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Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism

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Dietary intake of marine fatty acids from fish may protect against prostate cancer development. We studied this association and whether it is modified by genetic variation in cyclooxygenase (COX)-2, a key enzyme in fatty acid metabolism and inflammation. We assessed dietary intake of fish among 1,499 incident prostate cancer cases and 1,130 population controls in Sweden. Five single nucleotide polymorphisms (SNPs) were identified and genotyped in available blood samples for 1,378 cases and 782 controls. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by multivariate logistic regression. Multiplicative and additive interactions between fish intake and COX-2 SNPs on prostate cancer risk were evaluated. Eating fatty fish (*e.g.* salmon-type fish) once or more per week, compared to never, was associated with reduced risk of prostate cancer (OR: 0.57, 95% CI: 0.43–0.76). The OR comparing the highest to the lowest quartile of marine fatty acids intake was 0.70 (95% CI: 0.51–0.97). We found a significant interaction ($p < 0.001$) between salmon-type fish intake and a SNP in the *COX-2* gene (rs5275: +6365 T/C), but not with the 4 other SNPs examined. We found strong inverse associations with increasing intake of salmon-type fish among carriers of the variant allele (OR for once per week or more *vs.* never = 0.28, 95% CI: 0.18–0.45; $p_{trend} < 0.01$), but no association among carriers of the more common allele. Frequent consumption of fatty fish and marine fatty acids appears to reduce the risk of prostate cancer, and this association is modified by genetic variation in the *COX-2* gene.

Key words: epidemiology; prostate cancer; fish; omega-3 fatty acids; SNP

Increasing evidence from animal and *in vitro* studies shows that omega-3 (ω-3) fatty acids, especially long chain eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), protect against prostate cancer.[1–3] EPA and DHA are mainly found in fatty fish, and recent epidemiological studies showed that frequent consumption of fish is associated with reduced risk of prostate cancer.[2,4,5] Therefore, it has been suggested that high intake of fatty fish and marine fatty acids might be some of the most promising preventive dietary factors for prostate cancer. However, the mechanism for the potential protective effect remains unclear.

Polyunsaturated fatty acids, of which the main groups are omega-6 (ω-6) and ω-3 fatty acids, are converted in the body to eicosanoids, which are short-lived hormone-like lipids, such as prostaglandins and thromboxanes. These compounds have several biological effects, including modulation of the inflammatory and immune responses, cell differentiation and cellular growth.[3] One of the proposed mechanisms by which ω-3 fatty acids may affect carcinogenesis is through their suppressive effect on the biosynthesis of eicosanoids derived from arachidonic acid (AA; 20:4, an ω-6 fatty acid).[1] In general, AA-derived eicosanoids have proinflammatory effects and may promote carcinogenesis, whereas EPA-derived eicosanoids have anti-inflammatory effects and may inhibit prostate cancer growth.[1,3] A diet with a high ratio of ω-3 to ω-6 fatty acids results in a shift toward production of EPA-derived eicosanoids rather than AA-derived eicosanoids and, as a result, may inhibit the development of prostate cancer.

Cyclooxygenase-2 (COX-2), a key enzyme in eicosanoid synthesis, is overexpressed in prostate cancer tissue when compared to benign tissue from the same patients.[6–8] Also, use of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the activity of COX enzymes, is associated with a decreased risk of prostate cancer.[9] Taken together with our recent findings of an association between genetic variants of the *COX-2* gene and risk of prostate cancer,[10] this suggests that COX-2 may alter the effect of polyunsaturated fatty acids in the development of prostate cancer.

In a large Swedish population-based case-control study of prostate cancer, we studied the association between dietary intake of different fish species and fatty acids, especially marine fatty acids and the ratio of ω-3:ω-6 fatty acids, and risk of prostate cancer. Further, we aimed to explore interactions between fish intake, which ranged broadly in our source population, and genetic variation in the *COX-2* gene.

Methods

Study population

Cancer Prostate in Sweden (CAPS) is a population-based case-control study of prostate cancer etiology, with enrollment between January 1, 2001, and September 30, 2002. The study design and exposure assessment have been described in detail elsewhere.[11] Cases were all men between 35 and 79 years of age with pathologically verified adenocarcinoma of the prostate (ICD-10: C61) reported to 4 regional cancer registries in Sweden. Clinical data were obtained from linkage to the National Prostate Cancer Registry[12,13] for 95% of patients in the study. Control subjects were randomly selected from the Swedish Population Registry, and frequency matched to the expected distribution of the cases by age (in 5-year categories) and geographic residence. Advanced cases were defined as those with at least one of the following criteria: Tumor, Nodes, Metastasis (TNM) Stage[14] = T3/T4, N+, M+;

Abbreviations: AA, arachidonic acid; BMI, body mass index; CI, confidence interval; COX-2, cyclooxygenase-2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PSA, prostate-specific antigen; SNP, single nucleotide polymorphism.

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Gleason score = 8–10 or PSA level $\geq$ 100 ng/ml. Localized cases were those not meeting any of the above criteria.

In total, 1,895 prostate cancer cases were invited to the study. Of these, 1,499 (79%) agreed to participate by completing the questionnaire and 1,400 (74%) by donating a blood sample; 1,352 case patients (71%) did both. Of the 1,684 invited control subjects, 1,130 (67%) completed the questionnaire and 879 (52%) donated blood; 858 (51%) did both. All study participants granted informed consent at the time of enrollment in the study. This investigation was approved by the Ethics Committees at Karolinska Institutet and Umeå University.

Exposure assessment

The self-administered questionnaire assessed known and potential risk factors for prostate cancer.[11,15] The questionnaire included a validated food frequency questionnaire to measure average intake of foods and beverages during the preceding year.[16] The questionnaire assessed intake of 261 items, including individual dairy products, grains, starches, vegetables, fruits, meat, fish, eggs, sweets, beverages, additives (*e.g.*, butter, margarine and oil) and dietary supplements (*e.g.*, vitamins, minerals and fish oil). Participants were asked how often, on average, they ate salmon (*Salmo salar*), whitefish (*Coregonus lavaretus*) or char (*Salvelinus alpinus*) (hereafter referred to as ''salmon-type fish''); Baltic herring (*Clupea harengus membras*), herring (*Clupea harengus*) or mackerel (*Scomber scombrus*); cod (*Gadus morhua*), saithe (*Pollachius virens*) or fish fingers; caviar; or shellfish (*e.g.*, shrimp or crayfish): never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, 1 time per day, 2 times per day or 3+ times per day.

Questionnaire data about the average intake of food items were converted into average intake of energy and nutrients by linkage to the database of nutrients created by the Swedish National Food Administration.[17] To estimate total intake of ω-3 fatty acids, we summated intake of α-linolenic, eicosapentaenoic, docosapentaenoic and DHA. To estimate total intake of ω-6 fatty acids, we combined the intake of arachidonic and linoleic acids.

AA exists in limited levels in liver, meat and egg, but can be metabolized in humans from other fatty acids in the ω-6 fatty acid family. Linoleic acid is the parent fatty acid of the ω-6 family, and the main sources in a typical Swedish diet are vegetable oil (such as corn oil, sunflower oil, soy oil, rapeseed oil and margarine). α-Linolenic acid is the parent fatty acid of the ω-3 family, and can to a limited extent be converted to EPA and DHA. Conventional dietary sources of α-linolenic acid are rapeseed oil, soy oil, dark green leafy vegetables, flaxseed, walnuts and soybeans. EPA and DHA are mainly found in fatty fish, with levels that vary by the species of the fish, environmental factors and geographic area.[17] However, we were not able to take environmental factors and geographic area into account because the study questionnaire did not assess the origin of fish, such as the Baltic Sea or the Atlantic sea.

Selection of COX-2 single nucleotide polymorphisms

The *COX-2* gene, located on chromosome 1q25.2-q25.3, is less than 8 kb in length and includes 10 exons. To achieve complete coverage of the *COX-2* gene, we selected single nucleotide polymorphisms (SNPs) at a density of 1 SNP per kilobase and/or every missense mutation known. These SNPs were identified through public databases.[18,19] In total, we selected 16 SNPs from the *COX-2* gene, including SNPs located within the promoter, exons, introns and the 3′ untranslated region (3′ UTR). These SNPs were genotyped in 94 randomly selected control subjects from the CAPS study.

Five of the 16 SNPs—rs2745557 (+202 C/T), rs20432 (+3100 T/G), rs4648276 (+3935 T/C), rs5275 (+6365 T/C) and rs689470 (+8365 C/T)—had a minor allele frequency of more than 5% in the selected controls. We genotyped these 5 SNPs in all available samples (1,378 cases and 782 controls with extracted DNA) using the MassARRAY system (SEQUENOM, Valencia, CA) (for details see Shahedi *et al.*).[10] Assessment of quality control based on blinded duplicate samples yielded an estimated error rate of 0.0% (0/270 genotypes). All the 5 SNPs were in Hardy-Weinberg equilibrium among cases and controls respectively (all $p > 0.05$). When testing for linkage disequilibrium (LD), we found that all SNPs were in strong LD ($D' = 0.95$–1.0).[10]

Statistical methods

Baseline characteristics of cases and controls were compared using a two-sided *t*-test for continuous variables, and a χ^2-test for categorical variables.

The association between fish or fatty acids and prostate cancer was summarized in terms of odds ratios (ORs) and corresponding 95% confidence intervals (CI), and it was evaluated by age- and energy-adjusted unconditional logistic regression. Nutrient density was calculated by dividing the estimated intake of fatty acids and other nutrients by the total energy intake (*i.e.* the multivariate nutrient density model).[20] Participants with extremely high or low energy intake (<2,100 kJ/day or >21,000 kJ/day) were excluded from the analysis ($n = 16$). Intake of fatty acids was categorized into quartiles. A variable for ω-3:ω-6 ratio was created by dividing intake of ω-3 fatty acids by the intake of ω-6 fatty acids, and then categorizing the resulting ratio into quartiles. Categorization into quartiles was based on the distribution among controls, with the lowest quartile as the reference category for comparisons. Intake of individual seafood items was grouped into 3 categories (none, 1–3 times per month and 1 or more times per week). Total intake of salmon-type fish and herring/mackerel was grouped into 4 categories (none, 2 or fewer times per week, 3–4 times per week and 5 or more times per week).

As mentioned earlier, age- and energy-adjusted models (with age in 5-year intervals and total energy intake as a continuous variable) were fitted, as well as models adjusted for potential confounding factors, including level of education (0–9 years, 10–12 years, 13+ years), and intake of selected food groups and nutrient densities (fruit, vegetables, red meat, dairy products, fish other than the main exposure of interest, protein, carbohydrates, alcohol, fiber, saturated fat, fatty acids other than the main exposure of interest, food items rich in phytoestrogens, β-carotene, retinol, calcium, zinc, selenium, tocopherol, and vitamins A, C and D), categorized into quartiles based on the controls. The selection of covariates included in the final multivariate models was based on proportional ($\geq$10%) change in β-coefficients and previous subject matter knowledge. All covariates were tested, and those included in the final models were considered to be important confounding factors for the relation between the main exposure and prostate cancer, and are listed in the table footnotes (Tables II–IV). We used Pearson correlation coefficient analyses to evaluate whether dietary covariates were correlated. If the correlation coefficient between 2 covariates in the model or between a covariate and the main exposure was higher than 0.6, multicollinearity issues were considered and eventually one of the covariates was excluded from the model.[21] The Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model.[22]

To explore modifying effects of COX-2 SNPs on fish intake, formal statistical assessment of interaction effects was performed, considering both multiplicative and additive effect scales. In both approaches, frequencies of fish intake were represented by 2 indicator variables comparing medium and high fish consumer against never consumer, and each SNP was represented by an indicator variable (variant or not). On the multiplicative scale, interaction was assessed in a logistic regression model by a likelihood-ratio test of the product terms between the covariates representing fish intake and SNP genotypes. On the additive scale, interaction was assessed by the same product terms under a linear odds model. All interaction analyses were adjusted for age and total energy intake as described earlier. In addition, the association between prostate cancer risk and salmon-type fish intake were stratified by COX-2 alleles and trend tests, using the lowest levels of salmon-type fish

intake as a reference, were performed. Analyses were performed using the STATA System Software, version 8.2.

Results

Overall findings

Baseline characteristics and intake of nutrients among the study participants are presented in Table I. Most of the men were born in Sweden. We found no statistically significant differences between cases and controls with regard to body mass index, smoking history, level of education or intake of main groups of macronutrients. In addition, there was no difference in dietary mean intake of red meat, dairy products, all fish and seafood products combined, marine fatty acids or fish oil supplements. However, cases had a significantly higher energy intake than controls ($p = 0.02$).

Dietary intake of fish and prostate cancer risk

Estimates of prostate cancer risk by level of fish consumption are shown in Table II. High intake of salmon-type fish was associated with a significantly decreased relative risk of prostate cancer. After multivariate adjustment, risk of prostate cancer was 43% (95% CI: 24–57%) lower among men who ate salmon-type fish once or more per week, when compared with men who never ate salmon-type fish. Intake of herring and mackerel alone was not associated with risk of prostate cancer, but the combined intake of herring/mackerel and salmon-type fish was significantly associated with a 64% (95% CI: 28–82%) lower risk of prostate cancer for men who ate at least 5 servings of fatty fish per week. This finding was not substantially changed after additional adjustment for intake of EPA and DHA (data not shown). In contrast, intake of white fish (cod, saithe, fish fingers) or shellfish was significantly associated with an increased risk of prostate cancer. After multivariate adjustment, risk of prostate cancer was 45% (95% CI: 1.12–1.88) higher for men who ate white fish once or more per week, and 81% (95% C I: 1.28–2.56) higher for men who ate shellfish once or more per week, when compared with men who never ate white fish or shellfish, respectively. There was no association between prostate cancer and total intake of fish and seafood products: the OR comparing the highest to the lowest quartile of intake was 1.07 (95% CI: 0.85–1.35) (data not shown).

TABLE I – CHARACTERISTICS OF PROSTATE CANCER CASES AND CONTROLS WITH QUESTIONNAIRE DATA IN THE CAPS (CANCER PROSTATE SWEDEN) STUDY

Characteristics	Controls (n = 1,130)	Cases (n = 1,499)
Age, mean (years)	67.8	66.8
BMI, mean (kg/m^2)	26.3	26.2
Country of birth (n, %)		
Sweden	1,059 (94)	1,427 (95)
Other	71 (6)	72 (5)
Prostate cancer stage (n, %)		
Localized	–	828 (55)
Advanced	–	609 (41)
Unknown	–	62 (4)
Smoking history (n, %)		
Never	427 (38)	581 (39)
Ever	682 (60)	899 (60)
Missing	21 (2)	19 (1)
Total energy intake, median (kJ)	8,931	9,334
Proportion of energy intake (%) from:		
Fat[1] (%)	33	33
Protein[1] (%)	16	16
Carbohydrate[1](%)	50	50
Dietary intake, mean (g/day) of:		
Red meat	82	80
Dairy products	548	550
Fish and other seafood	40	41
Marine fatty acids[2]	0.60	0.57
Intake of fish oil supplements (n, %)		
Never	893 (79)	1,176 (78)
Ever	116 (10)	147 (10)
Missing	121 (11)	176 (12)

[1]Proportion of total energy intake derived from fat, protein, or carbohydrates.–[2]Sum of eicosapentaenoic, docosaapentaenoic and docosahexenoic fatty acids.

Dietary intake of long-chain fatty acids and prostate cancer risk

The relative risk of prostate cancer by level of fatty acids intake is shown in Table III. After multivariate adjustment, intake of ω-6 fatty acids was significantly associated with a 36% increased relative risk of prostate cancer in the highest when compared to the lowest quartile of intake. In separate analyses of linoleic acid and AA, only high intake of linoleic acid was associated with an increased risk of prostate cancer, and contributed the most to the positive association between omega-6 fatty acids and prostate cancer risk (data not shown).

We found no association between total intake of ω-3 fatty acids and prostate cancer risk. However, there was a statistically significant trend toward higher risk with increasing intake of α-linolenic acid. In contrast, high intake of marine fatty acids (EPA and DHA) was associated with a significantly decreased relative risk of prostate cancer; the risk was reduced by 30% in the highest compared to the lowest quartile of intake. The ratio of ω-3 to ω-6 fatty acids was associated with a significantly decreased relative risk of prostate cancer: subjects in the highest compared with the lowest quartile of ω-3:ω-6 consumption experienced a 29% lower risk. The association was even more pronounced for the ratio of EPA and DHA to ω-6 fatty acids, with a risk reduction of 34% in the highest compared with the lowest quartile of intake (Table III).

Additional adjustment for intake of fish oil supplement did not change the estimates for any of the associations. We repeated all analyses separately for cases with localized or advanced prostate cancer, and the estimates were similar across disease stages. For example, the OR comparing salmon-type fish once or more per week with men who never ate salmon-type fish was 0.56 (95% CI: 0.39–0.81, p for trend < 0.01) for advanced cases, and 0.58 (95% CI: 0.42–0.81, p for trend < 0.01) for localized cases (data not shown).

Interactions between intake of salmon-type fish and COX-2 polymorphisms

We explored each of the 5 identified SNPs in relation to increasing levels of salmon-type fish intake (Table IV). For each of the SNPs, we performed analyses separately for subjects homozygous for the more common allele and those who were heterozygous or homozygous for the variant allele. The interaction between salmon-type fish intake or combined intake of salmon/herring/mackerel and SNP (+6365 T/C) was significant on both the multiplicative ($p^{\text{salmon}} = <0.01$, $p^{\text{salmon/herring}} = 0.03$) and the additive scale ($p^{\text{salmon}} = <0.01$, $p^{\text{salmon/herring}} = 0.02$). We did not find any significant interactions between genotype and intake of salmon-type fish or herring/mackerel for any of the other 4 SNPs examined. In addition, we did not find any significant interactions between genotype and intake of white fish, shellfish, herring/mackerel or EPA/DHA fatty acids (data not shown). Among subjects who were heterozygous or homozygous for the variant allele (C) of the SNP (+6365 T/C), high intake of salmon-type fish was associated with a significantly decreased relative risk of prostate cancer. Following multivariate adjustment, risk of prostate cancer was 72% lower among men who ate salmon-type fish once or more per week, when compared with men who never ate salmon-type fish, whereas we found no significant association with salmon-type fish intake among subjects homozygous for the more common allele (T). We performed interaction and stratified analyses for cases with localized or advanced prostate cancer, and found no evidence of heterogeneity by disease stage (data not shown).

TABLE II – DIETARY INTAKE OF FISH AND ODDS RATIOS (OR) WITH 95% CIs FOR PROSTATE CANCER

Dietary intake of fish	Frequency	Controls (*n*)	Cases (*n*)	OR[1]	95% CI	OR	95% CI
Herring/mackerel	Never	169	219	1.00	(reference)	1.00[2]	(reference)
	1–3 per month	691	921	1.02	0.82–1.28	1.00[2]	0.79–1.27
	≥1 per week	223	288	0.96	0.73–1.26	1.00[2]	0.73–1.36
	p-value for linear trend			0.70		1.00	
Salmon-type fish	Never	174	277	1.00	(reference)	1.00[3]	(reference)
	1–3 per month	688	903	0.82	0.66–1.02	0.72[3]	0.57–0.90
	≥1 per week	222	249	0.65	0.50–0.85	0.57[3]	0.43–0.76
	p-value for linear trend			<0.01		<0.01	
Cod/saithe/fish fingers	Never	236	202	1.00	(reference)	1.00[4]	(reference)
	1–3 per month	600	846	1.58	1.27–1.96	1.41[4]	1.12–1.76
	≥1 per week	245	375	1.64	1.28–2.11	1.45[4]	1.12–1.88
	p-value for linear trend			<0.01		<0.01	
Shellfish	Never	450	450	1.00	(reference)	1.00[5]	(reference)
	1–3 per month	547	864	1.55	1.30–1.84	1.57[5]	1.30–1.88
	≥1 times per week	69	123	1.64	1.18–2.27	1.81[5]	1.28–2.56
	p-value for linear trend			<0.01		<0.01	
Salmon-type fish and herring/mackerel	Never	53	95	1.00	(reference)	1.00[6]	(reference)
	≤2 per week	921	1,214	0.74	0.53–1.02	0.64[6]	0.45–0.92
	3–4 per week	85	106	0.64	0.42–0.99	0.57[6]	0.35–0.90
	>5 per week	29	22	0.39	0.20–0.75	0.36[6]	0.18–0.72
	p-value for linear trend			<0.01		<0.01	

[1]Adjusted for age (in 5-year categories) and total energy intake.–[2]Adjusted for age (in 5-year categories), total energy intake, dietary intake of alcohol, food items rich in phytoestrogens, vitamin C, zinc, tocopherol, carbohydrates, saturated fat, selenium, shellfish, salmon-type fish (i.e., salmon, whitefish and char) and cod.–[3]Adjusted for age (in 5-year categories), total energy intake, dietary intake of alcohol, food items rich in phytoestrogens, vitamin C, fat other than ω-3, ω-6, EPA, or DHA, shellfish, cod and herring.–[4]Adjusted for age (in 5-year categories), total energy intake and dietary intake of shellfish, salmon-type fish and herring.–[5]Adjusted for age (in 5-year categories), total energy intake and dietary intake of food items rich in phytoestrogens, vitamin C, selenium, cod, salmon-type fish and herring.–[6]Adjusted for age (in 5-year categories), total energy intake, dietary intake of alcohol, food items rich in phytoestrogens, vitamin C, tocopherol, shellfish and cod.

TABLE III – DIETARY INTAKE OF FATTY ACIDS AND ODDS RATIOS (OR) WITH 95% CIs FOR PROSTATE CANCER

Fatty acid	Median (interquartile range)	Controls (*n*)	Cases (*n*)	OR[1]	95% CI	OR	95% CI
Omega-6 fatty acids[2] (g/day,·MJ)	0.66 (0.29–0.73)	281	367	1.00	(reference)	1.00[3]	(reference)
	0.78 (0.74–0.82)	281	319	0.88	0.71–1.11	0.93[3]	0.72–1.19
	0.88 (0.83–0.93)	281	358	0.94	0.76–1.18	1.03[3]	0.79–1.35
	1.05 (0.94–3.05)	281	445	1.16	0.93–1.47	1.36[3]	1.01–1.84
	p-value for linear trend			0.13		0.03	
Omega-3 fatty acids[4] (g/day,·MJ)	0.18 (0.07–0.19)	281	364	1.00	(reference)	1.00[5]	(reference)
	0.22 (0.20–0.23)	281	391	1.08	0.87–1.35	1.18[5]	0.91–1.52
	0.26 (0.24–0.28)	281	373	1.02	0.82–1.27	1.20[5]	0.88–1.63
	0.33 (0.29–1.4)	281	361	0.99	0.79–1.23	1.25[5]	0.88–1.78
	p-value for linear trend			0.78		0.27	
Alpha-linolenic acid (g/day,·MJ)	0.12 (0.05–0.13)	281	359	1.00	(reference)	1.00[6]	(reference)
	0.15 (0.14–0.16)	281	334	0.93	0.74–1.16	0.98[6]	0.77–1.26
	0.18 (0.17–0.19)	281	393	1.07	0.86–1.34	1.22[6]	0.93–1.61
	0.23 (0.20–0.60)	281	403	1.06	0.85–1.32	1.35[6]	0.99–1.84
				0.37		0.03	
Sum of EPA and DHA[7], g/day·MJ	0.03 (0–0.038)	277	398	1.00	(reference)	1.00[8]	(reference)
	0.05 (0.039–0.053)	281	409	1.03	0.83–1.28	0.98[8]	0.77–1.24
	0.06 (0.054–0.077)	280	369	0.97	0.77–1.21	0.91[8]	0.70–1.18
	0.11 (0.078–1.08)	279	308	0.80	0.64–1.00	0.70[8]	0.51–0.97
	p-value for linear trend				0.06		0.05
Ratio of omega-3:omega-6 fatty acids	0.22 (0.12–0.25)	281	441	1.00	(reference)	1.00[9]	(reference)
	0.27 (0.26–0.28)	281	390	0.89	0.72–1.10	0.89[9]	0.72–1.12
	0.30 (0.29–0.32)	281	360	0.83	0.67–1.03	0.83[9]	0.66–1.05
	0.37 (0.32–1.39)	281	298	0.71	0.56–0.88	0.71[9]	0.55–0.92
	p-value for linear trend				<0.01		<0.01
Ratio of EPA+DHA[3]:omega-6 fatty acids	0.03 (0–0.04)	281	449	1.00	(reference)	1.00[9]	(reference)
	0.05 (0.05–0.06)	281	390	0.87	0.70–1.09	0.84[9]	0.68–1.05
	0.08 (0.07–0.09)	281	355	0.81	0.65–1.01	0.77[9]	0.62–0.97
	0.13 (0.10–1.0)	281	295	0.69	0.55–0.87	0.66[9]	0.51–0.84
				<0.01		<0.01	

[1]Adjusted for age (in 5-year categories) and total energy intake.–[2]Sum of arachidonic and linoleic acids.–[3]Adjusted for age (in 5-year categories), total energy intake and dietary intake of food items rich in phytoestrogens, dietary intake of fat other than ω-6 fatty acids, red meat, dairy products, zinc, tocopherol, vitamin D and carbohydrates.–[4]Sum of alpha-linolenic, eicosapentaenoic, docosaapentaenoic and docosahexenoic acids.–[5]Adjusted for age (in 5-year categories), total energy intake and dietary intake of food items rich in phytoestrogens, vitamin C, saturated fat, fruit, vegetables, red meat, dairy products, zinc, tocopherol, vitamin D, carbohydrates and fiber.–[6]Adjusted for age (in 5-year categories), total energy intake and dietary intake of food items rich in phytoestrogens, vitamin C, saturated fat, red meat, dairy products, zinc, tocopherol, vitamin D, carbohydrates, fiber and alcohol.–[7]Sum of eicosapentaenoic acid (EPA), docosahexenoic acid (DHA) and docosaapentaenoic acid.–[8]Adjusted for age (in 5-year categories), total energy intake and dietary intake of food items rich in phytoestrogens, vitamin C, saturated fat, fruit, vegetables, red meat, dairy products, zinc, tocopherol, vitamin D, carbohydrates, fiber, alcohol, selenium, β-carotene and levels of education.–[9]Adjusted for age (in 5-year categories), total energy intake and dietary intake of fat other than ω-3and ω-6 fatty acids and vitamin D.

TABLE IV – ODDS RATIOS (OR) WITH 95% CIs FOR PROSTATE CANCER BY LEVELS OF INTAKE OF SALMON-TYPE FISH[1], STRATIFIED BY CYCLOOXYGENASE-2 ALLELES

refSNP ID and location	Nucleotide sequence	Dietary intake of salmon-type fish	Controls (*n*)	Cases (*n*)	OR[2]	95% CI	OR[3]	95% CI	*p*-value for multiplicative interaction[2]	*p*-value for additive interaction[2]
All cases		Never	174	277	1.0	(reference)	1.0	(reference)		
		1–3 per month	688	903	0.82	0.66–1.02	0.72	0.57–0.90		
		≥1 per week	222	249	0.65	0.50–0.85	0.57	0.43–0.76		
	p-value for linear trend				<0.01		<0.01			
rs5275+6365T/C	TT	Never	50	85	1.0	(reference)	1.0	(reference)	<0.01	<0.01
		1–3 per month	189	341	1.09	0.74–1.63	1.01	0.66–1.54		
		≥1 per week	49	96	1.14	0.69–1.89	1.10	0.64–1.89		
	p-value for linear trend				0.6		0.74			
	TC and CC	Never	45	149	1.0	(reference)	1.0	(reference)		
		1–3 per month	287	426	0.47	0.33–0.68	0.38	0.26–0.56		
		≥1 per week	100	116	0.36	0.23–0.55	0.28	0.18–0.45		
	p-value for linear trend				<0.01		<0.01			
rs20432+3100 T/G	TT	Never	67	162	1.0	(reference)	1.0	(reference)	0.17	0.14
		1–3 per month	335	566	0.71	0.52–0.98	0.65	0.46–0.91		
		≥1 per week	100	161	0.65	0.44–0.95	0.60	0.40–0.90		
	p-value for linear trend				0.03		0.02			
	TG and GG	Never	28	64	1.0	(reference)	1.0	(reference)		
		1–3 per month	135	172	0.59	0.36–0.96	0.47	0.28–0.81		
		≥1 per week	51	49	0.42	0.23–0.77	0.33	0.17–0.65		
	p-value for linear trend				<0.01		<0.01			
rs4648276+3935 T/C	TT	Never	75	175	1.0	(reference)	1.0	(reference)		
		1–3 per month	372	622	0.74	0.55–1.00	0.68	0.50–0.94		
		≥1 per week	110	174	0.68	0.47–0.97	0.63	0.43–0.93		
	p-value for linear trend				0.04		0.02			
	TC and CC	Never	24	54	1.0	(reference)	1.0	(reference)		
		1–3 per month	107	147	0.63	0.37–1.09	0.51	0.28–0.94	0.16	0.14
		≥1 per week	40	37	0.41	0.21–0.81	0.35	0.16–0.75		
	p-value for linear trend				0.01		<0.01			
rs2745557+202 C/T	CC	Never	63	164	1.0	(reference)	1.0	(reference)	0.10	0.09
		1–3 per month	340	543	0.64	0.47–0.88	0.58	0.41–0.81		
		≥1 per week	112	141	0.50	0.34–0.74	0.43	0.29–0.66		
	p-value for linear trend				<0.01		<0.01			
	CT and TT	Never	33	70	1.0	(reference)	1.0	(reference)		
		1–3 per month	141	228	0.79	0.49–1.26	0.66	0.40–1.10		
		≥1 per week	39	73	0.79	0.44–1.40	0.67	0.36–1.25		
	p-value for linear trend				0.4		0.2			
rs689470+8365 C/T	CC	Never	95	224	1.0	(reference)	1.0	(reference)	0.29	0.32
		1–3 per month	442	733	0.72	0.55–0.95	0.64	0.48–0.85		
		≥1 per week	140	195	0.58	0.42–0.81	0.53	0.37–0.75		
	p-value for linear trend				<0.01		<0.01			
	CT and TT	Never	6	8	1.0	(reference)	1.0	(reference)		
		1–3 per month	39	33	0.71	0.22–2.30	0.44	0.11–1.75		
		≥1 per week	11	15	1.30	0.33–5.06	1.07	0.19–6.14		
	p-value for linear trend				0.54		0.78			

[1]Salmon-type fish includes salmon, whitefish and char.–[2]Adjusted for age (in 5-year categories) and total energy intake.–[3]Adjusted for age (in 5-year categories), total energy intake, dietary intake of alcohol, food items rich in phytoestrogens, vitamin C, fat other than ω-3, ω-6, EPA or DHA, shellfish, cod and herring.

Discussion

We found that frequent consumption of fatty fish was strongly associated with a decreased relative risk of prostate cancer, whereas intake of lean fish and shellfish was associated with an increased risk. These results are further supported by our findings that high intake of marine fatty acids was associated with a significant reduction of prostate cancer risk. Moreover, a high ratio between intake of marine fatty acids and ω-6 fatty acids was strongly associated with a decreased prostate cancer risk, supporting our hypothesis that the fatty acids EPA and DHA are involved in the etiology of prostate cancer.

The inverse association between high intake of salmon-type fish and risk of prostate cancer was modified by a nucleotide sequence variant in the *COX-2* gene, and was seemingly confined to men who were C-allele carries of the SNP rs5275 (+6365 T/C). High salmon-type fish consumers with the C-allele had a 72% lower risk of prostate cancer, when compared to C-allele carriers with low salmon-type fish intake. No such association was found between intake of salmon-type fish intake and prostate cancer among men with the more common TT genotype. We applied both multiplicative and additive effect scales, and observed significant statistical interaction under both models.

Reviews of the literature on epidemiologic studies of the association between fish intake and/or fatty acids in adipose tissue, erythrocytes, serum or diet and the risk of prostate cancer[2,4,5] have revealed that 6 studies reported a significantly decreased risk of prostate cancer in association with high intake of fish, whereas 7 studies showed similar inverse but nonsignificant trends. However, no study found a significant positive association between dietary intake of fish, linoleic, or AA and prostate cancer risk, although α-linolenic acid intake was found to be associated with an increased risk in a majority of the studies, confirmed by Leitzmann *et al*. for advanced prostate cancer.[23] Only 3 out of 13 studies found a significantly reduced risk of prostate cancer in association with intake of EPA and DHA[2,4,5] while Leitzmann *et al*. found a borderline significant inverse relationship[23]; none reported a positive association with prostate cancer risk. Only a few studies have evaluated association between the ratio of ω -3 to ω-6 fatty acids and prostate cancer risk, with inconsistent results.[3,23] Some smaller studies have shown that a high ω-3:ω-6 ratio in serum is inversely related to prostate cancer progression.[24,25]

There are several possible explanations for the null findings in other studies. Almost all of them looked at total intake of fish and did not differentiate between species of fish; such misclassification might entail underestimation of any protective effect of fatty fish. The intake of marine fatty acids in some study populations may have been too low to show a potential protective effect, and/or the range of exposure may have been too narrow, limiting the ability to detect an association with prostate cancer.

There is some evidence of a stronger inverse association between fish intake and prostate cancer from studies conducted in countries with a high per capita intake of marine fatty acids, an indicator of high intake of fatty fish, when compared to results from studies conducted in countries with low per capita intake.[5] These findings are supported by another Swedish study that found a strong negative association between fish intake and prostate cancer.[26] Furthermore, the intake of fatty fish is relatively high in Sweden when compared with other countries,[27] and the intake of EPA and DHA in our study population in particular was relatively high when compared with intake in non-Swedish Western study populations.[28,29]

Even though herring and mackerel contain high levels of marine fatty acids, we did not find any inverse association with high intake of herring/mackerel alone. This lack of association may be because in Sweden it is common to eat pickled herring but in relatively small amounts on each occasion, while the intake of mackerel is not as common. Therefore, the contribution of herring/mackerel to the intake of marine fatty acids in the typical Swedish diet is much lower than that from salmon-type fish intake.

Our finding that intake of lean fish and shellfish was associated with an increased risk of prostate cancer is difficult to explain. However, the lack of an inverse association may be explained in part by the much lower levels of EPA and DHA in these types of seafood than in salmon-type fish and herring/mackerel,[30] or by the fact that fish fingers contain a relatively low proportion of fish meat.

To our knowledge, no other epidemiological studies have evaluated the interaction between intake of fish and polymorphisms in the *COX-2* gene in the etiology of prostate cancer. However, fish intake modified the association between COX-2 genotypes and colorectal adenoma in a case-control study.[31] In a small intervention study, the COX-2 expression was decreased among men with untreated prostate cancer consuming a low-fat diet supplemented with fish oil.[32] We recently found an association between 2 SNPs (+3100 T/G and +8365 C/T) in the *COX-2* gene and risk of prostate cancer.[10] However, the SNP (+6365 T/C) that interacted with fish intake in the present study was not independently associated with prostate cancer risk (OR = 0.93 (95% CI: 0.77–1.11). Although we did not detect any significant interactions between +3100 T/G or +8365 C/T and salmon-type fish intake, all 3 SNPs were in strong LD. Because these SNPs are not situated in the coding region of the gene, their biological relevance is unknown. However, an association study concluded that there are few existing functional COX-2 polymorphisms in the population, suggesting that there has been selective pressure against such SNPs because of the fundamental importance of the COX-2 enzyme in the maintenance of body homeostasis.[33] Although at present there are no functional data showing that the SNPs investigated in our studies affect the expression of COX-2 in the prostate, our findings suggest that +6365 T/C, or some other functional SNP in strong LD with this one, modifies the inverse association between salmon-type fish and risk of prostate cancer. Genetic variation in the *COX-2* gene may interact with fish consumption by influencing the synthesis and/or metabolism of eicosanoids, and could enhance the anti-inflammatory effect of marine fatty acids on prostate cancer risk. However, the precise mechanism of the effects of an interaction between COX-2 genetic variation and fish intake on prostate cancer development remains far from clear.

Emerging evidence that chronic inflammation is involved in the etiology of prostate cancer[34] is supported by previous findings that use of anti-inflammatory drugs (NSAIDs) is inversely associated with prostate cancer risk.[9] In addition, we recently reported that genetic variation in several inflammatory genes, including toll-like receptor 4[35] and toll-like receptor 1-6-10,[36] is associated with prostate cancer risk. It has been proposed that a protective effect of NSAIDs is mediated through inhibition of the COX enzymes. Overexpression of COX-2 in prostate cancer results in enhanced synthesis of prostaglandins, and malignant prostate tissue converts AA to prostaglandin 2 (PGE_2) at a 10-fold higher rate than benign tissue.[37] AA-derived eicosanoids favor the growth of malignant cells by increasing cell proliferation, impeding immune surveillance, inducing angiogenesis and inhibiting apoptosis.[1,38] In contrast, ω-3 derived eicosanoids have anti-inflammatory effects and may prevent prostate cancer growth by stimulating apoptosis and upregulating genes coding for antioxidant enzymes.[1,3]

Perhaps, the most prominent mechanism of the protective effect of ω-3 fatty acids may be *via* their suppressive effect on the biosynthesis of AA-derived eicosanoids. This inhibition occurs at several levels: (*i*) high intake of ω-3 fatty acids partly replaces AA incorporation into membrane phospholipids, resulting in decreased availability of precursors for AA-derived eicosanoids; (*ii*) ω-3 fatty acids have a higher affinity than ω-6 fatty acids for several enzymes (*e.g*., desaturases and elongases) in the metabolism of fatty acid conversion, and ω-3 fatty acids are therefore preferentially metabolized; and (*iii*) marine fatty acids, namely EPA and DHA, suppress COX-2 and lipooxygenases and compete with ω-6 fatty acids as the substrate for these enzymes.[1,3,39]

The ratio of ω-3/ω-6 fatty acids might be more important than the absolute intake of ω-3 fatty acids in inhibiting the development

of several diseases, including cancer, and various inflammatory and autoimmune diseases.[3] The ratio of ω-3/ω-6 fatty acids in Western diets is lower than in Far Eastern countries, where the incidence of prostate cancer is also lower.[3] In accordance with other studies, we found that the ω-3 fatty acid α-linolenic acid was associated with an increased risk of prostate cancer. Hence, the ratio of marine:ω-6 fatty acids may be a better measure of beneficial dietary fat intake than the ratio of ω-3:ω-6 fatty acids.

Our findings of a significant interaction between COX-2 polymorphism and salmon intake but not marine fatty acid intake may be explained by a higher degree of accuracy in the measurement of fish intake (directly from the questionnaire) than in the estimate of marine fatty acid intake. The reduced validity of the latter measurement may be because it is based on several assumptions, such as portion size, origin of the food items, analytical methods, type of dishes *etc*. Also, the range of dietary intake of marine fatty acids in our study population may be too narrow to provide sufficient power for interaction analysis.

Strengths of our study include its population-based design, large size and complete and rapid case ascertainment. The ethnic homogeneity of our study population reduces the risk of confounding by population stratification. Because there is limited PSA testing in our study population,[11] our results pertain mainly to non-PSA-detected, clinically significant prostate cancer. With detailed exposure information on dietary fish intake in our study population, we were able to distinguish among fatty fish, lean fish and shellfish. We were also able to evaluate risk associations with different fatty acids, and to adjust for other food items and nutrients, any or all of which may influence prostate cancer risk. However, we were unable to adjust for use of NSAIDs, since this was not evaluated in our study questionnaire.

Several other limitations may have influenced our results. Measurement error associated with the food frequency questionnaire is unavoidable, possibly leading to misclassification of dietary intake. However, because the possible role of fish and different fatty acids in prostate cancer development is not well known in the general Swedish population, such misclassification was likely nondifferential between cases and controls, leading to underestimation of the strength of any association. A potentially more serious concern is the relatively low participation rate, especially for blood donation, among eligible controls, since differential reasons for nonparticipation between cases and controls could introduce selection bias. While it is implausible that specific genotypes would influence individuals' willingness to join the study, participants and nonparticipants might differ in their intake of fish. Such bias should, however, have the same influence on all strata of COX-2 genotypes. The participation rate for the questionnaire only (79% for cases and 67% for controls) was higher than that for both questionnaire and blood donation. Therefore, we compared characteristics of participants who completed the questionnaire and donated blood with those of participants who only answered the questionnaire. Among both cases and controls, baseline characteristics (*e.g*., age, body mass index, level of education and smoking status), as well as dietary intake of fish, did not differ significantly between those who did and did not donate a blood specimen. However, controls who did not provide blood had a lower intake of macronutrients (protein, fat and carbohydrates) and total energy than controls who did provide blood. In addition, controls who did not provide blood were more likely to be missing information on fish intake. This difference could have occurred if controls who did not donate blood were less motivated to complete the questionnaire fully, which would have lead to lower calculated intake of food overall. However, if controls who did not donate blood truly consumed lower amounts of fish, then we would have underestimated the true protective effect of salmon-type fish intake on prostate cancer risk. Significant findings due to the play of chance following multiple comparisons are often a legitimate concern. In this study, however, we performed only a few global tests for interaction, and therefore did not adjust for multiple testing. Our analysis of the associations between fatty fish and prostate cancer was driven by a strong *a priori* hypothesis based on results from other studies. However, our finding of an interaction between fatty fish intake and COX-2 polymorphism was exploratory, and needs to be confirmed in other study populations.

In summary, we found that frequent consumption of fatty fish and marine fatty acids reduced the risk of prostate cancer and the protective effect of fish is modified by variation in the *COX-2* gene. Speculatively, the differences in fish intake and/or distribution of COX-2 polymorphisms could explain part of the international variation in prostate cancer incidence rates. Further studies of interactions between fish intake and polymorphisms in COX-2 and other genes involved in fat metabolism should be explored further, especially in other populations of different ethnicities.

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