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# Marine ω-3 polyunsaturated fatty acid intake and survival after colorectal cancer diagnosis

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## ABSTRACT

**Objective** Experimental evidence supports an antineoplastic activity of marine ω-3 polyunsaturated fatty acids (ω-3 PUFAs; including eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid). However, the influence of ω-3 PUFAs on colorectal cancer (CRC) survival is unknown.

**Design** Within the Nurses' Health Study and Health Professionals Follow-up Study, we prospectively studied CRC-specific and overall mortality in a cohort of 1659 patients with CRC according to intake of marine ω-3 PUFAs and its change after diagnosis.

**Results** Higher intake of marine ω-3 PUFAs after CRC diagnosis was associated with lower risk of CRC-specific mortality (p for trend=0.03). Compared with patients who consumed <0.10 g/day of marine ω-3 PUFAs, those consuming at least 0.30 g/day had an adjusted HR for CRC-specific mortality of 0.59 (95% CI 0.35 to 1.01). Patients who increased their marine ω-3 PUFA intake by at least 0.15 g/day after diagnosis had an HR of 0.30 (95% CI 0.14 to 0.64, p for trend <0.001) for CRC deaths, compared with those who did not change or changed their intake by <0.02 g/day. No association was found between postdiagnostic marine ω-3 PUFA intake and all-cause mortality (p for trend=0.47).

**Conclusions** High marine ω-3 PUFA intake after CRC diagnosis is associated with lower risk of CRC-specific mortality. Increasing consumption of marine ω-3 PUFAs after diagnosis may confer additional benefits to patients with CRC.

## Significance of this study

### What is already known on this subject?

- Marine ω-3 polyunsaturated fatty acids (ω-3 PUFAs) have been associated with lower risk of colorectal cancer (CRC).
- Marine ω-3 PUFAs suppress tumour growth and angiogenesis.
- Supplementation of ω-3 PUFAs enhances antitumour effects of chemotherapeutic agents in CRC and inhibits cancer-related cachexia.

### What are the new findings?

- Higher intake of marine ω-3 PUFAs after CRC diagnosis was associated with lower risk of CRC-specific mortality.
- Patients who increased their marine ω-3 PUFA intake after diagnosis had a lower risk of death from CRC, compared with those who did not change.

### How might it impact on clinical practice in the foreseeable future?

- Our findings provide the first line of population-based evidence for the benefit of marine ω-3 PUFAs on CRC survival.
- If replicated by other studies, our results support the clinical recommendation of increasing marine ω-3 PUFAs among patients with CRC.

## INTRODUCTION

Despite appreciable advances in treatment, colorectal cancer (CRC) still represents the third leading cause of cancer death in the USA, with about 49 700 individuals dying of the disease in 2015.[1] Substantial evidence indicates that dietary and lifestyle factors influence the likelihood of developing CRC,[2] but whether these risk factors impact survival of CRC remains largely unknown.[3] Understanding the role of modifiable indicators for prognosis is crucial to inform clinical practice and counselling to improve survival outcomes after cancer diagnosis.[4]

Marine ω-3 polyunsaturated fatty acids (ω-3 PUFAs), namely eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA), have been shown in laboratory studies to suppress tumour growth and angiogenesis, possibly through modulation of prostaglandin-endoperoxide synthase (PTGS) activity, alteration of cell surface receptor function and regulation of gene expression.[5] Supplementation of ω-3 PUFAs has been reported to enhance antitumour effects of chemotherapeutic agents in CRC.[6 7] Substantial, though inconsistent, evidence also suggests that ω-3 PUFAs can inhibit cancer-related cachexia by improving food intake, delaying the onset of anorexia and preventing body weight loss.[8 9] Therefore, it is plausible that intake of marine ω-3 PUFAs could provide an opportunity to improve survival among patients with CRC.

Despite these data, to our knowledge no study has yet examined the association between intake of marine ω-3 PUFAs and survival of patients with CRC. Therefore, we used data from two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), to assess whether high intake of marine

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ω-3 PUFAs after CRC diagnosis was associated with lower mortality.

## METHODS

### Study population

Details about the NHS and HPFS have been described elsewhere.[10 11] In brief, the NHS enrolled 121 700 US registered female nurses who were aged 30–55 years in 1976. The HPFS enrolled 51 529 US male health professionals who were aged 40–75 years in 1986. Similar follow-up procedures have been used in the two cohorts. Participants completed a mailed questionnaire inquiring about their medical history and lifestyle factors at baseline, and every 2 years thereafter. Dietary data were collected and updated using the food frequency questionnaires (FFQs) every 4 years. In the present analysis, we used 1984 for the NHS and 1986 for the HPFS as baseline, when we first collected detailed data on ω-3 PUFA intake. The follow-up rates have been 95.4% in the NHS and 95.9% in the HPFS for each of the questionnaires though 2010. This study was approved by the Institutional Review Board at the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

### Ascertainment of CRC cases

On each biennial follow-up questionnaire, participants were asked whether they had a diagnosis of CRC during the previous 2 years. For participants who reported CRC diagnosis, we asked for their permission to acquire medical records and pathological reports. Study physicians, blinded to exposure data, reviewed all medical records to confirm CRC diagnosis and to record the disease stage, histological findings and tumour location.[12] For non-responders, we searched the National Death Index to identify deaths and to ascertain any CRC diagnosis that contributed to death or was a secondary diagnosis.[13] For CRC deaths, we requested permission from next-of-kin to review medical records. In this analysis, we included participants who were diagnosed with CRC throughout follow-up and completed the FFQ after diagnosis (N=994 in the NHS and 665 in the HPFS) (see the flow chart in online supplementary figure S1).

### Measurement of mortality

Most of the deaths were identified through family members or the postal system in response to the follow-up questionnaires. We also searched the names of persistent non-responders in the National Death Index. The cause of death was assigned by study physicians blinded to exposure data. More than 96% of deaths have been identified using these methods.[13]

### Assessment of marine ω-3 PUFA intake

Detailed description of ω-3 PUFA intake assessment has been reported previously,[14 15] and provided in the online supplementary material. In each FFQ, we asked participants how often, on average, they consumed each food of a standard portion size during the previous year. Nine response options were provided, ranging from 'never or less than once per month' to '6 or more times per day'. We calculated the average daily intake for each nutrient by multiplying the reported frequency of consumption of each item by its nutrient content and then summing across from all foods. Use of fish oil supplement was also assessed and included in calculation of marine ω-3 PUFA intake, which was the sum of EPA, DHA and DPA consumption. We adjusted nutrient intake for total caloric intake using the nutrient residual method. FFQs have demonstrated good reproducibility and validity in assessing marine ω-3 PUFA intake,[16 17] as described in the online supplementary material.

Dietary intake reported on the first FFQ at least 1 year after diagnosis was used for postdiagnostic intake to avoid assessment during the period of active treatment. Categories of marine ω-3 PUFA intake (g/day) were predefined as <0.10, 0.10–0.19, 0.20–0.29 and 0.30 or more, consistent with prior analysis.[18] We also calculated the change of marine ω-3 PUFA intake by subtracting from the postdiagnostic intake the intake reported on the last FFQ before CRC diagnosis (prediagnosis intake).

### Covariate assessments

We collected information on body height, weight, smoking status and regular use of aspirin and non-steroidal anti-inflammatory drugs from each biennial questionnaire. We assessed mainly recreational or leisure-time physical activity using the validated questionnaire in 1980, 1982, 1986, 1988, 1992 and biennially thereafter in the NHS; and every 2 years in the HPFS. Physical activity was calculated by summing the products of time spent on a variety of activities with the average metabolic equivalent for that activity.[19]

### Statistical analysis

We calculated person-time of follow-up from the return date of the FFQ that was used for postdiagnostic assessment to death, or the end of the study period (1 June 2012 for the NHS, 31 January 2012 for the HPFS), whichever came first. In the main analysis, death from CRC was the primary end point, and deaths from other causes were censored. In secondary analyses, death from any cause was the end point.

We plotted the Kaplan-Meier curves and performed the log-rank tests across categories of marine ω-3 PUFA intake. Cox proportional hazards regression models were used to calculate HRs and 95% CIs of death, adjusted for marine ω-3 PUFA intake prior to CRC diagnosis and other potential predictors for cancer survival (see table 1 and footnote of table 2). We tested proportional hazards assumption by including the interaction term between marine ω-3 PUFA intake and time into the model, and did not find statistical evidence for violation of this assumption. We also stratified by lifestyle and clinicopathological factors, and calculated the HR of mortality per 1-SD increment (0.2 g/day) of marine ω-3 PUFA intake using the median intake of each category as a continuous variable. Test of interaction was performed using a likelihood ratio test by comparing the model with product terms between stratified covariate and marine ω-3 PUFAs to that without these terms. We used SAS V.9.3 for all analyses (SAS Institute, Cary, North Carolina, USA). All statistical tests were two-sided and $p<0.05$ was considered statistically significant.

## RESULTS

### Basic characteristics of participants at diagnosis

Among 1659 eligible participants with CRC, we documented 561 deaths, of which 169 were classified as CRC-specific deaths over a median of 10.4 years of follow-up. Other major causes of death included cardiovascular diseases (n=153) and other cancers than CRC (n=113). Participants with higher intake of marine ω-3 PUFAs were more likely to be physically active, to take multivitamins, to drink alcohol and to consume more vitamin D and fibre, and were less likely to smoke (table 1). Cancer subsite, differentiation and stage did not differ across categories of marine ω-3 PUFA intake.

**Table 1** Basic characteristics of patients with colorectal cancer at diagnosis according to postdiagnostic marine ω-3 polyunsaturated fatty acid intake*

| Variable | <0.10 g/day | 0.10–0.19 g/day | 0.20–0.29 g/day | ≥0.30 g/day |
|---|---|---|---|---|
| Participants (n, %) | 486 (29) | 358 (21) | 274 (17) | 541 (33) |
| Age, year | 69.7 | 68.7 | 66.9 | 68.7 |
| Height, inch | 66.8 | 66.8 | 66.9 | 66.9 |
| BMI, kg/m$^2$ | 26.1 | 26.6 | 26.0 | 26.4 |
| Physical activity, MET-hours/week | 17.9 | 16.9 | 19.9 | 23.0 |
| Pack-years of smoking | 18.1 | 18.2 | 16.2 | 15.9 |
| Current smokers, % | 7 | 7 | 6 | 5 |
| Multivitamin use, % | 58 | 56 | 58 | 67 |
| Fish oil use, % | 0 | 0 | 0 | 23 |
| Regular use of aspirin, %† | 38 | 43 | 43 | 39 |
| Menopausal hormone therapy, %‡ | 21 | 20 | 18 | 16 |
| Dietary consumption | | | | |
| Alcohol, g/day | 7.3 | 8.2 | 8.4 | 8.5 |
| Total folate, μg/day | 653 | 658 | 653 | 773 |
| Calcium, mg/day | 1169 | 1107 | 1180 | 1244 |
| Vitamin D, IU/day | 475 | 487 | 541 | 677 |
| Total fibre, g/day | 20.5 | 20.6 | 21.8 | 22.7 |
| Processed red meat, serving/week | 1.9 | 1.9 | 1.9 | 1.6 |
| Poultry, serving/week | 2.2 | 2.7 | 3.1 | 3.1 |
| Total fish, serving/week | 0.5 | 1.3 | 1.9 | 2.8 |
| Dark fish, serving/week | 0.0 | 0.1 | 0.4 | 0.8 |
| Tuna, serving/week | 0.3 | 0.7 | 0.8 | 1.0 |
| Other fish, serving/week | 0.2 | 0.5 | 0.6 | 0.9 |
| Ω-6 polyunsaturated fatty acids, g/day | 10.8 | 10.7 | 10.6 | 11.3 |
| Cancer subsite, % | | | | |
| Proximal colon | 42 | 43 | 40 | 45 |
| Distal colon | 29 | 32 | 31 | 31 |
| Rectum | 25 | 21 | 25 | 18 |
| Unspecified | 4 | 4 | 4 | 6 |
| Differentiation, % | | | | |
| Well differentiated | 14 | 12 | 130 | 14 |
| Moderately differentiated | 62 | 59 | 61 | 55 |
| Poorly differentiated | 12 | 13 | 12 | 13 |
| Unspecified | 12 | 16 | 14 | 18 |
| Stage, % | | | | |
| I | 35 | 33 | 31 | 34 |
| II | 30 | 30 | 26 | 31 |
| III | 21 | 23 | 26 | 20 |
| IV | 2 | 4 | 5 | 4 |
| Unspecified | 12 | 10 | 12 | 11 |

*Means are calculated for continuous variables. All variables are age-standardised except age.
†Regular users are defined as ≥2 standard (325 mg) tablets of aspirin per week.
‡Proportion of current postmenopausal hormone use is calculated among postmenopausal women only.
BMI, body mass index; MET, metabolic equivalent.

### Marine ω-3 PUFA intake after diagnosis and survival

The median interval between CRC diagnosis and marine ω-3 PUFA assessment was 2.8 years (IQR: 2.0–3.9 years). As shown in figure 1, participants who consumed higher amounts of marine ω-3 PUFAs after diagnosis tended to have a lower risk of CRC-specific mortality (p for log-rank test=0.02). In contrast, all-cause mortality did not appear to differ by categories of marine ω-3 PUFA intake (p=0.72).

Table 2 shows the HR estimates of mortality according to postdiagnostic intake of marine ω-3 PUFAs. Higher intake was associated with a dose-dependent reduction of CRC-specific mortality, even after adjusting for prediagnostic consumption and other potential determinants of survival (p for trend=0.03). Compared with patients who consumed <0.1 g/day, those who consumed at least 0.3 g/day of marine ω-3 PUFAs after CRC diagnosis had an HR for CRC-specific mortality of 0.59 (95% CI 0.35 to 1.01). We did not find any statistically significant association with all-cause mortality (p for tend=0.47). We observed similar results between the NHS and HPFS cohorts (p for heterogeneity by cohort=0.23 for CRC-specific mortality and 0.30 for all-cause mortality; see online supplementary table S1).

When marine ω-3 PUFAs were assessed according to dietary sources, those derived from foods and supplements both showed an inverse association with CRC-specific mortality, although the statistical power was limited for the analysis of supplemental fish oil due to low prevalence of use (see online supplementary table S2). Participants who consumed marine ω-3 PUFAs of at least 0.3 g/day from foods had an HR of 0.60

**Table 2** Postdiagnostic marine ω-3 polyunsaturated fatty acid intake and colorectal cancer-specific and all-cause mortality

| | <0.10 g/day | 0.10–0.19 g/day | 0.20–0.29 g/day | ≥0.30 g/day | p for trend* |
|---|---|---|---|---|---|
| Median intake (Interquartile range) | 0.06 (0.04 to 0.08) | 0.14 (0.12 to 0.16) | 0.24 (0.22 to 0.27) | 0.49 (0.36 to 0.80) | |
| Person-years | 3782 | 3094 | 2401 | 4294 | |
| Colorectal cancer-specific mortality | | | | | |
| Deaths (n=169) | 55 | 47 | 25 | 42 | |
| Age-adjusted HR (95% CI)† | 1 (referent) | 0.99 (0.65 to 1.50) | 0.74 (0.44 to 1.24) | 0.65 (0.42 to 1.03) | 0.04 |
| Multivariable-adjusted HR (95% CI)‡ | 1 (referent) | 0.98 (0.62 to 1.55) | 0.77 (0.44 to 1.37) | 0.59 (0.35 to 1.01) | 0.03 |
| All-cause mortality | | | | | |
| Deaths (n=561) | 164 | 135 | 85 | 177 | |
| Age-adjusted HR (95% CI)† | 1 (referent) | 1.09 (0.86 to 1.39) | 0.93 (0.71 to 1.23) | 0.96 (0.77 to 1.21) | 0.51 |
| Multivariable-adjusted HR (95% CI)‡ | 1 (referent) | 1.12 (0.87 to 1.45) | 0.90 (0.67 to 1.21) | 0.95 (0.73 to 1.25) | 0.47 |

*p for trend was calculated using median intake for each category of marine ω-3 polyunsaturated fatty acid intake.
†Cox proportional hazards regression model stratified by age groups at diagnosis (<60, 60–64, 65–69, 70–74 and ≥75 years), sex and cancer stage (I, II, III, IV and unspecified), with additional adjustment for age at diagnosis (continuous).
‡Further adjusted for prediagnostic intake of marine ω-3 polyunsaturated fatty acids (<0.10, 0.10–0.19, 0.20–0.29 and ≥0.3 g/day), grade of differentiation (1–3 and unspecified), subsite (proximal colon, distal colon, rectum and unspecified), pack-years of smoking (0, 1–15, 16–25, 26–45, >45), alcohol consumption (<0.15, 0.15–1.9, 2.0–7.4, ≥7.5 g/day), BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, ≥30 kg/m$^2$), physical activity (women: <5, 5–11.4, 11.5–21.9, ≥22 MET-hours/week; men: <7, 7–14.9, 15–24.9, ≥25 MET-hours/week), regular use of aspirin and NSAIDs (yes or no), postmenopausal hormone use (women only: never, current, past users) and intake of folate and vitamin D (in quartiles).
BMI, body mass index; MET, metabolic equivalent; NSAIDs, non-steroidal anti-inflammatory drugs.

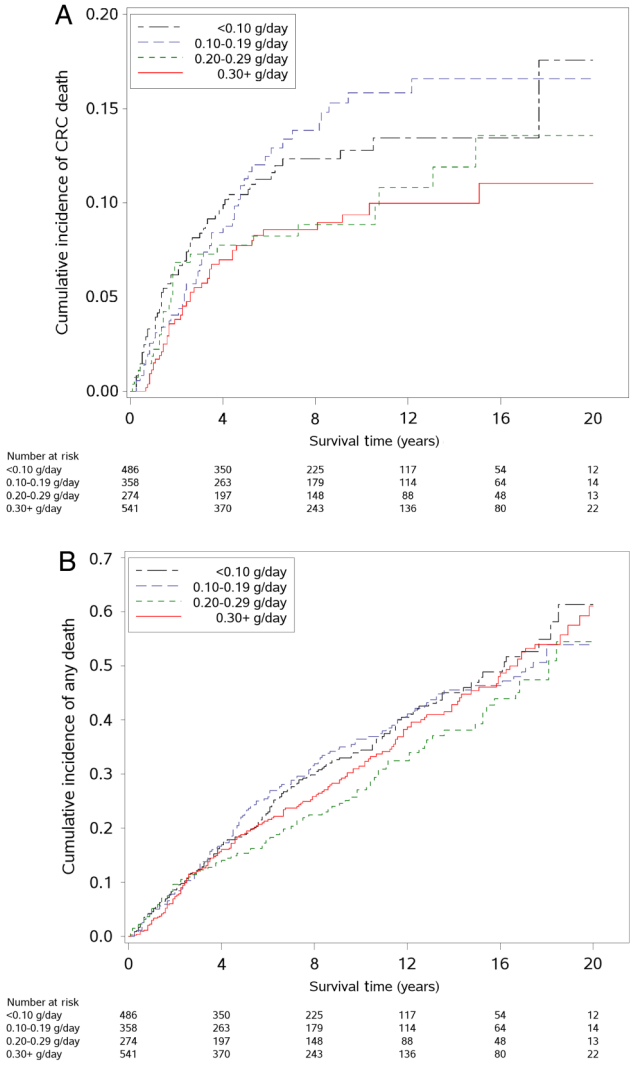


**Figure 1** Cumulative incidence of colorectal cancer (CRC)-specific death (A) and all-cause death (B) according to postdiagnostic intake of marine ω-3 polyunsaturated fatty acids. p Value for the log-rank test across categories of marine ω-3 polyunsaturated fatty acid intake was 0.02 for CRC-specific mortality and 0.72 for all-cause mortality.

(95% CI 0.35 to 1.04) compared with those who consumed <0.10 g/day (p for trend=0.06). Fish oil users had an HR of 0.63 (95% CI 0.24 to 1.71) compared with non-users.

To test the possibility that exclusion of patients who did not complete postdiagnostic FFQs due to early death, severe illness or CRC recurrence may have biased our results, we restricted our analysis to the 1293 participants who completed their FFQs within 4 years after diagnosis. The results were similar with an HR for CRC-specific mortality of 0.65 (95% CI 0.35 to 1.19, p for tend=0.08) comparing the highest to the lowest categories of marine ω-3 PUFA intake. In addition, to minimise bias associated with occult recurrences or other undiagnosed major illnesses which could influence dietary intake, we excluded 69 patients who died within 1 year after their postdiagnostic dietary assessment. Although statistical power was somewhat diminished, participants in the highest category of intake had an HR of 0.76 (95% CI 0.41 to 1.40) for CRC-specific mortality compared with those with the lowest intake.

### Marine ω-3 PUFA intake and survival within subgroups

In an exploratory analysis, we examined the influence of postdiagnostic marine ω-3 PUFA intake across strata of other predictors of cancer recurrence and mortality (see online supplementary figure S2). For CRC-specific mortality, we found a statistically significant interaction between marine ω-3 PUFAs and height (p=0.01), and the inverse association of marine ω-3 PUFA intake with mortality was stronger among tall participants. For all-cause mortality, the association with marine ω-3 PUFA intake differed by height, body mass index (BMI) and regular use of aspirin (p for interaction=0.003, 0.01 and 0.06, respectively). There appeared to be an inverse association among participants who were tall, had a BMI of <25 kg/m$^2$ or did not regularly take aspirin, with adjusted HRs of 0.85 (95% CI 0.74 to 0.99), 0.90 (95% CI 0.79 to 1.02) and 0.88 (95% CI 0.76 to 1.03) per 0.2 g/day increment of marine ω-3 PUFA intake, respectively. However, given the limited sample size and multiple comparisons conducted, these results should be interpreted cautiously.

The association between marine ω-3 PUFA intake and mortality did not differ across tumour subsites, differentiation levels and stages. We also performed a sensitivity analysis by excluding

56 patients with stage IV cancers. The results were essentially unchanged (data not shown).

### Change in marine ω-3 PUFA intake and survival

The correlation between prediagnostic and postdiagnostic intake of marine ω-3 PUFAs was modest (correlation coefficient, 0.50; p<0.001). We assessed whether changing marine ω-3 PUFA intake after diagnosis was associated with mortality (table 3). Compared with participants who did not appreciably alter their intake (amount of change <0.02 g/day), those who increased intake by at least 0.15 g/day had an HR of 0.30 for CRC-specific mortality (95% CI 0.14 to 0.64), whereas those who decreased their intake by the same amount had an HR of 1.10 (95% CI 0.59 to 2.08) (p for trend<0.001). Similar pattern was found for all-cause mortality (p for trend=0.03), and the corresponding HRs were 0.87 (95% CI 0.62 to 1.21) and 1.21 (95% CI 0.86 to 1.69), respectively.

## DISCUSSION

Higher intake of marine ω-3 PUFAs after CRC diagnosis was associated with lower risk of CRC-specific mortality. Patients with CRC who increased their intake from their levels before diagnosis experienced a substantial reduction in CRC-specific mortality and a moderate reduction in all-cause mortality. Our findings provide novel evidence for the potential benefit of increasing marine ω-3 PUFA consumption among patients with CRC.

Due to the high incidence rate as well as improved diagnosis and treatment, CRC represents the second most prevalent cancer in the USA. More than 1.2 million Americans are living with a diagnosis of CRC, among whom 64.9% live more than 5 years and 58.3% live more than 10 years.[20] Many of these cancer survivors are highly motivated to seek information about lifestyle changes to improve their prognosis. However, the evidence is limited for the influence of modifiable lifestyle factors on CRC survival.

Marine ω-3 PUFAs have demonstrated anti-CRC activity in animal and in vitro studies.[5] EPA and DHA treatment has been shown to reduce cellular proliferation and increase apoptosis of human CRC cells. A consistent 40%–60% reduction in size of xenograft CRC tumour has been observed in rodents supplemented with ω-3 PUFAs compared with controls.[21 22] As an alternative substrate for PTGS2 (cyclooxygenase-2), marine ω-3 PUFAs may compete with arachidonic acid and reduce the production of protumourigenic prostaglandin $E_2$.[23 24] Furthermore, incorporation of ω-3 PUFAs into cell phospholipid membranes changes the fluidity, structure and function of lipid rafts, resulting in altered downstream signalling by cell surface receptors, such as epidermal growth factor receptor.[25 26] Moreover, ω-3 PUFAs are highly peroxidisable and increase the levels of intracellular reactive oxygen species (ROS), a by-product of cell growth. Although moderately increased levels of ROS damage DNA and promote mutagenesis in cells, recent evidence indicates that high ROS levels exert an oxidative stress that can restrain tumour progression and metastasis by causing cell senescence or death.[27 28]

Several lines of evidence also support a beneficial effect of marine ω-3 PUFAs on cancer survival. In a randomised controlled trial (RCT) of 60 patients, supplementation of marine ω-3 PUFAs restored the decreased ratio of T-helper cells to T-suppressor cells and prolonged the survival of patients with cancer.[29] Recently, a phase II RCT showed that oral administration of EPA as the free fatty acid 2 g daily prior to surgery resulted in an increased content of EPA in tumour tissue, and reduced vascularity and mortality among patients with CRC cell liver metastasis.[30] Moreover, ω-3 PUFAs have been shown to potentiate the cytotoxicity of antineoplastic agents by overcoming multiple drug resistance and promoting an oxidative environment toxic to highly proliferative tumour cells.[31] In addition, ω-3 PUFAs have been suggested to have effects on mitigating cancer cachexia, partly due to its suppressive activity against inflammation and proteolysis, although current evidence remains inconsistent.[32] A recent cohort study reported that an increase in fish oil supplementation >24 months after diagnosis was associated with improved physical functioning among patients with stage II CRC.[33]

Consistent with these data, we found that patients who consumed higher marine ω-3 PUFAs after diagnosis had substantially lower risk of death from CRC. Although postdiagnostic marine ω-3 PUFA intake was not associated with overall mortality, patients who increased their intake from the levels before diagnosis demonstrated a moderate reduction in all-cause mortality. Moreover, we noted a potential benefit of higher marine ω-3 PUFAs for overall mortality among individuals who were

**Table 3** Change in marine ω-3 polyunsaturated fatty acid intake after diagnosis and colorectal cancer-specific and all-cause mortality

| | Decrease of ≥0.15 g/day | Decrease of 0.02–0.14 g/day | Change of <0.02 g/day | Increase of 0.02–0.14 g/day | Increase of ≥0.15 g/day | p for trend* |
|---|---|---|---|---|---|---|
| Median intake (Interquartile range) | −0.25 (−0.41 to −0.20) | −0.06 (−0.10 to −0.03) | 0 (−0.01 to 0.01) | 0.06 (0.04 to 0.10) | 0.37 (0.20 to 0.62) | |
| Person-years | 2271 | 3670 | 2208 | 2945 | 2477 | |
| Colorectal cancer-specific mortality | | | | | | |
| Deaths (n=169) | 36 | 51 | 35 | 34 | 13 | |
| Age-adjusted HR (95% CI)† | 1.02 (0.55 to 1.89) | 1.02 (0.63 to 1.63) | 1 (referent) | 0.96 (0.57 to 1.61) | 0.28 (0.13 to 0.57) | <0.001 |
| Multivariable-adjusted HR (95% CI)‡ | 1.10 (0.59 to 2.08) | 1.16 (0.71 to 1.91) | 1 (referent) | 1.10 (0.64 to 1.89) | 0.30 (0.14 to 0.64) | <0.001 |
| All-cause mortality | | | | | | |
| Deaths (n=561) | 108 | 161 | 88 | 127 | 77 | |
| Age-adjusted HR (95% CI)† | 1.26 (0.91 to 1.75) | 1.25 (0.95 to 1.65) | 1 (referent) | 1.24 (0.93 to 1.65) | 0.82 (0.59 to 1.13) | 0.005 |
| Multivariable-adjusted HR (95% CI)‡ | 1.21 (0.86 to 1.69) | 1.23 (0.93 to 1.63) | 1 (referent) | 1.21 (0.90 to 1.62) | 0.87 (0.62 to 1.21) | 0.03 |

*p for trend was calculated using median intake for each category of marine ω-3 polyunsaturated fatty acid intake.
†Cox proportional hazards regression model stratified by age groups at diagnosis (<60, 60–64, 65–69, 70–74 and ≥75 years), sex and cancer stage (I, II, III, IV and unspecified) with additional adjustment for age at diagnosis (continuous).
‡Further adjusted for prediagnostic intake of marine ω-3 polyunsaturated fatty acids (continuous), grade of differentiation (1–3 and unspecified), subsite (proximal colon, distal colon, rectum and unspecified), pack-years of smoking (0, 1–15, 16–25, 26–45, >45), alcohol consumption (<0.15, 0.15–1.9, 2.0–7.4, ≥7.5 g/day), BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, ≥30 kg/m$^2$), physical activity (women: <5, 5–11.4, 11.5–21.9, ≥22 MET-hours/week; men: <7, 7–14.9, 15–24.9, ≥25 MET-hours/week), regular use of aspirin and NSAIDs (yes or no), postmenopausal hormone use (women only: never, current, past users) and intake of folate and vitamin D (in quartiles).
BMI, body mass index; MET, metabolic equivalent; NSAIDs, non-steroidal anti-inflammatory drugs.

tall, had a BMI of <25 kg/m$^2$, or did not regularly use aspirin, although the possibility for chance findings cannot be excluded. Fatty acid composition and concentration have been shown to regulate growth hormone secretion,[22] and genetic variations in ω-3 PUFA metabolism have been associated with body height and weight.[34] Previous studies have also reported that ω-3 PUFA may have a stronger anti-CRC effect among individuals who do not regularly use aspirin,[35] an anti-inflammatory agent that shares antitumour pathways with ω-3 PUFA and has been proposed as a promising chemopreventive agent for CRC.[36 37] Given these preliminary data, further studies are needed to investigate whether marine ω-3 PUFAs interact with metabolic factors and aspirin to influence CRC development and progression.

Strengths of the current study include the prospective design, detailed collection of prediagnostic and postdiagnostic data, comprehensive medical record review of both CRC diagnosis and death and long-term follow-up. Some limitations are worth noting. First, data on cancer recurrence were unavailable. Nevertheless, because the median survival for metastatic CRC was approximately 10–12 months during much of the period of this study,[38] CRC-specific mortality should be a reasonable surrogate for cancer-specific outcomes. Second, treatment data are not collected in the cohorts. However, about 60% of patients had stage I or stage II disease, in which surgery alone would generally be the standard of care, and no interaction by disease stage was observed. Furthermore, although there are differences in the likelihood of use of adjuvant chemotherapy based on the factors such as socioeconomic status, the fairly homogenous nature of participants (health professionals) would likely increase the probability of at least standard therapy.[39 40] Comorbidities and access to healthcare may also confound our findings; however, given the population studied, we would expect the latter to be diminished. Moreover, although comorbidities have may influence overall survival,[41 42] such diseases are less likely to affect CRC-specific mortality,[43] the primary endpoint of this study. In addition, only a fraction of patients providing postdiagnosis data were included in this study. Therefore, both the statistical power and generalisability of our findings were limited. Further studies are needed in a larger population. Finally, we cannot exclude the possibility of residual confounding from other dietary or lifestyle factors. However, our results are robust to adjustment for multiple major risk factors of mortality.

In conclusion, marine ω-3 PUFA intake after diagnosis may lower the risk of CRC-specific mortality. Increasing consumption of marine ω-3 PUFAs after diagnosis may confer additional benefits to patients with CRC.

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