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A 22-year Prospective Study of Fish, *n*-3 Fatty Acid Intake, and Colorectal Cancer Risk in Men*

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Abstract

Background—Fish is the main dietary source of long-chain *n*-3 fatty acids, which have been suggested to play a protective role in colorectal cancer development in laboratory and animal studies. Human studies have not shown consistent results. We examined the association between intakes of fish and *n*-3 fatty acids from fish and colorectal cancer risk in men enrolled in the Physicians' Health Study (PHS).

Methods—The PHS began as a randomized trial to examine the effect of aspirin and β-carotene supplementation on cancer and cardiovascular disease. Fish intake was assessed at the 12 month follow-up using an abbreviated food-frequency questionnaire. Cox proportional hazards models were used to estimate multivariate relative risks (MVRRs) of colorectal cancer for categories of fish intake and quartiles of *n*-3 fatty acid intake.

Results—During 22 years of follow-up, 500 men had a confirmed diagnosis of colorectal cancer. Fish intake was inversely associated with colorectal cancer risk (MVRR (95% confidence interval (CI)) for highest vs. lowest category = 0.60 (0.40–0.91), $P_{trend} = 0.01$). The inverse association was observed for both colon and rectal cancers. Our findings for *n*-3 fatty acids were similar to those for fish; the MVRR (95% CI) of total colorectal cancer for the highest vs. lowest quartile of *n*-3 fatty acids was 0.74 (0.57–0.95), $P_{trend} = 0.01$.

Conclusions—Our results from this long-term prospective study suggest that intakes of fish and long-chain *n*-3 fatty acids from fish may decrease the risk of colorectal cancer.

Keywords

fish; *n*-3 fatty acids; colorectal cancer; prospective cohort; risk

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Introduction

Fish is the main dietary source of long-chain *n*-3 fatty acids, which have been suggested to play a protective role in colorectal cancer development (1, 2). While animal studies provide support for this hypothesis (3, 4), consistent results have not emerged from studies conducted with human populations. Of the fifteen prospective cohort studies that have examined the association between fish intake and colorectal cancer risk, seven reported inverse associations (5–11) (two of which were statistically significant (6, 8)), seven reported null associations (12–18), and two reported positive associations (19, 20). A recent meta-analysis (21) reported an overall summary relative risk (RR) (95% Confidence Interval (CI)) for colorectal cancer incidence of 0.88 (0.78–1.00) for the highest versus lowest category of fish intake based on 14 of these prospective cohort studies. The results of case-control studies have also been mixed (22–32).

N-3 fatty acids may protect against colorectal cancer by inhibiting the cyclooxygenase-2 (COX-2) enzyme and the production of arachidonic acid (*n*-6) derived eicosanoids (1, 2). In general, eicosanoids produced from arachidonic acid are proinflammatory while those produced from *n*-3 fatty acids are antiinflammatory (1, 33). Because *n*-3 and *n*-6 fatty acids compete for both the enzymes that convert shorter to longer chain fatty acids (1, 34) and the COX-2 enzyme (35–37), which converts the longer chain fatty acids to precursors for eicosanoid synthesis, higher *n*-3 fatty acid intake may result in decreased production of proinflammatory eicosanoids that could play a role in the development of colorectal cancer.

Aspirin also inhibits the COX-2 enzyme and regular use has been shown to decrease the risk of both colorectal adenoma and cancer (38). Although it is not known whether aspirin exerts its protective effect through COX-2 inhibition or other mechanisms, it is possible that *n*-3 fatty acids and aspirin may share a mechanism to decrease colorectal cancer risk.

We previously reported an inverse association between whole blood biomarker levels of long chain *n*-3 fatty acids and colorectal cancer risk from a case-control study nested within the Physicians' Health Study (PHS)(39). In that analysis, we also observed a statistically significant interaction between aspirin and *n*-3 fatty acids levels which indicated that the benefit of increasing *n*-3 fatty acid levels was only apparent among participants who were not taking aspirin. Here we report on the association between fish intake and colorectal cancer risk using data from the full PHS cohort followed for twenty-two years.

Methods

Study Population

This prospective cohort study was carried out using data from the PHS, a randomized, double blind, placebo-controlled, factorial trial designed to examine the effect of aspirin (325 mg every other day) and β-carotene (50 mg on alternate days) supplementation on the incidence of cancer and cardiovascular disease. The 22 071 participants had no history of myocardial infarction, stroke, transient ischemic attack, or cancer at the start of the study in 1982 (40). A baseline questionnaire inquired about previous medical diagnoses and lifestyle factors including height, weight, physical activity level, multivitamin use, alcohol intake, history of smoking, and other lifestyle habits. The research protocol was approved by the Institutional Review Board at Brigham and Women's hospital in Boston, MA and all subjects provided written informed consent. Because of the emergence of a statistically extreme ($P < 0.00001$) 44% reduction in the risk of first myocardial infarction, the aspirin component of the trial was terminated in January 1988 (40).

Identification of Cases

Participants reported new diagnoses, including colorectal cancer, on annual follow-up questionnaires. The end-point committee for the PHS obtained and reviewed the medical records, including the pathology report, to confirm the diagnosis of colorectal cancer. In addition, the histological details and the site and stage of the disease were recorded from the medical record. Information on deaths was gathered from family members, periodic searches of the National Death Index, and postal authorities. Death certificates and medical records were acquired to determine cause of death. Follow-up is over 99% complete for mortality and morbidity.

Measurement of Fish Intake

An assessment of fish intake was obtained at the 12-month follow-up using an abbreviated semiquantitative food-frequency questionnaire (FFQ) (41). The questionnaire asked about average intake of 4 types of fish or shellfish: 1) canned tuna fish, 2) dark meat fish (mackerel, salmon, sardines, bluefish, swordfish - 4–6 oz), 3) other fish (4–6 oz), and 4) shrimp, lobster, or scallops as a main dish. Seven frequency response categories were used on the questionnaire: rarely/never, 1–3 times/month, once per week, 2–4 times per week, 5–6 times per week, daily, and two or more times per day. This information was used to calculate both the average daily intake of fish and *n*-3 fatty acids from fish. For fish, we summed the frequency responses to each of the 4 fish/shellfish items. Intake of *n*-3 fatty acids was calculated by multiplying the frequency of intake of each fish/shellfish item with the grams of *n*-3 fatty acids per serving of that item (0.17g for other fish, 0.46g for shellfish, 0.69g for tuna fish, and 1.37 g for dark fish) and summing over all four items. *N*-3 fatty acid values per serving of type of fish were obtained from the US Department of Agriculture food composition tables (42).

Although a study of the reproducibility and validity of these questionnaire items has not been carried out in the PHS, this has been done in a similar population of 127 male health professionals using the same fish items (43). Correlations between two FFQs completed approximately one year apart were 0.48 for other fish, 0.54 for canned tuna fish, 0.63 for dark meat fish, and 0.67 for shrimp, lobster, and scallops (43). As a measure of validity, correlations between intakes from the second FFQ and 14 days of diet records were 0.23 for shrimp, lobster, and scallops, 0.39 for other fish, 0.42 for dark meat fish, and 0.56 for canned tuna fish (43). The correlation between eicosapentaenoic acid (EPA) intake estimated from the second FFQ and the percentage measured from adipose tissue from 118 of the 127 participants was 0.49 ($p<0.001$) (44). In addition, we further assessed the validity of the self-reported intakes of fish or *n*-3 fatty acids from fish by correlating these with the whole blood biomarkers of long chain *n*-3 fatty acid levels (45) in 456 participants from our previously reported nested case-control study (39). The Spearman correlation between these two variables was 0.24. Stronger correlations were observed between total fish intake and blood levels of docosahexaenoic acid (DHA) ($r=0.34$) as well as between intake of dark meat fish and DHA ($r=0.35$). These data suggest a reasonable validity of the self-reported fish intake in our study.

Statistical Analysis

We excluded 232 participants who died prior to or did not return the 12-month questionnaire, participants who developed cancer prior to return of the 12-month questionnaire, and those who did not respond to two or more questions regarding fish/shellfish consumption. We also excluded those who had missing information for one item and responded with “rarely/never” or “1–3 times per month” for the other three to minimize misclassification in the lower categories of fish intake. These exclusions left 21 406 participants for the analysis.

Participants were followed from the date of return of the 12-month follow-up questionnaire until the date of death, date of diagnosis of colorectal cancer, or date of last returned questionnaire until March 1, 2006, whichever came first. Dietary fish intake was divided into 4 categories (< 1 time per week, 1–2 times per week, 2–5 times per week, ≥ 5 times per week), and dietary *n*-3 fatty acid intake was categorized into quartiles.

We first examined the distribution of baseline risk factors among categories of fish intake using means or proportions. We used the Cox proportional hazards model (46) with age (in months) as the time metric to estimate the relative risk of colorectal cancer for categories of fish intake using the <1 time per week category as the referent and for quartiles of *n*-3 fatty acid intake using the lowest quartile as the reference group. We then conducted multivariate analyses to assess the independent association of fish intake with risk of colorectal cancer by adjusting for random aspirin assignment, smoking, body mass index (BMI), history of diabetes, physical activity, alcohol intake, multivitamin use, and red meat intake. Tests for trend were performed by assigning the median value to each category of consumption and modeling this as a continuous variable in separate Cox models. To test the assumption of proportional hazards, we fit a model that included an interaction term between age and fish intake (as a continuous variable) as well as a model that included an interaction term between age and *n*-3 fatty acid intake from fish (also as a continuous variable). We then conducted likelihood ratio tests and found no evidence of violation of the proportional hazards assumption.

To assess potential effect modification by aspirin assignment or BMI, we used Cox models to estimate relative risks of colorectal cancer for strata of aspirin assignment or BMI. We hypothesized that there could be effect modification by BMI because overweight and obesity are strong risk factors for colorectal cancer and overweight men may have a different dietary pattern than normal weight men. To formally test for interaction, we included a term that was the product of the natural log of *n*-3 fatty acid intake from fish (as a continuous variable) and randomized aspirin assignment or BMI (continuous) in a Cox regression model and used a likelihood ratio test. Because we were not able to adjust for colorectal cancer screening in our multivariate models, we examined the association between *n*-3 fatty acid intake from fish and colorectal cancer risk before and after 1995, the time at which we estimated that screening by colonoscopy became widely available, to assess the degree of potential confounding by colonoscopy utilization. In the examination of the association before 1995, participants contributed follow-up time from the date of return of the 12-month follow-up questionnaire to the date of diagnosis of colorectal cancer, date of death, date of last returned questionnaire, or December 31, 1994, whichever came first. For the analysis after 1995, we excluded participants who died, developed colorectal cancer, or were lost to follow-up before January 1, 1995. Participants then contributed follow-up time from January 1, 1995 to date of diagnosis, date of death, date of last returned questionnaire, or March 1, 2006.

Results

During the 22 years of follow-up we recorded 500 confirmed cases of colorectal cancer. Of these cases, 388 were colon and 112 were rectal cancers. Overall, 9.6% of men consumed fish <1 time per week, 31.1% 1 – <2 times per week, 48.3% 2 – <5 times per week, and 10.9% greater than 5 times per week. Men with higher fish intake were more likely to use multivitamins, and to drink alcohol and exercise more frequently (Table 1). They were also less likely to be current smokers and to have a history of diabetes.

After adjustment for age, fish intake was inversely associated with the risk of colorectal cancer (Table 2) ($P_{trend} = 0.05$). The multivariate RR (95% CI) for those consuming fish 5

or more times per week compared to less than once per week was 0.63 (0.42 – 0.95) (P_{trend} = 0.02) adjusting for random aspirin assignment, smoking, BMI, history of diabetes, physical activity, alcohol intake, multivitamin use, and red meat intake (Table 2). Additional adjustment for quartiles of dairy intake or beta-carotene assignment produced similar results (data not shown).

To assess whether change of dietary intake due to preclinical cancer could influence the association, we repeated the analysis by excluding cases that occurred during the first five years of follow-up. The multivariate RRs (95% CI) for increasing categories of fish intake after excluding these cases were 1.00 (0.70–1.43), 0.84 (0.60–1.20), and 0.66 (0.41–1.07) (P_{trend} = 0.03).

We also examined the association between each type of fish/shellfish and the risk of colorectal cancer. The multivariate RR (95% CI) comparing men who consumed fish/shellfish more than once per week compared to never was 0.98 (0.55–1.75) for dark fish, 0.76 (0.52 – 1.11) for other fish, 0.67 (0.31–1.42) for shrimp, and 0.95 (0.68 – 1.32) for tuna fish.

The RRs of colorectal cancer across quartiles of *n*-3 fatty acid intake from fish are shown in table 3. Overall, the results for *n*-3 fatty acids were very similar to those for fish intake. In the model adjusted for age only, *n*-3 fatty acids were inversely associated with the risk of colorectal cancer (P_{trend} = 0.05). In the multivariate model the RR (95% CI) for the highest versus lowest quartile was 0.76 (0.59 – 0.98) (P_{trend} = 0.02).

Because aspirin and *n*-3 fatty acids can both inhibit the COX-2 enzyme and may share a mechanism to decrease the risk of colorectal cancer, we assessed the possibility of an interaction between these two variables. We did not observe a statistically significant modification of the effect of *n*-3 fatty acid intake from fish by aspirin assignment ($P_{interaction}$ = 0.83) (Table 4).

Because the aspirin component of the trial lasted only 5 years, we further examined the possibility that any interaction between *n*-3 fatty acid intake and randomized aspirin assignment in relation to colorectal cancer could vary over time. There was no evidence of a statistically significant interaction when we limited the analysis to the first 10 years of follow-up ($P_{interaction}$ = 0.51) or when we started follow-up at year 10 ($P_{interaction}$ = 0.76). Although the inverse association was stronger among overweight men, the test for interaction between n-3 fatty acid intake and BMI was not statistically significant ($P_{interaction}$ = 0.14) (Table 4). For the analysis of the association between *n*-3 fatty acid intake from fish and colorectal cancer risk by time period, results showed that the inverse association was stronger for cases occurring in 1995 or later (Table 4), although the test for interaction was not statistically significant ($P_{interaction}$ = 0.18).

To further assess whether the inverse association between fish intake and colorectal cancer could be due to decreased red meat intake rather than an effect of fish itself, we examined the association between the ratio of red meat to fish intake and colorectal cancer risk. The RRs (95% CI) for increasing quartiles of the ratio of red meat to fish intake were 1.01 (0.78 – 1.31), 1.15 (0.89 – 1.48), and 1.08 (0.84 – 1.40), suggesting that the inverse association between fish intake and colorectal cancer is not solely due to decreasing red meat intake with increasing fish intake.

We also examined the association between fish intake and colon and rectal cancers separately. The RRs (95% CI) across increasing categories of fish intake were 0.91 (0.64 – 1.31), 0.90 (0.64 – 1.27), and 0.62 (0.38 – 1.00) (P_{trend} = 0.04) when we included only the

388 cases of colon cancer and 0.79 (0.43 – 1.46), 0.58 (0.32 – 1.06), and 0.65 (0.30 – 1.41) (P_{trend} = 0.29) for the 112 rectal cancer cases.

Discussion

We observed an inverse association between fish intake and colorectal cancer risk in this prospective study of U.S. physicians followed for twenty-two years. *N*-3 fatty acid intake estimated from fish was also inversely associated with risk and the trends were statistically significant for both of these associations. The inverse associations persisted after controlling for known risk factors of colorectal cancer and after further excluding cases diagnosed during the first 5 years after the dietary report, suggesting an independent association of fish intakes with low risk of colorectal cancer that is unlikely be affected by change of diet due to pre-cancer symptoms. The inverse associations were also similar for both colon and rectal cancer.

Shrimp and other fish were most strongly inversely associated with colorectal cancer risk. Given that dark meat fish and tuna fish contain higher amounts of *n*-3 fatty acids than does shrimp or other fish, this did not appear to support the hypothesis that *n*-3 fatty acids are the component of fish responsible for the inverse association with colorectal cancer risk. However, the CIs for the RRs for dark meat fish and tuna fish are wide and an inverse association cannot be excluded. Only 513 men were in the highest category of dark meat fish intake which would limit the power to detect an association. It is also possible that the participants in this study did not discriminate well between dark meat fish and other fish when they completed the abbreviated FFQ and the validity of the FFQ for assessing total fish intake may therefore have been better than for individual types of fish.

We did not find a statistically significant interaction between randomized aspirin assignment and *n*-3 fatty acid intake in this analysis as we did in our previous nested case-control study using blood levels of long-chain *n-3* fatty acids. One possible explanation for this difference may be the length of follow-up. Our previous nested, case-control study included cases that developed over the first 13 years of PHS follow-up while the cases in this analysis occurred over 22 years of follow-up. Aspirin use was monitored on annual follow-up questionnaires, and 71% of men reported regular aspirin use (three or more days per week) as of the 7-year follow-up questionnaire (47). However, when we ran an analysis with follow-up time through the end of 1995 here, there was again no statistically significant evidence of an interaction between *n*-3 fatty acid intake from fish and random aspirin assignment ($p_{interaction}$ = 0.44).

Another possible explanation for this difference is that blood levels of *n*-3 fatty acids may provide a more biologically relevant measure of intake than questionnaire based data. There may be metabolic steps that occur after intake (i.e., competition with *n*-6 fatty acids for enzymes and incorporation into cell membranes) that may make the blood measure a better assessment of what is occurring biologically in relation to pathways that *n*-3 fatty acids may share with aspirin. In addition, a study by Baylin et al (45) suggests that the whole blood measure of long-chain *n*-3 fatty acids may provide a better assessment of long term intake (particularly for DHA) than does the FFQ. In this study, the correlations between *n*-3 fatty acid intake as measured by FFQ and in adipose samples (which reflect long-term intake) were -0.08 for EPA, 0.26 for DHA, and 0.39 for total *n*-3 fatty acids. The correlations between the whole blood measurement and the adipose tissue measure were 0.20 for EPA, 0.49 for DHA, and 0.32 for total *n*-3 fatty acids.

While over thirty published studies have examined the association between *n*-3 fatty acid and/or fish intake and colorectal cancer risk, the results are inconsistent. For *n*-3 fatty acids,

five studies (5, 32, 48–50) suggest an inverse relationship while seven (12–14, 51–54) reported no association. The results for studies looking at fish intake are similarly mixed with eleven studies (5–11, 22–24, 30) reporting inverse, eleven reporting null (12–18, 25–28), and four reporting positive associations (19, 20, 29, 31). Two (20, 31) of these four positive associations were for smoked or salted fish and one was in females only (29). A systematic review (55) of nine prospective cohort studies that examined the association between *n*-3 fatty acid and cancer risk reported that there was "little to suggest that omega-3 fatty acids reduce the risk of any single type of cancer", including colorectal cancer.". In contrast, the recent meta-analysis (21) supports an inverse association between fish intake and colorectal cancer incidence. There are several potential explanations for the inconsistent results across studies, and plausible biological mechanisms support an inverse relation between *n*-3 fatty acids and colorectal cancer risk.

If *n*-3 fatty acids do indeed play a role in colorectal cancer development, null findings from epidemiologic studies could result from several factors, as reviewed by Larsson et al (1), including an intake of *n*-3 fatty acids that is too low to have any effect, low within-study variation in intake which reduces statistical power, and nondifferential misclassification of *n*-3 fatty acid intake which can bias results toward the null. Larsson et al (1) also suggest that studies should take into account other factors that can influence *n*-3 fatty acid metabolism or function such as intake of *n*-6 fatty acids and use of anti-inflammatory drugs (1). In addition to the possible explanations suggested by Larsson et al, there are others including differences in the length of follow-up and number of cases, inclusion of potential confounders in multivariate models, and the types of fish consumed.

Despite several possibilities, a clear explanation for the inconsistent results across studies is not readily apparent. Among the prospective studies of fish intake, those that reported null results include studies with both relatively small (13, 17, 18) and large (12, 15, 16) numbers of cases. Also, while most of the prospective studies of fish intake that reported inverse associations had follow-up times of < 10 years (5–8, 10, 11), our average length of follow-up was 17.6 years. In the meta-analysis by Geelen et al (21), the summary RR for studies in which the difference between the highest and lowest intake categories was ≥ 7 times per month was stronger [0.78 (0.66–0.92)] than the overall summary RR. The results of our study, in which the median intakes were 2.2 times per month for the lowest category and 26.1 times per month for the highest category are consistent with the findings from the meta-analysis.

Most of the potential confounders of the association between fish and colorectal cancer (such as BMI, physical activity, multivitamin use) are most likely negative confounders and not adjusting for these covariates would lead to RRs that are lower (in absolute magnitude) than the "true" RR. Therefore, inverse associations could be explained by a lack of adjustment for these covariates. Of the two previous prospective studies of fish intake and colorectal cancer reporting statistically significant inverse associations, Norat et al (6) adjusted for most potentially confounding variables while Kato and colleagues (8) did not. However, Norat et al (6) was not able to adjust for colonoscopy utilization, another potential negative confounder. To our knowledge, the only study to examine potential confounding by colonoscopy utilization was that by Giovannucci et al (17). This study reported no association between fish intake and colorectal cancer risk in an age and sex adjusted model and additionally adjusted for colonoscopy utilization but did not report the RR from this model.

There is also the possibility that some of the differences between studies could be explained by the type of fish consumed. Three of the prospective studies of fish intake and colorectal cancer risk that reported no association were conducted in Scandinavian countries (13, 15)

or in Japan (12), where smoked and salted fish are regularly consumed, and these studies did not distinguish between types of fish in their analyses. In fact, Knekt et al (20) reported a significant positive association between smoked and salted fish as well as between calculated N-nitrosodimethylamine (NDMA) intake and colorectal cancer risk and suggested that this finding may have been due to the nitrosamine content of these types of fish (56).

The finding of increased COX-2 expression in colorectal cancers and some colorectal adenomas (57, 58), provides support for the hypothesis that *n*-3 fatty acids could decrease colorectal cancer risk through the ability to inhibit the COX-2 enzyme and the production of eicosanoids derived from arachidonic acid, which could contribute to decreased cell proliferation and increased apoptosis (1). Fish oil supplementation has been reported to decrease proliferation in the rectal mucosa of patients with sporadic colorectal adenomas (59, 60) or to increase apoptosis in normal mucosa (61).

There are several limitations of this study that should be noted. First, fish intake was assessed only once on the 12-month follow-up questionnaire, and this measure may not be representative of fish intake over time. However, we would expect the resulting misclassification to be nondifferential and to bias RR estimates towards the null. In addition, PHS participants did not complete a full dietary assessment and the inverse association observed with fish intake could be due to some other unmeasured nutrient (such as vitamin D) that is correlated with fish intake.

There are also potential nondietary confounders that we were not able to take into account in our analyses. As mentioned previously, colonoscopy utilization is likely positively correlated with fish intake. We did examine the association between *n*-3 fatty acid intake from fish and colorectal cancer risk before and after 1995 to gauge the extent of potential confounding by colonoscopy utilization. Our results showed a stronger inverse association for cases occurring after 1995. However, there are other potential explanations for this difference and confounding by colonoscopy utilization may not be the most likely explanation. Because the PHS is a relatively homogeneous group, there may be less confounding by colonoscopy utilization than there would be in the general population. In the Health Professionals Follow-up Study, a similar group of men, 22.7% of men in the lowest quintile and 27.5% of men in the highest quintile of fish intake had a history of endoscopy at baseline in 1986. Despite the fact that there is some difference across quintiles, history of endoscopy is generally not a strong confounder of diet-disease associations in this cohort. In addition, in order for colonoscopy utilization to explain this difference, this variable would need to be negatively associated with colorectal cancer risk. While colonoscopy screening does lower colorectal cancer incidence in the long term through the removal of adenomas, this relationship may not be quite as clear in the early years of screening because it may also lead to the increased detection of slow growing cancers. Another potential explanation for the difference in results before and after 1995 is that *n*-3 fatty acids from fish could exert a protective effect early in colorectal carcinogenesis. However, findings from studies of *n*-3 fatty acids and colorectal adenoma risk are also inconsistent. Busstra et al (62) reported a nonsignificant inverse association between *n*-3 fatty acids measured in adipose tissue and the risk of colorectal adenoma. Using a measure of dietary *n*-3 fatty acid intake from a FFQ, Oh et al (54) observed no association for total colorectal adenomas and a nonsignificant inverse association for large adenomas. In addition, Giovannucci et al (63) reported a nonsignificant inverse association between dietary fish intake and colorectal adenomas.

We also do not have information on total energy intake in this cohort. Adjustment for energy intake accounts for extraneous variation in nutrient intake that is due to its correlation with total energy intake (rather than true differences in diet composition) and also adjusts for confounding by energy intake. However, because long-chain *n*-3 fatty acids are found in a

small number of foods, their correlation with total caloric intake is lower than other nutrients that are found in many foods. In the Health Professionals Follow-up Study, a similar cohort of men, the Spearman's correlation between EPA + DHA (the main long-chain *n*-3 fatty acids found in fish) and total energy intake is not strong (r = 0.18). Although we could not adjust for total energy intake, we did adjust for body mass index (an important determinant of total energy intake) and physical activity (the major determinant of between-person variation in total energy intake).

Our findings may also be limited by the validity of the FFQ for assessing fish intake. The correlation with the dietary records was low for shrimp/shellfish (r = 0.23). The correlations were higher, although still modest, for the other fish items. Albert et al (64) reported a strong inverse association between fish intake and risk of sudden death in this cohort; this result is consistent with the results from the GISSI randomized controlled trial (65) of *n*-3 fatty acids. This consistency lends support to the idea that these four FFQ items can discriminate fish intake between individuals. The correlation between fish intake and blood levels of long-chain *n*-3 fatty acids in this study is low. This could be partially explained by the fact that the FFQ and blood measures of intake reflected slightly different time periods. The blood samples were donated at baseline and reflect intake for some period of time before then (somewhere between a few weeks and a few months). The abbreviated FFQ was completed at the 12-month follow up and participants reported average intake over the previous year.

Fish intake may also be a marker of decreased meat intake which is associated with increased colorectal cancer risk (66). We addressed this issue by adjusting for red meat intake in our multivariate model and by examining the association between the ratio of red meat to fish intake and colorectal cancer risk. Although we did adjust for red meat intake, there is only a weak correlation between red meat and fish intake in this (r = −0.08) and no association between red meat intake and colorectal cancer risk (RR for highest vs. lowest quintile of red meat intake was 0.91 (0.71 – 1.16)) in this cohort.

Given that colorectal cancer takes many years to develop, it is possible that some of our study participants could have had undiagnosed colorectal cancer at the time that fish intake was assessed. This could result in bias if the preclinical disease altered the self-report of fish intake. To address this possible issue, we conducted sensitivity analyses excluding cases that developed during the first 5 years of follow-up and our results suggest little, if any, bias in our RRs resulting from preclinical disease.

Lastly, the participants are U.S. physicians, the majority of whom are Caucasian. Although the results of this study may not be directly generalizable to other populations, it is unlikely that the biological mechanism underlying the association between *n*-3 fatty acids and colorectal cancer would differ between populations.

In conclusion, the results from this large, prospective cohort of physicians followed for twenty-two years suggest that intake of fish and long-chain *n*-3 fatty acids from fish may decrease the risk of colorectal cancer. These findings are consistent with our previous study utilizing blood biomarker levels of long-chain n-3 fatty acids in a nested, case-control study within the same cohort (39).

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References

1. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr. 2004; 79(6):935–45. [PubMed: 15159222]
2. Reddy BS. Omega-3 fatty acids in colorectal cancer prevention. Int J Cancer. 2004; 112(1):1–7. [PubMed: 15305369]
3. Singh J, Hamid R, Reddy BS. Dietary fat and colon cancer: modulation of cyclooxygenase-2 by types and amount of dietary fat during the postinitiation stage of colon carcinogenesis. Cancer Res. 1997; 57(16):3465–70. [PubMed: 9270014]
4. Deschner EE, Lytle JS, Wong G, Ruperto JF, Newmark HL. The effect of dietary omega-3 fatty acids (fish oil) on azoxymethanol-induced focal areas of dysplasia and colon tumor incidence. Cancer. 1990; 66(11):2350–6. [PubMed: 2245391]
5. Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control. 1994; 5(1):38–52. [PubMed: 8123778]
6. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst. 2005; 97(12):906–16. [PubMed: 15956652]
7. Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, et al. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. Cancer Causes Control. 2002; 13(4):383–93. [PubMed: 12074508]
8. Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. Nutr Cancer. 1997; 28(3):276–81. [PubMed: 9343837]
9. Gaard M, Tretli S, Loken EB. Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. Eur J Cancer Prev. 1996; 5(6):445–54. [PubMed: 9061275]
10. Goldbohm RA, van den Brandt PA, van 't Veer P, Brants HA, Dorant E, Sturmans F, et al. A prospective cohort study on the relation between meat consumption and the risk of colon cancer. Cancer Res. 1994; 54(3):718–23. [PubMed: 8306333]
11. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med. 1990; 323(24):1664–72. [PubMed: 2172820]
12. Kobayashi M, Tsubono Y, Otani T, Hanaoka T, Sobue T, Tsugane S. Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. Nutr Cancer. 2004; 49(1):32–40. [PubMed: 15456633]
13. Pietinen P, Malila N, Virtanen M, Hartman TJ, Tangrea JA, Albanes D, et al. Diet and risk of colorectal cancer in a cohort of Finnish men. Cancer Causes Control. 1999; 10(5):387–96. [PubMed: 10530608]
14. Lin J, Zhang SM, Cook NR, Lee IM, Buring JE. Dietary fat and fatty acids and risk of colorectal cancer in women. Am J Epidemiol. 2004; 160(10):1011–22. [PubMed: 15522858]
15. Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. Int J Cancer. 2005; 113(5):829–34. [PubMed: 15499619]
16. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG. Red meat, chicken, and fish consumption and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2004; 13(9): 1509–14. [PubMed: 15342453]
17. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res. 1994; 54(9):2390–7. [PubMed: 8162586]
18. Phillips RL, Snowdon DA. Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. J Natl Cancer Inst. 1985; 74(2):307–17. [PubMed: 3856044]

19. Hsing AW, McLaughlin JK, Chow WH, Schuman LM, Co Chien HT, Gridley G, et al. Risk factors for colorectal cancer in a prospective study among U.S. white men. Int J Cancer. 1998; 77(4):549–53. [PubMed: 9679757]
20. Knekt P, Jarvinen R, Dich J, Hakulinen T. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. Int J Cancer. 1999; 80(6):852–6. [PubMed: 10074917]
21. Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, et al. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. Am J Epidemiol. 2007; 166(10):1116–25. [PubMed: 17823383]
22. Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. Am J Clin Nutr. 1999; 70(1):85–90. [PubMed: 10393143]
23. Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, et al. Food groups and risk of colorectal cancer in Italy. Int J Cancer. 1997; 72(1):56–61. [PubMed: 9212223]
24. Kune S, Kune GA, Watson LF. Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer Study. Nutr Cancer. 1987; 9(1):21–42. [PubMed: 3027675]
25. Kampman E, Verhoeven D, Sloots L, van ‘t Veer P. Vegetable and animal products as determinants of colon cancer risk in Dutch men and women. Cancer Causes Control. 1995; 6(3): 225–34. [PubMed: 7612802]
26. Bidoli E, Franceschi S, Talamini R, Barra S, La Vecchia C. Food consumption and cancer of the colon and rectum in north-eastern Italy. Int J Cancer. 1992; 50(2):223–9. [PubMed: 1730516]
27. Macquart-Moulin G, Riboli E, Cornee J, Kaaks R, Berthezene P. Colorectal polyps and diet: a case-control study in Marseilles. Int J Cancer. 1987; 40(2):179–88. [PubMed: 3038756]
28. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and colon cancer in Los Angeles County, California. Cancer Causes Control. 1992; 3(5):457–73. [PubMed: 1525327]
29. Steinmetz KA, Potter JD. Food-group consumption and colon cancer in the Adelaide Case-Control Study. II. Meat, poultry, seafood, dairy foods and eggs. Int J Cancer. 1993; 53(5):720–7. [PubMed: 8449595]
30. La Vecchia C, Negri E, Decarli A, D’Avanzo B, Gallotti L, Gentile A, et al. A case-control study of diet and colo-rectal cancer in northern Italy. Int J Cancer. 1988; 41(4):492–8. [PubMed: 3356484]
31. Chiu BC, Ji BT, Dai Q, Gridley G, McLaughlin JK, Gao YT, et al. Dietary factors and risk of colon cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev. 2003; 12(3):201–8. [PubMed: 12646508]
32. Kuriki K, Wakai K, Hirose K, Matsuo K, Ito H, Suzuki T, et al. Risk of colorectal cancer is linked to erythrocyte compositions of fatty acids as biomarkers for dietary intakes of fish, fat, and fatty acids. Cancer Epidemiol Biomarkers Prev. 2006; 15(10):1791–8. [PubMed: 17035384]
33. Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. Eur J Clin Nutr. 2002; 56 (Suppl 3):S14–9. [PubMed: 12142955]
34. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int J Vitam Nutr Res. 1998; 68(3):159–73. [PubMed: 9637947]
35. Culp BR, Titus BG, Lands WE. Inhibition of prostaglandin biosynthesis by eicosapentaenoic acid. Prostaglandins Med. 1979; 3(5):269–78. [PubMed: 121610]
36. Corey EJ, Shih C, Cashman JR. Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. Proc Natl Acad Sci U S A. 1983; 80(12):3581–4. [PubMed: 6304720]
37. Marshall LA, Johnston PV. Modulation of tissue prostaglandin synthesizing capacity by increased ratios of dietary alpha-linolenic acid to linoleic acid. Lipids. 1982; 17(12):905–13. [PubMed: 6298554]
38. Chan AT. Aspirin, non-steroidal anti-inflammatory drugs and colorectal neoplasia: future challenges in chemoprevention. Cancer Causes Control. 2003; 14(5):413–8. [PubMed: 12946035]
39. Hall MN, Campos H, Li H, Sesso HD, Stampfer MJ, Willett WC, et al. Blood Levels of Long-chain Polyunsaturated Fatty Acids, Aspirin, and the Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(2):314–21. [PubMed: 17301265]

40. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989; 321(3):129–35. [PubMed: 2664509]
41. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122(1):51–65. [PubMed: 4014201]
42. Composition of Foods. Agricultural Handbook Series No. 8. US Government Printing Office; Washington DC: 1963–1988.
43. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993; 93(7):790–6. [PubMed: 8320406]
44. 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(4):418–27. [PubMed: 1550093]
45. Baylin A, Kim MK, Donovan-Palmer A, Siles X, Dougherty L, Tocco P, et al. Fasting whole blood as a biomarker of essential fatty acid intake in epidemiologic studies: comparison with adipose tissue and plasma. Am J Epidemiol. 2005; 162(4):373–81. [PubMed: 16014782]
46. Cox D. Regression models and life-tables. J R Stat Soc Br. 1972; 34:187–220.
47. Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. Ann Intern Med. 1998; 128(9):713–20. [PubMed: 9556464]
48. Nkondjock A, Shatenstein B, Maisonneuve P, Ghadirian P. Assessment of risk associated with specific fatty acids and colorectal cancer among French-Canadians in Montreal: a case-control study. Int J Epidemiol. 2003; 32(2):200–9. [PubMed: 12714537]
49. Tavani A, Pelucchi C, Parpinel M, Negri E, Franceschi S, Levi F, et al. n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer. 2003; 105(1):113–6. [PubMed: 12672040]
50. Kojima M, Wakai K, Tokudome S, Suzuki K, Tamakoshi K, Watanabe Y, et al. Serum levels of polyunsaturated fatty acids and risk of colorectal cancer: a prospective study. Am J Epidemiol. 2005; 161(5):462–71. [PubMed: 15718482]
51. Terry P, Bergkvist L, Holmberg L, Wolk A. No association between fat and fatty acids intake and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2001; 10(8):913–4. [PubMed: 11489762]
52. Slattery ML, Potter JD, Duncan DM, Berry TD. Dietary fats and colon cancer: assessment of risk associated with specific fatty acids. Int J Cancer. 1997; 73(5):670–7. [PubMed: 9398044]
53. Tuyns AJ, Haelterman M, Kaaks R. Colorectal cancer and the intake of nutrients: oligosaccharides are a risk factor, fats are not. A case-control study in Belgium Nutr Cancer. 1987; 10(4):181–96.
54. Oh K, Willett WC, Fuchs CS, Giovannucci E. Dietary marine n-3 fatty acids in relation to risk of distal colorectal adenoma in women. Cancer Epidemiol Biomarkers Prev. 2005; 14(4):835–41. [PubMed: 15824153]
55. Maclean C, Newberry S, Mojica W, Khanna P, Issa A, Suttorp M, et al. Effects of Omega-3 Fatty Acids on Cancer Risk. Journal of the American Medical Association. 2006; 295(4):403–415. [PubMed: 16434631]
56. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. Environ Mol Mutagen. 2004; 44(1):44–55. [PubMed: 15199546]
57. Sano H, Kawahito Y, Wilder RL, Hashiramoto A, Mukai S, Asai K, et al. Expression of cyclooxygenase-1 and -2 in human colorectal cancer. Cancer Res. 1995; 55(17):3785–9. [PubMed: 7641194]
58. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology. 1994; 107(4):1183–8. [PubMed: 7926468]

59. Anti M, Marra G, Armelao F, Bartoli GM, Ficarelli R, Percesepe A, et al. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. Gastroenterology. 1992; 103(3):883–91. [PubMed: 1386825]
60. Anti M, Armelao F, Marra G, Percesepe A, Bartoli GM, Palozza P, et al. Effects of different doses of fish oil on rectal cell proliferation in patients with sporadic colonic adenomas. Gastroenterology. 1994; 107(6):1709–18. [PubMed: 7958682]
61. Cheng J, Ogawa K, Kuriki K, Yokoyama Y, Kamiya T, Seno K, et al. Increased intake of n-3 polyunsaturated fatty acids elevates the level of apoptosis in the normal sigmoid colon of patients polypectomized for adenomas/tumors. Cancer Lett. 2003; 193(1):17–24. [PubMed: 12691819]
62. Busstra MC, Siezen CL, Grubben MJ, van Kranen HJ, Nagengast FM, van't Veer P. Tissue levels of fish fatty acids and risk of colorectal adenomas: a case-control study (Netherlands). Cancer Causes Control. 2003; 14(3):269–76. [PubMed: 12814206]
63. Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. Relationship of diet to risk of colorectal adenoma in men. J Natl Cancer Inst. 1992; 84(2):91–8. [PubMed: 1310511]
64. Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, et al. Fish consumption and risk of sudden cardiac death. JAMA. 1998; 279(1):23–8. [PubMed: 9424039]
65. Marchioli R, Schweiger C, Tavazzi L, Valagussa F. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Lipids. 2001; 36 (Suppl):S119–26.
66. Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. Public Health Nutr. 2004; 7(1A):187–200. [PubMed: 14972060]

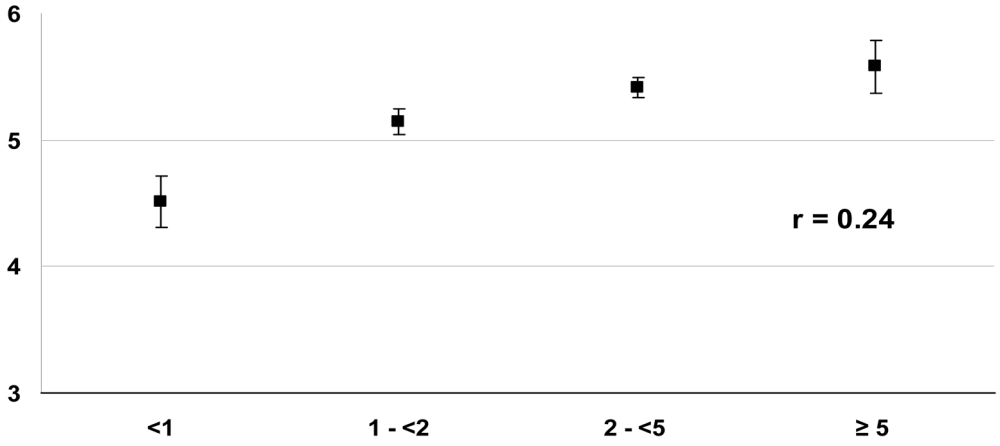

Figure 1.
Blood levels of long-chain *n*-3 fatty acids by category of fish intake. *Abscissa*, Fish intake (servings per week); *ordinate*, Mean blood level of total long-chain *n*-3 fatty acids (% of total fatty acids).

Table 1

Distribution of Baseline Risk Factors for Colorectal Cancer by Category of Fish Intake at 12 Months

	Average Frequency of Fish Intake (Times per Week)			
Variable	**< 1**	**1–<2**	**2–<5**	**≥5**
Number of men	2060	6656	10 350	2343
Age at randomization	54.0 ± 10.2 *	53.6 ± 9.6	53.6 ± 9.4	53.4 ±9.2
Smoking status - (%)				
Never	54.0	49.1	48.6	51.7
Past	33.6	38.4	41.1	40.2
Current	12.4	12.5	10.3	8.1
Multivitamin use - (%)				
Never	64.3	65.1	64.7	61.0
Past	16.3	16.6	15.4	15.7
Current	19.4	18.3	19.9	23.4
Diabetes - (%)	3.1	2.3	2.2	2.4
Aspirin Assignment - (%)	51.2	49.2	50.4	49.5
Vigorous Exercise - (%) †				
<once per week	31.8	29.7	25.8	24.1
1–4 times per week	52.7	54.8	58.0	56.9
≥ 5 times per week	15.5	15.5	16.1	19.1
Alcohol Intake - (%)				
≤1 time per week	53.4	42.1	36.3	36.8
2–6 times per week	26.9	34.0	37.7	38.7
≥ 1 drink per day	19.7	23.9	26.1	24.5
Body-mass Index ‡	24.6 ± 2.7	24.8 ± 2.8	24.8 ± 2.8	24.7 ± 2.8

* Plus-minus values are means ± SD

† Vigorous exercise defined as “exercise vigorous enough to work up a sweat.”

‡ Body Mass index is equal to the weight in kilograms divided by the square of the height in meters

Table 2

Relative Risk of Colorectal Cancer by Fish Intake

	Fish Intake				
	< 1 Time per Week	**1-<2 Times per week**	**2-<5 Times per week**	**≥5 Times per week**	**P Value for Trend**
Cases	54	162	243	41	
Person-years	35 661	116 957	182 668	40 886	
Age-adjusted RR (95% CI)	1.00	0.93 (0.68–1.26)	0.88 (0.66–1.18)	0.69 (0.46–1.03)	
Multivariate Adjusted RR[ǂ] (95% CI)	1.00	0.88 (0.65 – 1.20)	0.82 (0.61 – 1.10)	0.63 (0.42 – 0.95)	0.02

[ǂ]Multivariate model adjusted for age, smoking (never smoked, past smoking, current smoking), body-mass index (<23, 23 to 24.99, 25 to 26.99, ≥ 27), multivitamin use (never use, past use, current use), history of diabetes, random assignment to aspirin or placebo, vigorous exercise (< once per week, 1–4 times per week, ≥ 5–6 times per week), alcohol intake (≤ once per week, 2–6 times per week, ≥ once per day), and quartile of red meat intake

Table 3

Relative Risk of Colorectal Cancer by Dietary *n*-3 Fatty Acid Intake from Fish

	Dietary *n*-3 Fatty Acid Intake				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P Value for Trend**
Cases	137	139	118	106	
Person-years	91 686	99 676	93 282	91 528	
Age-adjusted RR (95% CI)	1.00	0.95 (0.75–1.21)	0.84 (0.66–1.08)	0.79 (0.61–1.02)	0.05
Multivariate Adjusted RR[≠] (95% CI)	1.00	0.93 (0.73–1.18)	0.81 (0.63 – 1.04)	0.76 (0.59 – 0.98)	0.02

[≠]Adjusted for same covariates as multivariate model in table 2

Table 4

Relative Risk* of Colorectal Cancer for Strata of Aspirin Assignment, BMI, and Time Period by Quartile of Dietary *n*-3 Fatty Acid Intake from Fish

	Dietary Intake of *n*-3 Fatty Acids from Fish								
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		
	No. of cases/ No. of person yrs.	RR (95% Confidence Interval	No. of cases/ No. of person yrs.	RR (95% Confidence Interval	No. of cases/ No. of person yrs.	RR (95% Confidence Interval	No. of cases/ No. of person yrs.	RR (95% Confidence Interval	P Value for Trend
Aspirin									
No	73/46 358	1.00 (ref)	78/49 824	1.00(0.73–1.38)	53/46 488	0.72(0.50–1.02)	55/45 295	0.79(0.55–1.12)*	0.08
Yes	64/45 329	1.00 (ref)	61/49 852	0.85(0.60–1.21)	65/46 794	0.92(0.65–1.30)	51/46 233	0.72(0.50–1.05)*	0.12
Body Mass Index									
<25	69/53 728	1.00 (ref)	71/57 094	0.99(0.71–1.38)	55/54 549	0.77(0.54–1.10)	59/53 925	0.85(0.60–1.21)//	0.24
≥ 25	68/37 958	1.00 (ref)	68/42 583	0.89(0.64–1.25)	63/38 733	0.87(0.62–1.23)	47/37 603	0.68(0.47–0.98)//	0.04
Time Period									
Before 1995	79/53 729	1.00 (ref)	72/58 066	0.87(0.64–1.20)	67/54 369	0.82(0.59–1.13)	72/53 656	0.89(0.65–1.23)†	0.54
1995 or later	58/43 126	1.00 (ref)	67/47 208	1.03(0.72–1.47)	51/44 139	0.82(0.56–1.20)	34/43 263	0.58(0.38–0.89)†	0.005

*Adjusted for same covariates as multivariate model in table 2 except random assignment to aspirin or placebo, p-value for interaction = 0.83

//Adjusted for same covariates as multivariate model in table 2 except BMI, p-value for interaction = 0.14

†Adjusted for same covariates as multivariate model in table 2, p-value for interaction = 0.18