

Assessment of marine ω -3 polyunsaturated fatty acid (PUFA) intake

We assessed dietary intake using the semiquantitative food frequency questionnaires (FFQs) in 1984, 1986, and every 4 years thereafter in the Nurses' Health Study (NHS); and in 1986 and then every 4 years in the Health Professionals Follow-up Study (HPFS). 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". In 1984, 1986, and 1990, the FFQ included 4 fish and seafood items: (1) dark-meat fish such as mackerel, salmon, sardines, blue-fish, or swordfish (3-5 oz [84-140 g]); (2) canned tuna (3-4 oz [84-112 g]); (3) other fish such as cod, haddock, halibut (3-5 oz [84-140 g]); and (4) shrimp, lobster, or scallops as a main dish (3.5 oz [98 g]). Since 1994 in the NHS and 1998 in the HPFS, the dietary questionnaire was expanded to include an additional fish item: breaded fish cakes, pieces, or fish sticks (1 serving, store bought). The average daily intake of marine ω -3 PUFA was calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items. The nutrient composition data were based primarily on the U.S. Department of Agriculture Nutrient Database that corresponded to each time when FFQs were administered and supplemented by other published sources and personal communications from other laboratories and manufacturers.

Reproducibility and validity of marine ω -3 PUFA intake assessment

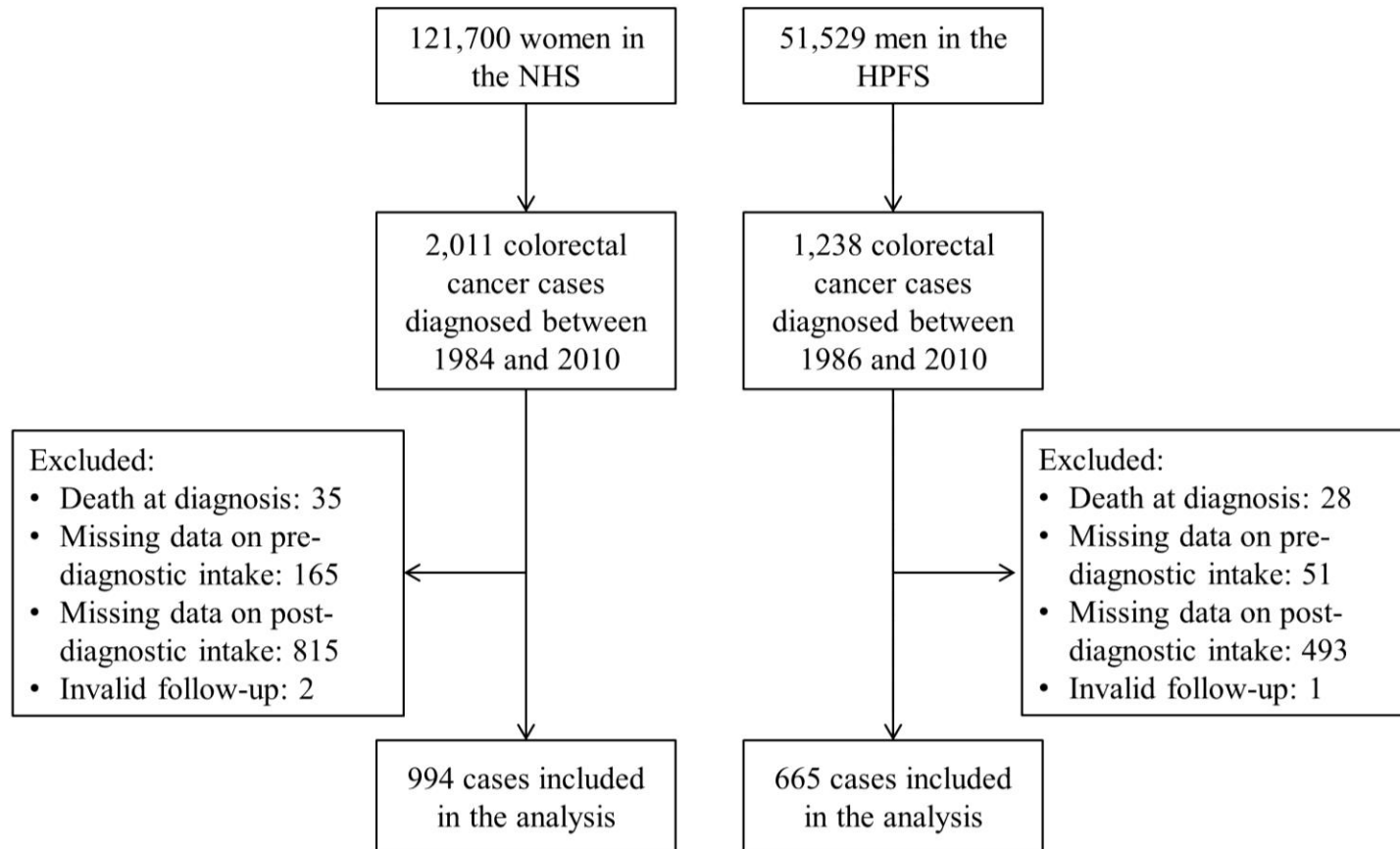
The reproducibility and validity of the food frequency questionnaire (FFQs) were assessed in a random sample of 118 men aged 45-70 years from the HPFS[1] who lived in the Boston area, completed two consecutive FFQs (in 1986 and 1987) and two 1-week dietary records approximately 6 months apart, and provided subcutaneous fat aspirate samples. The mean

eicosapentaenoic acid (EPA) intake from the two FFQs was the same (0.11 ± 0.08 vs. 0.11 ± 0.09 g/d), and was correlated with the EPA composition in adipose tissue ($r=0.49$).^[1] Recently, we conducted another large validation study among 627 women in the NHS who provided two blood samples and completed two FFQs one year apart. As a measure of reproducibility, the intraclass correlation coefficients were similar for total marine ω -3 PUFAs assessed by FFQs and plasma measurements (0.75 vs. 0.78). The FFQ-derived PUFA intake showed a moderate correlation with plasma levels ($r=0.58$ for total marine ω -3 PUFAs, 0.59 for EPA, 0.40 for DPA [docosapentaenoic acid], and 0.60 for DHA [docosahexaenoic acid]).

References

- 1 Hunter DJ, Rimm EB, Sacks FM, Stampfer MJ, Colditz GA, Litin LB, *et al.* Comparison of measures of fatty acid intake by subcutaneous fat aspirate, food frequency questionnaire, and diet records in a free-living population of US men. *Am J Epidemiol* 1992;**135**:418-27.

Supplementary Figure 1. Flowchart of participants' selection in the Nurses' Health Study and Health Professionals Follow-up Study



Supplementary Figure 2. Stratified hazard ratios and 95% confidence intervals of colorectal cancer-specific mortality (A) and all-cause mortality (B) per 0.2 g/day increment in post-diagnostic marine ω -3 polyunsaturated fatty acid intake.

Cox proportional hazards regression model was used with adjustment for the same set of covariates as in Table 2. Likelihood ratio test was used to calculate the *P* values for interaction. Medians were used as the cutoff for height (70 inch for men and 64 inch for women) and alcohol intake (7.5 g/day for men and 0.9 g/day for women), and predefined categories were used for physical activity (in MET-hours/week , 27 for men, 18 for women), consistent with prior analyses.

Figure 2 (A)

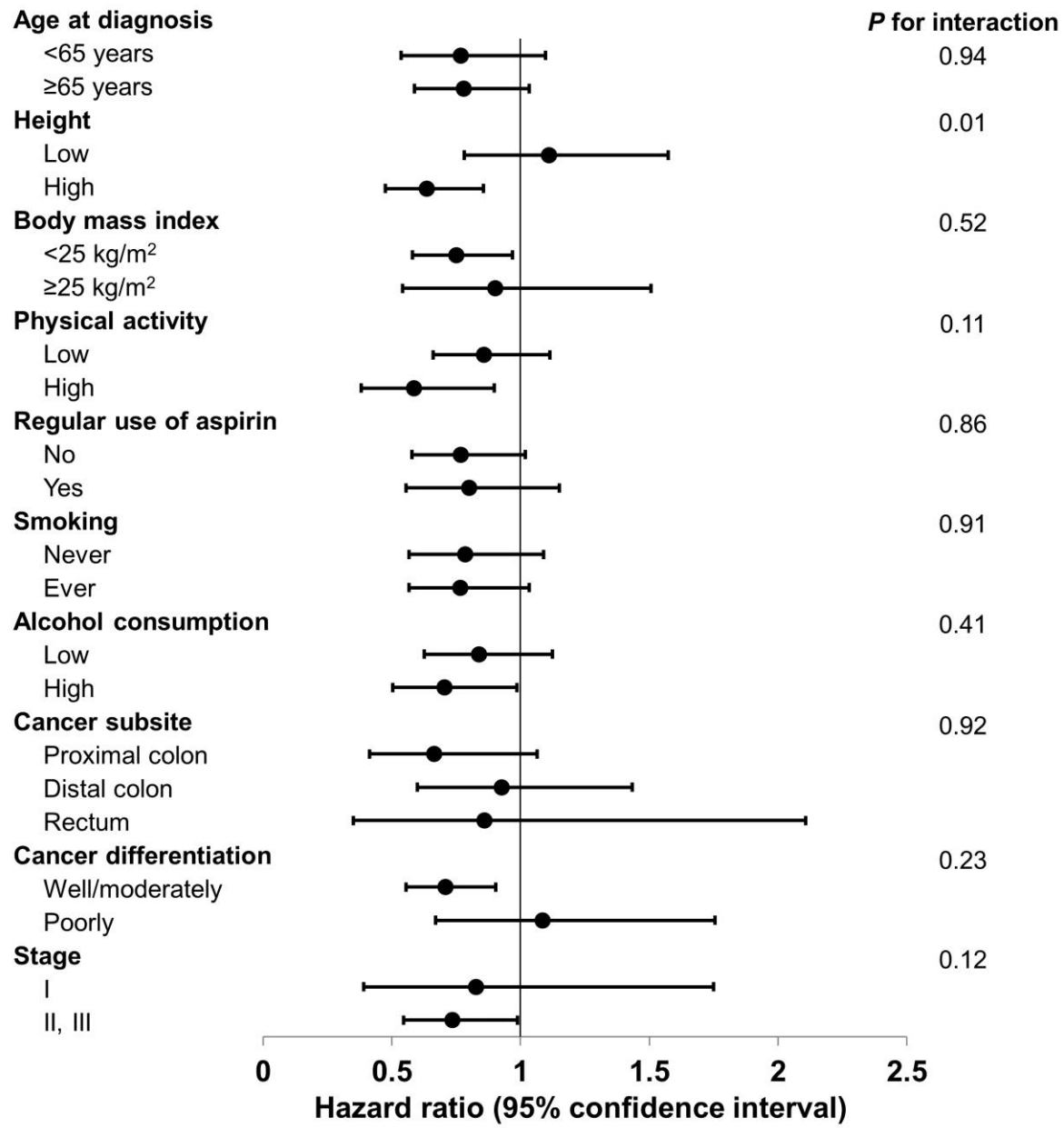
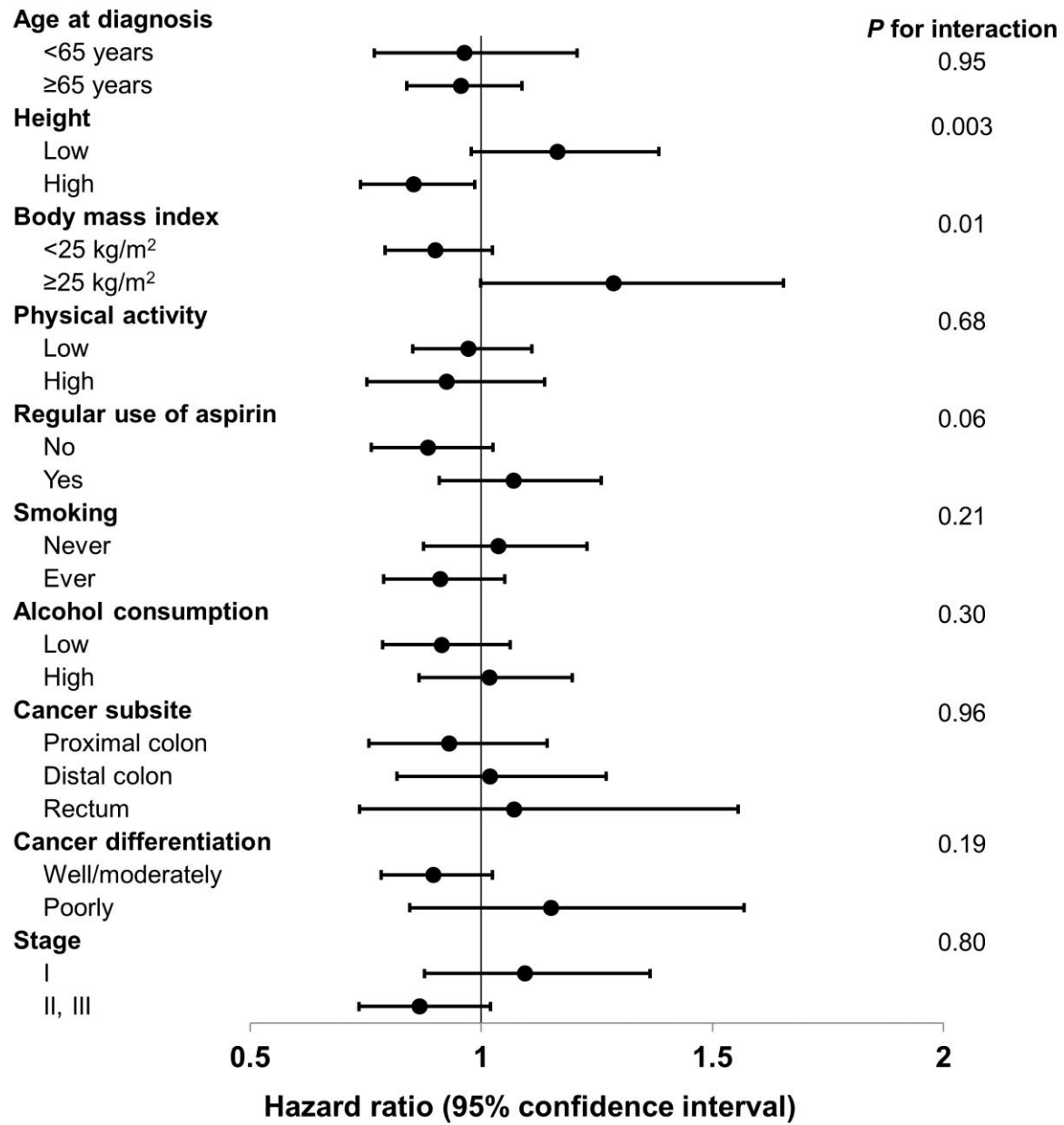


Figure 2 (B)



Supplementary Table 1. Post-diagnostic marine ω -3 polyunsaturated fatty acid intake and colorectal cancer-specific and all-cause mortality in women (Nurses' Health Study) and men (Health Professionals Follow-up Study)

	<0.10 g/day	0.10-0.19 g/day	0.20-0.29 g/day	\geq 0.30 g/day	<i>P</i> for trend *
Women					
Median intake (interquartile range)	0.06 (0.04-0.08)	0.14 (0.12-0.17)	0.24 (0.22-0.26)	0.50 (0.35-0.77)	
Person-years	2,699	1,928	1,385	1,847	
Colorectal cancer-specific mortality					
No. of deaths (n=111)	41	30	17	23	
Age-adjusted HR (95% CI) †	1 (referent)	0.93 (0.56-1.54)	0.78 (0.42-1.45)	0.74 (0.43-1.27)	0.26
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.72 (0.40-1.27)	0.69 (0.35-1.39)	0.47 (0.24-0.92)	0.04
All-cause mortality					
No. of deaths (n=281)	115	73	40	53	
Age-adjusted HR (95% CI) †	1 (referent)	0.96 (0.70-1.30)	0.82 (0.56-1.20)	0.74 (0.53-1.04)	0.07
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.90 (0.65-1.26)	0.72 (0.48-1.10)	0.72 (0.48-1.07)	0.10
Men					
Median intake (interquartile range)	0.06 (0.05-0.08)	0.13 (0.12-0.16)	0.24 (0.22-0.27)	0.49 (0.36-0.84)	
Person-years	1,084	1,166	1,016	2,447	
Colorectal cancer-specific mortality					
No. of deaths (n=58)	14	17	8	19	
Age-adjusted HR (95% CI) †	1 (referent)	1.10 (0.51-2.38)	0.66 (0.26-1.69)	0.51 (0.23-1.14)	0.04
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	1.45 (0.57-3.71)	1.03 (0.34-3.14)	0.70 (0.25-2.00)	0.24
All-cause mortality					
No. of deaths (n=280)	49	62	45	124	
Age-adjusted HR (95% CI) †	1 (referent)	1.39 (0.94-2.06)	1.17 (0.77-1.78)	1.28 (0.91-1.81)	0.42
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	1.55 (1.02-2.37)	1.25 (0.79-1.99)	1.33 (0.87-2.05)	0.64

Abbreviation: CI, confidence interval; HR, hazard ratio.

**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 \geq 75 years) and cancer stage (I, II, III, and unspecified) with adjustment for age at diagnosis (continuous).

‡Further adjusted for pre-diagnostic intake of marine ω -3 polyunsaturated fatty acids (<0.10, 0.10-0.19, 0.20-0.29, and \geq 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, \geq 7.5 g/d), BMI (<23, 23-24.9, 25-27.4, 27.5-29.9, \geq 30 kg/m²), 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).

Supplementary Table 2. Foods-derived marine ω -3 polyunsaturated fatty acid intake and fish oil supplements after colorectal cancer diagnosis and colorectal cancer-specific and all-cause mortality

	<0.10 g/day	0.10-0.19 g/day	0.20-0.29 g/day	\geq 0.30 g/day	<i>P</i> for trend *
Foods-derived marine ω-3 polyunsaturated fatty acid intake					
Colorectal cancer-specific mortality					
No. of deaths (n=169)	58	46	29	36	
Age-adjusted HR (95% CI) †	1 (referent)	0.86 (0.56-1.31)	0.84 (0.52-1.36)	0.63 (0.39-1.01)	0.05
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.88 (0.56-1.39)	0.89 (0.52-1.52)	0.60 (0.35-1.04)	0.06
All-cause mortality					
No. of deaths (n=561)	175	133	88	165	
Age-adjusted HR (95% CI) †	1 (referent)	1.00 (0.78-1.27)	0.89 (0.68-1.17)	1.00 (0.79-1.26)	0.98
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.99 (0.77-1.26)	0.88 (0.65-1.17)	0.97 (0.74-1.27)	0.84
Fish oil supplements					
<i>P</i>					
Colorectal cancer-specific mortality					
No. of deaths (n=150)	144	6			
Age-adjusted HR (95% CI) †	1 (referent)	0.62 (0.24-1.60)		0.33	
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.63 (0.24-1.71)		0.37	
All-cause mortality					
No. of deaths (n=523)	499	24			
Age-adjusted HR (95% CI) †	1 (referent)	0.72 (0.47-1.11)		0.14	
Multivariable-adjusted HR (95% CI) ‡	1 (referent)	0.80 (0.51-1.25)		0.32	

Abbreviation: CI, confidence interval; HR, hazard ratio.

**P* for trend was calculated using median intake for each category of foods-derived 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 \geq 75 years), sex and cancer stage (I, II, III, IV, and unspecified), with additional adjustment for age at diagnosis (continuous).

‡Further adjusted for pre-diagnostic intake of marine ω -3 polyunsaturated fatty acids (<0.10, 0.10-0.19, 0.20-0.29, and \geq 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, \geq 7.5 g/d), BMI (<23, 23-24.9, 25-27.4, 27.5-29.9, \geq 30 kg/m²), physical activity (women: <5, 5-11.4, 11.5-21.9, \geq 22 MET-hours/week; men: <7, 7-14.9, 15-24.9, \geq 25 MET-hours/week), regular use of aspirin and NSAIDs (yes or no), and intake of folate and vitamin D (in quartiles).