Dietary Fiber Intake Modifies the Positive Association between n-3 PUFA Intake and Colorectal Cancer Risk in a Caucasian Population1–3

Bledar Kraja,4–6,10 Taulant Muka,6,10 Rikje Ruiter,6,7 Catherine E de Keyser,6 Albert Hofman,6 Oscar H Franco,6 Bruno H Stricker,6–8,9 and Jessica C Kiefte-de Jong6,9

4Department of Biomedical Sciences, Faculty of Medicine, University of Medicine, Tirana, Albania; 5University Clinic of Gastrohepatology, University Hospital Center Mother Teresa, Tirana, Albania; 6Department of Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands; 7Department of Internal Medicine, Groene Hart Hospital, Gouda, Netherlands; 8Health Care Inspectorate, The Hague, Netherlands; and 9Department of Global Public Health, Leiden University College, The Hague, Netherlands

Abstract

Background: The association between dietary fat intake and the risk of colorectal cancer (CRC) is still unclear.

Objectives: We analyzed whether intakes of dietary polyunsaturated fatty acids (PUFAs) and saturated fatty acids (SFAs) were associated with CRC risk and whether these associations were modified by dietary fiber (DF) intake.

Methods: This study was embedded in the Rotterdam Study, a prospective cohort study among subjects aged ≥55 years (n = 4967). At baseline, diet was measured by a food-frequency questionnaire. CRC events were diagnosed on the basis of pathology data and medical records. Multivariable adjusted HRs were calculated using Cox regression models.

Results: During a mean follow-up period of 14.6 years, we identified 222 incident cases of CRC. There was no association between total PUFA, n-6 (ω-6) PUFA, or SFA intake and CRC risk. n-3 PUFA intake was associated with an increased risk of CRC (tertile 3 vs. tertile 1: HR = 1.44 [95% CI: 1.02, 2.04], P-trend = 0.04). When data were analyzed by food sources, only n-3 PUFAs from nonmarine sources were associated with an increased risk of CRC. A significant interaction between n-3 PUFA and DF intakes was found (P-interaction = 0.02). After stratification by median DF intake, an increased risk of CRC caused by n-3 PUFA intake was observed in participants with a DF intake less than the median (tertile 3 vs. tertile 1: HR = 1.96 [95% CI: 1.20, 3.19], P-trend = 0.01). No association was observed in subjects with DF intake equal to or higher than the median.

Conclusions: This study suggests that intake of n-3 PUFAs by adults is associated with an increased risk of CRC, which may be driven mainly by sources other than fish. Moreover, a complex interaction with DF intake may be present.

Keywords: diet, colorectal cancer, PUFAs, fiber intake, FAs

Introduction

Colorectal cancer (CRC)11 is a major cause of cancer-associated morbidity and mortality in the Western world and poses a substantial economic burden on individuals and society (1, 2). Diet is estimated to explain as much as 30–50% of the worldwide incidence of CRC (3). Although epidemiologic studies have identified several dietary components that are linked with an increased (red and processed meat intake) or decreased (dietary fiber [DF], fruit, and vegetables) CRC risk, the role of dietary fat on CRC risk remains controversial (4, 5).

Dietary fats consist of several subtypes of FAs: SFAs and unsaturated FAs of which the latter consist of MUFAs and PUFAs. PUFAs are further divided into n-3 PUFAs and n-6 PUFAs. Animal studies suggest that dietary fat intake is directly linked to an increased risk of CRC through the stimulation of the secr...
of bile acids, which can damage the colonic mucosa, increase cellular turnover, and increase the risk of endogenous mutation (6,7). However, findings from epidemiologic studies on the intake of dietary fat and CRC risk have been inconclusive (8–11). Differences in these results may be explained by modification of the association between dietary FAs and the risk of CRC by intake of DF (12, 13). DF intake can provide a healthy intestinal environment by reducing fecal bile concentration (14), which may mediate the effect of FAs on CRC risk (12). In addition, bile acid has shown to promote colonic carcinogenesis (15). Also, DF intake may enhance satiety through modifying gastric emptying and gastric hormone signaling that subsequently may have an impact on intestinal lipid absorption (16, 17). Furthermore, it has been shown that DF intake, such as β-glucan, may alter serum concentration of hormones or certain enzymes (e.g., lipoprotein lipase activity) that affect lipid metabolism and thus may offset the potential effects of PUFAs, such as its effect on inflammation and oxidative stress (18–20).

The primary objective of our study was to assess the association between PUFA (total PUFA, n–6 PUFA, and n–3 PUFA) and SFA intakes and the risk of CRC in a prospective cohort study. Secondly, we aimed to evaluate whether total fiber intake could modify the effect of dietary fat intake on CRC risk.

Methods

The Rotterdam Study. The study was performed within the framework of the Rotterdam Study, an ongoing prospective population-based cohort study. Its main objective was to investigate the incidence and determinants of diseases in the elderly (21). The first cohort was started in 1990 in Ommoord, a suburb of Rotterdam, Netherlands, and included 7983 men and women aged ≥55 y. Baseline measurements were obtained between 1990 and 1993. During this phase, information on current health status, use of medication, medical history, lifestyle, and risk indicators for chronic diseases were collected. Subsequently, the participants visited the study center for detailed clinical examinations and assessment of diet. Follow-up visits were held every 2–3 y (21). The vital status of the participants was obtained regularly from the municipal population registry. Morbidity and mortality were assessed by information from the general practitioner or, in case of hospitalization, by discharge reports from the medical specialists, as well as linkage with pathology registries. The Medical Ethics Committee of the Erasmus Medical Center approved the study and written consent was obtained from all participants.

Dietary assessment. Dietary intake was assessed by using a semiquantitative FFQ at baseline (1990–1993). Participants completed a checklist at home about foods and drinks they had consumed at least twice a month during the preceding year, as well as dietary habits and prescribed diets. Next, during their visit to the research center, they underwent a standardized interview with a trained dietitian based on the checklist, using a computerized validated 170-item semiquantitative FFQ, taking into account seasonal variations in fruit, vegetable, and fish intakes. For each item the frequency was recorded in times per day, week, or month. The number of servings per frequency was expressed in natural units (e.g., 1 slice of bread or 1 apple), household measures (e.g., 1 cup or 1 spoon), or grams (e.g., 150 g of cooked vegetables or mixed dishes). Nutrient intakes were calculated as the frequency of intake multiplied by the nutrient composition of the specified portion size. Nutrient estimates were based on the Dutch Food Composition Tables of 1993–2006 (22).

A validation study including 80 participants of the Rotterdam Study showed that the FFQ is a suitable instrument for ranking individuals by fat and fiber intakes in the Rotterdam Study (23). For example, as assessed by FFQ vs. multiple food records, partial Pearson correlation coefficients after adjustment for age, sex, energy, and within-person variation were 0.32 for saturated fat, 0.62 for polyunsaturated fat, and 0.62 for DF (23).

Case identification. The outcome of interest was diagnosis of CRC. The CRC status was ascertained from baseline until 31 December 2011. Two research physicians independently assessed the diagnoses on the basis of pathology data and medical records. All events were classified according to the International Classification of Disease, 10th edition (24). In case of discrepancy, consensus was sought or an oncologist decided. Only cases confirmed by the pathology department were considered in the analyses. The index date was defined as the earliest date found in the pathology reports.

Potential confounding variables. Information on current health status, medical history, and medication use; smoking behavior; education level; and socioeconomic status was obtained during the home interviews (1990–1993). Smoking habits were assessed by an interview asking participants whether they were currently smoking cigarettes, cigars, or a pipe. Education level was defined as low (primary education), intermediate (secondary general or vocational education), or high (higher vocational education or university). Household income was categorized as low (<1700 euro/mo), middle (1700–3000 euro/mo), or high (>3,000 euro/mo). Any history of cancer and diabetes mellitus was assessed at baseline and dichotomized. Baseline diabetes mellitus was defined as a nonfasting or postload serum glucose concentration of ≥11 mmol/L or use of glucose-lowering drugs. Serum total cholesterol was determined by an automated enzymatic procedure in a nonfasting blood sample (25). Uses of anti-inflammatory and antirheumatic products were reported by the participants at home interview. To assess dietary quality, the Dutch Healthy Diet (DHD) index was used as described previously (26). Briefly, the DHD index is a continuous score that represents compliance to the Dutch Guidelines for a Healthy Diet as assessed from the FFQ at baseline (26). To avoid overadjustment, the components of PUFA (and fish intake), SFA, and DF intakes were removed from the DHD index. Hence, the following DHD index components were available and were included in this study: intake of vegetable, trans fat, fruit, alcohol, and sodium. DF, fish, and meat intakes were measured by an FFQ. Total red meat included red meat (e.g., beefsteak and pork fricandeau) and processed meat (e.g., sausage and cold cuts). Processed meat included meats that were preserved by smoking, curing, or salting or with the addition of preservatives. Physical activity at the third visit to the research center (1997–1999) was assessed by means of an adapted version of the Zutphen Physical Activity Questionnaire and the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (27, 28). The questionnaire contained questions on walking, cycling, gardening, diverse sports, hobbies, and housekeeping. Total time spent on physical activity was calculated by the sum of minutes per week for each type of activity.

Physical height and body weight were measured with the participants standing without shoes and heavy outer garments. BMI was calculated as weight divided by height squared (expressed as kg/m2). Waist-to-hip ratio was calculated as the ratio of waist circumference over the hip circumference.

Population of analysis. In the first cohort of the Rotterdam Study, 7983 participants were included; dietary data were available for 4969 subjects. Subsequently, 2 participants were excluded because they had CRC at baseline, leaving 4967 participants for the final analysis.

Statistical analyses. Pearson’s correlation was used to assess the association between PUFA, SFA, and fiber intakes and their main dietary food sources. Person-years of follow-up were calculated from study entrance (1990–1993) to the date of diagnosis of CRC, death, or the censor date (date of last contact of the living), whichever occurred first. Follow-up was performed until 31 December 2011. To account for systematic measurement error and residual confounding, dietary intake was adjusted for total energy intake by using the residual method (29). Cox proportional hazards modeling was used to evaluate whether energy-adjusted n–3 PUFA, n–6 PUFA, total PUFA, and SFA intakes were associated with CRC. HRs and 95% CIs were reported. All FA intake variables were assessed in separate models, continuously and in tertiles (based on their distribution in our population and without making prior assumptions about optimal cutoffs). First, we calculated HRs for the following exposures: total PUFAs, n–6 and n–3 PUFAs, and SFAs. Subsequently, we tested, using a stepwise method,
the covariates that were selected on the basis of the literature on risk factors of CRC (4). Potential confounders that changed the effect estimates by ≥10% were included in the final multivariable model (the results are presented for the multivariable model only) (30). Hence, final multivariable models were adjusted for age, gender, energy-adjusted DF intake (continuously), and DHD index (continuously). Variables that were studied but did not alter the estimates by ≥10% included education, income status, smoking status, total physical activity, BMI, waist-to-hip ratio, total energy intake, energy-adjusted dietary intake of processed red meat and unprocessed red meat, energy-adjusted dietary total fish intake, presence of diabetes mellitus at baseline, family history of cancer, family history of diabetes mellitus, serum total cholesterol, and use of anti-inflammatory and antirheumatic drugs. In addition, mutual adjustment of the individual FAs did not alter the effect estimate by ≥10%. Tests for trend were performed by entering the categorical variables as continuous variables in multivariable Cox proportional hazards models. Moreover, as a sensitivity analysis, in the final multivariable regression model, a quartic term of the exposure of interest (continuously) was tested to verify whether a nonlinear association was present. If the quartic term was not significant, continuous analyses were reported without the quartic term. Effect modification of dietary FAs by DF intake was tested by adding the multiplicative interaction term between tertile levels of dietary FAs intake and DF to the final multivariable model. In addition, stratified analyses by median total DF intake (i.e., below and above median DF intake) was performed.

The proportional hazards assumption of the Cox model was checked by the visual inspection of log-minus-log plots and by performing a test for heterogeneity of the exposure over time. There was no evidence of violation of the proportionality assumption in any of the models (for time-dependent interaction terms, \( P < 0.05 \)). A multiple imputation procedure was used (\( n = 3 \) imputations) to adjust for potential bias associated with missing data. Rubin's method was used for the pooled regression coefficients (\( \beta \)) and 95% CIs (31). To explore the possibility of selection bias, we investigated whether there were differences in age, gender, and incidence of CRC among participants included in our analysis and participants who were excluded because of no data on dietary intake. Because plant- and marine-derived n–3 PUFAs have been shown to have opposing effects on health (32), we examined further the role of n–3 PUFAs from fish and other food sources in relation to CRC. Furthermore, we stratified by gender to examine whether there were gender differences. To identify potential reverse causality and to assess whether change in dietary intake caused by preclinical cancer could influence the results, we repeated the analysis by excluding subjects who developed CRC in the first 2 y of follow-up (33). A value of \( P < 0.05 \) was considered statistically significant but to account for multiple testing, we adjusted the \( P \) value from 0.05 to 0.0125 by applying the Bonferroni correction for the number of exposures studied (\( n = 4 \)). All analyses were performed using SPSS statistical software (version 21.0; SPSS, Inc.).

## Results

During the mean 14.6-y follow-up period (72,526 person-years), 222 participants were diagnosed with CRC (97 men and 125 women). Baseline characteristics are presented in Table 1. Mean intakes of total PUFAs and SFAs were 15.4 ± 7.8 g/d and 31.9 ± 11.8 g/d, respectively. As shown previously, the main food sources of n–6 PUFAs in our study were butter (including margarines and hard frying fats), vegetable oils, and whole grain, whereas butter, fish, and processed meat were the main food contributors to n–3 PUFAs intake (34). The highest correlations of SFAs with specific dietary food sources were for butter, potatoes, and nuts (Pearson's correlation = 0.61, 0.30, and 0.22, respectively; all, \( P < 0.05 \)), whereas for fiber the highest correlations were for whole grain, legumes, and fruits (Pearson's correlation = 0.50, 0.47, and 0.44, respectively; Supplemental Table 1).

### PUFA and SFA intakes and CRC

No association was observed between total PUFA or n–6 PUFA intake and CRC (Table 2). Also, no nonlinear associations were observed for total PUFA or n–6 PUFA intake (data not shown). No significant association with CRC was observed when analyzing n–3 PUFA intake as a continuous variable (Table 2). However, when n–3 PUFA intake was analyzed in tertiles, a significant positive association with CRC was observed [compared with tertile 1, tertile 3 HR = 1.44 (95% CI: 1.02, 2.04), \( P \)-trend = 0.04; Table 2]. No nonlinear association was observed for n–3 PUFA intake and CRC. (data not shown). No association was observed between SFA intake and CRC (Table 2). Also, the n–3:n–6 PUFA ratio intake was not associated with CRC (Supplemental Table 2). Similarly, no nonlinear associations were observed for SFA or n–3:n–6 PUFA ratio intake (data not shown).

### Effect modification by DF intake and sensitivity analysis

No significant interaction between DF and total PUFA intakes was observed (\( P \)-interaction = 0.84; Figure 1A) on the risk of CRC. There was no significant interaction between DF and n–6 PUFA intakes on the risk of CRC (\( P \)-interaction = 0.57). When data were stratified by median DF intake, tertile 2 of n–6 PUFA intake was associated with a reduced risk of CRC among subjects with fiber intake lower than the median [compared with tertile 1, tertile 2 HR = 0.58 (95% CI: 0.38, 0.90); Figure 1B]. In contrast, a significant interaction was observed between DF and n–3 PUFA intakes on the risk of CRC (\( P \)-interaction = 0.02). When data were stratified by median DF intake, an increased risk of CRC was observed for n–3 PUFA intake in subjects with DF intake lower than the median [compared with tertile 1, tertile 3 HR = 1.96 (95% CI: 1.20, 3.19), \( P \)-trend = 0.01]. No association was found between n–3 PUFAs and CRC in subjects with DF intake equal or higher than the median (Figure 1C). Also, no association was observed between tertiles of SFA intake and CRC when data were stratified by median DF intake (\( P \)-interaction = 0.28; Figure 1D).

### Additional analysis

There were significant differences in gender (58.9% male vs. 64.8% female), age (mean age, 67.6 y old vs. 75.7 y old), and incidence rate of CRC (3.1/1000 persons-years vs. 2.8/1000 persons-years) among participants included in our analysis and participants that were excluded because of no data on dietary intake. n–3 PUFA intake from food sources other than fish was associated with an increased risk of CRC (Supplemental Table 3), which was present only among participants with low DF intake (\( P \)-interaction = 0.01; Supplemental Figure 1). In contrast, no association was observed between n–3 PUFA intake from fish and CRC (Supplemental Table 3). Also, a borderline interaction between DF and n–3 PUFAs from fish was observed (\( P \)-interaction = 0.06). However, when data were stratified by median DF intake, tertile 3 of n–3 PUFA intake from fish was associated with a reduced risk of CRC among subjects with fiber intake lower than the median but with an increased risk among subjects with fiber intake equal or higher than median (Supplemental Figure 1). No gender differences were observed in the associations of FA intakes with risk of CRC (Supplemental Tables 4 and 5). Exclusion of CRC cases observed during the first 2 y of follow-up (\( n = 23 \)) did not substantially affect our results (data not shown). Moreover, after we applied the Bonferroni correction, only the association of n–3 PUFAs in all study participants and in subjects with DF intake lower than median remained significant (all study participants, tertile 2 of n–3 PUFAs, \( P = 0.01 \); subjects with DF intake lower than median, tertile 2 of n–3 PUFAs, \( P = 0.0003 \); tertile 3, \( P = 0.007 \)).

### Discussion

By using a large population-based cohort study, we showed that n–3 PUFA intake was associated with an increased risk of CRC.
BMI, kg/m² 26.4
Total fish intake, g/d 11.1
Total energy intake, kcal/d 2033
Total SFAs, g/d 34.5
n–3 PUFAs, g/d 1.0
Unprocessed red meat, g/d 80.4
Processed red meat, g/d 21.3

6

Income status (%) 0.14

Education, n (%) 0.97
Low education 864 (52.2) 860 (51.9) 844 (51.0) 761 (46.0) 872 (52.7) 935 (56.5)
Medium education 644 (38.9) 648 (39.1) 659 (39.8) 715 (43.2) 633 (38.2) 603 (36.4)
High education 147 (8.9) 148 (8.9) 152 (9.2) 180 (10.9) 151 (9.1) 117 (7.1)

P

P

P

P

P

P

P

P

3 Test was used for categorical variables; ANOVA was used for continuous variables.

4 Family history for all cancers.

In our study, additional sources of n–3 PUFAs, other than fish, may have driven the observed association between n–3 PUFA intake and CRC. Among n–3 PUFAs, longer-chain marine FAs [e.g., EPA (20:5n–3) and DHA (22:6n–3)] have a greater physiologic potency and a higher bioavailability than short- and medium-chain nonmarine FAs [e.g., α-linolenic acid (ALA; 18:3n–3)], suggesting possible differential effects of these PUFAs (45, 46). It has been shown that dietary n–3 PUFA intake promotes colon carcinoma metastasis in animal studies (47), whereas dietary administration of marine-derived n–3 PUFAs in rodent models has been reported to reduce CRC risk (45). Furthermore, ALA intake has been reported to increase the risk of prostate cancer, whereas DHA has been reported to reduce this risk (48). This evidence suggests that marine FAs may have different effects on cancer etiology than nonmarine FAs. The specific mechanisms underlying these different effects are unclear. A possible explanation is that ALA is less effective than EPA and DHA (the long-chain FAs) in displacing arachidonic acid (20:4n–6) from cell membrane phospholipids. The latter may influence eicosanoid signaling, which has been reported to be associated with the development and progression
of CRC (49). In addition, contrary to common beliefs, the current evidence does not support that an increase in ALA intake can enhance DHA synthesis (50). In fact, recently, it was reported that a higher ALA intake was associated with decreased tissue DHA concentrations (51), because of the feedback inhibition that controls DHA synthesis (52). DHA has been shown to have abundant anti-inflammatory properties (53). Nevertheless, we have recently shown that n–3 PUFA intake (mainly plant-derived n–3 PUFA intake) is associated with increased chronic inflammation (34), which may be associated with increased risk of CRC (54). Therefore, further research may be warranted in examining the potential role of different dietary sources of n–3 PUFAs on CRC risk.

Another insight provided in our study was the effect modification by DF intake, which might partly explain the contradictory results among previous studies. The possible interaction between

![Table 2](image)

**TABLE 2** Multivariable HRs (95% CIs) for CRC by dietary total PUFA and total SFA intakes (the Rotterdam Study, 4967 participants)

<table>
<thead>
<tr>
<th>Tertile of dietary total PUFA and total SFA intakes</th>
<th>T1 (low)</th>
<th>T2</th>
<th>T3 (high)</th>
<th>Continuous</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PUFA intake (median), g/d</td>
<td>8.7</td>
<td>13.4</td>
<td>21.7</td>
<td>4967</td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>1655</td>
<td>1656</td>
<td>1656</td>
<td>4967</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>75</td>
<td>75</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 [reference]</td>
<td>1.03 (0.75, 1.42)</td>
<td>0.95 (0.6, 1.32)</td>
<td>1.00 (0.97, 1.02)</td>
<td>0.77</td>
</tr>
<tr>
<td>n–6 PUFA intake (median), g/d</td>
<td>6.1</td>
<td>10.8</td>
<td>18.6</td>
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<tr>
<td>Participants, n</td>
<td>1656</td>
<td>1655</td>
<td>1656</td>
<td>4967</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>82</td>
<td>66</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 [reference]</td>
<td>0.81 (0.59, 1.12)</td>
<td>0.89 (0.69, 1.23)</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.47</td>
</tr>
<tr>
<td>n–3 PUFA intake (median), g/d</td>
<td>0.7</td>
<td>0.9</td>
<td>1.5</td>
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<tr>
<td>Participants, n</td>
<td>1656</td>
<td>1656</td>
<td>1655</td>
<td>4967</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>58</td>
<td>84</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 [reference]</td>
<td>1.54 (1.10, 2.15)</td>
<td>1.44 (1.02, 2.04)</td>
<td>1.21 (0.94, 1.56)</td>
<td>0.04</td>
</tr>
<tr>
<td>SFA intake (median), g/d</td>
<td>25.2</td>
<td>28.4</td>
<td>38.5</td>
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<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>1656</td>
<td>1656</td>
<td>1655</td>
<td>4967</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>65</td>
<td>79</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 [reference]</td>
<td>1.18 (0.84, 1.65)</td>
<td>1.13 (0.79, 1.62)</td>
<td>1.02 (0.99, 1.04)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

1 HRs (95% CIs) were estimated by using the Cox proportional hazards model adjusted for age, gender, energy-adjusted DF intake, and Dutch Healthy Diet index (excluding PUFA, fish, SFA, and DF components). Additional adjustment for other covariates did not change the effect estimate by >10%. CRC, colorectal cancer; DF, dietary fiber; T1, tertile 1; T2, tertile 2; T3, tertile 3.

2 Tests for trend were performed by entering the categorical variables as continuous variables in multivariable Cox proportional hazards models.

![Figure 1](image)

**FIGURE 1** Multivariable HRs (95% CIs) for the association of dietary FAs intake and CRC by levels of DF intake (the Rotterdam Study, 4967 participants). The figure shows (A) tertiles of total PUFA intake; (B) tertiles of n–6 PUFA intake; (C) tertiles of n–3 PUFA intake; (D) tertiles of SFA intake. HRs (95% CIs) were estimated by using the Cox proportional hazards model adjusted for age, gender, and DHD index (excluding PUFA, fish, SFA, and DF components). Additional adjustment for other covariates did not change the effect estimate by >10%. Tests for trend were performed by entering the categorical variables as continuous variables in multivariable Cox proportional hazards models. CRC, colorectal cancer; DHD, Dutch Healthy Diet; T1, tertile 1; T2, tertile 2; T3, tertile 3.
dietary FA and DF intakes has been previously shown in a population-based case-control study (17). Also, recently, an interaction has been reported of dietary n–3 PUFA and short-chain FA intakes produced from fiber with cytokines during colon inflammation and cancer (55). In addition, the studies reporting a positive association between n–3 PUFA intake and advanced CRC or CRC included subjects with low consumption of DF intake (median: 10–14 g/d; mean: 17–19 g/d) (36, 39), whereas the studies reporting no association between n–3 PUFA intake and CRC included subjects with a higher median DF intake (16–23 g/d) (40). DF intake in our study was higher than the studies mentioned previously (mean ± SD: 26.1 ± 7.2 g/d), but after stratifying by fiber intake, the positive association between n–3 PUFA intake and CRC was also observed in subjects with low fiber intake.

DF intake may decrease the risk of CRC mainly through increasing intestinal transit time and gastrointestinal bio- mass and changes of the composition of gut microbiota (18). Experimental evidence suggests that PUFAs and DF may operate together in the colon (13). Interaction of these dietary compounds in the colonic lumen can have substantial impact on the metabolism and kinetics of the colon epithelial cell population and may influence inflammation and neoplastic changes (13, 56). In addition, DF may influence FA-binding proteins (FABPs), which mediate the effect of dietary FAs between and within cells (57). FABPs have been shown to affect inflammatory state and, hence, colon cancer risk (58). A number of studies have also demonstrated that fat-to-fiber ratio has a substantial impact on diversity of gut microbes and their metabolic end products (19, 59). Additionally, recent studies suggest a possible interplay between the gut microbiota, diet, and lipid metabolism, which all have been implicated in CRC risk (60, 61). For example, the gut microbiota is affected by diet and, inversely, microorganisms can influence cancer risk by modifying metabolism of dietary components (e.g., fiber and linoleic acid found in vegetable oil), generating new components that are more biologically active (62).

Strengths of our study include its prospective design—the long follow-up and adequate adjustments for a broad range of possible confounders. However, there are several limitations that need to be taken into account. First, dietary intake was assessed at baseline, and there may have been changes in dietary fat and fiber consumption over time; e.g., because of gastrointestinal disorders as result of early carcinogenesis. Nevertheless, to reduce this potential reverse causality, we excluded CRC cases at baseline and we performed sensitivity analysis excluding CRC cases identified within 2 y of follow-up, which did not markedly influence our results. Moreover, it has been shown that dietary habits change very little over time in middle-aged adults (63). Also, the FFQ can introduce nondifferential misclassification in dietary intake. However, this is likely to bias results toward the null. Furthermore, FAs are derived from both endogenous and exogenous sources. This suggests that a combination of dietary assessment and adipose tissue or blood biomarkers of FAs may be optimal to address measurement error and risk of misclassification (64). Second, physical activity was measured in the third follow-up round in the Rotterdam Study. Therefore, we cannot fully exclude residual confounding by physical activity levels at baseline because these may vary over time. Finally, we found differences between participants included in our analysis and participants that were excluded because of missing data on dietary intake. However, it has been shown that using a selected source population for a cohort study usually leads to bias toward the null (65, 66) but may affect the generalizability of our results regarding mean dietary intake and the incidence of CRC.

In conclusion, the results from this prospective cohort show that n–3 PUFA intake was positively associated with CRC; however, future studies need to address the role of specific sources of n–3 PUFAs. In addition, we showed that a complex interaction with DF intake may be present.

Acknowledgments

BK, TM, RR, OHF, and JCK-dJ participated in the manuscript conception, statistical analyses, data interpretation, and manuscript writing and revising; RR, CEDK, and BHS participated in the data collection and acquisition of data on CRC. AH, OHF, and BHS designed the Rotterdam Study. All authors read and approved the final manuscript.

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