Short Communication

A Prospective Study of Intake of Fish and Marine Fatty Acids and Prostate Cancer[1]

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Abstract

Experimental studies suggest that marine fatty acids have an antitumor effect on prostate tumor cells. The aim of this study was to investigate whether high consumption of fish and marine fatty acids reduces the risk of prostate cancer in humans. We followed 47,882 men participating in the Health Professionals Follow-up Study. Dietary intake was assessed in 1986, 1990, and 1994, using a validated food frequency questionnaire. During 12 years of follow-up, 2,482 cases of prostate cancer were diagnosed, of which 617 were diagnosed as advanced prostate cancer including 278 metastatic prostate cancers. Eating fish more than three times per week was associated with a reduced risk of prostate cancer, and the strongest association was for metastatic cancer (multivariate relative risk, 0.56; 95% confidence interval, 0.37–0.86, compared with infrequent consumption, *i.e.*, less than twice per month). Intake of marine fatty acids from food showed a similar but weaker association. Each additional daily intake of 0.5 g of marine fatty acid from food was associated with a 24% decreased risk of metastatic cancer. We found that men with high consumption of fish had a lower risk of prostate cancer, especially for metastatic cancer. Marine fatty acids may account for part of the effect, but other factors in fish may also play a role.

Introduction

Among dietary factors postulated to influence prostate cancer development are long chain polyunsaturated ω-3 fatty acids, found mainly in fish. This hypothesis is largely based on studies in animal models and on cell lines from human prostate tumors showing that the fatty acids EPA[3] and DHA[3] suppress tumor cell growth (1, 2).

Data from studies on humans have been sparse. Populations with a high consumption of fish, for example in Japan and among Eskimos in Alaska, have lower incidence rates of prostate cancer than populations with Western food habits, where fish intake in general is lower (3–6). Previous epidemiological studies on consumption of fish and prostate cancer have mostly been conducted in Western countries and have yielded inconsistent findings (7–9).

The aim of this study was to investigate whether consistently high, long-term intake of fish and marine fatty acids EPA and DHA is protective against different stages of prostate cancer in the Health Professionals Follow-up Study.

Patients and Methods

Study Population. The Health Professionals Follow-up Study is a prospective cohort established in 1986 when 51,529 United States men, 40–75 years of age, completed a mailed questionnaire about demographic and medical information. To form the cohort for analysis, we excluded men with cancers diagnosed before 1986, men with missing data on date of birth, men without dietary data, and those with implausibly high or low scores for total energy intake, leaving 47,882 men eligible for follow-up. Follow-up questionnaires have been mailed to all surviving cohort members every 2 years, and the National Death Index was used to determine vital status for nonrespondents.

Dietary Assessment Method. Diet was assessed in 1986 using a validated 131-item semiquantitative food frequency questionnaire (10, 11) and was updated in 1990 and 1994. For each subject, the nutrient intake was calculated by multiplying the intake frequency for each food item by the nutrient content for a standardized portion size. We inquired about intake of canned tuna, dark meat fish (mackerel, salmon, sardines, bluefish, and swordfish), other (not specified) fish dishes, and seafood as a main dish. The intake of marine ω-3 fatty acids comprised EPA (20:5) and DHA (22:6), derived from all food products. The use of fish oil supplements was assessed in 1988.

Ascertainment of Cases. At each mailing cycle, participants indicated whether they had been diagnosed with cancer. Diagnosis of prostate cancer was confirmed by review of medical records (87% of the cases) or other confirmation data from the participant or his family. Analyses were performed for all cancer cases ($n = 2482$), for advanced cancer cases ($n = 617$), and for metastatic cancer cases ($n = 278$), respectively.

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[3] The abbreviations used are: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PSA, prostate-specific antigen; CI, confidence interval.

Table 1 Age-standardized mean values of baseline characteristics by level of total fish consumption (servings) in 1986 in the Health Professionals Follow-up Study

	Fish consumption			
	<2/month	2/mo to 1/week	2–3/week	>3/week
Participants (*n*)	7,696	8,149	20,079	11,958
Age (yrs)	53.8	54.0	54.2	55.6
Mean daily intake[a]				
Total energy intake (kcal)	1,857	1,903	2,002	2,098
Total fat intake (g)	75.7	74.3	71.5	66.1
Saturated fat (g)	27.0	26.1	24.5	21.5
Monounsaturated fat (g)	29.2	28.6	27.3	24.9
α-Linolenic acid (g)	1.1	1.1	1.1	1.1
Linoleic acid (g)	11.4	11.5	11.4	11.2
trans-Fatty acids (g)	3.2	3.1	2.8	2.4
Marine fatty acids (g)	0.1	0.1	0.3	0.6
Lycopene (μg)	9145	9410	10382	11799
Fructose (g)	49.8	48.9	49.1	49.3
Calcium (mg)	902	894	893	906
Vitamin D (IU)	319	336	357	421
Retinol (IU)	5066	5256	5424	5933
Beef, pork, or lamb as a main dish (servings/day)	0.3	0.3	0.3	0.2
Multivitamin use (%)	38	40	41	46
Fish oil supplement use in 1988 (%)	3	3	4	6
Ever tested for serum PSA level by 1996 (%)	60	62	64	70
History of vasectomy (%)	21	22	21	20
Routine rectal exam 1986–1988 (%)	40	44	46	48
Current smokers (%)	12	12	10	7
Body mass index (kg/m^2)	25.6	25.5	25.6	25.4
Physical activity (MET-hours/week)[b]	21.9	22.7	23.2	26.8

[a] Nutrients are adjusted for total energy intake.
[b] MET (metabolic equivalent)-hours/week, sum of the average time/week spent in each activity × MET value of each activity, MET value = caloric need/kg body weight/hour activity/caloric need/kg body weight/hour at rest.

Statistical Analysis. We computed person-time of follow-up for each participant from the date the baseline questionnaire was returned in 1986 to the date of prostate cancer diagnosis, death from any cause, or, January 31, 1998, whichever came first. The incidence rate for each category of exposure was calculated as the number of cases with prostate cancer divided by the person-time of follow-up. The incidence rate ratio (relative risk) was computed as the incidence rate across each category of exposure divided by incidence rate in a specific reference category. For the analyses of dietary intake, we formed a cumulative updated dietary variable to reduce within-person variation and better represent long-term intake (12).

We used pooled logistic regression with 2-year time increments to adjust for age (5-year categories) and other potential confounding factors. To adjust for testing of serum PSA, a propensity score for PSA screening was constructed based on a logistic model using 37 sociodemographic and dietary characteristics. Small differences in a large number of covariates related to PSA screening can accumulate into a substantial overall difference that may not be captured in a binary variable (PSA tested or not), and the PSA propensity score for each subject represents the entire collection of predictors collapsed into a single composite predictor, which was categorized into quintiles and included in the analyses.

Results

The age-standardized characteristics at baseline by level of fish consumption are shown in Table 1. Participants in the highest intake category of fish were more often users of multivitamin and fish oil supplements and were more often tested for PSA or had had a rectal exam than men in the lower intake categories.

The relative risks of prostate cancer by levels of fish consumption are shown in Table 2. Eating fish more than three times per week was associated with an overall decreased risk for prostate cancer, especially for metastatic cancer. The associations for the individual fish dishes (canned tuna, fish with dark meat, and other, unspecified fish dishes) were weaker, and intake of seafood (shrimp, lobster, and scallops) was unassociated with risk of prostate cancer. When fish intake was analyzed as a continuous variable, an increase in three servings of fish per week was associated with a relative risk of 0.75 (95% CI, 0.60–0.94) for metastatic prostate cancer. Corresponding analyses of marine fatty acids showed that each additional 0.5 g/day gave a relative risk of 0.76 (95% CI, 0.58–0.98) for metastatic prostate cancer. However, use of fish oil supplements, as compared with no use, was not associated with a decreased risk of prostate cancer.

Adjusting for potential confounding factors such as fatty acids, red meat, lycopene, fructose, vitamin D, retinol, exercise, body mass index, smoking, ancestry, vasectomy, PSA testing, or rectal exam did not change the association between intake of fish or marine fatty acids and prostate cancer.

Discussion

We found that a high intake of fish was associated with a lower risk of metastatic prostate cancer. A similar association was also found for dietary marine fatty acids from food. However, our findings suggest that the beneficial effect associated with eating fish may not necessarily be achieved by fish oil supplements.

The incidence of prostate cancer in Europe and North America is high. In epidemiological studies from these regions, an intake of fish once per week or more often, as

Table 2 Relative risks (RR) and 95% CIs for prostate cancer and total fish consumption assessed in 1986, 1990, and 1994 in the Health Professionals Follow-up Study (1986–1998)

Cancer status	Total fish consumption[a]			
	<2/mo	2/mo to 1/week	2–3/week	>3/week
All prostate cancer				
Case/person-time	320/73,601	487/99,162	1,181/232,606	494/110,076
Age-adjusted RR	1.00	1.06 (0.92–1.22)	1.06 (0.94–1.20)	0.91 (0.79—1.05)
Multivariate RR[b]	1.00	1.05 (0.91–1.21)	1.06 (0.93–1.20)	0.93 (0.80–1.08)
Advanced prostate cancer				
Case/person-time	83/74,501	119/100,692	303/236,343	112/111,671
Age-adjusted RR	1.00	1.06 (0.80–1.40)	1.12 (0.88–1.43)	0.83 (0.60–1.06)
Multivariate RR[b]	1.00	1.05 (0.79–1.39)	1.14 (0.88–1.46)	0.83 (0.61–1.13)
Metastatic prostate cancer				
Case/person-time	50/74,640	47/101,081	130/237,189	51/111,993
Age-adjusted RR	1.00	0.72 (0.48–1.07)	0.84 (0.60–1.16)	0.59 (0.40–0.88)
Multivariate RR[b]	1.00	0.71 (0.48–1.06)	0.82 (0.58–1.16)	0.56 (0.37–0.86)

[a] Total fish consumption comprises canned tuna, dark meat fish (mackerel, salmon, sardines, bluefish, and swordfish) and other, unspecified fish dishes.
[b] Adjusted for age, calories, and fatty acids [saturated fat, monounsaturated fat, linoleic acid (18:2), α-linolenic acid (18:3), and *trans*-fatty acids], lycopene, retinol, vitamin D, and physical activity.

compared with an intake of less than once per week, has yielded inconsistent results (7–9, 13, 14). The Health Professionals Follow-up study is a relatively health conscious cohort with a large number of frequent consumers of fish, which allowed us to examine the association for four, or more, servings of fish per week. Our result is in agreement with a small study from Japan (6), which is a country with a low incidence rate of prostate cancer and an intake of fish higher than that in most Western countries.

A potential mechanism for the apparent protective effect of fish on prostate cancer may be related to marine fatty acids. Both EPA and DHA can inhibit the biological activity of eicosanoids and androgens (15–17), which are both known to have a stimulating effect on prostate cancer cell growth (18, 19). In animal models and in human prostate cancer cell lines, EPA and DHA suppress cell growth (2). However, because intakes of fish and marine fatty acids are highly correlated, it is difficult to disentangle the effect of fatty acids from the effect of fish *per se*. Fish may contain alternative or additional potential protective agents, such as vitamin D and retinol, and a replacement of deleterious factors such as red meat confers the benefits of high consumption of fish. However, adjusting for vitamin D, retinol, or red meat in the analysis did not change the result for fish intake. In contrast, use of fish oil supplement was not associated with a reduced risk of cancer, but the precision was low because only 4% of men used fish oil supplements, and we lacked information about dose, frequency, and duration.

Our study has several strengths: diet was assessed prospectively and validated; we measured potentially confounding variables; follow-up rate was high; the number of cases was large; and information on digital rectal examination and PSA testing was available. The strongest inverse association between fish consumption and prostate cancer risk was found for the group of cases with advanced cancer, especially metastatic cancer. A major concern, although it is not likely to have influenced the results, is the possibility that high fish consumers were more likely to undergo PSA testing and rectal exams, and therefore, tumors among members in this group were detected at an earlier stage. However, the inverse association persisted after adjusting for the PSA propensity score. Moreover, if the inverse association for metastatic prostate cancer was caused entirely by more frequent screening and thus earlier detection, we would find a positive, not an inverse association as seen for all prostate cancers. Nor does the relative risk differ between men who had undergone PSA testing or rectal exam and those who had not. In addition, the association between intake of fish at baseline and risk of prostate cancer did not change when the 2 first years of follow-up were excluded, which indicates that it is not likely that men with early symptoms started to increase their intake of fish.

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