PUFA level was associated with a 4% lower risk of colorectal cancer (RR = 0.96; 95% CI, 0.92–1.00; **Table 2**). There was no evidence of a nonlinear association between blood n-3 PUFA levels and colorectal cancer risk (P for nonlinearity = 0.46).

Publication bias

There was no evidence of publication bias in the literature regarding colorectal cancer risk and n-3 PUFA intake (Begg $P = 0.53$, Egger $P = 0.18$), marine n-3 PUFA intake (Begg $P = 0.89$, Egger $P = 0.27$), or blood n-3 PUFA levels (Begg $P = 0.76$, Egger $P = 0.23$).

Discussion

The current meta-analysis of 20 prospective studies including 18,102 colorectal cancer cases and 1,360,046 subjects investigated the association between n-3 PUFA intake/blood n-3 PUFA levels and colorectal cancer risk. Our findings indicated that blood levels of n-3 PUFAs were inversely associated with a reduced risk of colorectal cancer. People with high blood levels of n-3 PUFAs had a 21% lower risk of colorectal cancer than those with low blood levels of n-3 PUFAs. A 1% increase in blood n-3 PUFA levels was associated with a 4% lower risk of colorectal cancer. For n-3 PUFA intake, we found a nonsignificant, weak inverse association between total n-3 PUFA intake and colorectal cancer risk, but significant inverse associations between EPA and DHA intakes and colorectal cancer risk were observed in both the highest versus lowest analysis and the dose–response analysis. People with high intakes of EPA and DHA had an 11% and 12% lower risk of colorectal cancer than those with low intakes of EPA and DHA, respectively. Each additional 0.1 g of EPA and DHA intake daily was associated with a 5% and 3% lower risk of colorectal cancer, respectively.

We found a significant inverse association between blood n-3 PUFA levels and colorectal cancer risk but did not find a significant association between n-3 PUFA intake and colorectal cancer risk. Differences in the association between intake and blood levels and the risk of colorectal cancer have also been observed in relation to vitamin B_6. A meta-analysis including 13 prospective studies indicated that blood pyridoxal 5′-phosphate (PLP; the active form of vitamin B_6) levels are inversely associated with a lower risk of colorectal cancer, while vitamin B_6 intake was not significantly associated with colorectal cancer risk (40). In epidemiologic studies, dietary assessment is often accompanied by measurement errors, as most studies assess dietary intake using a food frequency questionnaire. Fatty acids are especially prone to this because similar foods can have different fatty acid compositions not distinguished by the food description provided by the tools used to evaluate diet (41); in addition, it is difficult to calculate specific fatty acid intake (42). Measurement errors are likely to be nondifferential and thus would probably have led to results closer to null findings. There is a possibility of attenuation in the inverse association between n-3 PUFA intake and the risk of colorectal cancer because of measurement error in assessing n-3 PUFA intake. As most studies conducted a single assessment of fatty acid levels, there is also a possibility of measurement error in blood

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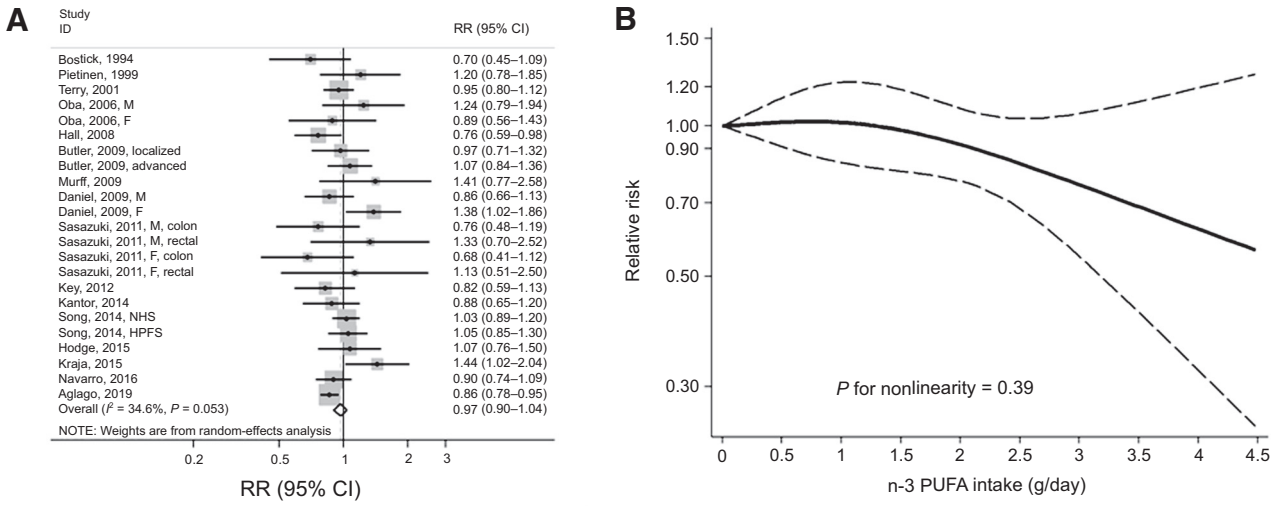

Figure 2.

A, Forest plot of prospective studies of colorectal cancer for the highest versus lowest category of n-3 PUFA intake, using a random-effects model. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from each prospective study, and the diamond indicates the pooled RR. **B,** Pooled dose–response association between n-3 PUFA intake and colorectal cancer. Data were modeled with random-effects restricted cubic spline models with 3 knots. The vertical axis is on a log scale.

Table 2. Summary of pooled RRs of colorectal cancer risk for n-3 PUFAs.

Variable	No. of studies	RR	95% CI	*P* for difference
		n-3 PUFA intake		
High versus low n-3 fatty acid intake				
All studies	17	0.97	0.90–1.04	
Sex				
Male	8	0.95	0.84–1.06	0.59
Female	10	0.99	0.89–1.09	
Geographic region				
United States	7	0.95	0.84–1.07	
Europe	5	0.98	0.83–1.15	0.83[a]
Asia	4	1.01	0.88–1.16	0.59[a]
Oceania	1	1.07	0.76–1.50	0.59[a]
Cancer sites				
Colon	9	0.94	0.83–1.06	0.49[b]
Proximal	4	0.84	0.72–1.00	0.11[c]
Distal	4	1.12	0.84–1.48	
Rectal	7	0.98	0.87–1.11	
Duration of follow-up				
<Median	9	0.98	0.86–1.11	0.89
≥Median	8	0.96	0.88–1.05	
Type of fatty acids				
ALA	7	1.01	0.92–1.12	
EPA	5	0.89	0.80–0.99	0.04[d]
DHA	5	0.88	0.81–0.96	0.05[d]
DPA	3	0.87	0.74–1.03	0.01[d]
Quality score				
<10	2	0.92	0.54–1.56	0.79
≥10	15	0.97	0.90–1.04	
Adjustment for age, BMI, smoking, alcohol, and physical activity				
Yes	11	0.95	0.88–1.01	0.79
No	6	0.99	0.82–1.19	

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Table 2. Summary of pooled RRs of colorectal cancer risk for n-3 PUFAs. (Cont'd)

Variable	No. of studies	RR	95% CI	*P* for difference
Increase of g/day in n-3 PUFA intake				
n-3 PUFA, 0.5 g/day	13	1.00	0.97–1.03	
ALA, 0.1 g/day	5	1.00	0.996–1.01	
EPA, 0.1 g/day	3	0.95	0.92–0.98	
DHA, 0.1 g/day	3	0.97	0.95–0.99	
DPA, 0.1 g/day	2	0.87	0.73–1.03	
Blood levels of n-3 PUFAs				
High versus low blood levels of n-3 fatty acids				
All studies	5	0.79	0.64–0.98	
Sex				
Male	2	0.41	0.18–0.94	0.49
Female	1	0.85	0.38–1.91	
Geographic region				
Asia	2	0.76	0.50–1.15	0.98
Non-Asia	3	0.80	0.62–1.02	
Cancer sites				
Colon	2	0.81	0.62–1.06	0.47
Rectal	1	1.08	0.69–1.67	
Duration of follow-up				
<Median	3	0.73	0.51–1.05	0.75
≥Median	2	0.83	0.64–1.08	
Type of fatty acids				
ALA	3	0.88	0.49–1.58	
EPA	5	0.82	0.67–1.00	0.75[e]
DHA	5	0.80	0.61–1.06	0.77[e]
DPA	3	0.72	0.46–1.12	0.60[e]
Quality score				
<10	2	0.81	0.59–1.11	0.87
≥10	3	0.75	0.53–1.08	
Adjustment for age, BMI, smoking, alcohol, and physical activity				
Yes	3	0.67	0.41–1.10	0.70
No	2	0.82	0.66–1.01	
Increase of 1% in blood levels of n-3 PUFAs				
All studies	3	0.96	0.92–1.00	

Abbreviation: No., number.
[a]*P* value difference in RRs of n-3 PUFA intake for Europe versus United States ($P = 0.83$), Asia versus United States ($P = 0.59$), and Oceania versus United States ($P = 0.59$).
[b]*P* value difference in RRs of n-3 PUFA intake for rectal cancer versus colon cancer.
[c]*P* value difference in RRs of n-3 PUFA intake for distal colon cancer versus proximal colon cancer.
[d]*P* value difference in RRs of n-3 PUFA intake for EPA versus ALA ($P = 0.04$), DHA versus ALA ($P = 0.05$), and DPA versus ALA ($P = 0.01$).
[e]*P* value difference in RRs of blood levels of n-3 PUFAs for EPA versus ALA ($P = 0.75$), DHA versus ALA ($P = 0.77$), and DPA versus ALA ($P = 0.60$).

measures. However, previous studies suggested that blood levels of fatty acids can be a reasonably good biomarker of habitual dietary fat intake showing the strong correlation between dietary PUFA intake and blood levels of PUFAs even if it is a single blood sample (28, 43).

In the subgroup analysis by type of n-3 fatty acids, intakes of EPA and DHA were associated with a lower risk of colorectal cancer. DPA intake showed a nonsignificant association, and ALA intake was not significantly associated with a risk of colorectal cancer. These results are in line with the findings from previous meta-analyses indicating null associations between intake of ALA and colorectal cancer (25, 44). Most of the previous studies of n-3 PUFAs and risk of disease have focused on long-chain n-3 fatty acids, and evidence for the association between ALA (short-chain n-3 fatty acids) and health outcomes was limited (45). Our results by type of n-3 fatty acids should also be interpreted with caution due to the relatively small number of studies. We could not find significant differences by sex, geographical region, cancer sites, and duration of follow-up. Although the differences were not significant, observed inverse associations were slightly stronger in men and colon cancer than women and rectal cancer. The previous meta-analyses showed positive associations in women and rectal cancer, which was different from inverse associations in men and colon cancer (25, 44).

Several case–control studies have investigated the association between n-3 PUFA intake and the risk of colorectal cancer and found that high n-3 PUFA intake was inversely associated with a lower risk of colorectal cancer (46–50). A meta-analysis of 8 case–control studies also reported a 24% lower risk of colorectal cancer in people who had high biospecimen n-3 PUFA levels than those who had low biospecimen n-3 PUFA levels (51). Experimental studies showed that colorectal tumor incidence was lower in the group with n-3 PUFA treatment in rats (5) and that n-3 PUFA-rich diets inhibited the growth of colorectal tumors in a mouse model (4). In addition, another animal study suggested that EPA is a candidate to reduce the risk of colorectal cancer, showing a decrease in the number and size of polyps in mice fed EPA diets (52). Given the results of our meta-analysis and previous

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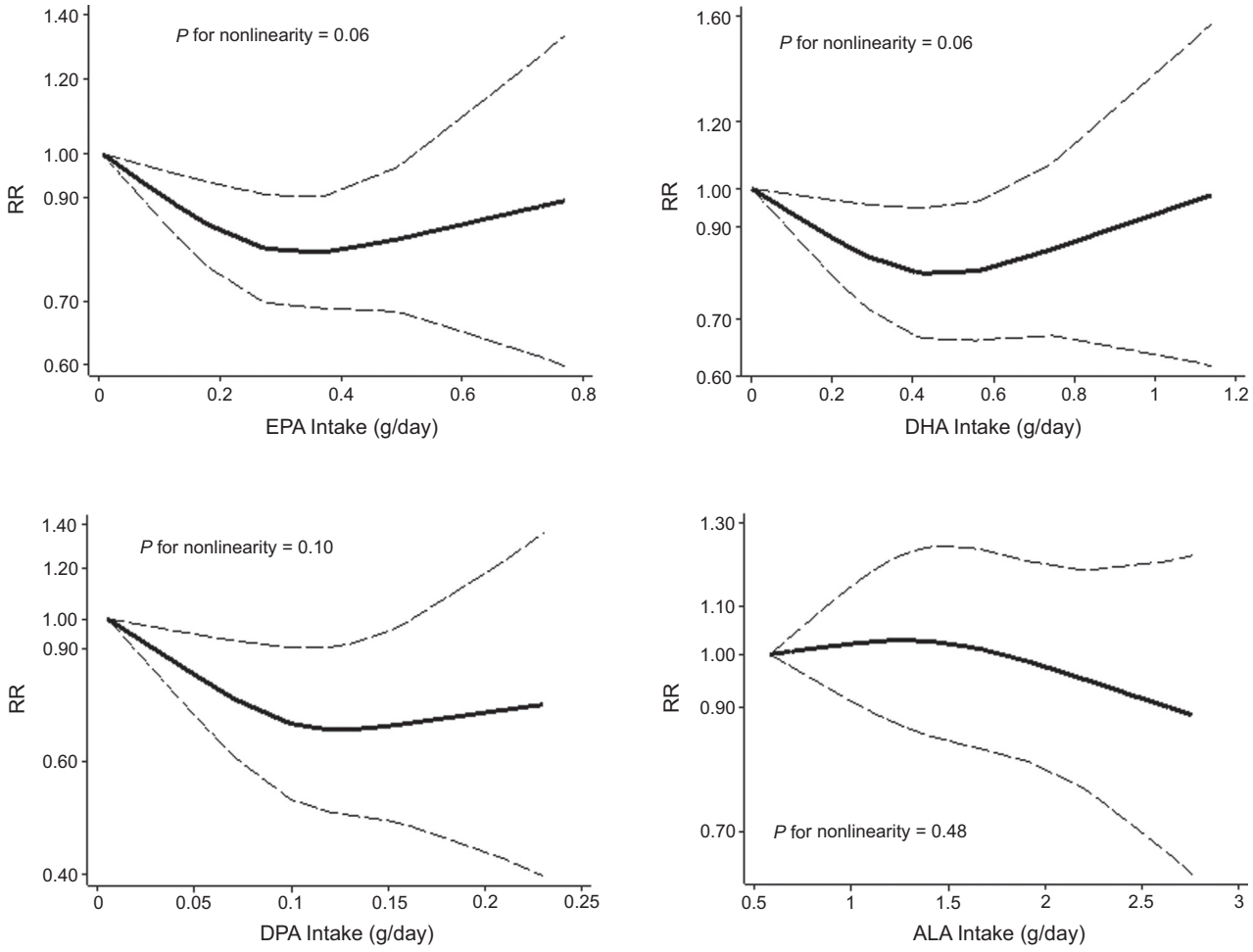

Figure 3.

Pooled dose–response associations of EPA, DHA, DPA, and ALA intake with colorectal cancer. Data were modeled with random-effects restricted cubic spline models with 3 knots. The vertical axis is on a log scale.

studies, n-3 PUFAs may have a beneficial effect against the development of colorectal cancer.

The potential protective effects of n-3 PUFAs in regard to the risk of colorectal cancer are biologically plausible. The most prominent mechanism for the anticancer activity of n-3 PUFAs is inhibition of the production of arachidonic acid–derived eicosanoids, which are positively associated with inflammation and carcinogenesis (53). This suppressive effect on the biosynthesis of arachidonic acid–derived eicosanoids results in reduced cell proliferation (54) and increased cell apoptosis (55). In addition, n-3 PUFAs may contribute to a decreased risk of colorectal cancer by affecting gene expression or signal transduction and alteration of free radical production (53). Recent experimental animal studies have shown that n-3 PUFAs have anti–colorectal cancer effects by modulating profiles of eicosanoid metabolites (4) and regulating the DNA methylation process (5). An intervention study conducted on humans also reported that high n-3 PUFA intake was associated with elevated apoptosis in the normal sigmoid colon of patients polypectomized for adenomas/tumors (56).

To the best of our knowledge, this is the first comprehensive meta-analysis to investigate the risk of colorectal cancer in relation to both n-3 PUFA intake and blood n-3 PUFA levels. Compared with previous meta-analysis (25) (including 8,775 cases) examining the association between n-3 PUFA intake and colorectal cancer risk, our meta-analysis (including 18,102 cases) included more than twice as many cases of colorectal cancer. The large sample population enhanced the statistical power of the results of the meta-analysis. In addition, this quantitative assessment included only prospective studies, and thus, our results were relatively free from recall or selection bias that could be of concern in retrospective studies. Despite these strengths, our meta-analysis has several limitations. First, our results for n-3 PUFA intake had the possibility of some degree of misclassification because most studies included in the meta-analysis evaluated n-3 PUFA intake by a single assessment with a food frequency questionnaire. We tried to supplement for measurement error in the assessment of n-3 PUFA intake by conducting a meta-analysis for both n-3 PUFA intake and blood n-3 PUFA levels. Second, because the current meta-analysis was based on observational studies, there was the possibility of potential effects of unknown or residual confounding factors on our results. When we conducted a limited analysis of studies adjusted for age, BMI, smoking, alcohol consumption, and physical activity,

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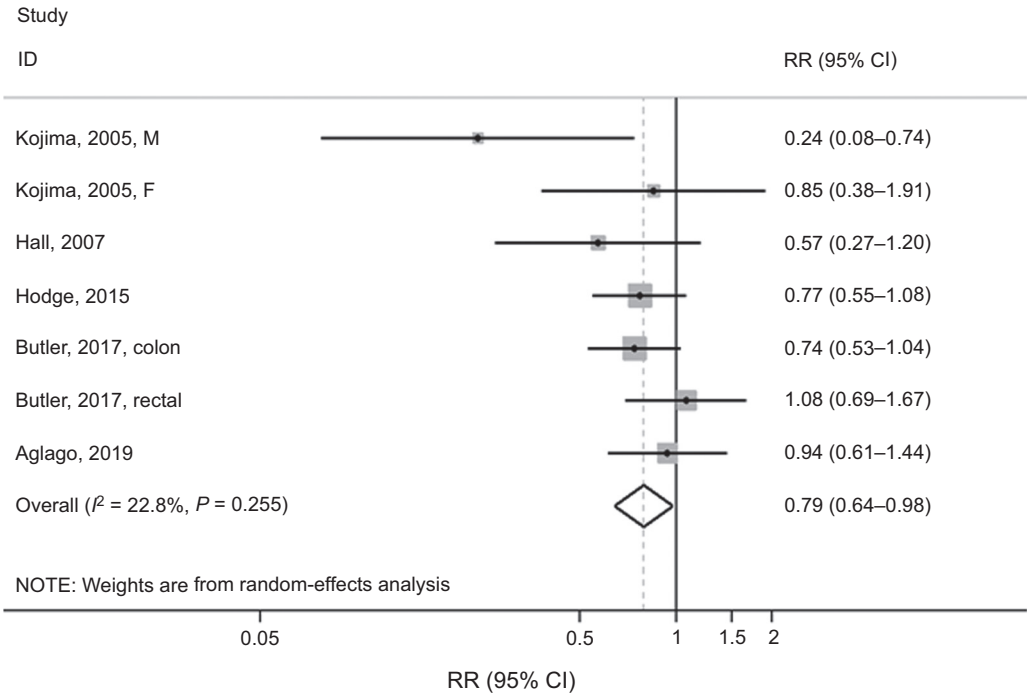

Figure 4.
Forest plot of prospective studies of colorectal cancer for the highest versus lowest category of blood levels of n-3 PUFAs using a random-effects model. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from each prospective study, and the diamond indicates the pooled RR.

significant differences were not observed. However, the possibility of residual confounding cannot be completely ruled out. Third, the analysis of blood n-3 PUFA levels included a relatively small number of studies due to the limited published data. Nevertheless, a significant inverse association between blood levels of n-3 PUFAs and risk of colorectal cancer was found. Fourth, the highest and lowest categories of intake or blood levels of n-3 PUFAs varied among the studies, which is an inherent limitation in this meta-analysis. However, we explored the dose–response association between the intake and blood levels of n-3 PUFAs and the risk of colorectal cancer through linear and nonlinear dose–response analyses and performed a highest versus lowest analysis. Finally, when interpreting the results of blood levels of PUFAs, it should be noted that we combined results from different blood matrices (whole blood, serum, and plasma).

In conclusion, the current meta-analysis of 20 prospective studies indicated that high blood levels of n-3 PUFAs are inversely associated with a low risk of colorectal cancer and high n-3 PUFA intake was suggestively associated with a low risk of colorectal cancer. Our findings suggest that high blood levels of n-3 PUFAs may decrease colorectal cancer risk, but it is impossible to identify a causal relationship between n-3 PUFAs and colorectal cancer risk because of the observational nature of prospective studies included in the meta-analysis. Further large randomized controlled trials of n-3 PUFA supplementation, prospective cohort studies using food diaries as a dietary assessment tool, and large prospective cohort or nested case–control studies on blood n-3 PUFA levels are needed to verify the association between n-3 PUFA intake/blood n-3 PUFA levels and the risk of colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Kim, J. Kim
Development of methodology: Y. Kim
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Kim
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Kim, J. Kim
Writing, review, and/or revision of the manuscript: Y. Kim, J. Kim
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Kim
Study supervision: J. Kim

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Intake or Blood Levels of n-3 Polyunsaturated Fatty Acids and Risk of Colorectal Cancer: A Systematic Review and Meta-analysis of Prospective Studies

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